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Rajani Mathur
Pranabesh Chakraborty *Editors*

Essentials of Pharmacodynamics and Drug Action

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Raja Chakraverty • Rajani Mathur •
Pranabesh Chakraborty
Editors

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Foreword

Going through the pages of *Essentials of Pharmacodynamics and Drug Action*, by **Raja Chakraverty, Rajani Mathur, and Pranabesh Chakraborty**, I am excited. Describing pharmacology in terms of dynamics and the mechanism of drug action is very much clarified in a very simple language in this book. Pharmacology is the science of drugs or medicine. One of the important pillars of pharmacology is kinetics. This book emphasizes pharmacodynamics, which explores the effects of medicines and at the same time it will be helpful for the learners to develop concepts for ensuring therapy as well as the rational use of drugs.

Drugs are substances used for preventive, promotive, and curative purposes. Currently, civilization depends upon “drugs or medicines.” An important issue in drug development research depends on the basic concepts of drug action. Drugs acting on different systems, such as autonomic nervous system, central nervous system, gastrointestinal system, and cardiovascular system, are narrated in this book. Very interestingly, immunomodulation-related drugs are also discussed along with hormones and antimicrobials. Tables and supplementary figures will help in the meaningful learning.

The beauty of this book lies in its simple language, lucid explanations, and understandable clarification of complicated mechanisms of action. Analysis of various human diseases and the pharmacological agents governing them provides a reference resource for academicians, researchers, and clinical practitioners. Academicians can help the young learners in the development of concepts, researchers can innovate further in drug development, and clinicians can use this book for ensuring therapy.

I hope that this book *Essentials of Pharmacodynamics and Drug Action* will be used from students to teachers, researchers to professionals, and this will help to redesign the facets and spectrum of the colorful subject “Pharmacology.”

My best wishes to the authors for such initiative.

Long live Pharmacology!

Medical College and Hospital
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Anjan Adhikari

Preface

Essentials of Pharmacodynamics and Drug Action: While a textbook with a strong clinical emphasis is required to train future doctors, pharmacists, or nurses, it does a great deal of disservice to future researchers. How are drugs discovered and how do they act? How are their mechanisms of action elucidated? These are all relevant questions for research-oriented undergraduate and postgraduate students of health sciences. They must not only know the answers but also be equipped to address recent evidence of drug discovery from the laboratory and clinical trials.

Essentials of Pharmacodynamics and Drug Action is a comprehensive book curated for all types of medical professionals and students dealing with drugs and their mechanisms of action lucidly and attempts to do just that. Rather than merely stating that beta lactams inhibit cell wall synthesis, this textbook will explain every observation and experiment that backed this conclusion, and will do so for the mechanism of action for every class of drugs across therapeutic domains discussed. This textbook was written for you: students, young faculty members, clinical practitioners, and future researchers. We will be happy for your constructive feedback regarding the same to help us improve upon this work in subsequent editions.

Happy Reading everyone!

Kolkata, West Bengal, India
New Delhi, Delhi, India
Kolkata, West Bengal, India

Raja Chakraverty
Rajani Mathur
Pranabesh Chakraborty

Contents

1	Principles of Pharmacokinetics: The Dynamics of Drug Action	1
	Raja Chakraverty and Tatini Debnath	
2	Pharmacodynamics: Mechanism of Drug Action	5
	Dipesh Chakraborty	
3	Principles of Therapeutics and Gene-Based Therapy	41
	Anamika Sengupta	
4	Drugs Acting on Autonomic Nervous System	57
	Moitreyee Chattopadhyay and Bhaskar Pal	
5	Drugs Acting on Central Nervous System	89
	Dipesh Chakraborty and Ria Das	
6	Drugs Acting on Renal and Cardiovascular Function	123
	Raja Chakraverty and Tatini Debnath	
7	Drugs Affecting Gastrointestinal Functions	145
	Moitreyee Chattopadhyay and Sweety Gupta	
8	Pharmacotherapy of Microbial Diseases	169
	Pranabesh Chakraborty and Dipesh Chakraborty	
9	Hormones and Hormones Antagonists	199
	Arshvir Kaur, Raja Chakraverty, and Rajani Mathur	
10	Drugs Used for Immunomodulation	229
	Subarna Ganguli and Tatini Debnath	

Editors and Contributors

About the Editors



Raja Chakraverty is a Pharmacologist by training and currently serves as an ICMR Scientist in the Department of Critical Care Medicine at IPGME&R, Kolkata, and co-ordinates research in the area of Antimicrobial Resistance. He is a well-known biomedical scientist who studied Pharmaceutical Technology at the UG, PG, and doctoral level. He has 11 years of rich teaching and research experience. Dr. Chakraverty has been awarded many accolades including Best Paper awards and Best Researcher Award in 2021 at various national seminars and has travelled abroad for academic discourses and invited orations. Dr. Chakraverty is a prolific writer who has published around 60 highly cited full-length articles in peer-reviewed journals and several book chapters and two authored books. Dr. Chakraverty is also a leading Editor for various journals. He is a life member of the Indian Pharmacological Society.



Rajani Mathur is a distinguished faculty member at DIPSAR (Delhi Institute of Pharmaceutical Sciences and Research), New Delhi, with an impressive academic and research background. She holds a BPharm, MSc, and PhD in Pharmacology. Dr. Mathur has made significant contributions to the field of Pharmacology through groundbreaking research work at AIIMS (All India Institute of Medical Sciences), New Delhi, and DIPSAR.

Her research interests encompass various critical areas, including drug development for cancer angiogenesis, pediatric NAFLD (non-alcoholic fatty liver disease), pharmacovigilance, and materiovigilance, as well as the standardization and validation of medicinal plants.

Dr. Mathur's remarkable achievements have garnered widespread recognition and honors. She has been acknowledged with certificates of appreciation, best paper presentation awards, and scholarship grants for her exemplary work. Her expertise is recognized internationally, as evident from her active membership in the International Society for Pharmacoeconomics and Outcomes Research.

In addition, Dr. Mathur has been elected as a member of prestigious organizations such as the National Academy of Medical Sciences, India, and the International Union of Radio Science. Her significant contributions to the field of Pharmacology are also evident from her invention being published in *The Patent Office Journal*.

As an accomplished writer, Dr. Mathur has made valuable contributions to journals and editorial boards worldwide. Her research has been presented at numerous international conferences, where she received accolades for her outstanding work.



Pranabesh Chakraborty is serving as a UGC Adjunct Professor and Former Director at the School of Pharmaceutical Science & Health Care Technology at Maulana Abul Kalam Azad University of Technology (formerly West Bengal University of Technology), India. He has also served as the director and adviser for academic and research affairs at Bengal School of Technology and Bengal School of Technology & Management.

Throughout his career, the author has shown exceptional dedication to education and research, having served as the Principal of the first pharmaceutical college in West Bengal, Gupta College of Technological Sciences. Additionally, he was the Principal at Kanak Manjari Institute of Pharmaceutical Sciences under Sambalpur University.

The author's contributions to academia and research are evident through his extensive list of publications, including more than 50 publications, books, and book chapters.

Recognized for his exemplary work, the author has received several prestigious awards, such as the ATI Visistha Chikitsa Medal and the Best Principal Award in 2010. His dedication to public service is evident from his honorary life membership in ACCP (Association of Colleges of Chest Physicians, India).

The author has also played a significant role in establishing and supporting various academic and research associations, including the Pharmaceutical Technologists Association (PTA), Indian Pharmaceutical Graduates Association (IPGA), Indian Society for Technical Education (ISTE), and more. His involvement as a founder member of several research scholar associations showcases his commitment to fostering scholarly communities.

In the realm of publishing, the author has held esteemed positions as the Chief Editor in a Society Journal and the Editor in one of the International Journals.

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Principles of Pharmacokinetics: The Dynamics of Drug Action

1

Raja Chakraverty and Tatini Debnath

Abstract

The term “pharmacokinetics” is derived from the ancient Greek words “pharmakon” and “kinetikos,” meaning “drug” and “putting in motion,” respectively. It serves as a fundamental concept in pharmacology, elucidating how the body interacts with pharmaceutical substances and how these substances influence the body’s response. Pharmacokinetics explores the processes of liberation, absorption, distribution, metabolism, and excretion (LADME) of drugs, providing valuable insights for optimizing drug administration and utilization.

Keywords

Pharmacokinetics · Absorption · Elimination · Kinetics

1.1 Introduction

Liberation is the phase in which a drug is released from its formulation and is essential for subsequent absorption into the body. Absorption primarily occurs in the small intestine through passive diffusion, and pharmacokinetic parameters governing absorption include the absorption rate constant and bioavailability. Distribution involves the dissemination of a drug across fluids and tissues in the body, with parameters such as the apparent volume of distribution and unbound fraction being

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relevant. Metabolism refers to the transformation of a drug into metabolites within the body. Parameters associated with metabolism include metabolic clearance, which is the rate of drug metabolism relative to drug concentration in plasma (Craig 1995; Moore et al. 1987; Dudley 1991).

Excretion is the elimination of a drug from the body, often through renal clearance. Pharmacokinetic parameters related to excretion include renal clearance and fraction excreted unchanged. Several additional pharmacokinetic parameters contribute to understanding a drug elimination, including the elimination rate constant, half-life, clearance, area under the curve, steady-state concentration, non-renal clearance, total body clearance, and intrinsic clearance (Bennett et al. 1979; Nicolau et al. 1995; Hatala et al. 1996; Hutchin & Cortopassi 1994; Tran Ba Huy et al. 1981).

In addition to pharmacokinetic parameters, other pharmacokinetic values such as the acid dissociation constant, bioavailability, solubility, and absorption capacity play crucial roles in drug absorption and distribution. Pharmacokinetic studies typically involve healthy volunteers or patients and aim to estimate the dynamic interactions between drugs and the body. These studies provide valuable data for optimizing drug design, dosing strategies, individualized treatment, and risk assessment (Hitt et al. 1997; Zhanel et al. 2001; Kuti et al. 2002).

Indeed, a comprehensive understanding of pharmacokinetic parameters is vital for assessing the absorption, distribution, metabolism, and excretion (ADME) of drugs within the body. These parameters help in determining the fate of a drug in the body and its overall pharmacological and therapeutic effects. Here is a summary of the key pharmacokinetic parameters mentioned:

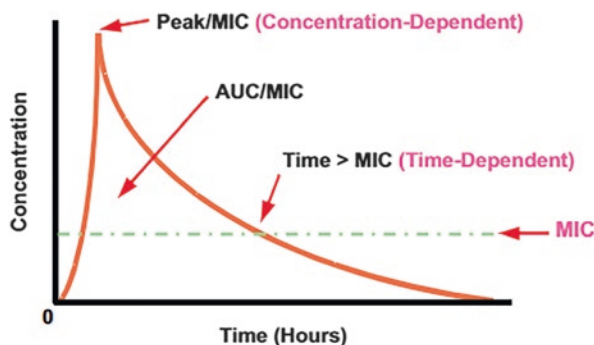
1.2 Absorption

- Absorption rate constant: Reflects the rate at which a drug is absorbed into the bloodstream.
- Bioavailability: Represents the fraction of the administered drug dose that reaches systemic circulation unchanged, typically influenced by factors such as absorption, metabolism, and excretion (Nicolau et al. 1999, Donskey et al. 2004).

1.3 Distribution

- Apparent volume of distribution: Provides an estimate of the theoretical volume into which a drug distributes throughout the body, indicating the extent of distribution beyond the plasma.
- Unbound fraction: Indicates the proportion of the drug that is not bound to plasma proteins, which is typically the fraction responsible for pharmacological activity.

Fig. 1.1 Pharmacokinetic plasma drug concentration profile



1.4 Metabolism

- Metabolic clearance: Reflects the rate at which a drug is metabolized in the body relative to its concentration in plasma.

1.5 Excretion

- Renal clearance: Indicates the rate at which a drug is eliminated from the bloodstream by the kidneys relative to its concentration in plasma.
- Fraction excreted unchanged: Represents the proportion of the administered drug dose that is excreted unchanged in urine relative to the overall rate of drug elimination.

These pharmacokinetic parameters collectively provide insights into the behavior of drugs in the body, helping in the optimization of dosing regimens, prediction of drug interactions, and assessment of drug safety and efficacy. Understanding these parameters is fundamental in clinical pharmacology and pharmacotherapy for effective and safe drug administration (Fig. 1.1) (Jumbe et al. 2003; Fink et al. 1994).

1.6 Conclusion

Clinical pharmacokinetics integrates pharmacokinetic principles into clinical practice to tailor drug therapy to individual patients, optimize dosing regimens, enhance safety, and monitor therapeutic outcomes. It plays a vital role in precision medicine and evidence-based medicine, contributing to the safe and effective use of drugs in patient care.

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Pharmacodynamics: Mechanism of Drug Action

2

Dipesh Chakraborty

Abstract

Pharmacodynamics is the study of mechanisms behind drug actions. It helps us understand the behaviour of drugs inside a body and the way body reacts to the drugs. Every class of drug preserves a unique mechanism of action mostly through different receptor proteins and sometimes involving associated secondary messengers. Pathway or the mechanism a drug follows determines the onset of action, drug interactions, adverse drug reaction, etc. After administration of drugs, showing the pharmacological effects involves many interconnected phases and transportation of drug molecules to the site of action is really crucial and for that our body uses different enzymes, ion exchange pumps, and specialized proteins. On reaching the site of action, drugs are attached as signals or signalling molecule and upon binding to its specific ligand binding site the transducer mechanism takes place. So, in this chapter we have focused on the molecular basis of the drug action which will not only serve as a first-hand guide to pharmaceutical and medical graduates but also to students from biological sciences.

Keywords

Pharmacodynamics · Agonist · Antagonist · Transporter · Receptor · Second messenger · Apoptosis

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Abbreviations

ABC	ATP-binding cassette
AF-1	N-terminal activation region
AQP	Aquaporin
ATPBD	ATP-binding domain
BAX	Bcl-2-associated X protein
Bcl-2	B-cell lymphoma 2
CNS	Central nervous system
CRE	cAMP response element motif
CREB	cAMP response element binding protein
DAG	Diacylglycerol
DCT	Distal convoluted tubule
DHP	Dihydropyridine
Elk-1	ETS like-1 protein
FADD	Fas-associated death domain
GAP	GTPase-activating protein or GTPase-accelerating protein
GAT	GABA transporter
GEF	Guanine nucleotide exchange factors
HREs	Hormone response elements
IKK	I κ B kinase
IP3	Inositol triphosphate
IRAKs	Interleukin-1 receptor-associated kinase 1
MAPK	Mitogen-activated protein kinase
mTOR	Mammalian target of rapamycin
NCor	Nuclear hormone receptor co-repressor
PDE	Phosphodiesterases
PG	Prostaglandin
PIAS	Protein inhibitor of activated STAT
PIP2	Phosphatidylinositol-4,5 bisphosphate
PKA	Protein kinase A
PLC	Phospholipase C
PTPs	Protein tyrosine phosphatase
RAS	Renin-angiotensin system
SERCA	Sarcoendoplasmic reticulum calcium ATPase
SERMs	Selective oestrogen receptor modulators
SGLT1	Glucose symporter
SMAC	Second mitochondria-derived activator of caspase
SMRT	Silencing mediator of retinoid hormone receptor
SOC	Suppressor of cytokine signalling
SRC	Steroid receptor co-activator family
TLRs	Toll-like receptors
TRADD	Tumour necrosis factor receptor type 1-associated DEATH domain protein
TRAIL	TNF-related apoptosis-inducing ligand

In order to restore the body's normal physiology in the presence of impaired body function, or usually what we refer to as 'disease', medicine or 'drug' is crucial. Disease, as its name suggests, creates discomfort in the body as a result of any degree of biochemical modification that results in altered physiology. Drugs become crucial for halting biochemical alterations and returning the body to normal physiology, or what we call a 'fit body'.

We will choose paracetamol as the simplest example because it is widely available and typically used as an analgesic and an antipyretic. We understand that the administered drug must have some specific mechanism of action by which they are able to decrease the temperature and function as antipyretics, so once we feel feverish, the pill becomes our first choice, and, within half an hour, the fever begins to subside.

If we focus specifically on the medication in question, the most widely accepted theory explaining its antipyretic effects is that it inhibits the CNS cyclooxygenase enzyme, which is essential for the conversion of arachidonic acid to the prostaglandins H₂ (PGH₂) that cause fever.

Pharmacodynamics, a fundamental idea in pharmaceuticals and biopharmaceuticals, is the simple understanding of how a medicine interacts with the body. Now, when we refer to pharmacodynamics as the mechanism behind the action of any drug, we must keep in mind that the same mechanism of action of a drug can result in the easing of the condition and that it can also bring about adverse effects. Having in-depth knowledge of pharmacodynamics is helpful in creating a logical and superior therapy plan (Ayoub 2021). Even though some genetic variants may cause some disparities in the outcome of treatments, a balanced approach of pharmacokinetics and pharmacodynamics will always result in a safer and more effective therapy.

2.1 Basic Concepts of Pharmacodynamics

The effect of a drug is an outcome of the interaction between the active pharmaceutical ingredient and the specific macromolecular components, which are predominantly proteins with specialized structures, capable of binding to the endogenous ligands or signals to carry on day-to-day biochemical processes and thereby maintaining normal body physiology. These macromolecules are known as receptors (Feher 2017).

In cases of altered secretion or hindered availability of those endogenous signals or ligands, our bodies start feeling diseased, and we need the administration of drugs that may mimic the effects of the endogenous signal or may do the opposite. So, the drug actually changes the magnitude of intrinsic cell signalling rather than creating a novel response. While designing a therapeutic approach against a disease, the first thing to be understood is the reason or pathophysiology of the disease and, thereby, the target to neutralize the disease. Now, this 'target' of drug action will mostly be different receptors through which the drug will be exerting its action. The

better the target is observed, the better the chance is of getting successful therapeutics.

Depending upon the location, the receptors can be of two types:

- Membrane-embedded receptors: These receptors are mostly found in the plasma membrane, having a ligand binding side at the extracellular domain and effector side in the cytosolic domain.
- Receptors Inside specific intracellular compartments.

Apart from the physiological receptors, there are a few proteins named acceptors that may alter the pharmacokinetics of a drug by attaching to it by virtue of the protein binding property of the drug. Albumin is the most important drug-binding protein. Though lipoprotein, globulin, and α 1-acid glycoprotein also have drug-binding properties, the drugs, which are highly protein-bound drugs, poorly penetrate the tissues.

A physiological receptor is one that treats the endogenous signalling molecule or chemical messengers as its ligand and thereby plays an important role in normal biochemical pathways. These physiological receptors are predominant in the body and very specific with ligand selectivity and action.

2.2 Concepts of Agonism and Antagonism

As already mentioned, drugs that mimic the action of normal endogenous chemical messengers when administered to treat a disease are called agonists. This does mean an agonist attachment will always lead to the same effect that upon attachment of the endogenous chemical would have resulted. If the drug gets attached to the specific location where endogenous agonists get attached, then the drug will be called a primary agonist. If attached to a site other than the primary recognition site, then it is called an allosteric or allotropic agonist. Drugs that act to counter the actions of endogenous chemical messengers are called antagonists. These events of antagonism may be the result of few possibilities, like competitive antagonism in which a drug molecule competes with an endogenous messenger to occupy the specific recognition site (syntrophic interaction) and thereby does not allow the endogenous material to get attached to the receptor. The drug molecules can also hinder the action of endogenous chemical messengers by getting attached to a site other than the primary site and causing a conformational change in the primary site ligand binding site, resulting in the unavailability of the site for endogenous molecules to sit. This is called allosteric antagonism. Again, a drug can interact with the endogenous chemical messenger to ultimately decrease the activity, which is called chemical antagonism. There are a few drugs that work on the same receptor as the endogenous substance but work exactly oppositely; these are called functional antagonisms. Molecules that are only partly active, irrespective of concentration, are known as partial agonists. An inverse agonist is a type of ligand that gets attached to exactly the same region of the receptor as an 'agonist', counteracting the effects

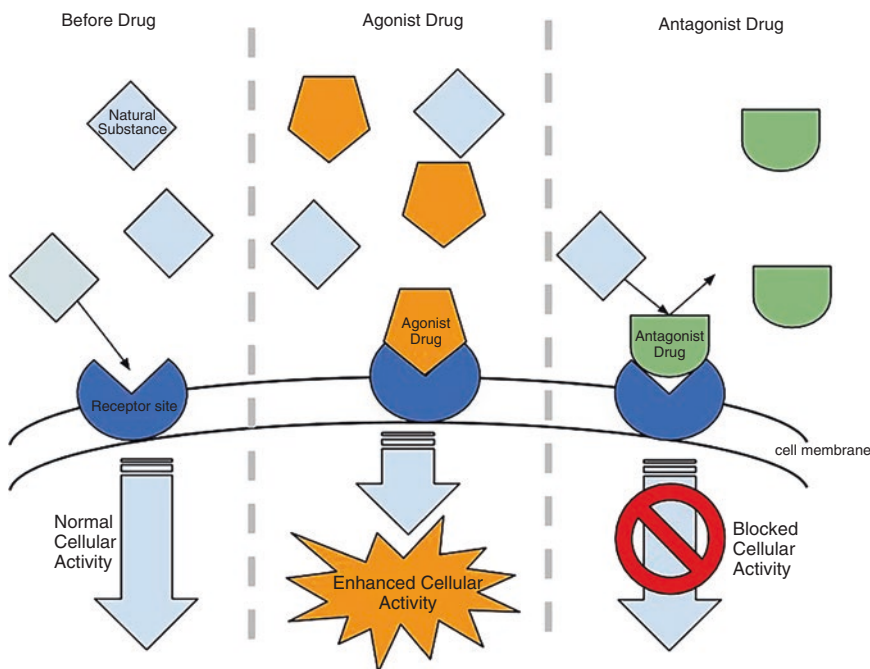


Fig. 2.1 Activity of agonist and antagonist (<https://en.wikipedia.org/wiki/Agonist-antagonist>)

of the former while also having the opposite effect by preventing spontaneous receptor activation (shown in Fig. 2.1).

2.3 Drug-Receptor Interaction

So, the receptors are proteins capable of accepting or binding the ligands and thereby can initiate a transducer mechanism to give the needed pharmacological effect. Most of the transmembrane signalling follows some very well-maintained, coordinated, and well-strategized mechanisms to bypass the barrier created by the plasma membrane, like:

- Lipid-soluble ligands can cross the membrane and act on intracellular receptors.
- There are some transmembrane receptors that have enzymatic activity that gets activated when a ligand is added to the extracellular domain, causing a conformational shift.
- Few receptors are present that work through the activation of tyrosine kinase.
- Transmembrane protein corridors that are permeable to specific ions are called an ion channel.
- Transmembrane receptor protein stimulates G protein which ultimately activates secondary messengers.

2.4 Molecular Basis of Different Transport Mechanisms

For normal biochemical processes to continue in the body, material exchange across the plasma membrane is crucial. Hydrophobic or lipophilic molecules can cross the membrane without the aid of outside energy; instead, they can freely diffuse from one concentration to another until equilibrium is reached. The technique is referred to as passive transport or diffusion since it requires no external energy. The concentration, charge of particles, electrical potential differential across the membrane, and concentration all together contribute a crucial role in the passive diffusion of charged species over the membrane.

Extent of concentration gradient, solute's molecular weight, total distance to be travelled, the membrane's permeability, and its surface area all affect how quickly particles diffuse over the membrane, according to Fick's law of diffusion. Any solute molecule's diffusion coefficient is equal to the proportionality factor of Fick's law, which is defined as the mass of solute diffusing through a unit area in a unit time (square metres per second). The diffusion coefficient is influenced by the polarity, size, temperature, and charge of the molecule due to the difference in charges between protons and electrons.

Due to the nonpolar nature of the membrane lipid bilayer, the process does not occur through passive transport in the case of polar or lipophobic substances. Polar molecules are repelled by the lipid bilayer's nonpolar environment, making it impossible for them to get through. The phospholipids' hydrophilic heads draw polar molecules to them, while their hydrophobic tails repel them. As a result, the polar molecules are unable to get through the membrane, creating a barrier.

The cell involves the transporter proteins in the membrane to maintain easy flow of polar substances as the energy needed for transportation is dispersed by the difference of concentration of molecule (concentration gradient) in the preferred direction. If the movement is from a region of higher concentration to one of lower concentration, the process is referred to as facilitated transport. The amount of free energy is minimal when polar molecules are distributed unevenly (as shown in Fig. 2.2).

Active transport is the process by which a polar molecule is moved against the concentration gradient from a region of lower to greater concentration. To make the movement in the cell spontaneous, an external source of energy must be given to the mediator protein. Active transports can broadly be classified into two types in terms of source of energy and different machineries responsible for doing the transportation. Primary active transport takes place when there is no electrochemical gradient present and is propelled by metabolic energy, such as that created by the hydrolysis of ATP. The only molecules that can perform primary active transport are ion pumps. When one solute is moved in the direction of its growing electrochemical potential while another, usually an ion, is helped to diffuse in the direction of its falling electrochemical potential, this is known as secondary active transport. Secondary active transport is of two types: the subtype which includes transport of both the solute to same direction are called symport and if they are going to opposite direction are called antiport.

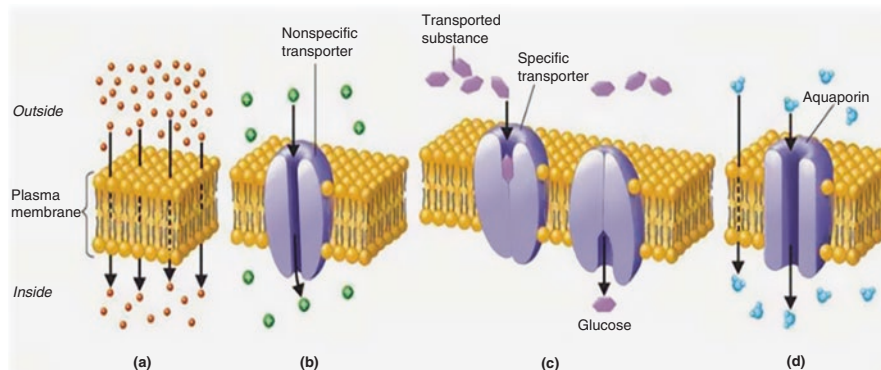


Fig. 2.2 Different types of passive transports (<https://microbenotes.com/passive-transport/>). (a) Simple diffusion through the lipid bilayer. (b) Facilitated diffusion through a nonspecific transporter. (c) Facilitated diffusion through a specific transporter. (d) Osmosis through the lipid bilayer (left) and an aquaporin (right)

Most of the ion pumps in which we are interested are transport ATPases, which are bifunctional molecules capable of moving the substrate against the dominant electrochemical gradient as well as hydrolysing ATP.

Between 60% and 70% of a cell's energy is used by ATP pumps. The cell contains cations such as potassium, calcium, and sodium, as well as anions such as proteins, nucleic acids, phosphate ions, sulfate ions, and chlorine. ATP pumps account for 60–70% of a cell's energy use. Within the cell exists cations such as potassium, calcium, and sodium, as well as anions such as proteins, nucleic acids, phosphate, sulfate, and chlorine.

2.4.1 Important Transporter Proteins

The first enzyme to be shown to be an active ion transporter was Na^+K^+ -ATPase, also referred to as the Na^+ - K^+ pump or Na^+ pump. Additional enzyme transporters include vacuolar-type H^+ -ATPase pumps, SERCA (smooth endoplasmic reticulum or Ca^{2+} ATPase), gastric H^+ -ATPase, PMCA (plasma membrane calcium ATPase), V-type ATPases², etc.

Let us discuss a few important details about the transporters, adenosine triphosphate (ATP) is the primary energy source in cells. Polar molecules must actively move against concentration gradients in order to be transported, which costs energy. A vast class of transporters known as ATPases hydrolyse ATP to move molecules across membranes.

A broad class of transporters known as 'ATPases' hydrolyse ATP to transfer molecules across membranes. Based on their physiological functions and structural characteristics, these carrier ATPases are classified into five subclasses:

2.4.1.1 P-Type ATPases

P-type ATPases are the largest, most diverse, integral membrane proteins that use the energy from hydrolysis of ATP for transportation of cations and lipids across biological membranes. As the name suggests, P-type ATPases' mechanism is via phosphorylated protein intermediates. P-type ATPases can be classified into sub-classes on the basis of substrate specificity.

These subfamilies briefly include(Wardhan et al. 2017):

1. **P1A-ATPases:** Play a very important role in the transportation of K^+
2. **P1B-ATPases:** Transports heavy metals.
3. **P2-ATPases:** Most prominent examples include:

Sarcoendoplasmic Reticulum Calcium ATPase (SERCA)/ Ca^{2+} -ATPase, which is a prime regulator of calcium homeostasis inside the cell, primary function of SERCA is to reuptake Ca^{2+} back to sarcoendoplasmic reticulum using the energy coming from hydrolysis of ATP following the event of muscle contraction, this aids in keeping the concentration of Ca^{2+} in the cytosol between 50 and 100 nM. Muscle pathogenesis is greatly influenced by SERCA (Xu and Van Remmen 2021).

The **Na^+ - K^+ ATPase pump** is expressed at significant levels in both distal convoluted tubule (DCT) of kidney and ascending limb of the Henle loop (also in proximal tubule, collecting ducts, the ascending limb of the Henle loop in descending quantity). Whole mitochondria surround it in the basolateral membranes of healthy kidneys. This is present in sperm cells, grey matter and the brain in addition to the kidney. There are three subunits in it: α , β , and γ . Significantly smaller than the catalytic subunit α (110 kDa), the regulatory β subunit (55 kDa) is a transmembrane protein with a highly glycosylated conformation that contributes to the stability and translation efficiency of the α subunit of the enzyme. It also possesses an ATP-binding domain and a phosphorylation site. The γ subunit, a tissue specific FXYD protein, regulates affinity for pump kinetics and sodium, potassium, and ATP and helps in further characterization and stabilization of Na^+ / K^+ -ATPase pump.

Na^+ - K^+ ATPase is a great target for cardiac glycosides like digoxin and digitoxin in case of heart failure by blocking the Ca^{2+} to leave through indirect inhibition of Na^+ / Ca^{2+} exchange causing Ca^{2+} accumulation at the intracellular domain. Research indicates that individuals with heart failure exhibit 40% reduced levels of total Na^+ / K^+ -ATPase.

For the glomerular filtrate to be reabsorbed and for H^+ to be excreted in the proximal tubule, Na^+ / K^+ -ATPase, located in the basolateral membrane is necessary.

Na^+ - K^+ ATPase is important for preserving membrane potential and controlling cell volume. The Na^+ / K^+ -pump in astrocytes plays a great role in maintenance of a low K^+ level around neurons, it also becomes important in maintenance of osmotic balance in the inner ear of mammals, age-related degeneration of photoreceptors is influenced by loss of Na^+ / K^+ -pump activity, or its reduced expression, which has been identified as a critical factor in the loss of vision, transmembrane receptor's activity can largely be modified under the influence of Na^+ - K^+ ATPase (Pivovarov et al. 2019) (as shown in Fig. 2.3).

4. **P3-ATPases:** Plasma membrane H^+ pumps (transports H^+).
5. **P4-ATPases:** These are mainly effective in transportation of phospholipids. The flippase activity of P4-ATPases gives rise to phosphatidylserine membrane asymmetry by forcing phosphatidylserine to translocate to the cytosolic leaflet transport phospholipids. It makes certain phospholipids easier to migrate inward from the extracellular leaflet domain to the cytosolic leaflet domain, phosphatidylserine is exposed on the outer leaflet when this process is triggered during apoptosis or blood clotting, as a result of specific enzyme scramblases breaking down the lipid asymmetry of the plasma membrane. Phosphatidylserine, which is normally constrained within the cytosolic leaflet, goes through externalization by activating scramblase at the plasma membrane. Phospholipid serine exposure in turn triggers a number of biological functions, including blood coagulation and macrophage identification of apoptotic cells (Hankins et al. 2015).
6. **P5-ATPases:** Substrate unknown.

All P-type ATPases consist of two soluble cytoplasmic domains, first one is the ATP-binding domain and another the actuator domains (ATPBD and A domain).

- **F-type ATPases:** Comprising two primary functional domains, the outer membrane domain contains the enzyme's catalytic domain, which involves converting ADP and inorganic phosphate into ATP. The proton pump's process is similar to that of the mitochondrial F-ATPase, which produces ATP via a proton gradient rather than by using ATP consumption to make acid.
- **Ecto-type ATPases:** Ecto-ATPase is ubiquitous in eukaryotic cells. They hydrolyse extracellular tri- and/or diphosphate nucleosides and, when isolated, exhibit type E ATPase activity (i.e., Ca^{2+} or Mg^{2+} dependent activity and insensitive to type-specific inhibitors). Ecto-ATPases are glycoproteins; they do not form phosphorylated intermediates in the catalytic cycle; they appear to be present in very high abundance, and they present particular experimental problems in the solubi-

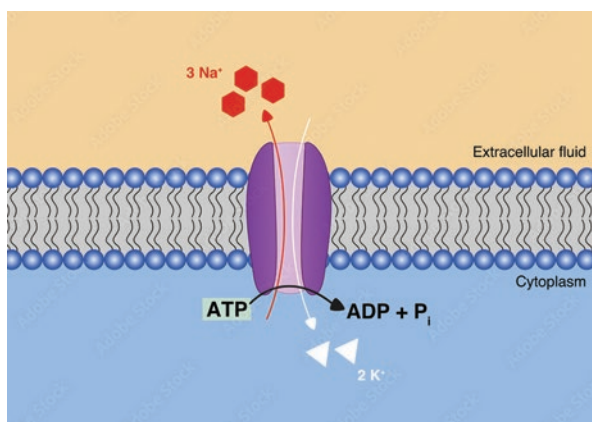


Fig. 2.3 Na^+K^+ ATPase pump mediated transportation of Na^+ and K^+ ion across the cell membrane (Skaliora et al. 2015; Williams et al. 2014)

lization and purification of Mg^{2+} -ATPase T-tubes belonging to the this enzyme, may play two major roles in completing ATP/ADP-induced signal transduction. Several other functions have been discussed and the identification of several molecules cell adhesion and bile acid transport proteins have been proposed based on isolation of cDNA clones and immunological work (Plesner 1995).

- **A-type ATPases:** These are so named as it is found in archaea. The variety of rotor subunit sizes and the coupling ions used by archaeal A1AO ATP synthases to utilise enzymes to synthesize ATP with H^{+} , Na^{+} , or even H^{+} and Na^{+} are two of their most remarkable characteristics (Grüber et al. 2014).

2.4.1.2 ATP-Binding Cassette Transporters

The ATP-binding cassette (ABC) transporters are abundantly available, membrane-bound, ATP-dependent transport proteins. These are expressed in the blood–brain barrier, blood–testis barrier, liver, kidney, intestine, and placenta. ABC transporters are responsible for transporting ions, amino acids, peptides, sugars, hydrophobic compounds, and metabolites across intracellular as well as plasma membranes.

These pumps work against the substrates' electrochemical gradient to move them across membranes and into cellular vesicles by releasing energy from the hydrolysis of ATP. There are a total of 49 ABC genes found in human which are arranged in 8 subfamilies. Certain genes, like X-linked adrenoleukodystrophy and cystic fibrosis, have already been linked to serious hereditary diseases. ABC transporters have an ATP-binding cassette, sometimes referred to as a 'nucleotide-binding domain' (NBD), that contains highly conserved motifs such as the Walker A and Walker B sequences.

The ABC-transporter ABCA4 acts as a phospholipid-ethanolamine and retinylidene-PE flippase in the outer segment membranes of rod and cone cells; floppases, however, are ABC transporters that mediate the movement of phospholipids in the opposite direction. Phospholipid transport is unidirectional and ATP-dependent and is mediated by P4-ATPases and ABC transporters. P4-ATPases are clearly involved in the development of membrane asymmetry in a range of organisms and cell types, but ABC transporters appear to have more specialized roles, such as the excretion of lipid components found in bile (Vasilou et al. 2009).

2.4.1.3 Aquaporins (AQPs)

Monomers of aquaporins consist of six helical segments at transmembrane domain and in around the cytoplasmic and extracellular two short helical segments which surrounds the cytoplasmic and extracellular vestibules connecting through a small aqueous pore. Numerous cell types involved in fluid transportation, such as the lung, kidney, exocrine glands, eye, and gastrointestinal tract, express mammalian aquaporins. Aquaporins are expressed also in astrocytes in all throughout central nervous system. Aquaporins play important role in cell migration which allows entry of water inside protruding lamellipodia in migrating cells, also help in maintaining skin hydration. High levels of glycerol (works as humectant which has the capacity to retain water) concentration in the stratum corneum is maintained by AQP3. AQP7 helps in exit of glycerol from adipocytes, thus prevents intracellular accumulation of glycerol and triglyceride (Shechter 1986).

2.5 Different Types of Transports Based on Direction of Movement and Associated Transporters

Under symport, the ions and solutes are translocated in the same direction, with the ions travelling from low to high solute concentration in the opposite direction of the solute, which moves down its concentration gradient. The oligopeptide symporter (PepT), glucose symporter (SGLT1), GABA symporter (GAT), and several others are examples.

The brain, heart, kidney nephrons, and intestinal epithelial cells all contain glucose symporter (SGLT1) molecules. Per glucose (or galactose) molecule imported into the cell against the gradient, two Na^+ ions are imported down its gradient of concentration. GABA is an inhibitory neurotransmitter found in the synaptic cleft of the nervous system. The GAT symporter controls its concentration. Moving a solute across a membrane requires a symporter coupled with Na^+ or Cl^- ions.

PepT, also known as the oligopeptide symporter, is a protein that aids in the reabsorption of nitrogen in the kidney and intestine. It is a key entry point for drugs like beta-lactam antibiotics. Per dipeptide or tripeptide molecule, one H^+ ion is transported by this symporter against the gradient of its concentration from a high to low concentration (shown in Fig. 2.4).

Proteins responsible for carrying on antiport are called antiporters. Some prominent examples can be **$\text{Na}^+/\text{Ca}^{2+}$ antiporter** which helps in exchange of three Na^+ going inside (down the electrochemical gradient) the cardiac muscle cell and one Ca^{2+} going out of (against the electrochemical gradient) the cell for maintaining low calcium concentration.

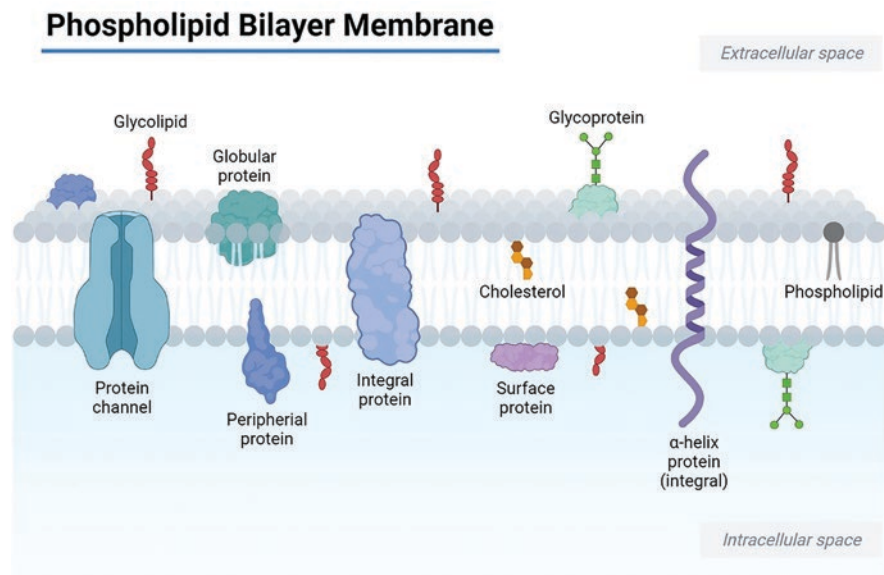


Fig. 2.4 Types of secondary active transporters and their mechanism of transportation (<https://microbenotes.com/passive-transport/>)

The $\text{Cl}^-/\text{HCO}_3^-$ antiporter facilitates the electroneutral exchange of a single Cl^- ion along an electrochemical gradient with a single bicarbonate (HCO_3^-) ion across the same gradient. It offers a method for balancing the ATP-driven H^+ efflux in cells that engage in transcellular net H^+ transport. The Na^+/H^+ **antiporter** is a crucial component in preserving the cytoplasmic pH because it helps move one Na^+ ion down its electrochemical gradient and one H^+ ion against it.

2.6 Cellular Pathways Activated by Physiological Receptors

Receptors can be divided into four main classes and all of them have unique structures, mechanism of signal transduction, specificity towards ligand and onset of action after attachment to ligand as well as difference in outcome. G protein-coupled receptors, ion channel receptor, tyrosine kinase-coupled receptors, and nuclear receptors are the subclasses. G protein-coupled receptors being responsible for many of the diseases in human become a great target for the pharmaceutical scientists in course of designing therapeutics. In most of the cases in biological system, the living cells try to come back to its original state once it has done the process of signalling as mere having forward reaction eventually may lead to activation of any biomolecule or pathway, would surely be giving rise to imbalanced physiology. Once the process of signalling is done, in most of the cases there are few special proteins which help in getting the cell back to its original state. G protein coupled receptor being the one of the most important family of receptor, we would start our discussion with it only.

2.6.1 G Protein-Coupled Receptor and Its Mechanism of Signal Transduction

G protein-coupled receptors are so named for their ability to associate with heterotrimeric G proteins ($\text{G}\alpha\beta\gamma$) and produce signal transduction. GPCRs in vertebrates are commonly divided into five families based on their sequence and structural similarity

- (a) Rhodopsin type (family A),
- (b) Secretin type (family B),
- (c) Glutamate (family C),
- (d) Adhesion type, and
- (e) Frizzled/taste.

GPCR is the largest protein family and most important physiological receptor as 'drug target'. GPCR is also called seven transmembrane receptors or serpentine receptors due to its structural orientation and shape.

2.6.1.1 G Protein Activation

1. Dimerization is a very crucial part of the entire process. This might control the GPCR complex's specificity and affinity for G proteins. Dimerization makes sure that the receptor will be successfully phosphorylated, that the arrestin will bind to the receptor both during the initial phase of the action and again when the action is terminated, and that signalling molecules will be removed from the cell surface. The first step in the activation of a single membrane-spanning receptor is dimerization.
2. Agonists bind to the GPCR's ligand binding domain, which causes a structural alteration.
3. A conformational alteration in the receptor causes the ligand binding site to move to the second and third intracellular loops, where it links with the heterotrimeric G protein.
4. The G protein subunit becomes dissociated and changes its bound GDP to GTP as a result (shown in Fig. 2.5).
5. GTP binding triggers the α subunit, causing it to dissociate from the receptor and the other two subunits ($\beta\gamma$ dimer). The $\beta\gamma$ heterodimer and the GTP-bound α subunit both become functional signalling molecules.
6. Once one G protein is activated, the agonist-bound GPCR and the G protein have a brief interaction before the receptor can interact with other G proteins.

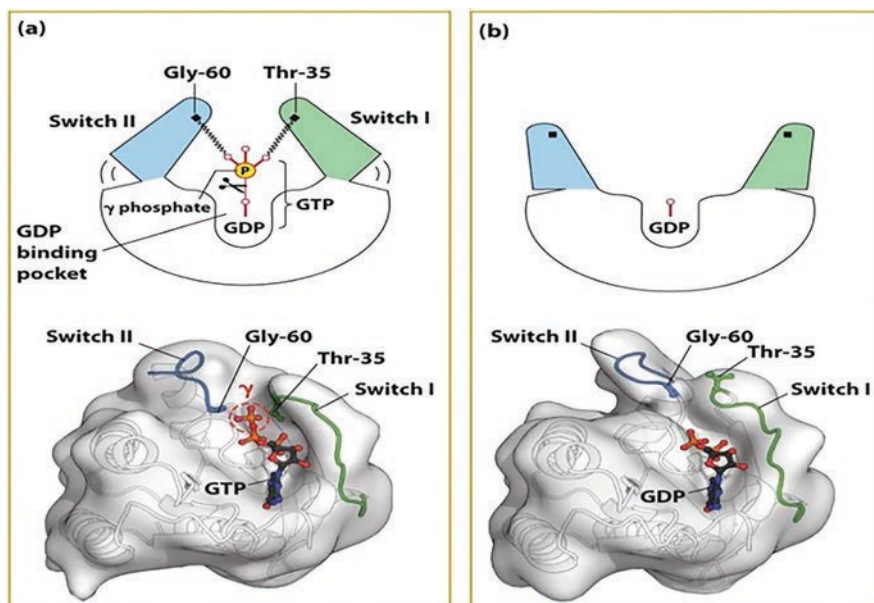


Fig. 2.5 Conformational changes due to exchange of GDP for GTP (<https://quizlet.com/328693546/chapter-15-signal-transduction-and-g-protein-coupled-receptors-flash-cards/>). (a) GTP-bound "on" state. (b) GDP-bound "off" state

7. GTP-bound α subunit can bind to and regulate effectors like phospholipase C β (via Gq α) or adenylyl cyclase (via Gs α), depending on its nature. The $\beta\gamma$ subunit has the ability to control numerous effectors, including enzymes and ion channels (PI3-K, for example).
8. Until the α subunit containing GTP hydrolyses to GDP, losing one phosphate and returning to the typical inactive phase, G protein remains active.
9. The slow intrinsic rate of GTP hydrolysis of the α subunit is regulated by the regulators of G protein signalling (RGSs) protein family.
10. Due to their significant acceleration of GTP hydrolysis, the RGS proteins are appealing targets for pharmacological targeting (Ross and Wilkie 2000).
11. The receptor and $\beta\gamma$ subunit combine together to form the inactive receptor-G protein complex, having all the subunits together which on attachment of ligand can again be made active, following the same process mentioned above.

G protein coupled receptors (shown in Fig. 2.6), upon ligand binding, initiate GPCR effector pathways, which are signalling cascades. GPCR conformational alterations trigger intracellular pathways involving effector proteins like ion channels and enzymes. These pathways control a variety of cellular reactions, including neurotransmission, hormone regulation, and sensory perception. GPCR effector pathways are viable targets for therapeutic interventions as well as essential mechanisms in cellular communication.

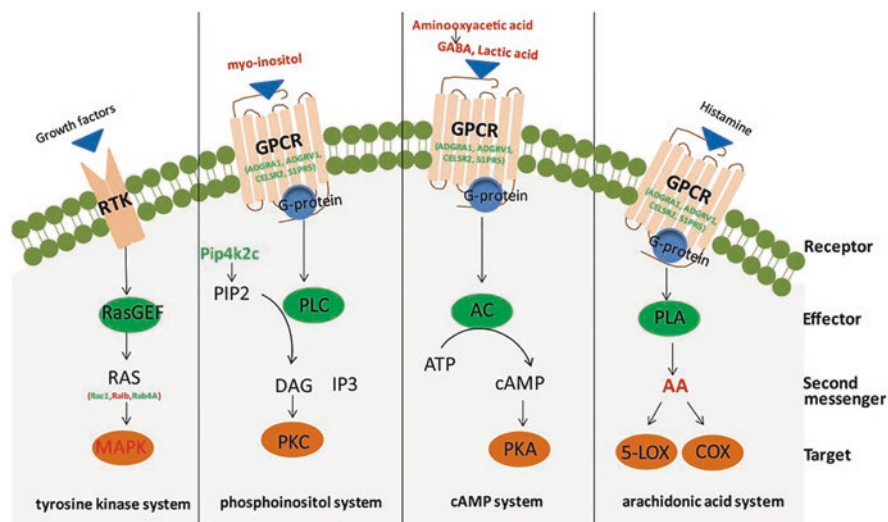


Fig. 2.6 Effector pathways of GPCR upon binding of different neurotransmitters (Purves et al. (2018) Neuroscience. 6th Ed. Oxford University Press) (<https://www.biorender.com/template/gpcr-effector-pathways>)

2.6.1.2 Activation of Secondary Messengers and Transducer Mechanisms

Second messengers are molecules that relay and amplify signals received at receptors on the cell surface.

2.6.1.3 Adenylyl Cyclase-cAMP Pathway

1. Under the influence of GTP carrying Gs α subunit, cAMP is synthesized from ATP by membrane-bound glycoprotein adenylyl cyclase (Gi α subunit can inhibit activity of adenylyl cyclase) with the release of pyrophosphate and, in the presence of Mg^{2+} , hydrolysed into 5'-AMP by the enzyme phosphodiesterase (as shown in Fig. 2.7).
2. A wide range of stimuli can activate monomeric GTPases which play a crucial role (operate as binary switches) in regulating cell functions as well as GTP binding proteins. It can be influenced directly or indirectly through a second messenger (like cAMP) upon the addition of extracellular stimuli. The activity of GTPases is very much influenced by guanine nucleotide exchange factors. GEFs are responsible for catalysing the reaction resulting in the exchange of guanosine diphosphate for guanosine triphosphate by activating GTPase activity.

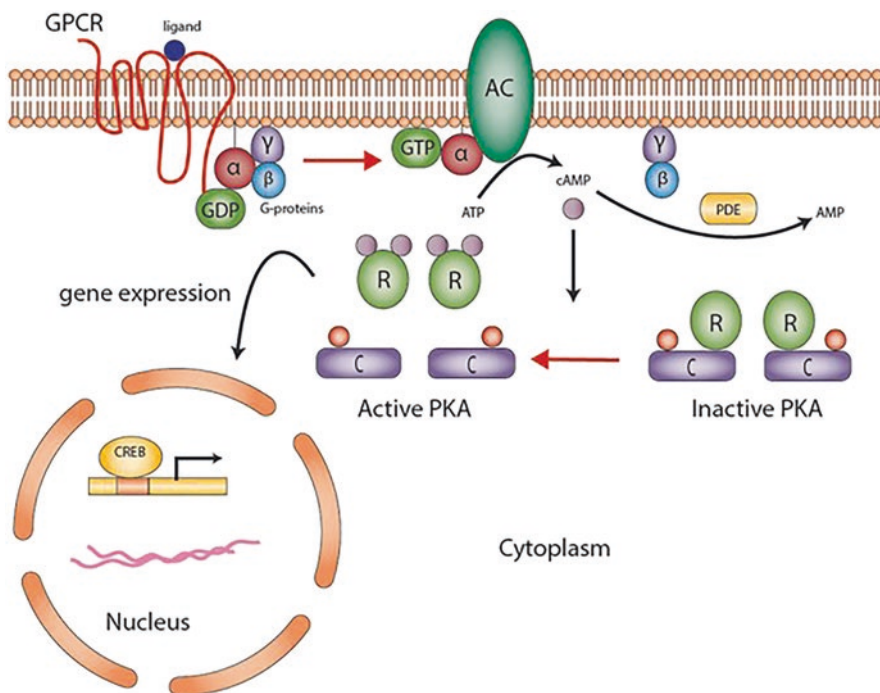


Fig. 2.7 Adenylyl cyclase-cAMP pathway (Pierre et al. 2009)

3. Cyclic AMP generated by adenylyl cyclases from ATP works through some additional biological messengers. Among them the most important targets are as follows:
 - (a) PKA (cAMP-dependent protein kinase A)
 - (b) EPACs (cAMP-regulated guanine nucleotide exchange factors)
 - (c) CREB (cAMP response element binding protein)
 - (d) Cyclic nucleotide-gated ion channels
 - (e) Cyclic nucleotide-regulated phosphodiesterases (PDEs)
 - (f) ABC transporters (MRP4 and MRP5)

Among the above mentioned targets, the first three are most widely functional, the rest of the three comes into play in some specialized cells.

4. Cyclic AMP-dependent protein kinase A (PKA) is a holoenzyme of heterotetramer complex, having two catalytic (C) domains (which on exposure to other protein can readily phosphorylate them) which is bound reversibly to a regulatory (R) subunit dimer. When cAMP is in little concentration, the R subunits are capable of inhibiting the catalytic subunits and stopping them from phosphorylating other proteins and thereby activating them.
5. When adenylyl cyclases are activated, the concentration of cAMP also increases, upon binding of four cAMP molecules two to each R subunit of the R₂ C₂ complex (regulator-catalytic domain complex) of PKA, a conformational change takes place resulting in the R subunits that lower affinity of R to C subunits. This causes detachment of R subunits from C subunits leaving the catalytic domain of PKA exposed which now can easily phosphorylate other proteins.
6. The active catalytic subunits keep on phosphorylating serine and threonine residues on specific proteins. The R and C subunits achieve isoform-specific interactions with other proteins in the cellular environment.
7. PKA can phosphorylate different physiological targets such as many metabolic enzymes, different sorts of transporters, regulatory factors, ion channels, transcription factors, and other kinases too.
8. A very important example is the phosphorylation of the transcription factor CREB-binding protein (CBP) which can interact with RNA polymerase II and enhance the transcription of over a hundred genes whose DNA promoter regions contain the cAMP response element motif (CRE), e.g., angiotensinogen, insulin, glucocorticoid receptor, etc.
9. The cyclic GMP-dependent protein kinase (PKG) can also be activated by stimulation of receptors that raise intracellular cGMP concentrations. PKG can phosphorylate in the same manner as PKA, although certain substrates are specific to PKG. PKG may also occasionally be activated by cAMP.
10. Another important second messenger cyclic AMP-regulated guanine nucleotide exchange factors (GEFs) are extracellular signals on attachment of which membrane receptors go through conformational changes and activate different signalling pathways. These possess crucial roles in the regulation of phagocytosis, co-ordinates cell cycle, gene expression, apoptosis, etc.

11. Cyclic nucleotide phosphodiesterases (PDEs) are signal functions which are regulated through gene transcription rate and also by second messengers (cyclic nucleotides/ Ca^{2+}) and can interact with β arrestin protein and different kinases. Cyclic nucleotide phosphodiesterases catalyse hydrolyzation of 3',5'-phosphodiester bond of both the cAMP and cGMP resulting in the termination of their action. PDE3 forms are good targets for the treatment of asthma, cardiovascular diseases, and neurological disorders. A widely known PDE5 inhibitor (e.g., sildenafil) which increases cellular accumulation of cGMP in the smooth muscle and increases relaxation and improves its capacity is used to treat COPD and problems related to erectile dysfunction (Manganiello and Degerman [n.d.](#)).

2.6.1.4 IP3-DAG Pathway

Like the adenylyl cyclase-cAMP pathway, another important GPCR-mediated transducer mechanism is the IP3-DAG pathway.

1. In this pathway, after the activation of GPCR (Gq/Gi) it, in turn, activates PLC β , a form of cytosolic enzyme phospholipase C by releasing the $\beta\gamma$ dimer and activating the G protein's α subunit through the exchange of GDP with GTP. $\beta\gamma$ dimer is covalently attached and anchored to some lipids in the cytosolic domain of the membrane.
2. Different isoforms of PLC β can be activated by the $\beta\gamma$ dimer and the active α subunit (Gq-GTP bound), while PLC γ isoforms are activated by phosphorylation of tyrosine kinase (shown in Fig. [2.8](#)).
3. Upon stimulation PLCs can translocate to the plasma membrane and being activated, it catalyses the hydrolysis of phosphatidylinositol-4,5-bisphosphate (PIP2), a membrane phospholipid and produces two intracellular signalling molecules. The first one which can travel in cytosol, i.e., inositol-1,4,5 trisphosphate (IP3), and diacylglycerol (DAG) which stays in the membrane.
4. Different protein kinases, which support signalling pathways, are activated by both molecules. In the endoplasmic reticulum, IP3 diffuses and activates the IP3 receptor in the membrane, releasing the Ca^{2+} that has been stored there. Protein kinase C (PKC) is activated by membrane-embedded DAG.
5. Ca^{2+} is released from the endoplasmic reticulum into the cytoplasm, which multiplies the amount of Ca^{2+} in the cytoplasm several times in a matter of seconds.
6. Ca^{2+} /calmodulin-sensitive protein kinases and calmodulin-sensitive enzymes, like cyclic AMP PDE, are then activated by the cytosolic Ca^{2+} .
7. CaM-kinases are very important and essential for proper functioning of cell through influencing gene transcription, cell survival, cell death mechanism (apoptosis), reorganization of cytoskeleton, activation of a contractile protein, myosin and in maintaining the learning and memory (Hudmon and Schulman [2002](#)).
8. While studying the biochemical pathways, we need to keep a thing in mind that most of the reactions that take place in the body are reversible, so that no absolute stagnant phase is prevailing. Any molecular pathway or signalling that

2.6.1.5 Role of Calcium as Second Messenger

One of the most significant second messengers in the control of gene expression, contraction, secretion, metabolism, and electrical activity is calcium. The plasma membrane's Ca^{2+} channels allow Ca^{2+} to enter the cell. The membrane of the endoplasmic reticulum (ER) contains the sarcoplasmic reticulum (SR) Ca^{2+} -ATPase (SERCA), which permits Ca^{2+} to enter ER/SR and be stored there, and membrane Ca^{2+} pumps that extrude Ca^{2+} to the extracellular space maintain the basal Ca^{2+} level in cells in the 100-n range in accordance with its role as a signal.

There are a total of five subtypes of calcium channels. L type calcium channel, activated on high voltage found in skeletal muscle, smooth muscle, bone, ventricular myocytes, apart from that N type, P type, R type, and T type are also present. Among all the calcium channels, the most widely targeted and well researched are L type and T type calcium channels. L type calcium channels are mainly targeted in antihypertensive and antianginal therapeutics. Though nowadays antianginals are also made to target T type calcium channels also. Selective T types calcium channel blockers are antiepileptic class of drugs (present in Table 2.1).

2.6.2 Ion Channel Receptor

These are the most basic physiological receptors in terms of both structure and mode of action. The lipid bilayer of body plasma membrane makes a barrier which is merely impermeable to ions, but the exchange of ions between the intracellular and extracellular domains of the membrane is still a very important mechanism that sustains the electrochemical gradients, which are essential for preserving a membrane potential. As an illustration, we can discuss Na^+K^+ -ATPase, which, as was previously noted in the chapter, uses ATP to move K^+ within cells and Na^+ outside of them. The processes of secondary symport and antiport are involved in non-excitabile cells.

A sizable family of ion channels found in the membrane is primarily responsible for passive ion fluxes down the cellular electrochemical gradients. These are the fastest acting receptors and a common target for modern drugs (examples include potassium channel blockers like amiodarone, calcium channel blockers like amlodipine, and sodium channel blockers like phenytoin). Ion transporters are specialized transport proteins that open up channels for particular ions to enter or exit cells. Numerous factors can stimulate the proteins, but the most common ones are ligand- or voltage-gated. Ion channels that are voltage-gated mainly react to variations in the membrane potential of the cell, while ligand-gated ion channels create a passageway for ions to enter or exit the channel in response to the attachment of a specific ligand. Ion channel receptors can be broadly categorized into six types depending upon the manner of activation:

- (a) Voltage-activated ion channels,
- (b) Ligand-activated ion channels,

Table 2.1 Different types of calcium channel

Type	Sensitivity	Location	Drugs/chemicals acting
L type (long-lasting channel or k/a DHPR channel)	Voltage activated, DHP sensitive	Ventricular myocytes, nodal cells, Smooth muscle, skeletal muscle, cortical neurons, bone (osteoblasts), endocrine cell, retina	Blocker: Verapamil, diltiazem, and 1,4-dihydropyridines (DHPs) like nitrendipine, nifedipine, nimodipine Agonist: Bay K8644 (may have role in neuroprotection) (Wang et al. 2013)
N type (neural type)	Voltage activated, non-DHP sensitive	Nerve terminal and dendrites of neurons (CNS/PNS)	Blocker: ω -conotoxins, cilnidipine, desipramine, nicardipine, carvedilol, ziconotide Agonist: NA
P (Purkinje)/Q type	Voltage activated, non-DHP sensitive	Nerve terminal and dendrites of neuron, cerebellum (Purkinje and granule cells)	Blocker: Agatoxin-IVA Agonists: NA
R (residual) type	Voltage activated, non-DHP sensitive	Cell body, dendrites, nerve terminal, cerebellum (granule cells)	Blocker: SNX-482 Agonists: NA
T (transient type)	Voltage activated, non-DHP sensitive	Nodal cell of heart skeletal muscle, neurons, bone (osteocyte), thalamus	Blocker: Trimethadione, zonisamide, pimoizide, most of the antiepileptic drugs and antianginal/hypertensive drugs which target L type calcium channels Agonist: NA

- (c) Store-activated ion channels,
- (d) Stretch-activated ion channels, and
- (e) Temperature-activated ion channels.

2.6.2.1 Voltage-Gated Ion Channels

Majority of voltage sensitive ion channels (as shown in Fig. 2.9) are found in muscle and nerve cells. Na^+ , K^+ , Ca^{2+} , and Cl^- channels are the voltage-gated channels that are most commonly found.

In order to generate strong and robust action potentials that cause rapid depolarization from resting membrane potentials of -70 mV to approximately $+30$ mV in milliseconds, voltage-gated Na^+ channels are primarily responsible. Voltage-gated channels must quickly complete the function because they are primarily used in highly excitable cells. The Na^+ ion channel has a domain made up of charged amino acids that functions as a voltage sensor. When the voltage changes, this domain causes a conformational change in the pore, or channel, as it is called. When positive voltages appear, this domain opens up, depolarizing the membrane. Local anaesthetics like lidocaine and tetracaine target Na^+ channels in pain neurons. These medications inhibit fast depolarization, block ion channel pore function, and block pain perception. They are also effective in treating cardiac arrhythmias.

Voltage-gated Ca^{2+} channels, which are expressed in smooth muscle and essentially maintain vascular tone, share structural characteristics with Na^+ ion channels. Ca^{2+} concentration within cells plays a crucial role in controlling the phosphorylation of the Ca^{2+} /calmodulin-sensitive myosin kinase.

The most prevalent type of voltage-gated K^+ channel differs structurally from other voltage-gated channels and is also the most readily available. The primary function of K^+ channels is to sustain the resting membrane potential within the range of -70 to -90 mV after a depolarization in response to any kind of stimulus. A few types of epilepsy arise from naturally occurring Kv channels mutations.

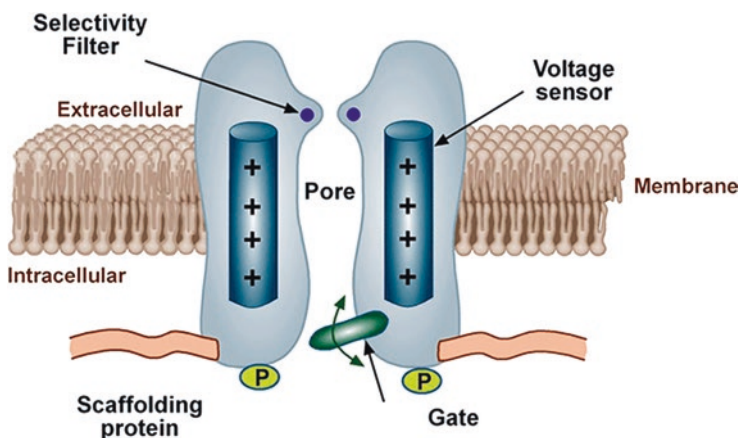


Fig. 2.9 Structure of a voltage-gated ion channel (<https://www.itaca.edu.es/ion-channels.htm>)

Drugs like retigabine may be able to target this Kv channel in the process of developing treatments for epilepsy.

2.6.2.2 Ligand-Gated Channels

When a particular ligand attaches itself to a particular location in the channel protein, these channels become active. Most synaptic transmission by neurons in both the central nervous system and the peripheral nervous system is caused by the activation of these channels. These receptors differ structurally from traditional ligand-gated channels and are activated by the addition of intracellular small molecules or signalling molecules.

Hyperpolarization and the heart-expressed cAMP-gated (HCN) channel are the causes of the slow depolarization seen in phase 4 of the action potentials of the AV and SA nodal cells (Biel et al. 2009). Furthermore, cyclic nucleotide-gated (CNG) channels are essential for vision, including the sulfonylurea ‘receptor’ (SUR1), which is linked to the control of the ATP-dependent K⁺ channel (KATP) in pancreatic beta cells, and the IP₃-sensitive Ca²⁺ channel, which is in charge of releasing Ca²⁺ from the ER.

2.6.3 Transmembrane Receptors Linked to Intracellular Enzymes

These physiological receptors possess ligand binding domains at extracellular sites and on cytoplasmic domain it has intrinsic enzymatic activity. The cytoplasmic domain of receptor tyrosine kinases (RTKs) containing intrinsic tyrosine kinases includes insulin and epidermal growth factor (EGF). Apart from the α and β chains that make up the insulin receptor, these compounds are composed of single polypeptide chains with large cysteine-rich extracellular domains, brief transmembrane domains, and an intracellular region that occasionally contains two protein tyrosine kinase domains each.

Cell survival, proliferation, and differentiation are all facilitated by the activation of growth factor receptors. Neuronal angiogenesis, axonal migration, and guidance are caused by ephrin receptor activation. Growth factor receptors are monomeric when they are inactive.

1. When a ligand is bound, the receptor dimerizes and the kinase domains on several tyrosine residues undergo cross-phosphorylation. Phosphorylation of these tyrosine residues results in further activation of the receptor kinase because some of them are located in the kinase’s activation loop.
2. SH2 domain docking sites are created when tyrosine residues are further phosphorylated, which are present in many signalling proteins and comprise more than 100 proteins in the human genome (Ren et al. 2008).
3. After activation of the receptor, large signalling complexes form on the receptor, which ultimately result in cell proliferation. PLC γ , which increases intracellular Ca²⁺ levels and activates PKC, is one of the molecules that are drawn to

phosphotyrosine-containing proteins by their SH2 domains, as previously mentioned.

4. The α and β isoforms of phosphatidylinositol 3-kinase (PI3-K) possess SH2 domains that enable them to bind to phosphorylated receptors. PIP3, or phosphatidylinositol 3,4,5 trisphosphate, is a molecule that forms extra membrane docking sites for signalling molecules like protein kinase B (PKB, also known as Akt). Once they dock, they become active and raise the concentration of PIP3.
5. PKB regulates multiple signalling pathways, including those that involve the BCL2 associated agonist of cell death (Bad) protein, which is essential for apoptosis, and mTOR. Not only do phosphotyrosine-presenting proteins attract enzymes, but they also attract dormant adaptor molecules with SH2 domains, such as Grb2. Guanine nucleotide exchange factors (GEFs) such as Sos are then drawn to these molecules, and this can activate the small GTP binding protein Ras.
6. Extracellular receptors only activate members of the Ras and Rho subfamilies.
7. A significant portion of human cancers are caused by spontaneous activating mutations in Ras; therefore, compounds that block Ras are highly desirable for use in cancer treatment.
8. Rho, Rac, and Cdc42 are members of the Rho family and are in charge of communicating signals from the membrane to the cytoskeleton. GTPase-activating proteins (GAPs) inhibit all small GTPases, while GEFs, which are controlled by multiple mechanisms, activate all small GTPases (Etienne-Manneville and Hall 2002).
9. When members of the Ras family are activated, a cascade of protein kinases known as the mitogen-activated protein kinase (MAP kinase, or MAPK) pathway is triggered. One of the main ways that growth factor receptors communicate with the nucleus and promote cell growth is through activation of the MAPK pathway. Rap, a MAP kinase kinase kinase (MKKK), is the pathway's initial enzyme.
10. Rap causes MAP kinase kinase (MKK) known as MEK to become phosphorylated and activated.
11. MAP kinase ERK is phosphorylated by MEK. Phosphorylation of closely spaced tyrosine and threonine residues in the kinase activation loop activates ERK, an intriguing member of the kinase family.
12. To regulate gene transcription and encourage cell division, ERK phosphorylates two transcription factors in the nucleus: CREB and Elk-1 (Manning and Davis 2003).

2.6.3.1 JAK-STAT Receptor Pathway

These are receptors for growth hormone and prolactin, as well as cytokines like γ -interferon, which communicate with the nucleus more directly than receptor tyrosine kinases. These lack intrinsic enzymatic activity; instead, they function by binding to the cytosolic domain of Janus kinase (JAK) (intracellular kinase). JAKs can easily phosphorylate other proteins such as signal transducers and activators of transcription (STATs), following dimerization brought on by ligand binding.

Translocating to the nucleus, STATs control transcription. The JAK-STAT pathway refers to the entire pathway (Harrison 2012). These proteins are monomers in their basal state; they dimerize when they bind an agonist ligand, which phosphorylates the type I monomer's kinase domain and activates the receptor. A gene-regulatory protein known as a Smad is subsequently phosphorylated by the activated receptor. In cells, Smads are found in multiples; upon being phosphorylated on a serine residue by the activated receptor, Smad controls genes that lead to morphogenesis and transformation after separating from the receptor, migrating to the nucleus, and joining transcription factors. To stop signalling, phosphorylated Smads compete with inhibitory Smads, such as the Smad6 or Smad7 isoforms (shown in Fig. 2.10).

JAK/STAT signalling pathway activation and inhibition. The activation process is indicated by black arrows. Negative regulation was indicated by red-dotted arrows. JAK/STAT signalling pathway activation:

1. Growth factors and cytokines bind to their respective receptors, which causes the receptor to dimerize and attract related JAKs;
2. JAK activation causes the receptors to become tyrosine phosphorylated, which creates docking sites for STAT;
3. Tyrosine phosphorylates STATs;
4. STATs split off from the receptor to form homodimers or heterodimers; and
5. STAT dimers enter the nucleus, bind to DNA, and control transcription (Manson et al. 2015).

JAK/STAT signalling pathway negative regulation: The CIS/SOCS (suppressor of cytokine signalling), PTPs (protein tyrosine phosphatase), and PIAS (protein

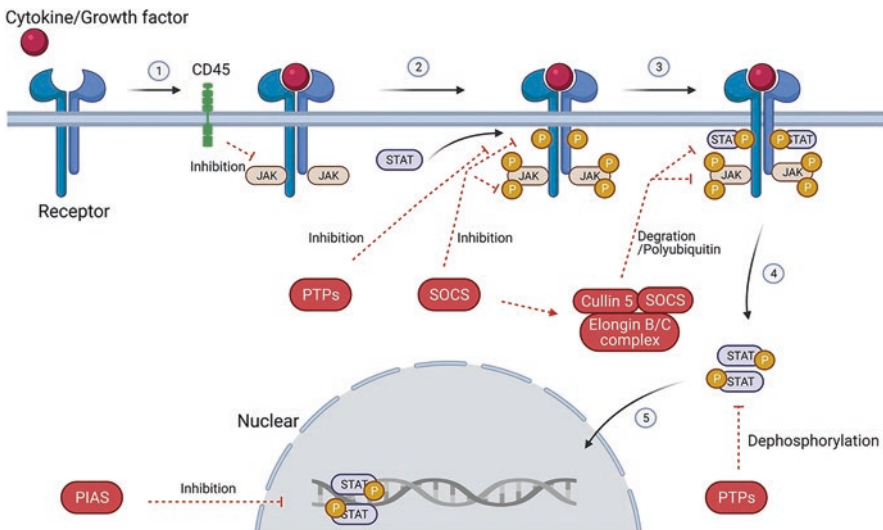


Fig. 2.10 JAK-STAT receptor activation and signalling pathway (Li et al. 2023)

inhibitor of activated STAT) families of proteins are the three primary protein types implicated in the negative regulation of the JAK/STAT signalling pathway.

To prevent JAK/STAT signal transduction, PIAS primarily interacts with STAT dimers to inhibit STAT binding to DNA. Through three different mechanisms, the CIS/SOCS family inhibits the JAK/STAT pathway:

1. binding to a tyrosine kinase receptor to prevent the recruitment of STAT;
2. binding directly to JAK to prevent its kinase activity; and
3. forming an elongin B/C-cullin5 complex that breaks down JAK or STAT bound to the SOCS protein by polyubiquitination and proteasome degradation.

PTPs block the JAK/STAT pathway through three different mechanisms:

1. dephosphorylating the STAT dimer;
2. interacting with the receptor to dephosphorylate the associated JAK; and
3. blocking the phosphorylation of JAK in the case of CD45 (a transmembrane PTP).

2.6.3.2 Toll-Like Receptors

1. Within the haematopoietic cell, Toll-like receptors (TLRs), a family of over ten single membrane-spanning receptors, are highly expressed and mediate innate immune system signalling.
2. The TIR domain, which is a cytoplasmic region devoid of intrinsic enzymatic activity, a short membrane-spanning domain, and a large extracellular ligand binding domain are all contained within a single polypeptide chain to form these receptors (Hu et al. 2021).
3. TLR ligands include lipids, viruses, peptidoglycans, and lipopeptides, among other pathogen products (as depicted in Fig. 2.11).
4. Inflammation is brought on by pathogenic microorganisms when these receptors are triggered. As is the case with all single membrane-spanning receptors, ligand binding to TLRs initiates dimerization. As a result, a signalling complex can be formed by signalling proteins adhering to the receptor.
5. A group of adaptor proteins, such as Mal and myeloid differentiation protein 88 (MyD88), are drawn to the intracellular TIR domain by means of ligand-induced dimerization. These proteins then draw in the interleukin-associated kinases, or IRAKs.
6. The complex is stabilized by the combination of IRAKs and MyD88, which occurs after the IRAKs autophosphorylate.
7. Additionally, TRAF6 is brought into the complex by the phosphorylation event, which makes it easier for TRAF6 to interact with a ubiquitin ligase and attach a polyubiquitin molecule to it.
8. This complex can now be interacted with by the adaptor TAB1 and the protein kinase TAK1. TAK1 is a member of the family of MAP kinases that activates NF- κ B kinases. Many inflammatory genes are transcriptionally activated when NF- κ B transcription factors are phosphorylated, which causes them to translocate to the nucleus (Jin and Lee 2008).

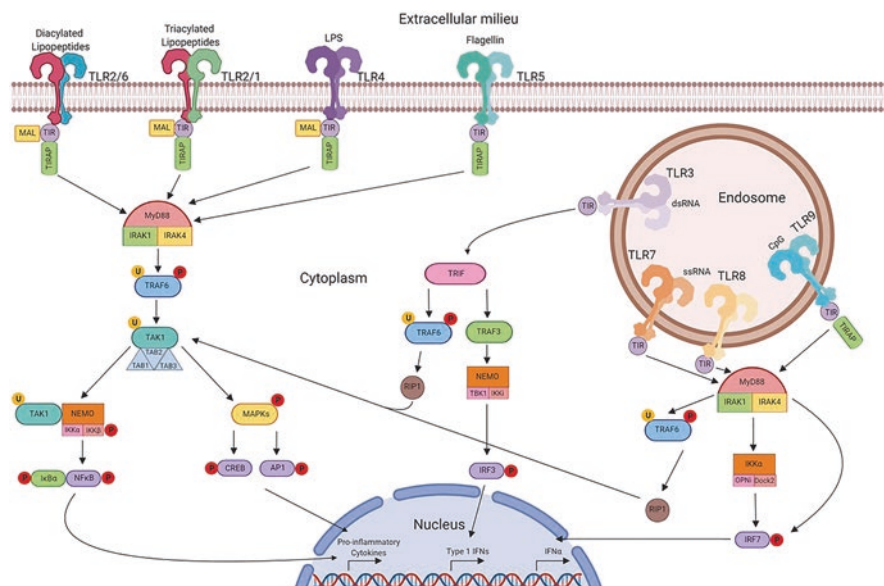


Fig. 2.11 Toll-like receptor activation and signalling pathway (<https://blog.cellsignal.com/immunology-what-are-toll-like-receptors-and-how-do-they-invoke-tumor-tolerance>)

2.6.3.3 TNF- α Receptors

1. Tumour necrosis factor α (TNF- α) and Toll-like receptors share a mechanism of signalling to NF- κ B transcription factors due to the lack of enzymatic activity in the receptor's intracellular domain.
2. Another single membrane-spanning receptor is the TNF- α receptor, which has three domains: a transmembrane domain, an extracellular ligand binding domain, and a death domain in the cytoplasm.
3. Comprising TNF-receptors 1 and 2, TNF- α binds to this complex. The binding of the adaptor protein TRADD by the death domains during trimerization brings in the receptor-interacting protein 1 (RIP1) so that a receptor–adaptor complex can form at the membrane.
4. Following RIP1's polyubiquitination, the I κ B kinase (IKK) complex and TAK1 kinase are drawn to the ubiquitinated molecules (Skaug et al. 2009).
5. The transcription of inflammatory genes is triggered by the complex's p50/p65 heterodimer, which enters the nucleus when IKKs activation loop within it is phosphorylated (Ghosh and Hayden 2008). This process also releases I κ B α . Infliximab and adalimumab, two TNF- α humanized monoclonal antibodies, are essential for the treatment of rheumatoid arthritis and Crohn's disease, even though there are currently no drugs that block the cytoplasmic portions of the TNF- α signalling pathway (as shown in Fig. 2.12).

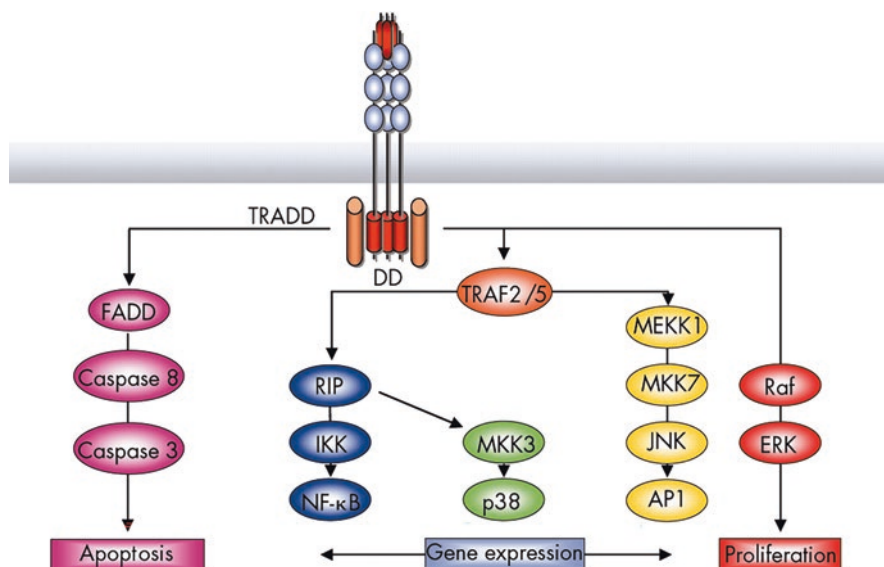


Fig. 2.12 Signalling of TNF- α receptors (<https://doi.org/10.1136/ard.2005.042523>)

2.6.4 Nuclear Hormone Receptors and Transcription Factors

The 48 receptors that make up the nuclear hormone receptor superfamily in humans react to a wide range of ligands. Receptor proteins are transcription factors that have the ability to control gene expression that governs many physiological processes, including metabolism, development, and reproduction.

Among the well-known members of this family are receptors for circulating steroid hormones, which include thyroid hormone, oestrogens, glucocorticoids, and vitamin D. More members of the family serve as receptors for a variety of lipids, fatty acids, bile acids, and lipid metabolites. The latter receptors monitor the cell's metabolic state by responding to variations in locally available molecules (McEwan and Nardulli 2009). There is a single polypeptide chain with four main domains found in nuclear hormone receptors. Both the activation region (AF-1), which is crucial for transcriptional regulation, and the DNA-binding domain, which has two zinc fingers and binds to DNA, are highly conserved regions found in the N-terminal domain. The entire ability of the nuclear receptor to activate transcription is governed by phosphorylation and other mechanisms that also affect the N-terminal activation region (AF-1). The C-terminal half of the molecule contains some sets of amino acid residues that bind co-repressors and co-activators in a second activation region (AF 2), the hinge region, which may be involved in binding DNA, and the ligand binding domain (abbreviated LBD), which binds hormones and ligands (shown in Fig. 2.13).

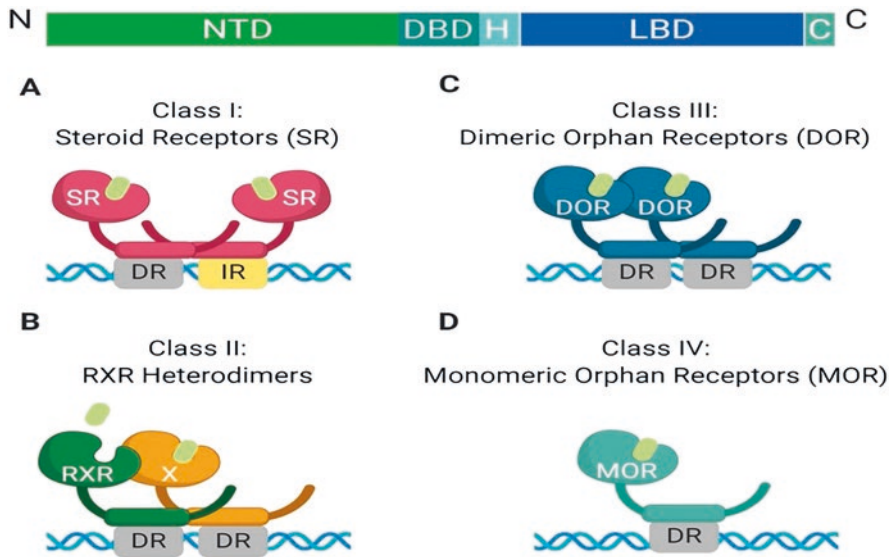


Fig. 2.13 Nuclear receptors superfamily (<https://www.biorender.com/template/nuclear-receptors-superfamily>)

2.6.4.1 Signalling Pathway of Nuclear Receptor

1. Steroid receptors, including glucocorticoid receptors, are found in the cytoplasm in their inactive state. When a ligand is bound, these receptors move to the nucleus.
2. Ligand binding causes a significant conformational change in helix 12, which forms the ligand binding domain from a bundle of 12 helices (Privalsky 2004). The nuclear hormone receptor (OR) undergoes a conformational shift in helix 12 (black bar) in response to an agonist and co-activator binding, which stimulates gene transcription.
3. This conformational shift also affects the binding of the co-regulatory proteins necessary for the activation of the receptor–DNA complex.
4. The majority of nuclear hormone receptors function as dimers when bound to DNA; some function as homodimers, while others as heterodimers.
5. Each type of receptor has specific hormone response elements (HREs), which are repeating DNA sequences to which receptor dimers bind. AGGTCA half-sites on the oestrogen receptor, for instance, are placed with a three-base spacer in an inverted repeat.
6. Upstream or, in certain situations, inside the regulated genes are the regions of the DNA that react to hormones. Frequently, a programme of metabolic regulation or cellular differentiation is carried out by activating a large number of genes via an agonist-bound nuclear hormone receptor (Kalaany and Mangelsdorf 2006).

7. Co-repressor binding prevents activation from taking place. The fact that these receptors need to bind their ligand, in order to regulate their target genes is one of their key characteristics.
8. The silencing mediator of retinoid hormone receptor (SMRT) and the nuclear hormone receptor co-repressor (NCoR) are examples of co-repressors. Co-activators include the p160 family proteins, the steroid receptor co-activator (SRC) family, and others (Privalsky 2004).
9. The ratio of co-repressors to co-activators in the complex influences not only the ligand but also the activity of nuclear hormone receptors in a given cell.
10. Heme acetylase, an enzyme that modifies chromatin to prepare DNA for transcription, is one of the enzymes that co-activators bring into the transcription complex.
11. Histone deacetylase is one of the proteins that co-repressors enlist to support transcription inhibition by keeping DNA tightly packed.
12. Nuclear hormone receptors have the ability to differentially regulate the genes that they target based on the type of bound ligand and the combination of co-activators and co-repressors attached to the complex.
13. The capacity of some medications to function as specific regulators of gene expression and receptor function is explained by this characteristic. Tamoxifen and raloxifene are classified as selective oestrogen receptor modulators (SERMs), while substances like 17 β -estradiol are considered oestrogen receptor agonists in all tissues.
14. Thus, distinct co-activator and co-repressor combinations bind to the receptor–DNA complex differently depending on the tissue, resulting in gene-specific functions. By attracting co-repressors to the transcription factor complex (shown in Fig. 2.14).

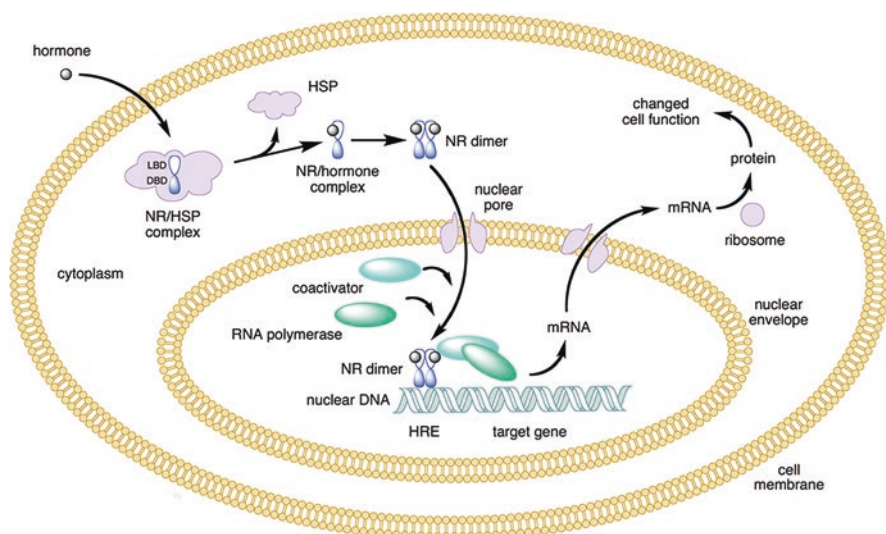


Fig. 2.14 Signalling pathway of nuclear receptor (https://en.wikipedia.org/wiki/Nuclear_receptor)

2.7 Apoptosis

A highly controlled series of biochemical events known as apoptosis cause the cell to round, the cytoplasm to contract, the nucleus and nuclear material to condense, and the cell membrane to alter. Ultimately, this results in the presentation of phosphatidylserine on the cell's exterior. Macrophages identify phosphatidylserine as an indication of apoptosis and engulf the dying cell, phagocytizing it.

Notably, the apoptotic cell's membrane does not rupture during this process, and neither does the cell's nuclear material nor cytoplasm. Therefore, the apoptotic process does not trigger an inflammatory response, in contrast to necrotic cell death. Comprehending the mechanisms that govern apoptosis is crucial, as the process is essential for healthy cells and deviations from these pathways have been linked to numerous illnesses, including cancer, neurodegenerative disorders, and autoimmune illnesses (Bremer et al. 2006). Therefore, the aim of major drug development efforts to treat diseases involving dysregulated apoptotic pathways is to maintain or restore normal apoptotic pathways (Fesik 2005). It might be possible to get rid of undesirable cells by specifically triggering apoptotic pathways (in Fig. 2.15).

1. Apoptosis is triggered by two main signalling pathways. Apoptosis can be brought on by internal pathways triggered by DNA damage, misfolded proteins, or the loss of cell survival factors, or it can be brought on by external signals that share characteristics with ligands, such as $\text{TNF-}\alpha$.

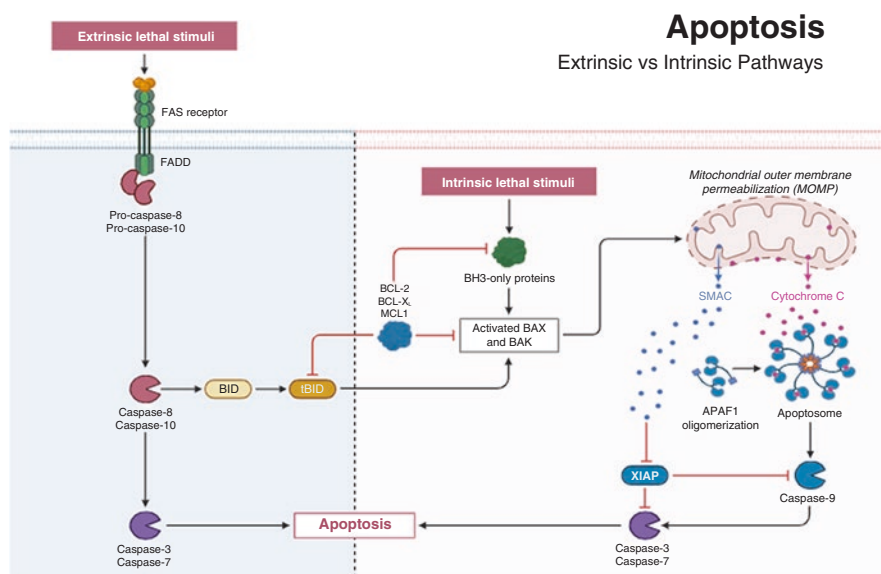


Fig. 2.15 Comparison in pathways of intrinsic and extrinsic apoptosis (<https://www.assaygenie.com/blog/cleaved-caspase-3-and-apoptosis>)

2. No matter how it is initiated, the apoptotic programme is executed by a broad family of cysteine proteases known as caspases (Wilson and Hunt 2002).
3. A type of cytoplasmic proteases called caspases are highly selective and inactive in healthy cells until they receive apoptotic signals (Danial and Korsmeyer 2004). Ligands or signals such as TNF, FAS, Apo-1, or TNF-related apoptosis-inducing ligand (TRAIL) can trigger the external apoptosis signalling pathway.
4. The transmembrane FAS and TRAIL receptors are without enzymatic activity. Their cytoplasmic death domain can bind intracellular adaptor proteins, and they have short transmembrane domains in addition to large external ligand binding domains.
5. These receptors recruit adapter proteins to the death domain, form a receptor dimer, and undergo a conformational change upon binding TNF, FAS ligand, or TRAIL.
6. To form a complex of RIP1, TRADD/two pathways leading to apoptosis, adaptor proteins such as TRADD, FADD, or TRAF2 recruit the receptor-interacting protein kinase (RIP1) and caspase 8.
7. External ligands like TNF, FAS, or TRAIL can activate apoptosis at particular transmembrane receptors. Upon activation, the receptor trimers and adaptor molecules like TRADD bind to the intracellular death domain.
8. The effector caspase, caspase 3, is recruited by the adaptors and activated, resulting in the cleavage and activation of caspase 8, which in turn activates the caspase pathway and causes apoptosis.
9. Additionally, an intrinsic pathway controlled by Bcl-2 family members like Bcl-2 and BAX can start apoptosis. Damage to DNA or distorted proteins are mediated by p53 to activate BAX.
10. When this pathway is activated, cytochrome *c* is liberated from the mitochondria and a complex containing caspase 9 and Apaf-1 is created.
11. The complex triggers apoptosis by activating caspase 3, by caspase 9 (from inactive procaspase).
12. FADD/TRAF2 and caspase 8, which cause caspase 8 to become activated. Different adaptors known as FADD/MORT are recruited by the FAS and TRAIL receptors. These adaptors have the ability to attract and subsequently activate caspase 8 through autoproteolytic cleavage.
13. The apoptotic programme is initiated by caspase 3, which is activated by stimulation of its proteolytic activity, independent of the upstream complexes that activate caspase 8. Caspases 6 and 7 carry out the last stages of apoptosis, which results in the cell death-associated DNA fragmentation, structural protein degradation, and enzyme degradation.

The internal apoptosis pathway can be activated by signals such as

1. DNA damage due to any reason can lead to increased transcription of the p53 gene which is also known as 'father of cell division', involves damage to the mitochondria by pro-apoptotic members of the Bcl-2 family of proteins like BAX, Bad, and Bak and creates a pore.

2. Additionally, Bcl-2, Bcl-X, and Bcl-W are anti-apoptotic Bcl-2 members that function as negative regulators of the system and prevent mitochondrial damage.
3. p53 transcription is triggered when DNA damage happens, stopping the cell at a checkpoint in the cell cycle until the damage is fixed.
4. Apoptosis is triggered by pro-apoptotic Bcl-2 members like BAX if the damage cannot be healed.
5. When BAX is activated, the anti-apoptotic proteins relocate to the mitochondria where they are phosphorylated. This leads to the release of cytochrome *c* and a protein known as the 'second mitochondria-derived activator of caspase' (SMAC).
6. SMAC binds to the inhibitors of apoptosis proteins (IAPs), which normally prevent caspase activation and render them dormant.
7. Cytochrome *c* interacts with caspase 9 and an additional protein known as apoptotic activating protease factor-1 (Apaf-1) in the cytosol.
8. This complex causes caspase 9 to become activated, which in turn activates caspase 3.
9. When caspase 3 is activated, the same downstream pathways as the external pathway mentioned earlier are activated. This leads to membrane blebbing, DNA condensation, and the cleavage of proteins, cytoskeletal elements, and DNA repair proteins, all of which culminate in cell death and macrophage engulfment.

2.7.1 Receptor Desensitization and Regulation of Receptors

In addition to initiating the regulation of physiological processes and biochemical events, receptors are also subject to a variety of homeostatic and regulatory controls. These controls include covalent modification, relocation within the cell, association with other regulatory proteins, and control over the synthesis and degradation of the receptor. Effector and transducer proteins are controlled in a comparable way. Receptors can receive modulatory inputs directly or indirectly from other receptors, and their own signalling outputs nearly always regulate the receptors in response. When agonists are used to stimulate cells repeatedly, they typically result in a state of desensitization, which lessens the impact of additional or repeated exposure to the same drug concentration. This state is also known as adaptation, refractoriness, or down-regulation. This quick occurrence, known as tachyphylaxis, has significant therapeutic implications.

Desensitization may occur from a reduction in the number of synthesized and available receptors at the cell surface (in case of downregulation of receptor number) or from a temporary blockage of the receptor to agonist. A major factor in causing quick desensitization is the phosphorylation of GPCR receptors by particular GPCR kinases (GRKs). When GRKs phosphorylate agonist-occupied GPCRs, it makes it easier for cytosolic proteins known as arrestins to bind to the receptor, which causes G protein to decouple from the receptor (as shown in Fig. 2.16). (Shah et al. 2022; Striessnig et al. 2015; Morrow and Marx 2015; Wu et al. 2016; Marks 2000)

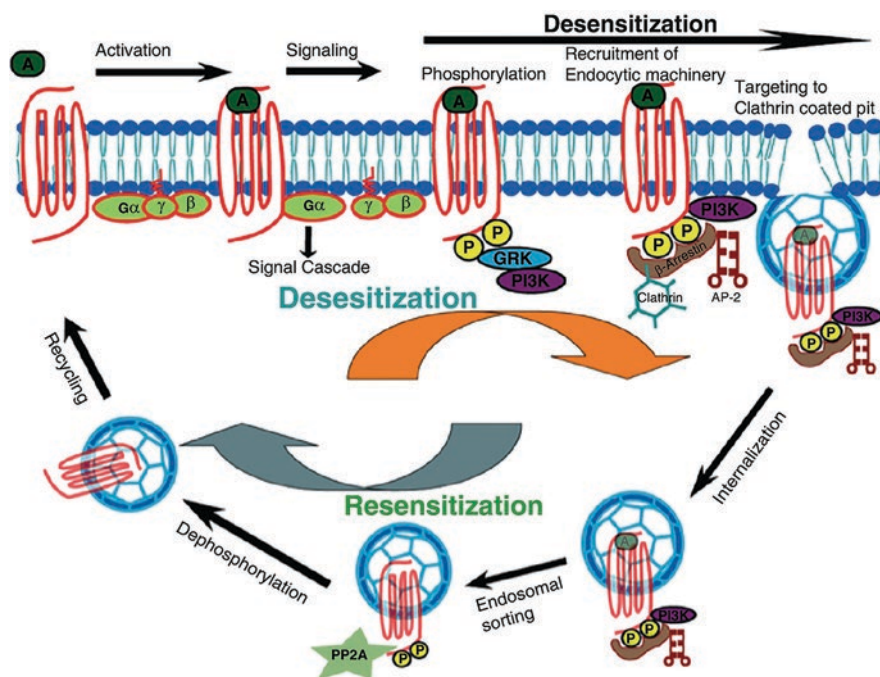


Fig. 2.16 Schematic representation of receptor desensitization (Mohan et al. 2012)

The β -arrestins bind to proteins like PDE4, which inhibits cyclic AMP signalling, clathrin and β 2-adaptin, this actually plays a great role in the internalization of receptors from the membrane, creating a scaffold for further signalling processes.

A tissue's reaction to pathological conditions, such as cardiac ischemia, can result in supersensitivity. This is because new receptors are synthesized and recruited to the myocyte's surface. Similar agonist- and antagonist-induced modifications to receptor-effector systems appear to be the basis for the actions of a number of classes of CNS-active agents (Nargeot et al. 1997).

2.7.2 Diseases Resulting Due to Receptor Malfunction

Disease may arise due to modifications in receptors and the signalling effectors that they immediately interact with. Some highly specialized signalling systems, such as the androgen receptor deficiency and testicular feminization syndrome, may exhibit a relatively limited, albeit dramatic, phenotypic disorder as a result of receptor loss. A number of conditions, including myasthenia gravis and some types of insulin-resistant diabetes mellitus, are caused by deficiencies in widely used signalling pathways. These conditions arise from autoimmune depletion of either insulin or nicotinic cholinergic receptors. Receptors, effectors, and coupling proteins that are constitutively active, aberrant, or ectopic may cause supersensitivity, subsensitivity,

or other undesirable reactions(Smit et al. 2007). An important development is the emergence of aberrant receptors, which are the byproducts of oncogenes that cause cancer by converting healthy cells into cancerous ones. Oncogenic potential exists for almost any kind of signalling system.

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Principles of Therapeutics and Gene-Based Therapy

3

Anamika Sengupta

Abstract

This chapter focuses on the history and evolution of gene-based therapies from its inception in the early 1970s to the landmark discovery of the CRISPR-Cas9 gene editing, which was ultimately recognized and awarded the Noble Prize in 2020. This chapter reviews essential requirements of traditional gene therapy approach and lists the gene-based therapies currently marketed in different countries, in conjunction with their associated limitations and concerns. This chapter also discusses in-depth CRISPR-Cas9 technology as an efficient alternative for site-specific gene alteration that practically eliminates many red flags raised by traditional gene therapy methods. The limitations associated with the CRISPR-Cas9 gene editing methods have been afforded their due attention within the scope of the discussion.

Keywords

Gene therapy · Vectors · Genome editing · CRISPR-Cas9

3.1 Introduction

Human gene-based therapies aim at inactivating, modifying, manipulating, or replacing mutants and disease-causing genes to either inhibit or alter their cellular expression. The ultimate objective is to treat genetic diseases via the modification or/rectification of cell functions expressing the gene.

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The foundation of the advanced twenty-first century gene therapy (with the potential to treat heritable diseases and cancer at the genetic level) was originally laid by James Watson and Crick (1953) through the definition of the double helical DNA structure and later refined by Nirenberg and Leder (1964) by deciphering the RNA code words (codons) for protein synthesis. Both geneticists and scientists have since invested decades of dedicated work to gain better understanding of genetic theories, developing gene-based therapeutics for treating multiple inherited disorders and overcoming associated roadblocks linked with clinical trials using viral vectors (e.g. the death of Jessie Gelsinger, participant of a clinical trial, 1999) (ClinicalTrials.gov [n.d.](#); Abbott et al. 2020). Gene-based therapies and attempts of therapeutic gene transfer in the twenty-first century promise viable treatment and even certain cure for many hematological, immunological, and metabolic disorders that were previously considered untreatable.

3.2 History of the Evolution of Gene-Based Therapies

The foundation for gene-based therapies was laid with the establishment of genetic engineering techniques using plasmids for gene transfer (Akinsheye et al. 2011; Anders et al. 2016). The myriad milestones achieved between 1973 and 2000 are summarized in Fig. 3.1.

The twenty-first century has subsequently been marked by multiple clinical trials employing a variety of vectors, first gene therapy commercialized by China, the establishment of gene editing technique of CRISP-Cas9, and the establishment of USA-FDA guidelines for research and development relative to gene therapy (Basak et al. 2015). Figure 3.2 summarizes said achievements between 2001 and 2020.

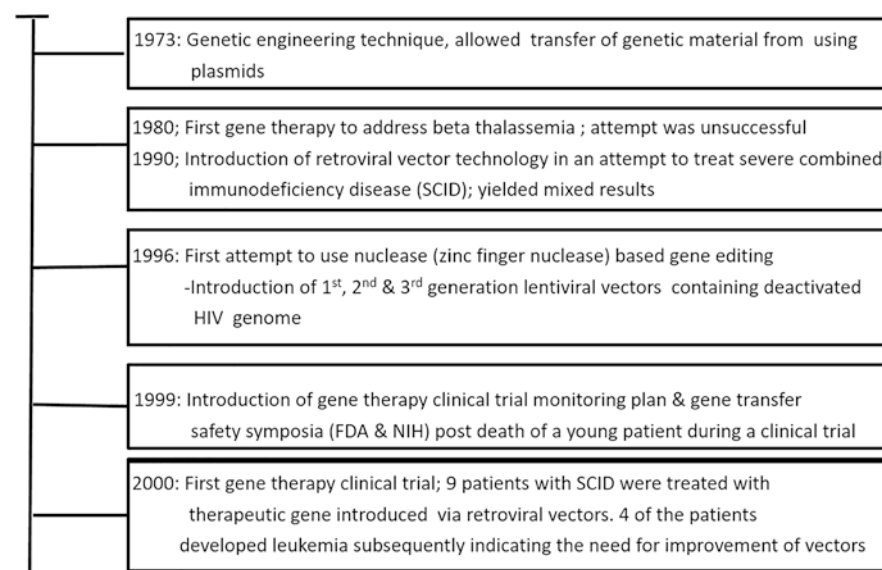


Fig. 3.1 Achievement in the field of gene therapy between 1973 and 2000

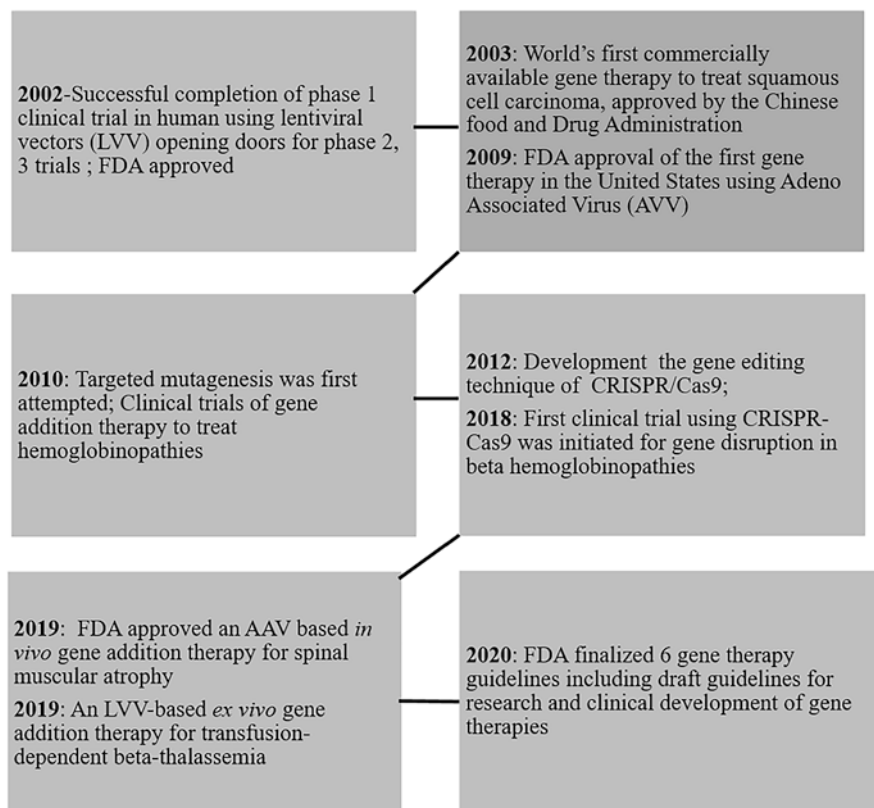


Fig. 3.2 Achievement in the field of gene therapy between 2001 and 2020

Gene-based therapeutic approaches can be classified into three broad categories:

1. **Ex vivo or in vitro gene therapies:** Diseased target cells are identified and removed from the body, genetically manipulated to correct the mutant gene, the corrected cells are re-introduced into the patient's body using viral vectors (lentiviral vectors or retroviral vectors).

Attempts have been made to correct blood-related disorders by ex vivo gene-based therapy. Examples include thalassemia (inability of the body to produce sufficient normal hemoglobin due to defective alpha- or beta-hemoglobin genes), Fanconi anemia (inability of the bone marrow to produce sufficient red blood cells), and sickle cell anemia (a single base pair change in the sixth codon of the beta-hemoglobin gene leading to misfolded globin chains, low oxygen-carrying capacity of hemoglobin, and altered shape of RBCs) (Basak and Sankaran 2016). A corrected copy of the defective gene is introduced into the genome of hematopoietic stem cells isolated from the bone marrow of the patient with the help of recombinant viral vectors. The modified stem cells with the potential to mature into healthy bone marrow cells are re-introduced into the patient's bone marrow (Broughton

et al. 2020). Chemotherapy that precedes this kind of ex vivo gene therapy kills all stem cells in the marrow with the defective gene. The long-term goal of this type of gene therapy is either to eliminate or significantly reduce the need for regular blood transfusion by patients with the above-mentioned blood disorders.

2. **In vivo gene therapies:** For diseases involving the brain, spinal cord, or liver (most of which are non-dividing cells), in vivo gene therapies are preferred. In the process, a recombinant vector (adenoviral or adeno-associated viral vectors) containing the correct gene (expected to replace the defective gene) is administered either into the target cells, into blood, or into the cerebrospinal fluid of the patient (Charlesworth et al. 2019).

Attempts have been made with in vivo gene therapy to treat Fabry disease and is currently under clinical trials. Fabry disease is a rare lysosomal disorder caused by a mutant GLA gene that produces a defective lysosomal enzyme called alpha galactosidase A. The defective enzyme is unable to break down its substrate globotriaosylceramide in the lysosomes of different cells, causing it to accumulate (particularly in cells lining the blood vessels of the skin as well as cells of major organs like the kidney, heart, and even the nervous system). This leads to extensive cell damage in early life (Cong et al. 2013). Via in vivo gene therapy, the correct version of the GLA gene is introduced into the affected cells of the patient using recombinant viral vectors. The hope is that the therapeutic gene via homologous recombination will get inserted into the genome of the recipient cells and help them produce normal alpha-galactosidase A enzymes, thus restoring normal lysosomal function in the patient's affected cell types (Cross 2018; Daley 2019).

3. **In situ gene therapies:** In this approach, a viral vector containing the therapeutic gene is injected directly into the affected organ or specific area of the body. For example, injection of the therapeutic gene into certain tumors might be required to treat certain cancers. Or, injection of a therapeutic gene into certain areas of the brain may effectively treat neuropathies (Food US. Drug Administration 2020; Hu et al. 2018).

Attempts to treat metastatic prostate cancer via in situ gene therapy are envisioned to reduce the mortality associated with the specific cancer. Using viral vectors, specific therapeutic genes are transduced into the tumor with the aim of generating localized cytotoxic activities or a generalized immune response in the tumor that would affect the systemic disease (Hacein-Bey-Abina et al. 2008; Haapaniemi et al. 2018).

3.3 Role of Vectors in Gene-Based Therapies

A vector in gene-based therapies helps in the delivery of the therapeutic gene to the target cells as shown in Fig. 3.3. Specific types of viruses have been used as vectors in different gene therapy approaches as mentioned in the above sector. The advantages associated with the use of viral vectors include (Kim et al. 1996):

1. The capability of a virus to rapidly infect cells.
2. The ease of modifying the viral genome for delivery of the therapeutic gene into the target cells.
3. Attenuation of the virus to avoid virulence (in the patient) is easily achievable.

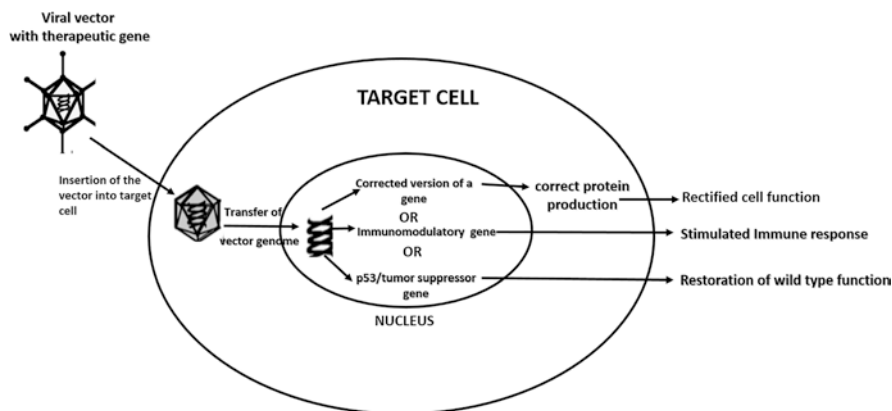


Fig. 3.3 Diagrammatic representation explaining the role of vectors in gene-based therapies

3.3.1 Common Viral Vectors Used Include

3.3.1.1 Adeno-Associated Viral (AAV) Vectors

The AAV vectors are safe for *in vivo* gene therapies as they can persist in patients for a lifetime and are non-integrative in nature. Thus, if the target cell is a dividing cell, the therapeutic gene is not passed onto the progeny cells affecting the long-term impact of the gene-based therapy. AAV vectors are thus used to deliver therapeutic DNA genes into the target cell that is non-dividing in nature (such as non-dividing cells of the liver, nervous system, eye, etc.). Delivery of relatively smaller genes or DNA fragments is appropriate for conveyance by AAV vectors. The actual size of therapeutic DNA may determine the diseases it can target. An important drawback associated with AAV vector use is the innate immune response it invokes in the patient following the first administration. And, as a consequence, patients are often limited to a one-time administration of the therapeutic gene. This characteristic property of AAV vectors is considered as a disqualifying criterion for clinical trials as it limits treatment efficacy (Kleinstiver et al. 2016). Patients with prior exposure to adeno-associated viruses through natural infections may have antibodies against the virus which may attack and destroy the vector before delivery of the therapeutic genes to the target cells. Much work has been dedicated by the scientific community to combat this daunting challenge, some of which involve the use of synthetic viral capsids unrecognizable by the host's immune system. Utilization of enzymes that can neutralize the AAV specific antibodies in the host is another approach (Kleinstiver et al. 2015; Kulcsár et al. 2017).

3.3.1.2 Adenoviral Vectors

Adenoviral vectors have very similar properties to AAV vectors in targeting non-dividing cells of the host. However, they are capable of delivering larger DNA fragments or genes due to their comparatively larger genome size. Strong immune response invoked in the host by adenoviral vectors can cause severe inflammation in the host, thus decreasing the effectiveness of the gene therapy.

3.3.1.3 Comparative Lentiviral and Retroviral Vectors

Both lentiviral and retroviral vectors are capable of integrating their genomes into the host cell genomes and thus are used to transfect dividing cells. The transfected genetic material is copied into all progeny cells and continues to function beyond the original cell lineage receiving the treatment. This makes the treatment longer lasting and thus more attractive. Lentiviral and retroviral vectors are capable of carrying larger therapeutic RNA fragments which are converted into DNA via reverse transcription during the integration process into the host genome. They are ideal for ex vivo treatment approach (shown in Fig. 3.3).

Major hurdles that prevented easy translation of traditional gene-based therapies from bench side to bedside:

Although the idea of correcting a mutant disease-causing gene was quite attractive to the scientific community during the 1990s, clinical translation from bench side to bedside has posed many challenges, some of which are listed below.

- *Short life of the treatment:* Integration of therapeutic DNA into the genome of target cells is not guaranteed, and the degree of acceptance or rejection varies between different target cell types. Sometimes, for longer lasting effect, patients have had to go through multiple rounds of gene therapy (expensive and thus considered a major drawback) (Maguire et al. 2009; Garcia-Bloj et al. 2019).
- *Immune response:* Introduction of a foreign gene specifically through viral vectors often triggers unpredictable acute immune response in the patient which may put the patient's life at risk. An example is the case of Jesse Gelsinger (1999) (Naldini et al. 1996).
- *Viruses as vectors:* Attenuated viruses (retrovirus, adenovirus, adeno-associated virus, and lentivirus) are preferred as vectors for gene-based therapies. These viruses are genetically manipulated before introduction into patients such that they are no longer capable of replication in the host cell. But, at times, the recombinant viruses mutate back to the replication competent form under suitable environment of the host cell. This may lead to viral infection and unpredicted complications.
- *Multigene disorders:* Disorders like diabetes, Alzheimer's and cardiovascular diseases which involve defect in multiple genes have been challenging for gene therapy resolution.

3.4 Gene-Based Therapies or Gene Medicines Marketed

The use of gene therapy as treatment still has its limits. Two thousand six hundred clinical trials have been conducted in the field of gene-based therapies. Limited quantities of these viable therapeutic drugs have been vetted and authorized for global marketing in different countries. Table 3.1 lists commercial gene therapeutics currently available (Nirenberg and Leder 1964).

Table 3.1 Commercial gene-based therapies currently available in Europe and the United States of America

Brand name	Therapeutic approach	Function of the therapeutic gene	Vector used	Target disease	Vendor	Approving country and year
ZOLGENSMA®	Single dose of survival motor neuron 1 (SMN1) gene	Production of SMN protein for motor neuron survival and function	Adeno-associated virus	Spinal muscular atrophy in children	Novartis	USA 2019
(ZYNTEGLO®)	Administration of patient's hematopoietic stem cells carrying an inserted copy of functional beta-globin gene	Production of normal beta-globin protein for hemoglobin synthesis	Lentiviral vectors	Beta-thalassemia major	bluebird bio	Europe 2019
Luxturna	RPE65 cDNA	Synthesis of RPE65 protein retinal pigment epithelium (RPE)	Adeno-associated virus	Leber congenital amaurosis (retinal disease)	Spark Therapeutics	USA 2017
STRIMVELIS®	Human ADA cDNA sequence	Synthesizes adenosine deaminase enzyme	Retroviral vectors	Severe combined immunodeficiency disease (ADA-SCID)	uniQure Orchard Therapeutics	Europe, 2012 Europe 2016
KYMRIAH®	Genetically engineered chimeric T cell obtained from the patient	Targets CD19 receptors on patient's cancerous B cells	Lentiviral vectors	B-cell acute lymphoblastic leukemia	Novartis	USA 2017
YESCARTA®	Genetically engineered chimeric T cell obtained from the patient	Target CD19 receptors on the cancerous B cells	–	Large B-cell lymphoma that has failed conventional treatment	Kite Pharma	USA 2017
(IMLYGIC®)	Gene for human GM-CSF	Stimulate immune response against cancer cells	Herpes simplex virus	Melanoma	Amgen Inc.	USA, Europe, 2015

3.5 Gene Editing: A New Approach to Gene Therapy

3.5.1 Basic Principle of Gene Editing

Genome editing can be essentially defined as an effort to make permanent site-specific modifications in the DNA sequence of the mutated target gene. It is a one-time delivery attempt of a therapeutic gene sequence into target cells. The genomic modifications may range from a single-nucleotide base pair change to an extended deletion, inversion or integration of entire gene sequences. If/when successful, the corrected DNA encodes for the correct protein, thus restoring normal function of the target cell type (Nishimasu et al. 2018).

Genomic editing approaches attempt to retain the normal physiological expression of the target gene, as the regulatory components of the target gene are left unaltered. Efforts of genome editing were initially cumbersome and depended heavily on processes such as site-specific mutagenesis, cleavage, synthesis, and DNA repair. Fortunately, the discovery of novel nucleases marked significant advancements in the field of genomic editing. These novel engineered nucleases are capable of binding to specific loci on the target DNA and introducing double-stranded breaks in specific sequences of the target gene, thus making permanent editing of the sequence achievable. Introduction of the double-strand breaks on the target DNA molecule (by nucleases) is followed by recombinant repair processes (for 100% reconstitution of the target gene sequence) required for restoration of normal cell functioning (O'Connell et al. 2014). The common types of novel nucleases used in genome editing processes include (shown in Table 3.2):

Table 3.2 The characteristic features of the novel nucleases used in genome editing

Characteristics features	Meganucleases (MNs)	Zinc finger nucleases (ZFNz)	TALENs	CRISPR-Cas9
Length of target DNA	14–40 nbp long	9–18 nbp long	30–40 nbp long	22 nbp + protospacer adjacent motif (PAM) sequence
Binding mechanism	Interactions between DNA and proteins	Interactions between DNA and proteins	Interactions between DNA and proteins	Interactions between DNA and RNA (Watson–Crick base pairing)
DNA breaks and repair process induced	Double-stranded breaks	<i>FokI</i> (a restriction endonuclease) induced double-stranded break	Double-stranded break induced by <i>FokI</i> (a restriction endonuclease)	Single/double-strand breaks by Cas9
Design	Large size of the recognition sites—a limitation	Specificity of zinc finger motifs assembled in arrays are often affected, leading to challenges	Target specificities are well defined	Complementarity with the target DNA makes it easy. Expression vectors for Cas9 available. Direct delivery of pre-loaded Cas9-RNA complex possible

- **Meganucleases (MNs)**
- Zinc finger nucleases (ZFNs)
- Transcription activator-like effector nucleases (TALENs)
- Cas nuclease used in the CRISPR-Cas9 system

3.6 CRISPR-Cas9 Model of Gene Editing: Recognized by Nobel Prize for Chemistry in 2020

The CRISPR-Cas9 genome editing technique (pioneered by Dr. Emmanuelle Charpentier and Dr. Jennifer Doudna) was adapted from the genome editing system employed by common bacteria (like *Streptococcus pyogenes*) for protection against viral attacks (Pearson et al. 2004). When infected with viruses, the bacteria insert pieces of the viral DNA into their own DNA in a particular pattern called the “clustered regularly interspaced short palindromic repeats (CRISPR).” This creates memory imprints of the virus, allowing the bacteria to “remember” the virus and prepare itself for a future attack by the same family of viruses. If and when attacked again, the bacteria use the elaborate CRISPR arrays to produce complementary RNA segments that attach to and cleave specific DNA segments of the invading bacteriophage (with an endonuclease like cas9), successfully thwarting and disabling it (Papanikolaou and Bosio 2021).

The CRISPR-Cas9 genome editing technique uses the same model of DNA editing (as used by the bacteria to defend against viral attacks described above). The main components of the genome editing system includes a Cas9 endonuclease which introduces double-stranded cut on the identified sequence of a target DNA (Ran et al. 2013). The Cas9 enzyme is associated with a piece of engineered RNA that has 2 components, namely the trans-activating rRNA (tracrRNA) and a single guide RNA (sgRNA) which is about 20 nbp long (small). Figure 3.4 shows the basic components of the CRISPR-Cas9 model of gene editing. A protospacer adjacent motif (PAM) which is a DNA motif specific for each type of Cas9 is also a requirement. The PAM sequence is needed as a guide to bind the Cas9 nuclease to its target DNA. When the engineered RNA with the Cas9 and PAM are introduced into target cells, the sgRNA recognizes the target DNA sequence via RNA–DNA interactions (Watson–Crick base pairing) (Regulatory Focus n.d.). The associated Cas9 nuclease cleaves the DNA at the targeted location (similar to the bacterial defense process). The cellular DNA repair machinery thereafter adds or deletes DNA segments with the mutation or replaces an existing DNA segment with a customized DNA sequence. In a more targeted approach, this can be achieved by providing a repair template containing the desired sequence. This helps to avoid truncations leading to null mutations. Many of the advantages associated with the CRISPR-Cas9 genome editing include the relative ease of manipulating genomic targets, the ability to concurrently edit multiple sites on a gene, and the higher predictability of off-target binding.

The CRISPR-Cas9 gene editing tool has been successfully incorporated into a variety of monogenic disorders’ treatment protocols (including cystic fibrosis, hemophilia, and sickle cell disease), all currently in different phases of clinical trials

(Watson et al. 1953). In-depth research on the role of CRISPR-Cas9 in the treatment and prevention of cancer, cardiovascular diseases, mental illness, and human immunodeficiency virus (HIV) infections is formally underway.

3.7 Delivery of the CRISPR-Cas9 Gene Editing Tool

The CRISPR toolkit packaged into adeno-associated viral vectors (AVV) for direct delivery into target cells is a common approach (Slaymaker et al. 2016). Although this approach increases the longevity of expression, it may also enhance off-target effects (OTEs), immunotoxicity, and insertional oncogenesis.

The CRISPR toolkit can also be introduced into target cells via electroporation and micro-injection which would avert viral vector-associated risk factors. This *ex vivo mode of delivery* (described earlier in the chapter) is much safer and is associated with enhanced technical feasibility as well as better quality control of the target cells (Teichler Zallen 2000). Associated challenges with the *ex vivo* delivery include concerns regarding survival and retention of engineered cells' function under *in vivo* conditions (following re-engraftment into the patient). The high-voltage shock required to permeate the cell membrane during electroporation could trigger toxicity leading to permanent damage of the treated cells (bluebird bio 2021).

Delivery of CRISPR components *in vivo* occurs either systemically (through intravenous injections) or directly (injected into the target tissues). With systemic delivery, tissue-specific promoters enable the expression of the CRISPR toolkit in the target cells of the specific organ. Challenges associated with *this* delivery include attack by blood borne proteases and nuclease, opsonization and clearance via the body's phagocytic system. Reaching the target tissue through the tight knit vascular endothelium and the efficient uptake by the target cells via endocytosis are likewise additional concerns (shown in Fig. 3.4).

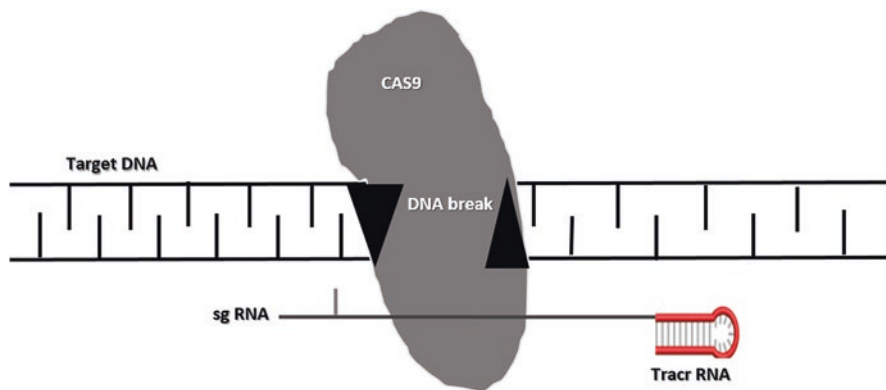


Fig. 3.4 The CRISPR-Cas9 toolkit; sgRNA-single guide RNA, tracrRNA: trans-activating rRNA; Arrowheads indicate the break points on the DNA induced by the nuclease Cas9

3.8 Limitations Associated with the CRISPR-Cas9 Gene Editing Technique

Off-target effects (OTEs) The major limitation associated with the CRISPR is the high frequency (>50%) of “off-target effects” (OTEs). Engineering the nuclease Cas9 variants to reduce OTEs while maintaining their ability to edit a gene has been attempted. SpCas9-HF1 is a high-fidelity engineered Cas9 variant with 4 mutated residues that influence binding between Cas9 and the target DNA. Compared to wild type Cas9, the off-target effect of SpCas9-HF1 is low to undetectable. Other variants include evoCas9 and HiFiCas9 characterized by changes in their amino acid residues in the nucleotide recognition domain. Another approach toward reduction of OTEs may involve the reduction of Cas9-DNA interactions and prioritizing DNA:RNA heteroduplex interactions for facilitating genomic edits (Uddin et al. 2020).

Toxicity due to DNA damage The trigger of target cell apoptosis due to CRISPR-induced double-stranded breaks is another major limitation. It is most commonly caused by the activation of the tumor suppressor gene p53 in the target cells. p53 suppressed cells respond well to the CRISPR but subsequently increase the chances of selection for oncogenic cell survival (Haapaniemi et al. 2018). Large deletions and complex rearrangements of gene sequences are among other unintended consequences that invariably question the safety of using CRISPR-Cas9 genome editing. Cas9 variants (dCas9 with inactivated nuclease domains) may mitigate the risks associated with double-stranded breaks while providing therapeutic utility (Garcia-Bloj et al. 2019). Other variants (Cas9n, which induce single-stranded breaks) may also offer additional alternatives for consideration.

Immunotoxicity Similar to the traditional gene therapy approaches, the CRISPR system also raises concern for immunogenic toxicity. In a study (Charlesworth et al. 2019), using human subjects, more than 50% of the subjects had pre-existing immunity against the most commonly used bacterial ortholog of Cas9 (SaCas9 and SpCas9). For this cohort of patients, the use of CjCas9 nuclease would be the only option. Since the efficacy and safety protocols of CjCas9 are not yet well established, the authorized use of CjCas9 would still be questionable at best.

Ethical Concerns The genome editing process is, thus far, limited to somatic cells and thus the changes introduced are not heritable. This is a valid and a legitimate concern, with limitation. There are clearly ethical challenges and safety issues associated with germline cell genome editing. There are likewise unanswered questions related to whether the CRISPR-CAS9 gene editing technology would be morally permissible for use in the enhancement of human traits like height, intelligence, etc. And even if that were granted, it would most surely raise concerns of misuse and abuse. In the USA, genome editing of embryos is strictly prohibited.

3.9 Utilization of the CRISPR-Cas9 Gene Editing Technology in Therapeutics

CRISPR battling SARS CoV-2 A CRISPR-based COVID-19 detection assay, called SARS-CoV-2 DETECTR (characterized by high accuracy (95%) and short turn-around time (40 min)) is currently underway. The assay involves reverse transcription of the extracted RNA and simultaneous amplification (using the RT-LAMP method). The endonuclease used is called Cas12. The guide RNA recognizes a nucleoprotein gene (N gene) and an envelope gene (E gene) of the SARS-CoV-2. Visualization involves the cleavage of a fluorescent reporter molecule, producing a single band close to the sample band (on the application strip (negative test)). The resulting appearance of one or two higher bands is indicative of a positive SARS-CoV-2 test. The discovery of the Cas13 (an RNA-guided RNA-targeting endonuclease) and the development of a PAC-MAN (prophylactic antiviral CRISPR in huMAN cells—that utilizes a CRISPR-Cas13d variant) aim toward the provision of therapeutic options for COVID-19 patients.

Role of CRISPR-Cas9 in immunotherapy approach to treat cancers The first phase 1 clinical trial using CRISPR was approval by the United States Food and Drug Administration in 2018. The aim was to help cancer patients fighting rare conditions characterized by relapsing tumors and fewer treatment options (such as melanoma, multiple myeloma, synovial sarcoma, and round cell liposarcoma).

In this trial, the α and β chains of the endogenous T cell receptor (TCR) and the programmed cell death-1 protein (PD-1) were knocked out using CRISPR. Lentiviral vector-mediated delivery of the modified TCR gene (specific for recognizing NY-ESO-1 antigen highly expressed in relapsed tumors) was attempted. This trial (conducted in both pre-clinical and clinical settings) marks the first attempt at using CRISPR's novel abilities of gene editing for treating cancers.

3.9.1 Gene Disruption Using CRISPR-Cas9 for the Treatment of Blood Disorders

Vertex Pharmaceuticals and CRISPR Therapeutics both used CRISPR for gene disruption in a clinical trial that initially aimed at therapeutically benefitting patients with blood disorders, namely sickle cell anemia (SCD), followed by a β -thalassemia clinical trial in the USA. This therapy was called CTX001 and aimed at increasing fetal hemoglobin (HbF) levels, thereby providing clinical benefit for a disease that involves β -hemoglobin, namely SCD and β -thalassemia (Akinsheye et al. 2011).

The trial used CRISPR ex vivo approach for targeted disruption of the enhancer of *BCL11A* gene in erythroid-specific target cells (erythropoietic progenitor cells collected from a patient). The disruption led to elevated HbF gene expression (Basak and Sankaran 2016) in the modified target cells. Delivery of the genetically edited target cell into patients via intravenous infusion (post-busulfan treatment to destroy

unaltered hematopoietic stem cells from the bone marrow) yielded promising results. Significant increase in HbF expression (46.6% HbF and 94.7% erythrocytes expressing HbF) was noted after 4 months of CTX001 transfusions in a patient with sickle cell disease. Then again, in a β -thalassemia patient, 9 months post-therapy exhibited significant increase in fetal hemoglobin expression.

3.10 Future Outlook and Conclusion

Clinical gene-based therapy has made significant progress in the past decade. Improvement of the vector systems and the successful use of lentiviral and adeno-associated viral vectors in multiple clinical trials were highly regarded landmark achievements. Introduction of the genome editing techniques using designer nucleases was likewise considered breakthrough discoveries in the field. These remarkable achievements provide rays of eternal hope that diseases previously considered incurable may at least be treatable someday soon. Given that the field anticipates exponential growth in the coming decade, surely some practical consideration is due in advance toward some of the identified areas:

- *Pricing:* Most of these gene-based therapies are innovative and thus tend to be extremely expensive. If the costs of such therapies are not effectively managed, reimbursement of the likely expenses from funding sources (like the health insurance companies) would remain a challenging. Accessibility would therefore be largely limited to the super wealthy patients, much to the detriment of the common person as an end result then, gene therapy might finally end up “gold medicine for the wealthy.”

Engineering of gene-based therapeutic products should be streamlined and quality controlled: Currently, two approaches are being discussed for the manufacturing of gene-based therapeutic products: the “centralized” and the “decentralized.” Per the centralized model, collection of the patient sample (target cells) should be pursued at a local hospital followed by shipment to a remote central facility for genetic engineering. The engineered sample in a frozen state would be shipped back to the original location for patient treatment. This system based on centralized expertise of licensed/certified operators working under carefully regulated standards is expected to be error-free. However, transportation could have adverse impact on the viability of the engineered cells hence increasing chances of treatment failure. Transportation may likewise add to the cost of the therapies.

Decentralized manufacturing would allow cell collection and processing locally. The advantage to this process is its close proximity to the patient which would increase chances of treatment personalization to cater to the patient’s individual need. A major disadvantage of this process would be user variability and bias due to difference in location, availability of resources, and expertise/skillset of specialized persons involved in the process at each location. This variability, however, can be avoided through the introduction of manufacturing automation using a closed

system that allows minimal user interaction. Successful decentralization would regularly require “technology transfer” between specialists (Wirth et al. 2013).

Collaboration For the establishment of regulatory protocols for quality assurance of gene-based therapies (often considered as “living drugs”) and for obtaining large scale marketing authorization, close collaboration between scientists, industrialists, law makers, and regulatory agencies should be embraced.

In conclusion, recent advances made in the field of gene-based therapies have been exemplary and worthy of mention. Significant milestones have been achieved with overwhelming benefit to patients stricken with life-threatening genetic conditions. There is tremendous potential for exponential growth in the field of gene-based therapeutics even though still in its toddler stage. The FDA-approval of CRISPR-based gene therapy trials in phase I/II (after a thorough risk-to-benefit ratios’ analysis) for treatment of severely debilitating monogenic diseases and some types of cancer is positively inspiring. The potential outcome of these trials will dictate the future use of not only gene editing techniques for treatment of a wide array of diseases but may also open up new avenues for significant advancement.

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Drugs Acting on Autonomic Nervous System

4

Moitreyee Chattopadhyay and Bhaskar Pal

Abstract

The autonomic nervous system is largely distributed throughout the body and controls the autonomic and visceral functions, which occur without consciousness. In periphery, it contains nerves, ganglia, and plexuses, which innervate the heart, blood vessels, glands, smooth muscle, and other visceral organs. The concept of neuronal transmission was developed to demonstrate the presence of physiologically active molecules and transmission of neuronal impulses from the postganglionic nerve fibres to the effector cells. The transmission of neuromodulators including the biogenic amine, an amino acid, or a peptide occurs, which affects the synthesis and release of neurotransmitter by acting on presynaptic neurons. The pharmacotherapies used in autonomic complications exert their pharmacological action by modulating the critical phases of neuronal transmission. Therefore, in this article we discussed about the autonomic neurohumoral transmission, the synthesis, storage, release of transmitter and drug acting on parasympathetic and sympathetic autonomic nervous system. The drug used in different autonomic complications including glaucoma, myasthenia gravis, Alzheimer's disease is discussed. Furthermore, the receptors involved in autonomic cholinergic, adrenergic, and ganglionic agonist as well as antagonists are also demonstrated.

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Keywords

Neuromodulators · Cholinergic · Adrenergic · Presynaptic neurons ·
Pharmacotherapy · Neurohumoral transmission

Abbreviations

AChE	Acetylcholinesterase
ADR	Adverse drug reaction
ANS	Autonomic nervous system
BChE	Butyrylcholinesterase
BP	Blood pressure
CHF	Congestive heart failure
COMT	Catechol- <i>O</i> -methyltransferase
COPD	Chronic obstructive pulmonary disease
DAT	Dopamine transporter
GA	General anaesthesia
i.o.p	Intraocular pressure
IBS	Irritative bowel syndrome
MAO	Monoamine oxidase
NET	Norepinephrine transporter
NMJs	Neuromuscular junctions
NO	Nitric oxide
NPY	Neuropeptide Y
PG	Prostaglandin
RMP	Resting membrane potential
SERT	Serotonin transporter
TCA	Tricyclic antidepressant
UTI	Urinary tract infection
VIP	Vasoactive intestinal peptide

4.1 Introduction**4.1.1 Neurohumoral Transmission in Autonomic Nervous System**

Neurohumoral transmission signifies the transmission of signals or humoral response from the presynaptic nerve to postsynaptic nerve through synapse and neuroeffector junction. The transmission of neuromodulators including the biogenic amine, an amino acid, or a peptide occurs, which affects the synthesis and release of neurotransmitter by acting on presynaptic neurons. Non-synaptic nerve terminals also release the biogenic amines, which further affect the function of other neurons. The concept of neuronal transmission was developed to demonstrate the presence of physiologically active molecules and pass the information from one neuron to

Table 4.1 Difference between sympathetic and parasympathetic ANS (Waldman 2009; Cartwright and Carvounis 2018)

	Sympathetic	Parasympathetic
Source	Dorso-lumbar (T1-L2/L3)	Cranio-sacral (iii, vii, ix, x; S ₂ –S ₄)
Spreading	Widely	Limited to trunk, neck, and head
Effects	Excitatory	Inhibitory
Neurotransmitters	Noradrenaline, adrenaline	Acetylcholine
Activation	During stress	During relaxation
Pre:post gang fibre ratio	1:20–1:100	1:1–1:2
Stability	Acts on wider areas	Locally degraded

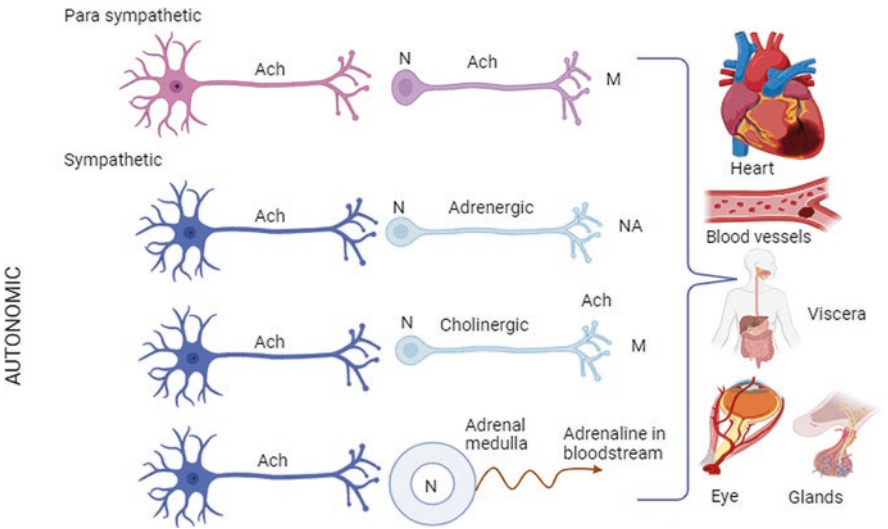


Fig. 4.1 The schematic outlines of efferent ANS, the neurochemical release and their receptors in synapse. *Ach* acetylcholine, *N* nicotinic, *M* muscarinic, *NA* noradrenaline

another neuron or effector organ. In the year 1921, the experiment of Otto Loewi with two frog hearts and vagus stimulation identified two new substances Vagusstoff, later identified as acetylcholine by Loewi and Navratil, and the stimulator, Acceleranstoff, a substance like epinephrine. Though later Von Euler in 1946 discovered noradrenaline from the extract of bovine splenic nerve (Neurohumoral transmission in the autonomic nervous system 2023; McCorry 2007; McCoy and Tan 2014; von Euler 1971). The ANS is broadly classified as sympathetic and parasympathetic system as depicted in Table 4.1 and Fig. 4.1.

4.1.2 Neurochemical Transmission

1. **Axonal Conduction:** The RMP (–70 mv) is achieved through the high accessibility of resting axonal membrane to K⁺ in axoplasm coupled with low Na⁺ gradients by an energy-dependent process, Na⁺/K⁺-ATPase pump. Initiation of

action potential occurs due to the sudden enhancement of Na^+ influx \rightarrow resulting in rapid depolarization and positive overshoot. The termination of depolarization occurs with closure of Na^+ -channels and delayed K^+ efflux. Thus action potential (AP) propagate and ionic progress generate local circuit currents, which activate the adjacent resting channels in axon at next excitation region of the axonal membrane and propagation of AP occurs without decrement (Katz and Chase 1971; Zucker et al. 2012; Steps in neurohumoral transmission - autonomic nervous system: Pharmacology 2023; Byrne 2023). Tetrodotoxin (puffer fish) and saxitoxin (few shellfish) selectively obstacle the axonal conduction by preventing Na^+ permeability and abolish impulse generation. Batrachotoxin (South American frog) generates paralysis by enhancing the Na^+ permeability by inducing depolarization (Venkatesh et al. 2005; Cusick and Sayler 2013; Finol-Urdaneta et al. 2018).

2. **Transmitter Release:** The generation of AP in nerve terminals induces the sequence of events which triggers the impulse transmission (excitatory or inhibitory) across the neuroeffector junction. The neurotransmitters are extensively produced in axonal terminals and stored in the synaptic vesicles. In the resting condition, spontaneous and slow release of the transmitter occurs, which generates the electrical responses in the postjunctional membrane [miniature end-plate potentials (mepps)] and regulates the physiological responsiveness in effector organs. When Ca^{2+} enters inside the axonal cytoplasm, the effector organ responds. All the objects of the storing vesicles (enzymes, other proteins, transmitters) escape to synaptic cleft by exocytosis (Mesulam 2009; Thesleff 1988; Reichardt and Kelly 1983).

Most of the mediators like PG, NO, endocannabinoids enter their target sites by either diffusion (Scherma et al. 2016) or active transport. Synaptobrevin (vesicle protein) complexes with SNAP-25 and syntaxin 1 (plasma membrane protein) initiate vesicle fusion (Shiff and Morel 1997). Several other proteins including synaptogyrin, synaptotagmins, synaptophysin, and synapsin play in membrane fusion and exocytosis.

3. **Transmitter Action in Postjunctional Neuron and Generation of Postjunctional Potential—**The transmitter combines with particular receptors in the synaptic cleft that depends on the nature of the following changes:
 - Potentiate the permeability to cation (Na^+ , Ca^{2+}) influx, resulting in membrane depolarization which is referred to as excitatory postsynaptic potential (EPSP).
 - Potentiate the permeability to anion (Cl^-) influx, resulting in membrane hyperpolarization, that is inhibitory postsynaptic potential (IPSP) (Fig. 4.2).
 - Increasing the accessibility to K^+ efflux, and K^+ gradient moves out from the cell, resulting in hyperpolarization and membrane potential (IPSP) (Neurohumoral transmission in the autonomic nervous system 2023; Katz and Chase 1971; Zucker et al. 2012; EPSPs and IPSPs 2015).
4. **Induction of Postjunctional Activity:** The super threshold EPSP initiates AP in postsynaptic neurons or muscles (skeletal or cardiac) by activating voltage-gated channels. EPSP may induce spontaneous depolarization with Ca^{2+} release caus-

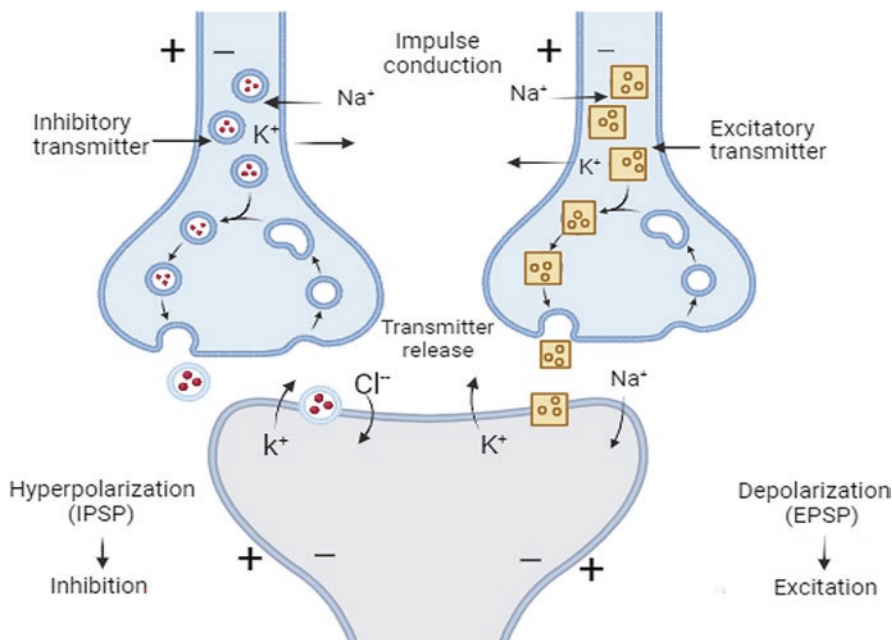


Fig. 4.2 Schematic illustration of the sequence of neurochemical transmission. *EPSP* excitatory postsynaptic potential, *IPSP* inhibitory postsynaptic potential

ing contraction (smooth muscle) and secretion (glands). IPSP (neurons and smooth muscle) resists the excitatory potentials generated by other neurons at the same time and stabilizes the postjunctional membrane (EPSPs and IPSPs 2015).

5. **Termination or Dissipation of the Transmitter:** A combination of transmitters with receptors is either rapidly terminated locally (ACh) or reuptake into the presynaptic nerve by diffusion or active transport (NA). Specialized transporter proteins (NET, DAT, SERT) are produced in axonal membranes. The rate of disposing of transmitted impulses across junction occurs by an efficient protein (AChE for cholinergic synapse), and when the activity of these proteins is inhibited termination occurs. The dissipation rate of transmitter depends on the rate in which signals are transmitted across the junction (1–1000/s) (Laghaei et al. 2018; Blakely and Edwards 2011).

Co-transmission: After activation most of the neurons produce different pharmacologically active substances along with primary transmitters, the cotransmitters. In case of ANS, peptides (VIP, NPY, substance P, somatostatin, etc.), NO, purines (ATP, adenosine), PG are cotransmitters. In the autonomic cholinergic transmission, VIP acts as neuromodulator and paracrine mediator, which act locally in receptor-bearing cells. Furthermore, VIP modulates smooth muscle activity (potent vasodilator), secretion of epithelial cell, and blood flow in GIT (Hashimoto et al. 1997). NO is another potent cotransmitter in parasymp-

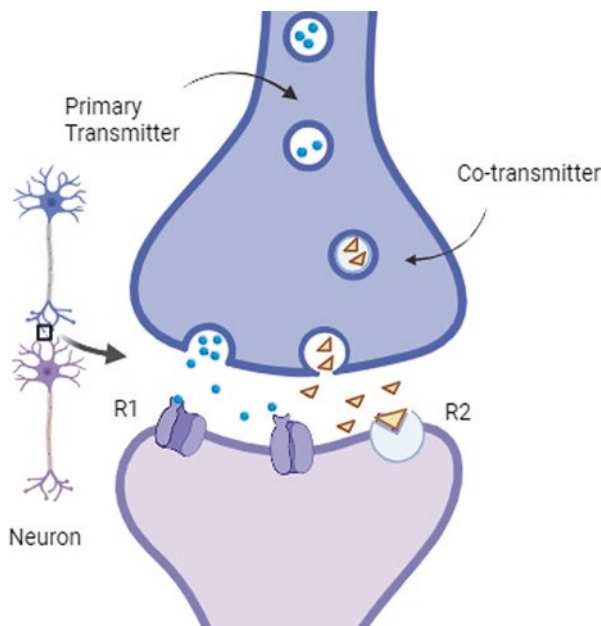


Fig. 4.3 Cotransmission; R1—transmitter receptor, R2—cotransmitter receptor

pathetic neurons acting as vasodilator and also modulating vascular tone, blood pressure as well as hemodynamics (Levine et al. 2012).

The adrenergic neurons produced NPY, which is potent vasoconstrictor and also shows pharmacological action in CVS and GIT (McAuley et al. n.d.). The cotransmitters are stored in storage vesicles and released with primary transmitter. After secretion of cotransmitters, it affects the prejunctional regulation and post-synaptic sensitivity of primary transmitters. The action is represented in Fig. 4.3.

The neurotransmitters of autonomic nervous system are compacted in Table 4.2.

4.2 Sympathetic System

The adrenergic transmission in neuroeffector junction is mediated by noradrenaline (post-ganglionic sympathetic neurons and CNS), dopamine (extrapyramidal system and mesolimbic neuron), and adrenaline (adrenal medulla) which are collectively stated as adrenergic transmission, and all these amines are termed as catecholamines.

Tyrosine is hydroxylated to DOPA by tyrosine hydroxylase (TH) and DOPA to dopamine (DA) by aromatic L-amino acid decarboxylase (AAADC). Dopamine enters into the storage vesicles by VMAT2 transporter. Dopamine gets converted into norepinephrine (NE) by dopamine- β -hydroxylase (D β H) and stored in vesicles along with cotransmitters (NPY, ATP). The fusion involves the interaction between

Table 4.2 Receptors, agonist, antagonist, and prominent pharmacological actions of epinephrine, dopamine, and serotonin (Epinephrine n.d.; Ormsbee 1984; De Ponti 2004; Acetylcholine n.d.)

Neurotransmitters	Receptors	Agonist	Antagonist	Pharmacological actions
Epinephrine and norepinephrine	α (α_1 , α_2), β (β_1 , β_2 , β_3)	α_1 -Phenylephrine, methoxamine α_2 -Clonidine, brimonidine β_1 -Dobutamine, epinephrine β_2 -Albuterol, formoterol β_3 -Mirabegron	α_1 -Prazosin, doxazosin α_2 -Yohimbine β_1 -Metoprolol, atenolol β_2 -Nadolol β_3 -L748,328 $\beta_1 + \beta_2 + \alpha_1$ -Carvedilol	↑ Secretion of glands (α_1), but ↓ insulin secretion (α_2). Contraction (α_1) and relaxation (β_2) of urinary tracts + Inotropic, chronotropic, dromotropic effects (β_1) on heart Renin release from kidney (β_1) Mydriasis (α_1), ↑ aqueous secretion (β_2) in eye Glycogenolysis (α_1 , β_2) in the liver and lipolysis (β_3) in adipose tissue
Acetylcholine	Muscarinic (M_1 , M_2 , M_3) (M_4 and M_5 —under research) Nicotinic (N_M , N_N)	M_1 -Oxotremorine M_2 -Methacholine M_3 -Bethanechol N_M -Nicotine, succinylcholine N_N -Epibatidine	M_1 -Pirenzepine M_2 -Triptiramine, oxybutynin (weak) M_3 -Tolterodine, Solifenacin M_1/M_3 -Triotropium bromide N_M -Atracurium N_N -Mecamylamine	Learning memory and motor function (M_1), contraction of skeletal muscle (N_M) Histamine secretion and acid secretion in gastric gland (M_1) CA release from adrenal medulla (N_N) — Inotropic chronotropic, dromotropic effects (M_2) in the heart Pupil contraction, ↑ NO release, ↓ BP, ↑ glands secretion and smooth muscle contraction (M_3)
Dopamine	D_1 , D_2 , D_3 , D_4 , D_5	D_1 -SKF82958, pergolide (partial) D_1/D_5 -Dihydroxidine D_2 -Bromocriptine D_2/D_3 selective-ropinirole D_3 -Quinpirole	D_1 -Ecopipam D_2 -Haloperidol D_3 -Raclopride, BP-897	Hypokinesia, tremor, speech, mood Non-specific awakening in hepatic coma Tachycardia, postural hypotension, ↓ sympathetic outflow The excitatory transmitter in CTZ, ↑ nausea and vomiting ↓ Prolactin, ↑ GH secretion, ↑ g.f.r, natriuretic effect, +inotropic effect, vasoconstriction (large dose)

(continued)

Table 4.2 (continued)

Neurotransmitters	Receptors	Agonist	Antagonist	Pharmacological actions
Serotonin	5HT ₁ , 5HT ₂ , 5HT ₃ , 5HT ₄₋₇	5HT _{1A} -Buspirone 5HT _{1D} -Sumatriptan 5HT _{2B} - α -methyl-5-HT 5HT _{2C} -MK 2.2 5HT ₃₋₂ -methyl-5-HT 5HT ₄ -Cisapride	5HT _{1A} -WAY 100135 5HT _{2A/2C} -Risperidone 5HT ₃ - Ondansetron 5HT ₄ -GR 113808	↓Gastric acid and ↑mucus secretion ↑Peristalsis (5HT ₄) in diarrhoea. ↓BP, bradycardia, apnoea and pain (5HT ₃) Behavioural changes, hunger, sleepiness (injected in brain) Platelet aggregation (5HT _{2A})

↑ = increase; ↓ = decrease; + = positive

specialized proteins including VAMPs (vesicle-associated membrane proteins) and SNAPs (synaptosome-associated proteins), following that the neurochemicals bind with particular receptor and exert the pharmacological actions.

4.2.1 Synthesis, Storage, and Destruction of Catecholamines

Synthesis Catecholamines are originated from amino acid phenylalanine as illustrated in Fig. 4.4 (Neurohumoral transmission in the autonomic nervous system 2023; Carlsson 1966; Burnstock and Costa 1975). Tyrosine hydroxylase hydrolyses phenylalanine to tyrosine in the liver, and alpha-methyl-*p*-tyrosine prevents this conversion by inhibiting the enzyme. The 3-hydroxylation and decarboxylation convert tyrosine to dopamine. β -hydroxylation of dopamine gives NE, further N-methylation in chromaffin forms epinephrine. Dopa decarboxylase produces serotonin from 5-hydroxy-L-tryptophan.

Storage CAs are stored in vesicles in sympathetic nerve terminals, which prevent the leakage and intraneuronal metabolism of transmitters. The vesicular membrane takes up dopamine from axoplasm. NA and ATP are stored in complex form (4:1)

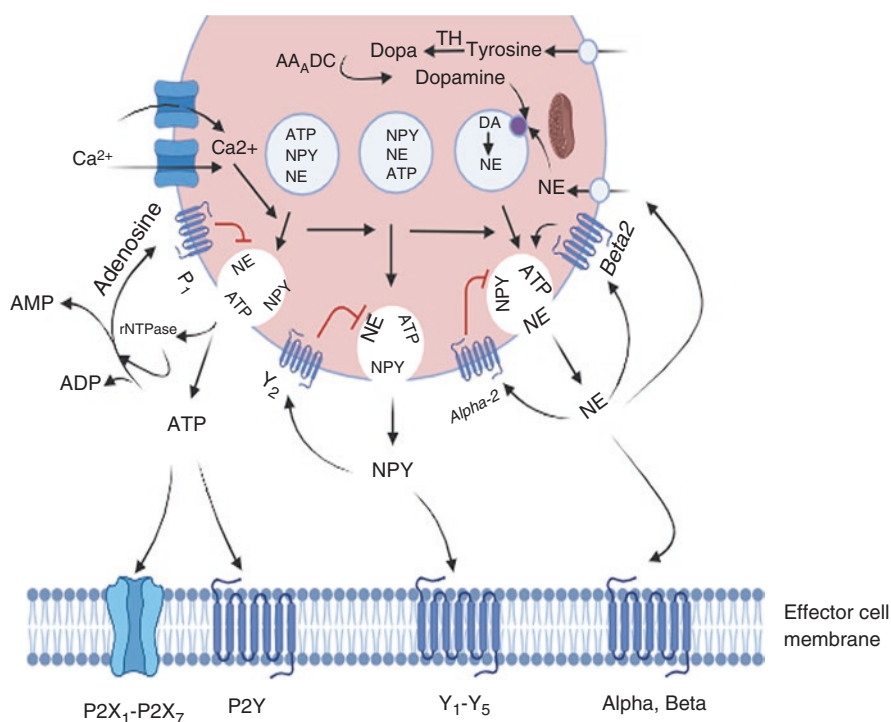


Fig. 4.4 Illustration of adrenergic neuronal transmission showing the site for production, storage, exocytosis, and receptors

and absorbed in chromogranin (protein) (Burnstock and Costa 1975; Joh and Hwang 1987).

4.2.2 Metabolism

After releasing NA from vesicles into cytoplasm, NA is metabolized by MAO, while circulated and administered CAs are metabolized by COMT in liver. The neuronal metabolism of CAs is inhibited by MAO and COMT inhibitors. MAO and COMT are widely distributed in the kidney, liver, brain, in a few postsynaptic nerves and glial cells (Weiner 1964). MAO converts CA into aldehyde and acid that are excreted through urine.

Adrenoceptors: The brief outline is given in Table 4.3.

The adrenergic neurotransmission in the neurons and effect modified in the presence of various drugs is elaborated in Table 4.4 and Fig. 4.5.

Table 4.3 Location, mechanism, agonist and antagonist of adrenoceptors (Lancaster 1980; Reid 1984)

Receptors	Location and function	Mechanism	Agonist	Antagonist
α_1	Glands—secretion UT—contraction Gut—relaxation Heart—+inotropic Eye—mydriasis Liver—glycogenolysis Uterus—contraction	\uparrow PLC and PLA2, activates Na^+/H^+ exchanger, modulates K^+ channels, \uparrow Ca^{2+} channels, and MAPK signalling	Phenylephrine Methoxamine Midodrine Metaraminol	Prazosin Doxazosin Nipradilol Labetalol
α_2	Pancreas— \downarrow insulin secretion Platelets—aggregation Smooth muscle contraction, \uparrow BP	Inhibits AC and cAMP, \downarrow PKA	Clonidine Apraclonidine Brimonidine Guanabenz	Yohimbine
β_1	Heart—+ chronotropic, dromotropic and inotropic effect Kidney—rennin release Posterior pituitary—ADH release	Activate AC, \uparrow cAMP generation \uparrow PKA and activate Ca^{2+} channels (L-type)	Dobutamine Epinephrine	Metoprolol Atenolol
β_2	GIT—relaxation UT—relaxation Blood vessels—dilation, \downarrow BP Bronchioles—bronchodilation Liver—glycogenolysis Eye— \uparrow aqueous secretion	Activate AC \uparrow cAMP \uparrow PKA and activate Ca^{2+} channels	Albuterol Formoterol Celiprolol Carteolol Bopindolol	Nadolol
β_3	Adipose tissue—lipolysis	Activate AC \uparrow cAMP \uparrow PKA and activate Ca^{2+} channels	Mirabegron	L748,328

\uparrow = increase; \downarrow = decrease

Table 4.4 Modification of adrenergic transmission in presence of various drugs (Vardanyan and Hruby 2016; Patrick 2023b)

Steps	Activity	Drugs	Function
Synthesis of NA	Prevention Using identical path	α -met-p-tyrosine α -met-dopa	NA exhausted NA replacement
Axonal reuptake	Blocking	Guanethidine, cocaine	\uparrow NA, \downarrow tyramine
Vesicular reuptake	Blocking	Reserpine	NA depletion
Neuronal impulse combined NA release	Prevention	Bretylium	Impaired adrenergic transmission
Neuronal NA assembly	Alter diffusion	Amphetamine	\uparrow NA (indirectly acting)
Metabolism of NA	MAO-inhibitor MAO-A inhibitor MAO-B inhibitor COMT-inhibitor	Nialamide Moclobemide Rasagiline Entacapone	\uparrow NA \uparrow NA and tyramine \uparrow DA \uparrow NA and DA
Receptors	Agonism Antagonism	Clonidine Salbutamol Dobutamine Phenylephrine Prazosin Yohimbine Esmolol Propranolol	α_2 - \downarrow NA release, \downarrow BP β_2 -bronchodilation β_1 -cardiac stimulant α_1 - \uparrow BP, bradycardia α_1 - \downarrow BP, improve urine flow α_2 - \uparrow BP, \uparrow heart rate β_1 - \downarrow BP, \downarrow heart rate β_1 + β_2 - \downarrow CO, \downarrow force of contraction

\uparrow = increase; \downarrow = decrease

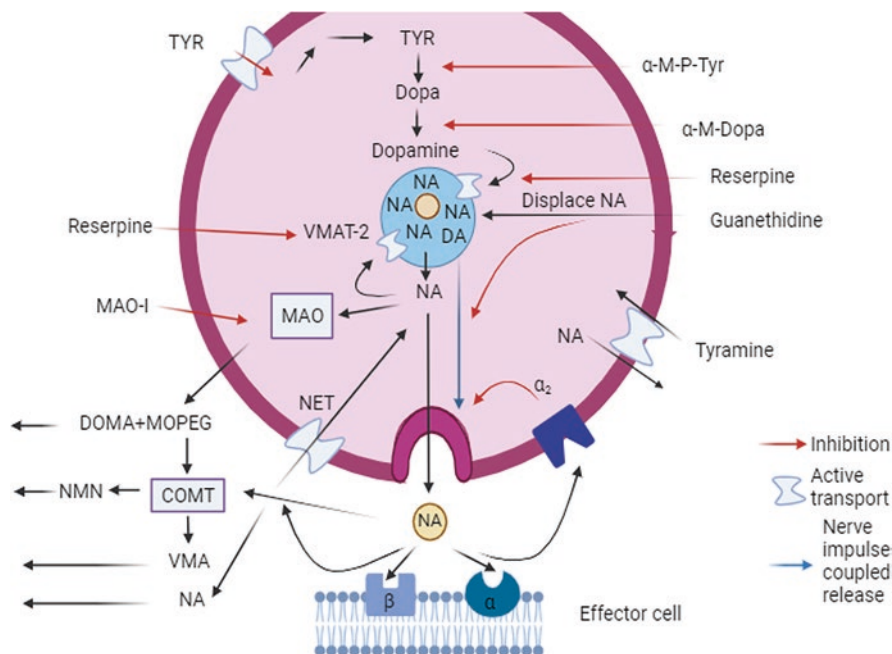


Fig. 4.5 Adrenergic transmission and its modification by drugs. Try: tyrosine, MAOI: monoamine oxidase inhibitor, α -M-P-Tyr: α -methyl phenyl tyrosine, COMT: catechol-*o*-methyl transferase, α -M-dopa: α -methyl dopa, NMN: nor-metanephrine, VMA: vanillyl mandelic acid, DOMA: 3,4-dihydroxy mandelic acid, NET: norepinephrine transporter, MOPEG: 3-methoxy,4-hydroxy phenyl glycol, VMAT-2: vesicular monoamine transporter

4.3 Sympathomimetics

The sympathomimetics mimics the action of the NA, Adr with wide pharmacological actions (Table 4.5). The uses and side effects and toxicity (Table 4.6) are discussed.

Table 4.5 Pharmacological action of sympathomimetics (Patrick 2023b; Vardanyan and Hruby 2006; Frishman and Silverman 1979)

Organ	Actions
Heart	Cardiac stimulant, ↑heart rate, ↑cardiac output, ↑contractile force, ↑isometric tension, ↑excitability
Blood vessels	Vasoconstriction (α), vasodilatation (β_2), ↑mean BP (systolic and diastolic)
GIT	Relaxation, ↓peristalsis
Bladder, prostate	Bladder contraction (β_2 , β_3) and relaxation (α_1), ↑prostatic muscle tone, Vas deferens contraction
Uterus	Contraction (β) and relaxation (α_1)
Spleen capsule	Contraction (non-evident in man)
Skeletal muscle	Ach release, tremors, ↑tension
CNS	Restlessness, tremor, apprehension, and headache
Pancreas	Hyperglycaemia, ↓insulin secretion
Liver	Glycogenolysis, lipolysis, vasodilatation
Eye	Mydriasis, ↓intraocular pressure
Lung	Relaxing bronchial muscle, bronchodilator
Others	Increases haematocrit and plasma protein concentration, accelerates blood coagulation, promotes fibrinolysis, sweating, and pilomotor activity (systemic)

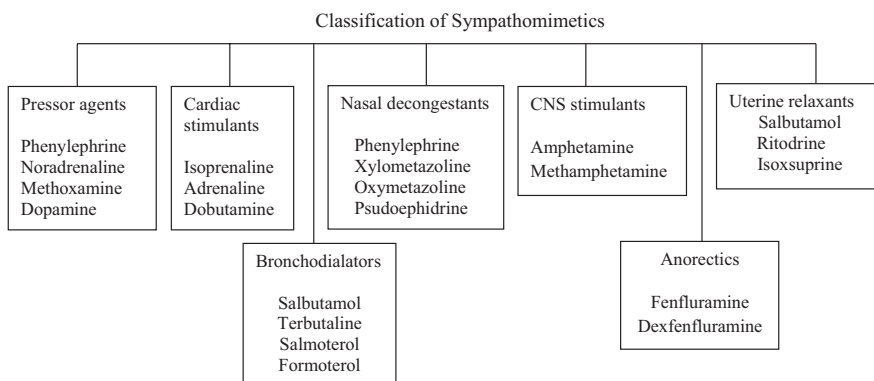
↑ = increase; ↓ = decrease

Table 4.6 Side effects and toxicity of sympathomimetics (Sympathomimetic drugs n.d.; Aviado 1965; Solanki et al. 2014)

Drugs	Toxicity
Methoxamine (selective α_1)	Uterine hypertonus, anxiety, bradycardia, piloerection
Dopamine (D1 and D2)	Arrhythmia, dizziness, orthostatic hypotension
Phenylephrine (selective α_1)	Nervousness, headache, dizziness
Dobutamine (β)	Palpitation, headache, chest pain
Isoprenaline (β_1 , β_2)	Stomach upset, fatigue, blurred vision
Xylometazoline (α) oxymetazoline (α_1 , α_2) Pseudoephedrine (α)	Runny nose, sneezing, dryness, nervousness, dizziness, blurred vision
Amphetamine (D2, 5HT) methamphetamine (α , β)	Appetite loss, dry mouth, fever, trouble sleeping, constipation
Formoterol (β_2)	Arrhythmia, tremor, tachycardia
Salmeterol (β_2)	Anaphylaxis, bronchospasm
Terbutaline (β_2)	Appetite, muscle cramps, mode changes
Salbutamol (β_2)	Hypokalemia, tremors
Fenfluramine (β_2 , 5-HT _{1A}) dexfenfluramine (5-HT)	↓Appetite, drowsiness, pyrexia Dry mouth, nausea, depression, diarrhoea
Ritodrine (β_2)	Dry mouth, drowsiness, dry skin, ↑urination
Isoxsuprine (β)	Skin rash, dizziness, shortness of breathing

↑ = increase; ↓ = decrease

4.3.1 Classification of Sympathomimetics



4.3.2 Therapeutic Uses

1. **Acute Hypotension:** Intravenous infusion of ephedrine or mephentermine is used to treat such condition. These drugs are also used to manage postural hypotension but not completely cured (Rorabaugh 2007).
2. **Prevent Local Bleeding:** Adrenaline and phenylephrine prevent capillary and arteriolar bleeding associated with surgery or trauma (Murdoch et al. 2021).
3. **Nasal Decongestant:** Phenylephrine, pseudoephedrine are used to provide relief from nasal congestion, which may occur due to allergic reaction or cold stress. Higher dose of these drugs also constricts blood vessels and increases BP. β_2 agonists are also used to treat asthma, COPD, and other airway tract symptoms (Eccles 2006).
4. **Peripheral Vascular Disease:** Isoxsuprine is used to treat Buerger disease, frost bite, night leg cramps, and other peripheral vascular disorders (Cacione et al. 2016).
5. **Cardiac Arrest, CHF:** Adrenaline stimulates heart during cardiac arrest, i.v. infusion of dobutamine is used to manage CHF and isoprenaline is used in complete A-V block (Grose 1986).
6. **Allergic Reaction:** Adrenaline is used in the management of different allergic diseases including urticaria, anaphylaxis, angioedema by antagonizing histamine, potent mediator for different hypersensitivity reactions (Ring et al. 2018).
7. **Ocular Disease:** Phenylephrine is used to prevent allergic conjunctivitis, facilitate fundus diagnosing by dilating pupils, and also decrease the intraocular pressure (Murdoch et al. 2021).

8. Uterine Relaxant: The drug of choice in dysmenorrhoea and threatened abortion is isoxsuprine. Ritodrine infusion can be used to postpone labour (Weikel et al. 1959).

4.4 Sympatholytics

The sympatholytics are those agents that oppose the action of sympathetic system. The drugs are classified and their pharmacological actions (Table 4.7), therapeutic uses and side effects and toxicity (Table 4.8) have been elaborated.

Table 4.7 Pharmacological action of sympatholytics (Sympatholytic drugs n.d.; Vongpatanasin et al. 2011)

Organs	Actions	
	α -blockers	β -blockers
Blood vessels	Vasodilatation, \downarrow BP, \uparrow peripheral resistance	\downarrow NA release, \downarrow sympathetic outflow
Heart	Tachycardia, \uparrow NA (α_2)	\downarrow HR, \downarrow CO, \downarrow force of contraction, depressant and membrane stabilizing action (high dose)
Respiratory tract	Nasal stiffness	\uparrow Bronchial resistance (β_2)
Eye	Miosis	\downarrow Aqueous secretion, \downarrow i.o.t
Kidney	\downarrow Renal blood flow, \downarrow g.f.r	\downarrow Rennin release
Miscellaneous	\uparrow Intestinal motility, loose motion \downarrow Smooth muscle tone in sphincter and prostate Inhibits ejaculation	Behavioural changes, \downarrow anxiety, \downarrow tremor \uparrow LDL/HDL ratio, glycogenolysis, lipolysis Local anaesthetics

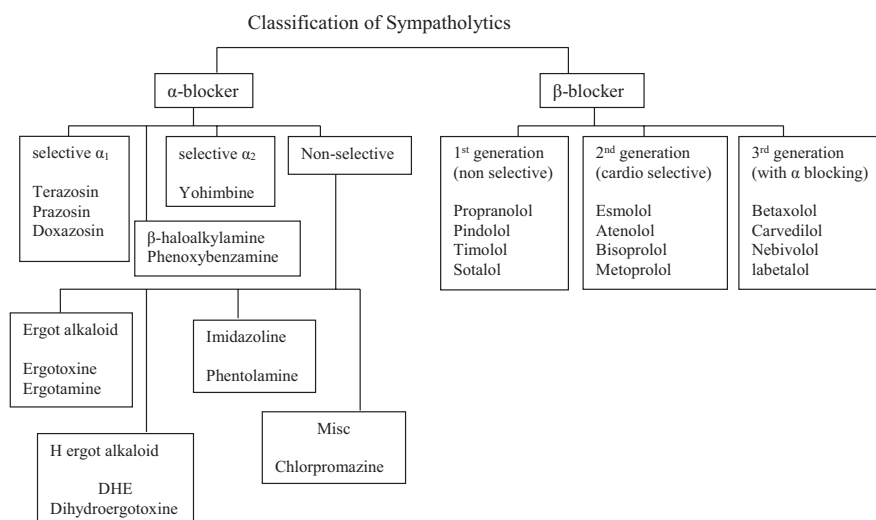
\uparrow = increase; \downarrow = decrease

Table 4.8 Side effects and toxicity of sympatholytics (Engelman 1988)

α -blockers	Side effects	β -blockers	Side effects
Phentolamine Tolazoline	Postural hypotension, failure of ejaculation	Propranolol Pindolol Timolol Sotalol	Bradycardia \downarrow CO, hypoglycaemia \downarrow AV conduction Diarrhoea, headache
Prazosin Alfuzosin Terazosin Doxazosin	Postural hypotension, runny nose, blurred vision, stomach pain, UTIs	Esmolol Atenolol Bisoprolol Metoprolol Betaxolol	Irritation, dizziness Heart failure Diarrhoea, joint pain Allergic reaction Heart burn, tiredness

\uparrow = increase; \downarrow = decrease

4.4.1 Classification of Sympatholytics



4.4.2 Therapeutic Uses

1. Pheochromocytoma: Phenoxybenzamine is used to treat pheochromocytoma, tumours of adrenal medulla and sympathetic neurons which produce larger amount of CAs in bloodstream. Phentolamine is used to control BP and pseudo-obstruction of bowel in pheochromocytoma patients. The β -blockers are also used to prevent tachycardia and arrhythmia in pheochromocytoma patients (Brimijoin et al. 2016; Watanabe 2011).
2. Hypertension: Phentolamine and phenoxybenzamine are used to control BP in clonidine withdrawal symptoms. The β -blockers are also used in hypertension, but these are not the first drug of choice (Armstrong et al. 1993).
3. Prostate Hypertrophy: Prazosin prevents benign hypertrophy of prostate (BHP) by minimizing the prostatic urethra and bladder smooth muscle tone. Terazosin, tamsulosin, and doxazosin are preferable due to less frequency of dosing (once/day). Most of the evidence suggests that terazosin and doxazosin induce apoptosis in prostate. Finasteride (5 α -reductase inhibitor) is also used in BHP by reducing the growth and size of prostate (Nambiar and Meyer 2018).
4. PIPE Therapy for Impotence: Papaverine injection with or without phentolamine in corpus cavernosa is used to prevent impotence. PIPE therapy requires proper training and facilities (Garg et al. 2011).
5. Angina: β -blockers are minimizing the frequency of anginal attack, but high dose can increase the ventricular size and decrease the coronary flow.
6. CHF: Metoprolol, carvedilol, and bisoprolol are used in the management of mild to moderate CHF. The β -blockers are minimizing sympathetic activity and

decrease remodelling in patient with CHF. Most of the clinical trials with metoprolol, carvedilol, and bisoprolol have shown that chronic exposure to these drugs reduces the disease progression in CHF patient, by improving left ventricular function and minimizing hospitalization and mortality rate (Chavey et al. 2003).

7. Arrhythmia: Propranolol (i.v) minimizes adrenergically induced extrasystole in ventricular and supraventricular tachyarrhythmia. Esmolol is also used as an alternative therapy for paroxysmal supraventricular tachycardia.
8. Migraine: Propranolol is used in migraines (Limmroth and Mummel 2000).
9. Glaucoma: The topical β -blockers are used in glaucoma (wide angle and angle close) and decrease the intraocular pressure (IOP) by blocking sympathetic outflow in ciliary epithelium and by reducing aqueous secretion (Kriegelstein 1982).
10. Anxiety: Propranolol exerts anxiolytic effects (off-label use) by blocking the action of adrenaline though not approved by FDA (Beta-blockers for anxiety: uses, benefits, and side effects n.d.).

4.5 Parasympathetic System

The major neurochemical of parasympathetic cholinergic neuron is acetylcholine. In somatic, autonomic, and central sites, it also plays a major role.

Acetylcholine is formed by the reaction of choline and acetyl coenzyme A in the presence of choline acetyltransferase (ChAT). ACh formed is stored in a vesicle with cotransmitters. Fusion process occurs through the interaction between special proteins including VAMPs and SNAPS. The exocytosis of ACh can be blocked by botulinum (Bot) toxin. ACh is metabolized into acetate and choline by acetylcholinesterase (AChE).

4.5.1 Acetylcholine: Synthesis, Storage, and Destruction of ACh

- The acetylation reaction of choline and acetyl coenzyme A is catalysed by choline acetyltransferase and acetylcholine is formed in axoplasm of cholinergic axons. Choline enters into the axoplasm from the extracellular matrix by Na^+ :choline cotransport (active transport) (Neurohumoral transmission in the autonomic nervous system 2023; Lepor 1990).
- The acetylcholine moves to cytoplasm which is stored into storage vesicles. The choline reuptake (rate-limiting step in ACh production) in presynaptic nerve is inhibited by hemicholinium (Fig. 4.6). The vesicle associated transporter (VAT) actively transports ACh into storage vesicles by using proton electrochemical gradients, which are inhibited by vesamicol (Lepor 1990; Benarroch 2021).
- The exocytosis of ACh along with cotransmitter (VIP, ATP) occurs on depolarization through Ca^{2+} entry and fusion of vesicles (Dale and Haylett 2009).
- The ACh is locally hydrolysed by cholinesterase (AChE and BChE) readily after releasing from vesicles and choline is reuptake into presynaptic nerve.

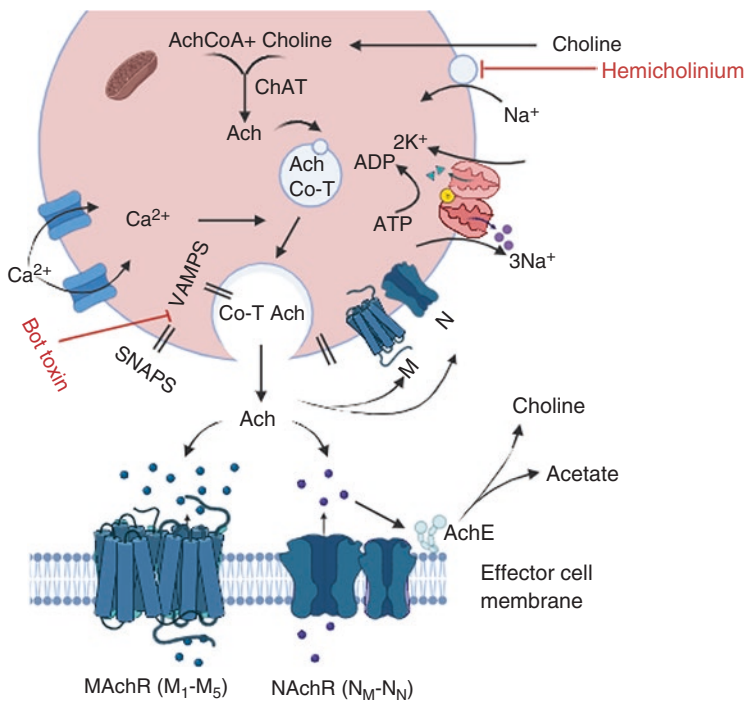


Fig. 4.6 Illustration of cholinergic transmission, showing the production, storage, and exocytosis of acetylcholine

Table 4.9 Pharmacological action of cholinesterase (evansm22 2022; Aboul Ezz et al. 2013; Colovic et al. 2013; Gupta et al. 2017; Duyzen et al. 2009; Ord and Thompson 1950)

Organ	Actions
CNS	Hydrolyses acetylcholine, BCeE ↑risk of AD, affects emotional behaviour and social stress in mice
Heart	Regulates the cardiac parasympathetic responses ↑the risk of cardiac death (BChE)
Blood	Maintains shape and size of RBCs (RBC membrane), potential marker for anaemia
Others	Fat metabolism (BChE), ↑life span of CVS patient by ↑ plasma BChE activity

↑ = increase; ↓ = decrease

Botulinum toxin (Thesleff 1988) affects cholinergic transmission by inhibiting the release of ACh , whereas the toxin of spider (black widow) potentiates the extensive release and depletion.

The pharmacological action of cholinesterase (Table 4.9), details of cholinceptors (Table 4.10) are given below.

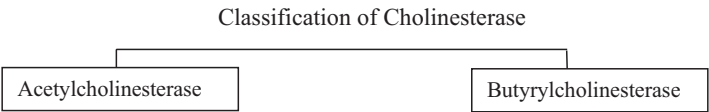
Table 4.10 Location, mechanism, agonist, and antagonist of cholinceptors (Broadley and Kelly 2001; Dowd 2017)

Receptors	Location and function	Mechanism	Agonists	Antagonists
M1	Autonomic ganglia—depolarization Gastric gland—↑histamine and gastric acid secretions CNS—learning and memory	Coupled with $G_{q/11}$ ↑PLC, ↑IP3 and DAG signalling pathway → ↑ Ca^{2+} and PKC → depolarization	Oxotremorine, Men-343A	Telenzepine, pirenzepine
M2	SA node—↓heart beat AV node—↓conduction velocity Atrium and ventricle—↓contractility Smooth muscle contraction	Coupled with G_i/G_o ↓AC, ↓ cAMP K^+ channel opening and closing of Ca^{2+} channels → hyperpolarization and inhibition	Methacholine	Triptamine, methoctramine
M3	Iris—miosis Smooth muscle contraction Glands secretion	Coupled with $G_{q/11}$ ↑PLC, ↑IP3 activating DAG signalling pathway → ↑ Ca^{2+} and PKC → depolarization	Bethanechol	Darifenacin, solifenacin
M4	CNS mainly in forebrain, striatum, cerebral cortex—↓ transmitter release, analgesics, catalepsy	Coupled with G_i/G_o inhibits AC, ↓cAMP inwardly rectifying K^+ channel opening, voltage-gated Ca^{2+} channel closing → hyperpolarization	Pilocarpine, bethanechol, methacholine	Atropine, tolterodine, darifenacin
M5	Substantia nigra—↑DA release VTA (ventral tegmentum area)—drug seeking behaviour	Coupled with $G_{q/11}$ ↑PLC, ↑IP3 and DAG ↑ Ca^{2+} and PKC → depolarization	Bethanechol, methacholine	Solifenacin, fesoterodine, scopolamine
N _M	Neuromuscular junction—depolarization Skeletal muscle contraction	Binds with $\alpha_2, \beta, \gamma, \delta$ subunits → Na^+ and K^+ channel opening	PTMA, nicotine	Tubocurarine, α -bungarotoxin
N _N	Autonomic ganglia—depolarization Adrenal medulla—CA release	Binds with α or α, β subunits → Na^+ , K^+ , Ca^{2+} channels	DMPP, nicotine	Hexamethonium, trimethaphan

↑ = increase; ↓ = decrease

4.6 Cholinesterase

4.6.1 Classification of Cholinesterase



4.6.2 Cholinoceptors

4.7 Parasympathomimetics

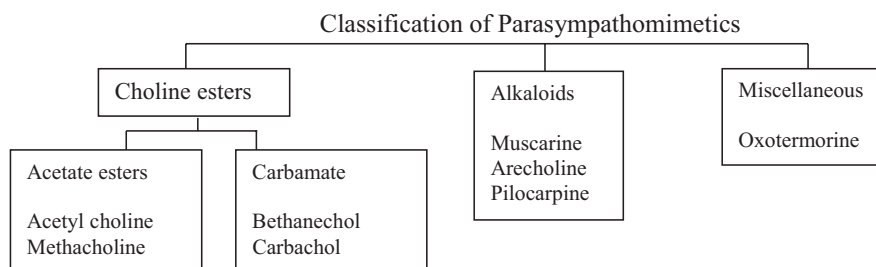
These drugs mimic the action of the cholinergic system. The pharmacological actions are given in Table 4.11.

Table 4.11 Muscarinic, nicotinic, and CNS actions of parasympathomimetics (Shiroma and Costa 2015; Finkbeiner et al. 1977; Dautrebande 1962)

Muscarinic actions	
Heart	Hyperpolarize SA node, ↓diastolic depolarization ↓ impulse generation → bradycardia ↓Force of contraction in atrium, ↓conduction, and ↑refractory period in AV node → ↑P-R interval→ AV block ↓ Contractility in ventricle
Blood vessels	Dilation, ↓BP, NO release (PL _C -IP ₃ /DAG) → vasodilatation
Smooth muscle	↑ Peristalsis and tone in GIT → abdominal cramp and evacuation of bowel ↑ Peristalsis in uterus, relax bladder, and sphincter Constriction of bronchial muscle → bronchospasm → asthma
Glands	↑Secretion, salivation, ↑ gastric secretion, sweating
Eye	Miosis, ↑aqueous outflow, ↓i.o.p in glaucoma, ciliary muscle contraction
Nicotinic action	
Autonomic ganglia	Stimulate sympathetic and parasympathetic ganglia (high dose) Ach (high dose) use after atropine → tachycardia, ↑BP, ↑CAs release
Skeletal muscle	Contraction of fibre (iontophoretic Ach), twitching (intraarterial)
CNS action	
i.v. injection cannot penetrate BBB → no central effect, direct injection (brain) → arousal response, depression, and neurological effects	

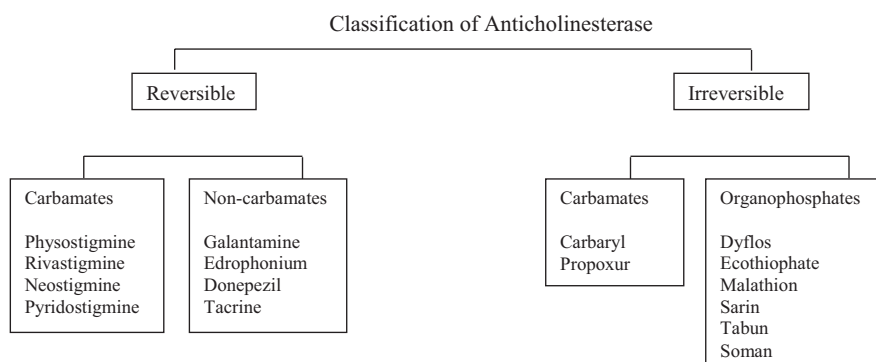
↑ = increase; ↓ = decrease

4.7.1 Classification of Parasympathomimetics



4.7.2 Anticholinesterase

4.7.3 Classification of Anticholinesterase



Mechanism of action: The three different sites of AChE instate the binding domain for AChE inhibitors depending on the specificity distinction between AChE and BChE. After binding with a specific region, these agents act by inhibiting the cholinesterase (both AChE and BChE) (Takács et al. 2017).

Edrophonium and tacrine bind with choline subsite, but edrophonium reversibly binds with the active centre of AChE and the quaternary structure simplifies renal elimination. Donepezil binds to the active centre and propidium binds to the peripheral anionic region of AChE. The carbamates are readily hydrolysed by AChE (physostigmine and neostigmine) but more slowly than Ach (Kitz 1986).

The pharmacological actions (Table 4.12), therapeutic uses and side effects (Table 4.13) of these category are summarized.

Table 4.12 Pharmacological actions of anticholinesterase (Anticholinesterase inhibitors [n.d.](#); Hobbiger 1976)

Organ	Actions
Eye	Conjunctival hyperaemia, miosis, ↓i.o.p
GI tract	↑gastric contractions, ↑gastric acid secretion, ↑gastric motility, ↑peristalsis
Neuromuscular junction	Depolarization, neuromuscular blocking
CVS	Bradycardia, ↑BP
Ganglia	Depolarization, stimulated by muscarinic receptors
Skeletal muscle	Depolarization of end plates, blocks neuromuscular transmission, weakness paralysis
CNS	Generalized alerting response, improves cognitive function, excitement, tremor, confusion, convulsion, and coma
Miscellaneous	Smooth muscle stimulation, glands secretion, bronchoconstriction

↑ = increase; ↓ = decrease

Table 4.13 Side effects and toxicity of anticholinesterase (Anticholinesterase inhibitors [n.d.](#); Hobbiger 1976)

Drugs	Side effects
Galantamine	Stomach and bowel problem
Edrophonium	↓Heartbeats, convulsion eye redness, shallow breathing
Donepezil	Dizziness, trouble sleeping, tremor, diarrhoea
Tacrine	Diarrhoea, anorexia, myalgia
Echothiophate	Headache, eye irritation, blurred vision
Physostigmine	Vomiting, ↑salivation, ↓heartbeats
Rivastigmine	Stomach pain, diarrhoea, loss of appetite
Neostigmine	Muscle twitching, dizziness, chest pain
Pyridostigmine	Stomach pain, diarrhoea, muscle cramps, ↑ salivation

↑ = increase; ↓ = decrease

4.7.4 Therapeutic Uses

Miosis: Pilocarpine is used to constrict the pupil (Fig. 4.7) and increase the ciliary muscle tone as well as outflow facility, resulting in decrease the i.o.p in glaucoma (Patrick 2023a).

Myasthenia Gravis: The autoimmune disorder myasthenia gravis occurs due to the generation of antibody to the nicotinic (N_M) cholinergic receptors (Li et al. 2014).

Edrophonium is used to diagnose myasthenia gravis, neostigmine followed by pyridostigmine and corticosteroids are used for the treatment. These drugs are used

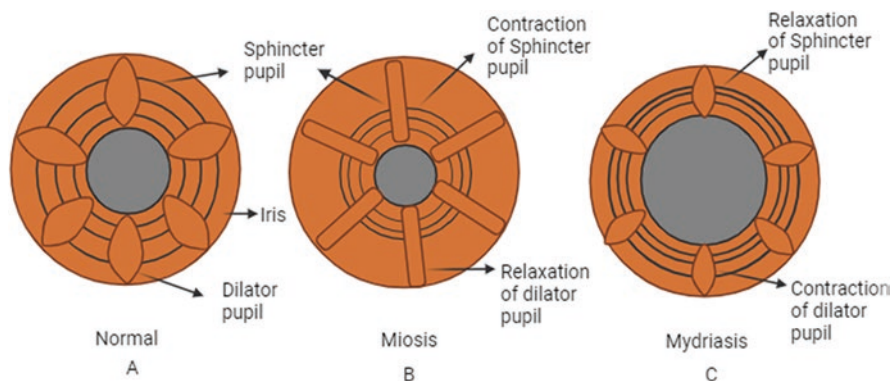


Fig. 4.7 Autonomic controlling of pupil (a), and region of action of miotics (b) and mydriatics (c)

to prevent the structural damage that occurs in muscle end plates and also stimulate the Ach receptors in NMJs (Pruitt and Ilse 2012).

Post-operative Paralytic Ileus: Neostigmine is subcutaneously administered to prevent paralytic ileus after surgical procedure (Phillips and Vincent 2016).

Post-operative Decurarization: Neostigmine i.v. is used to prevent muscle paralysis induced by neuromuscular blocking agents (Luckey 2003).

Cobra Bite: The neurotoxin from cobra venom can be counteracted by neostigmine along with atropine, which prevents the paralysis of respiratory tract (Hristovska et al. 2017).

Belladonna Poisoning: Physostigmine (i.v) is used as antidote in belladonna poisoning, by antagonizing the central and peripheral actions of belladonna (Naphade and Shetti 1977).

Alzheimer's Disease: Rivastigmine, donepezil, and galantamine are commonly used anticholinesterase for the management of AD (Hasgul et al. 2022; Grossberg 2003).

4.8 Parasympatholytics

These are the agents that antagonize the activity of cholinergic system. The pharmacological actions (Table 4.14), therapeutic actions, and side effects (Table 4.15) are discussed.

Table 4.14 Pharmacological action of parasympatholytics (Parasympatholytics, DrugBank Online 2023; Gardenhire and Rau 2008; Kunznetsov 1971)

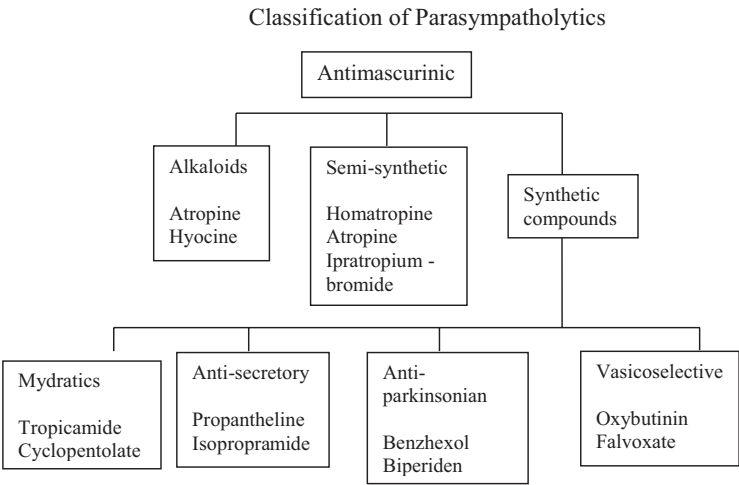
Organ	Actions
CNS	Stimulate CNS, cortical excitation, hallucination, respiratory depression (high dose), ↓tremor and rigidity
CVS	Tachycardia, facilitate AV conduction, ↓PR interval, vasomotor stimulation, ↑BP, prevent vasodepressor activity of cholinergic drugs
Eye	Autonomic control of iris, mydriasis, cycloplegia, ↑i.o.p
Gland	↓Sweat, saliva, and lacrimal secretion, dry skin, ↓acid and mucus secretion in stomach
Smooth muscle	Relaxation, ↓tone of contraction of stomach and intestine, constipation, ↓spasm, relax uterus and bladder
Others	↑Body temp (high dose), atropine fever (children), mild anaesthetic action in the cornea

↑ = increase; ↓ = decrease

Table 4.15 Side effects and toxicity of parasympatholytics (Kunznetsov 1971)

Drugs	Side effects
Atropine Hyoscine	Chest pain, cough, blurred vision, dilated pupil, belladonna poisoning (overdose) Tachycardia, anaphylaxis, decreased BP
Homatropine Ipratropium bromide	Eye redness, blurred vision Bladder pain, shortness of breath, cough, back pain
Tropicamide Cyclopentolate	Flushing, skin rash, unusual behaviour, hallucination Eye redness, blurred vision
Propantheline Isopropamide	Dry mouth, headache, stomach upset, nervousness Constipation, dizziness, blurred vision
Benzhexol Biperiden	Xerostomia, dizziness Confusion, nervousness, hallucination
Oxybutynin Flavoxate	Dry mouth, sleepiness, diarrhoea, constipation, stomach pain Dry mouth, drowsiness, blurred vision

4.8.1 Classification of Parasympatholytics



4.8.2 Therapeutic Uses

Antisecretory: Preanaesthetic medication—Atropine and hyoscine are used as preanaesthetic medication (irritant GA-ether), to reduce secretion of salivary and tracheobronchial. Atropine is used to prevent halothane-mediated ventricular arrhythmia. Additionally, vasovagal attack and laryngospasm (skeletal muscle) are also regulated by atropine (Chen et al. 2022).

Pulmonary Embolism: Atropine reduces pulmonary secretion, excessive salivation, and sweating (Mirakhur 1991).

Antispasmodic: Nervousness, drug-induced vomiting can be reduced by anticholinergics (Wall et al. 2014).

Constipation, IBS, abdominal discomfort, and evacuation of the bowel are obtained by anticholinergics (Alreshq et al. 2019). Gastric hypermotility, pylorospasm, abdominal cramps may be suppressed but dry mouth, intestinal colic, and other anticholinergic activities are dose depending (Patrick 2023a).

Respiratory Diseases: Ipratropium bromide aerosol is used in COPD and asthmatic bronchitis (Appleton et al. 2006). Tiotropium bromide is another alternative drug used in the management of COPD.

Mydriatic and Cycloplegic: Tropicamide (with phenylephrine), cyclopentolate, and homatropine are used to dilate pupil during diagnosing. Atropine ointment is preferred for children but cyclopentolate is a more rapidly acting drug (Alingil and Erda 1992). To improve fundoscopy antimuscarinic along with phenylephrine is used. Atropine is used in the treatment of iritis, corneal ulcers, and choroiditis by inducing mydriatic-cycloplegia and pain-relieving action in the cornea (Miller 2008).

Cardiac Action: Atropine is used in the management of bradycardia (sinus) and heart blocking (partial) in MI and digitalis toxicity (Scheinman et al. 1975).

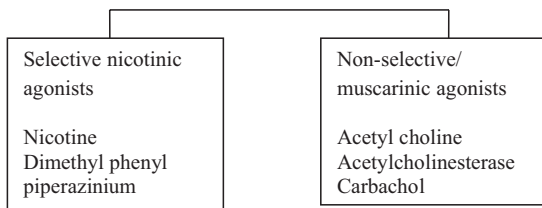
Central Action: Benzhexol, trihexyphenidyl, and biperiden are commonly used in drug-induced PD. Hyoscine, dicyclomine are used to prevent vigorous motion sickness (Kostelnik et al. 2017; Spinks and Wasiak 2011).

4.9 Drugs Acting on Autonomic Ganglia

4.9.1 Ganglionic Stimulants

4.9.1.1 Classification of Ganglionic Stimulants (Bissada et al. 1978; Volle 1980)

Classification of Ganglionic stimulants [109, 110]

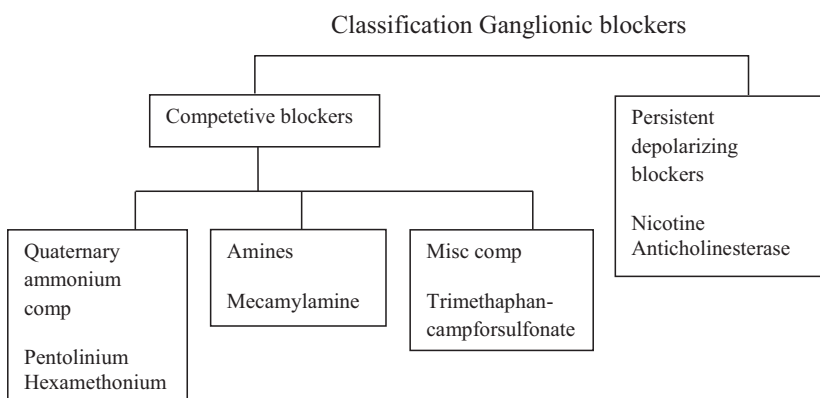


Therapeutic Uses: Ganglionic stimulants are used to relieve from nicotinic withdrawal symptoms and smoking mitigation. Varenicline is used with counselling and education to help people with smoking cessation. Nicotine is also used to stop tobacco use (Jiloha 2014; Varenicline: a novel, potent, and A4B2-selective nicotinic receptor partial agonist for smoking cessation n.d.).

4.9.2 Ganglionic Blocking Agents

These agents show high alterations on various organs as summarized in Table 4.16.

4.9.2.1 Classification Ganglionic Blockers



4.9.3 Therapeutic Uses

Ganglionic blockers are superior agents for the management of chronic hypertension. Trimethaphan i.v. infusion is used in hypertensive crises to produce hypotension (↓BP during surgical process to minimize haemorrhage). Succinylcholine is

Table 4.16 Effect on organs (van Rossum 1962; Bissada et al. 1978)

Organ	Actions
Heart	Tachycardia
Intestine	↓Motility
Blood vessels	Vasodilatation, ↓BP
Salivary glands	↓Salivation
Iris	Mydriasis
Male sexual organs	Impotence
Sweat glands	↓Sweating
Ciliary muscle	Cycloplegia
Bladder	↓Tone

↓ = decrease

used to produce endotracheal intubation. Neuromuscular blockers are mainly used as combined therapy with narcotic or volatile anaesthetic agents as skeletal muscle relaxant to improve surgical process. Mecamylamine alone or combined with nicotine in smoking mitigation (Lancaster and Stead 1998; Agarwal and Mathur 2016; Marsch et al. 2011; Varon and Marik 2003).

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Drugs Acting on Central Nervous System

5

Dipesh Chakraborty and Ria Das

Abstract

Central nervous system is the part of the body which is responsible for accepting, processing, and creating response against the external stimuli or the sensory information. Brains and spinal cord create the machinery which plays the biggest role in maintaining and coordinating balance between the outer world and the living body. These responses are spontaneous, fast, and well-coordinated. Acceptance of stimuli and creating a message out of it and thereby responding to the stimuli involve many ion channels and chemical messengers, here especially neurotransmitters play a big role in creating an integrated cell-to-cell communication. So, diseases which affect the central nervous system need medications which largely target either some ion channels or neurotransmitters. Here, in this chapter we have covered the mechanistic approaches of designing therapy with drugs acting on CNS.

Keywords

Central nervous system · Neurotransmitter · Action Potential · Cell signaling · Therapeutics

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Abbreviations

AEDs	Antiepileptic drugs
AMPA	α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic
cAMP	Cyclic adenosine monophosphate
CDD	Childhood disintegrative disorder
CDK	Cyclin-dependent kinases
CNS	Central nervous system
DDC	Dopa decarboxylase
DNA	Deoxyribonucleic acid
GABA	Gamma-aminobutyric acid
GABA-A	Gamma-aminobutyric acid type A
GAD	Generalized anxiety disorder
GAPs	GTPase-activating proteins or GTPase-accelerating proteins
GDP	Guanosine diphosphate
GEF	Guanine nucleotide exchange factors
GPCR	G protein-coupled receptors
GPi	Globus pallidal segment
GTP	Guanosine triphosphate
IP3	Inositol trisphosphate
MAO-A	Monoamine oxidase A
MAO-B	Monoamine oxidase B
MAOIs	Monoamine oxidase inhibitors
MDD	Major depressive disorder
NMDA	N-methyl-D-aspartate
NMDAR	N-methyl-D-aspartate receptor
PD	Parkinson's disease
PNS	Peripheral nervous system
RGS	Regulator of G protein signaling proteins
SAD	Seasonal affective disorder
SNpc	Substantia nigra pars compacta
SNRIs	Serotonin and norepinephrine reuptake inhibitors
SSRIs	Selective serotonin reuptake inhibitors
TCAs	Tricyclic antidepressants

The communication system of the body that has the ability to respond to the changes may be external or internal through coordination of specialized nerve cells, neurons, because of the nervous system. The changes to which the body responds are the stimulus. There are two divisions within the nervous system: the PNS or peripheral nervous system and the CNS or central nervous system. The nervous system in which the nerves that link the spinal cord and brain to the body's other organs are known as the peripheral nervous system, while the brain and spinal cord are parts of the central nervous system. Over 100 billion unique nerve cells make up the human CNS and are composed of the spinal cord and brain. It regulates our movements, senses our environment, and shapes who we are. Even though the brain and spinal

cord contain endogenous stem cells, it has many distinct physiological and anatomical traits, such as confinement within skeletal systems (the skull and vertebrae) that both protect and impede access, separation by tight connections between endothelial cells and the circulation of systemic blood that both prevent intravenous therapeutic delivery and act as a barrier to toxins and a limited capacity for self-repair (Payne et al. 2019).

5.1 Organization of CNS

The brain and spinal cord are the parts of the CNS. Situated in the dorsal cavity of the body, the brain and spinal cord are so vitally crucial that they are protected by bone. Inside the cranial vault is the brain, and inside the vertebral column's vertebral canal is the spinal cord. The brain and spinal cord are connected at the foramen magnum, despite the fact that they are thought of as different organs.

Seeing, hearing, feeling, taste, and smelling are among the five senses, as well as movement, consciousness, thought, and speech are governed by the brain (Thau et al. 2022). The brain consists of four lobes, namely: temporal lobe (crucial for giving emotional meaning to sensory information and digesting it, it also plays a role in the establishment of long-term memory; this area also contains certain facets of language perception), occipital lobe (brain area responsible for visual processing, which contains the visual cortex), parietal lobe (the parietal lobe combines touch, navigation, and spatial awareness with other senses), and frontal lobe (situated near the front of the brain, is home to most dopamine-sensitive neurons and is primarily involved in reward, attention, short-term memory, planning, and motivation) (Fig. 5.1 shows lobes of brain) (Becker 2012; Anon 2018; Nyulangone 2019; Waxenbaum et al. 2023).

The brain extends into the spinal cord. Via the web of peripheral nerves that connect to the brain, it transmits and receives messages (Thau et al. 2022).

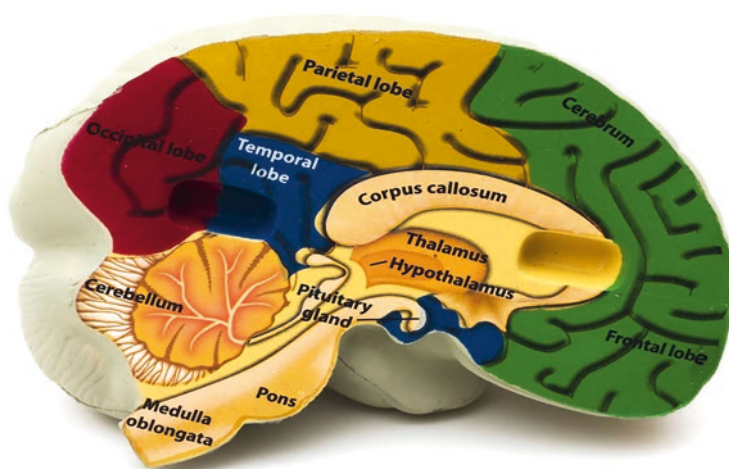


Fig. 5.1 Lobes of brain Bailey (2019)

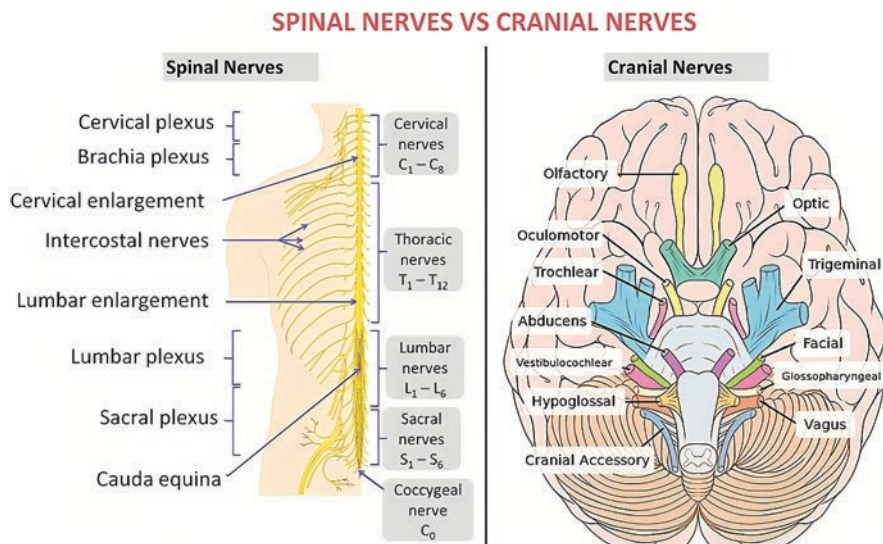


Fig. 5.2 The spinal and the cranial nerves How many spinal and cranial nerves are present in the human body (2023)

There are 31 pairs of spinal nerves that emerge from each of the five segments that make up the spinal cord: the cervical, thoracic, lumbar, sacral, and coccygeal. There are three sulci, one anterior fissure, and four surfaces in the spinal cord. Inside, it is made up of white matter encircling a core of gray matter. The segmental and vertebral arteries are the source of the blood supply to the spinal cord. Twelve pairs of cranial nerves exist: olfactory, optic, oculomotor, trochlear, trigeminal, abducens, facial, auditory, glossopharyngeal, vagus, accessory, hypoglossal. Each pair of nerves divides to supply the body's and brain's two halves (Fig. 5.2 shows spinal and cranial nerves) (Augustine et al. 2004; Blumenfeld 2018; Mihailoff and Haines 2018).

5.2 Functions of CNS

The nervous system's brain is in charge of reactions, feeling, movement, emotions, communication, processing thoughts, and memory. The human brain is shielded from external threats by the meninges, cerebrospinal fluid, and skull. It is incredibly sensitive and vulnerable to even the smallest impact. It also possesses a blood–brain barrier that shields the brain from any dangerous material floating in the blood. Located within the vertebral column, the spinal cord is an essential component of the central nervous system (CNS). The spinal cord's functions include carrying sensory data from the sense organs back to the brain and transmitting motor orders to the body's extremities from the brain. Meninges, cerebrospinal fluids, and bone all protect the spinal cord.

1. The system regulates both intentional and unintentional bodily movements.
2. It keeps the body in equilibrium.

3. By performing tasks like temperature regulation and other things, it keeps the body in a state of homeostasis.
4. It is in charge of detecting the stimuli, interpreting them, and generating the proper reaction.
5. The brainstem gives rise to the cranial nerves III–XII, which innervate the head and neck and, via the spinal accessory nerve, also extend some of their function into the trapezius muscle.
6. Autonomic centers are located in the medulla, which is the spinal cord's rostral extension, which regulate respiration and blood pressure regulation among other essential processes.
7. The pons, which lies between the medulla and the midbrain, aids with breathing, posture, and balance maintenance. Via the corticopontocerebellar tract, the pons transmits data from cerebrum to cerebellum.
8. The midbrain, located at the most rostral part of the brainstem, is engaged in relay routes of auditory and visual, as well as ocular motility. These processes are facilitated by the lateral and medial geniculate nuclei, respectively (Fig. 5.3 shows various functions of brain).

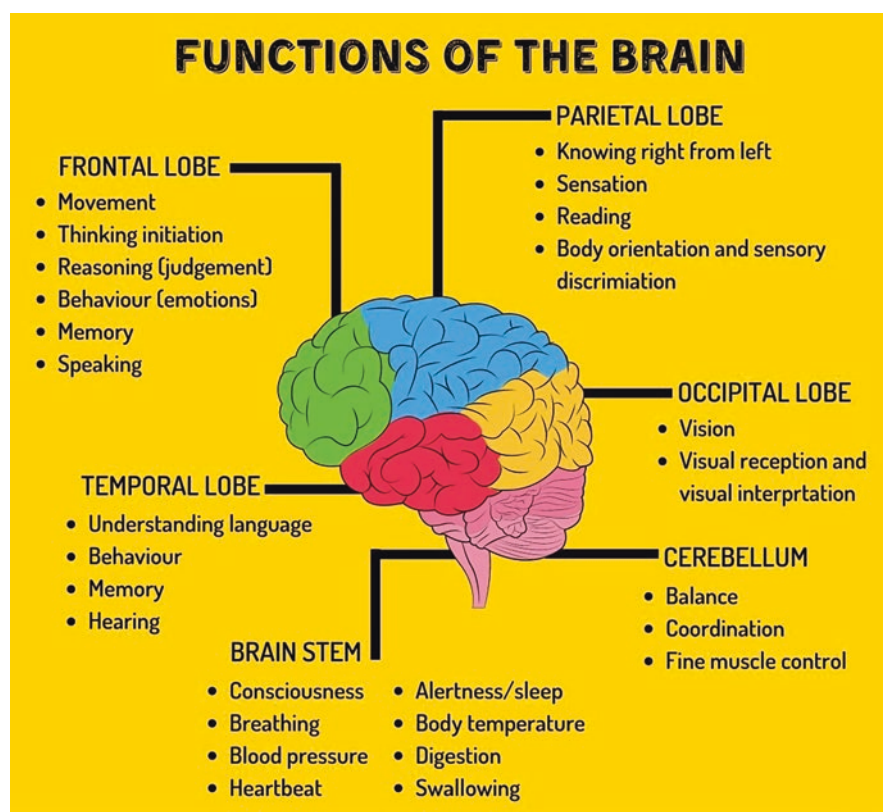


Fig. 5.3 Function of different lobes of brain Functions of the brain (2021)

9. Position and head motions, movement planning and execution, and posture maintenance are all coordinated by the cerebellum, which is located in the posterior fossa. The cerebellum's well-known role in motor function is not the only one it plays to have a crucial part in other cognitive and sensory-motor processes that include auditory pathways related to speech recognition and other cognitive processes.
10. The brainstem and the cerebral hemispheres are separated by the thalamus and hypothalamus. A key processing area for motor information heading toward the brainstem and spinal cord and sensory information heading toward the cerebral cortex is the thalamus. Hormones that modify anterior pituitary hormone release by stimulating or inhibiting it are secreted into the hypophyseal portal blood by the hypothalamus, which regulates pituitary gland secretions. Hypothalamic cell bodies are also responsible for controlling the antidiuretic hormone and oxytocin releases from the posterior pituitary.
11. The substantia nigra, putamen, caudate, globus pallidus, ventral striatum, and subthalamic nucleus are the components of the basal ganglia, sometimes known as basal nuclei. These nuclei help regulate movement by receiving input from almost the whole neocortex and projecting to a relatively limited area of the frontal lobe via basal ganglia-thalamocortical circuits.
12. The amygdala interprets emotional data and uses the hypothalamus and hormone release to influence the autonomic system.
13. The hippocampus is mostly engaged in memory.
14. Through the integration of motor functions and the processing of sensory information, the cerebral cortex plays a major role in perception and higher motor function. There are three main sensory and motor areas in the cortex: primary, secondary, and tertiary. The core of cortical function is its capacity to combine various information and deliver direction in response (Fig. 5.4 shows functions of spinal nerves).
15. Signal transmission (Fig. 5.5 shows functions of cranial nerves) via ascending and descending routes through the spinal cord, connecting the peripheral and central neural systems. The cell bodies of the spinal nerves terminate at the conus medullaris at the level of L1/L2, making the spinal cord shorter than the spinal column as a result of uneven growth during development. The spinal nerves L2 through C1 form the cauda equina, a structure that spreads caudally as the spinal nerves leave the spinal column at their corresponding levels in the lumbar cistern or subarachnoid space. The safe performance of lumbar punctures, typically in the space between the L3 and L4 or L4 and L5 vertebral bodies, is made possible by this subarachnoid space free of the spinal cord (Haines 2014; Mancall and Brock 2011; Moore et al. 2013; Patton et al. 2019; Wang 2009; Wineski 2018; Birch et al. 2016; Britannica.com n.d.; Sulaiman et al. 2020; Britannica 2023).

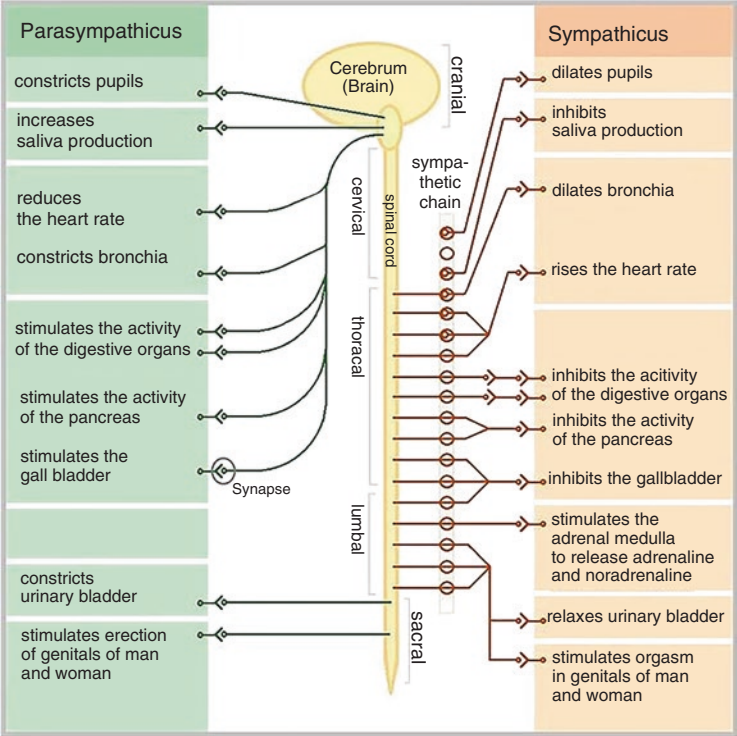


Fig. 5.4 Function of spinal nerves Libretexts (2024)

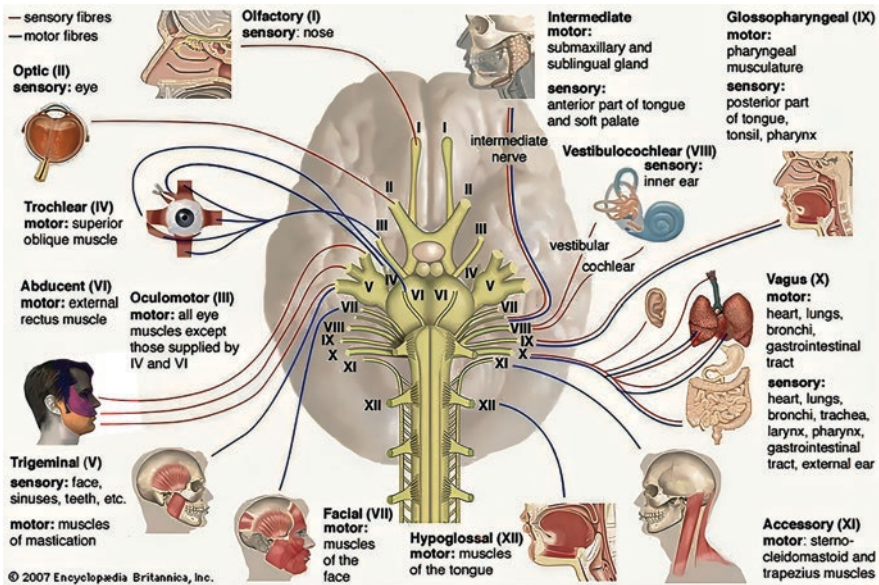


Fig. 5.5 Function of cranial nerves Ratcliff et al. (2024)

5.3 Role of Neurotransmitters in Signaling in CNS

The endogenous substances known as neurotransmitters (as shown in Fig. 5.6) facilitate communication between neurons across the nervous system. By chemical synaptic transmission, they facilitate the brain’s ability to perform a multitude of operations. The functions of daily living are greatly influenced by these endogenous substances. Neurotransmitters are released from presynaptic brain cells and bind to postsynaptic receptors, which initiates chemical synaptic transmission. Changes in the concentrations of particular neurotransmitters (Table 5.1 shows explanation of different neurotransmitters) have been acknowledged in numerous neurological conditions, such as depression, schizophrenia, Parkinson’s disease, and Alzheimer’s (Sheffler et al. 2023).

5.3.1 Classification of Neurotransmitters

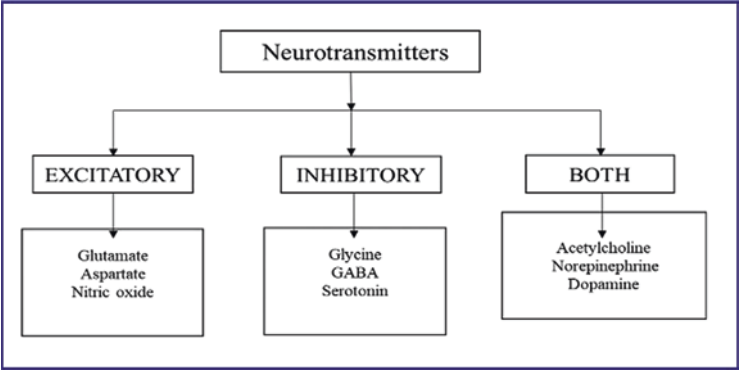


Fig. 5.6 Classification of neurotransmitters (Kumar et al. 2020)

Table 5.1 Explanation of different neurotransmitters (Blanpied et al. 2005; Patri 2019; Tranquillini and Reggiani 1999; Abe et al. 1995; Baldo 2018; Baldo and Rose 2020; Ferrando and Eisendrath 1991)

Name of neurotransmitter	Type	Origin	Function	Importance	Drugs
Glutamate	Excitatory	Produced by the enzyme glutaminase in the CNS from glutamine as a component of the glutamate–glutamine cycle in nearby glial cells or in the presynaptic neuron	In CNS most potent excitatory neurotransmitter glutamate is essential to several brain processes, such as synaptic plasticity (learning and memory), neuronal network creation during development, and central nervous system repair	Glutamate, a plentiful amino acid, is essential for protein structure as well as for nutrition, metabolism, and signaling. It is the primary excitatory neurotransmitter in the CNS	One glutamate antagonist that is now being used to treat Parkinson’s symptoms is amantadine
Aspartate	Excitatory	Oxaloacetate transamination is a common method of synthesizing aspartate	In the central nervous system, the excitatory neurotransmitter aspartate increases the probability of generating action potential binding to its receptors and helps electrical signals to travel across the brain and makes it easier for neurons to communicate with one another	The excitatory neurotransmitter aspartate, an amino acid, is involved in many bodily metabolic processes and is also thought to be involved in a number of physiological and neuroprotective processes	Aspartate is reabsorbed into the presynaptic membrane, where it opens an ion channel and becomes inactive. Aspartate, however, is an excitatory neurotransmitter that raises the possibility of postsynaptic membrane depolarization. Aspartate does not activate glutamate receptors of the AMPA type, but it is an extremely selective agonist for those of the NMDAR type

(continued)

Table 5.1 (continued)

Name of neurotransmitter	Type	Origin	Function	Importance	Drugs
Glycine	Inhibitory	Serine-hydroxymethyltransferase, a mitochondrial enzyme, converts serine to glycine. Glycine is quickly taken out of the synaptic cleft by certain membrane transporters after it gets released from the presynaptic cell	Precursors for several essential metabolites, including glutathione, hem, creatine, porphyrins, and purines, are glycine. In the CNS, glycine functions as a neurotransmitter and has a variety of roles, including immunomodulatory, cryoprotective, antioxidant, and anti-inflammatory in peripheral and neurological tissues	It supports the health and proliferation of cells. One of the amino acids required for the body to synthesize the antioxidant glutathione is glycine. In order to combat free radicals, which can otherwise lead to oxidative stress and harm DNA, proteins, and cells, cells create glutathione	Based on their chemical structure, the five main groups of glycine antagonists that have been found so far are quinoxalinedione, pyridozino quinoline, benzodiazepines, tetrahydroquinolines, and indoles
GABA	Inhibitory	Vitamin B6 is required as a cofactor for the enzyme glutamate decarboxylase, which converts precursor glutamate into GABA in the cytoplasm of presynaptic neurons	It is a significant neurotransmitter that inhibits nerve transmission, which lowers neural excitability	The body finds it challenging to unwind following a stress-induced neurotransmitter release when GABA levels are too low. Mood disorders, anxiety, depression, and sleeplessness are caused by low GABA activity. Natural brain relaxant GABA has a calming effect on people	Antihypertensive medications, which treat high blood pressure, can interact with GABA (gamma-aminobutyric acid). GABA may have a hypotensive effect. Blood pressure may drop too low if GABA is used alongside blood pressure-lowering drugs. Keep a careful eye on your blood pressure

Serotonin	Inhibitory	Serotonin is nearly entirely produced in neurons in the CNS that originate in the raphe nuclei, which are situated in the brainstem's midline	It stabilizes emotions and aids in blood coagulation	It elevates your mood and promotes healthy sleeping habits	Combining a number of serotonergic medications typically results in serotonin syndrome. A variety of antidepressants fall under this category, including tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), and norepinephrine and serotonin reuptake inhibitors (SNRIs)
Acetylcholine	Both	Choline acetyltransferase is the enzyme that converts choline and acetyl-coenzyme A into acetylcholine in the nerve terminal's cytoplasm	Acetylcholine causes blood vessels to dilate, smooth muscle contraction, a rise in body secretions, and a slowing of the heart rate	In synapses and myoneural junctions, acetylcholine is crucial for the transfer of nerve impulses	A few cholinergic medications, including arecoline, muscarine, and pilocarpine, imitate acetylcholine's parasympathetic nervous system stimulation action. But these medications are not very useful in treating anything. Other cholinergic medications, including scopolamine and atropine, block acetylcholine's function, which in turn inhibits all parasympathetic nervous system activity
Dopamine	Both	The brain's ventral tegmental region, hypothalamus, and substantia nigra manufacture this neurotransmitter	Dopamine affects emotions, attention, movement, and learning	It functions as the brain's "feel good" reward system, intensifying the experience	Central dopamine antagonist medications are widely used to treat a wide range of medical complaints. Among the most often utilized are prochlorperazine, droperidol, promethazine, and metoclopramide

5.4 Stages of Synaptic Transmission of Neurotransmission

5.4.1 Generation of Action Potential

The mechanism of voltage-gated ion channels, which are proteins with ionic-selective pores spanning the cell membrane, is responsible for both the creation and propagation of action potentials. Variations in the field of electricity across the membrane cause ion channels to shift in structural shape. Owing to these structural alterations, channels or pores open up, allowing ions to move along their electrochemical gradient. Ion-borne charge produces an electrical current that quickly changes the cell's membrane potential with characteristics that rely on voltage and time. The action potential is the name given to this quick, fleeting change in membrane potential. Action potentials cause exocytosis in secretory cells, initiate contractions in muscle cells, and transfer information across neurons (as shown in Fig. 5.7) (Egri and Ruben 2012).

- **Reaching Threshold:** The resting membrane potential may vary in response to an external stimulus from a different cell or neuron. An action potential does not, however, always follow a modification of the resting membrane potential. “Reaching threshold” is the process by which the resting potential of the membrane shifts from -70 to -55 mV in response to a single stimulus or a combination of stimuli.
- **Depolarization:** As a result, the membrane of the nerve cell opens up voltage-gated sodium (Na^+) channels. Ions are propelled into the cell by the concentration gradient because the quantity of Na^+ is less inside the cell than it is outside. Because the ions in question are positively charged sodium ions, the huge input of ions will cause the internal voltage of the cell to lower. When the membrane potential approaches zero, this is referred to as depolarization.
- Sodium channel blockade-acting medications have many different clinical uses. Class 1 antiarrhythmics are among them, in general. Examples include class 1A

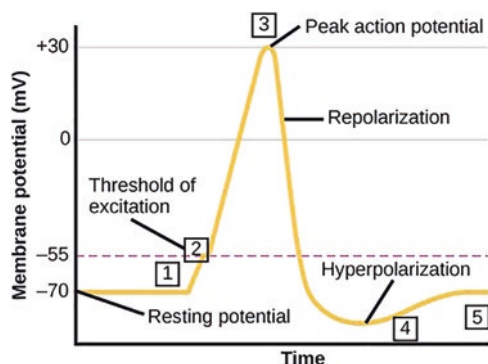


Fig. 5.7 Generation of action potential (Patidar 2009)

antiarrhythmics quinidine and procainamide, class 1B antiarrhythmics lidocaine, mexiletine, and phenytoin, class 1C antiarrhythmics flecainide and propafenone, and class 1D antiarrhythmics lamotrigine and carbamazepine.

- Numerous cell types have Ca^{2+} channels that mediate Ca^{2+} inflow as a consequence to action potentials and subthreshold depolarizing signals. These channels activate upon membrane depolarization. The second type messenger of electrochemical signaling is Ca^{2+} , which enters the cell via voltage-gated Ca^{2+} channels and starts a variety of cellular activities. Neurotransmitters are released from the presynaptic neuron into the synaptic cleft, and Ca^{2+} channels are essential for this process. Using pharmacological and biophysical criteria, four different types of Ca^{2+} channels (L, N, P, and T) have been found. The excitation–secretion coupling of certain neurons and endocrine cells is mediated by L-type Ca^{2+} channels. Neurotransmitter release is a function of N-type Ca^{2+} channels, which are only found in neurons. Only Purkinje cells contain P-type Ca^{2+} channels, which are responsible for recurrent spikes brought on by depolarization. In endocrine cells and neurons, depolarization-induced repeated spikes are mediated by T-type Ca^{2+} channels, which deactivate more slowly than any other Ca^{2+} channel.
- Pharmacologically, diltiazem, nifedipine, and verapamil block L-type Ca^{2+} channels, while ω -agatoxin blocks P-type Ca^{2+} channels.
- **Repolarization:** As long as the membrane potential is not higher than +30 mV, Na^+ will keep entering the cell due to its robust concentration gradient. This happens when the membrane's voltage-gated potassium channels open. With potassium (K^+) leaving the cell the membrane potential starts to return to its resting voltage. When this happens, the membrane voltage returns to its resting membrane potential, which is around -70 mV. This is known as repolarization.
- **Hyperpolarization:** The membrane voltage must drop below -70 mV for potassium ions to truly attain equilibrium. A brief overshoot occurs when the membrane potential falls below -70 mV due to little delay in the closure of K^+ channels. Hyperpolarization refers to this time frame (Moore et al. 2013; Hall and Hall 2020; Rubin et al. 2012; Champney 2016; Dokken and Fairley 2022; Catterall 2011; Wright et al. 2009).

5.4.2 Docking of Synaptic Vesicles

There are various phases of synaptic vesicle exocytosis:

1. Neurotransmitters are loaded into synaptic vesicles through active transport.
2. The next step, called tethering, involves moving freshly filled synaptic vesicles to the functional zones of synapses.
3. Next, the presynaptic membrane is docked to the synaptic vesicles (as shown in Fig. 5.8).
4. Following a priming phase while expecting a calcium signal, the status of synaptic vesicles becomes fusion competent.
5. A calcium signal starts the fusion process.

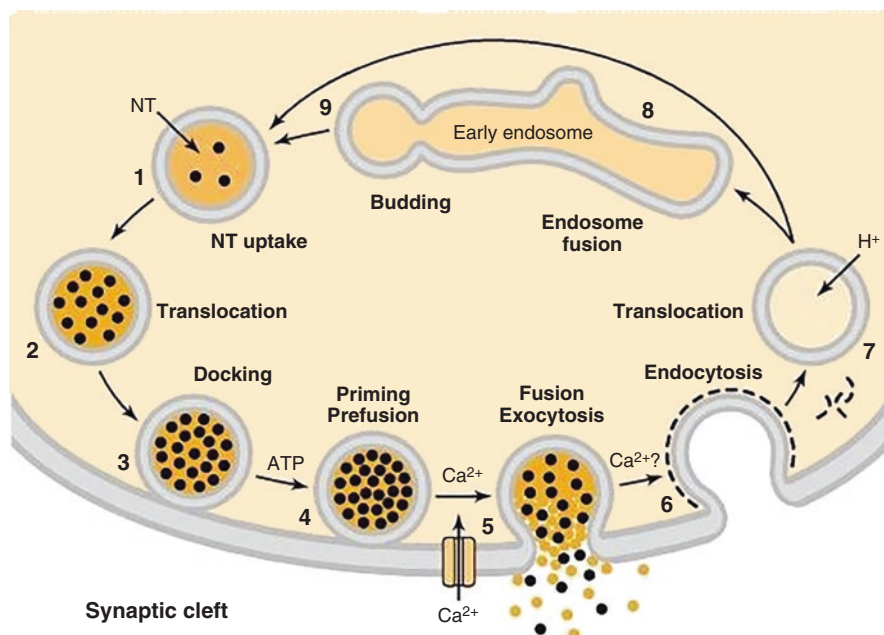


Fig. 5.8 Steps of docking of synaptic vesicles (Shaib 2018)

6. After being coated with clathrin, fused synaptic vesicles are ready for endocytosis.
7. Endocytosed synaptic vesicles are acidified by proton pumps after shedding their clathrin covering.
8. Later on, the synaptic vesicles unite with early endosomes. Upon being prepared, synaptic vesicles emerge from endosomes.
9. Synaptic vesicles emerge from endosomes when they are ready.

Certain synaptic vesicles have the ability to bypass the endosomal intermediate stage and proceed straight from step 7 to step 1 (Shaib 2018).

5.4.3 Release of Neurotransmitter

A crucial aspect of synaptic transmission is the neurotransmitter released from neurons. When presynaptic neurons experience neuronal activity, neurotransmitters are produced from their synaptic vesicles. They then disperse across the synaptic junction and attach to particular receptors to modify postsynaptic neurons (as shown in Fig. 5.9) (Fon and Edwards 2001).

The transmission signal would not have reached a distinct end point if the released neurotransmitter was not eliminated from the synapse in some manner. Neurotransmitters are known to be eliminated via reuptake, which occurs through specific reuptake channels, sometimes referred to as transporters, that allow the

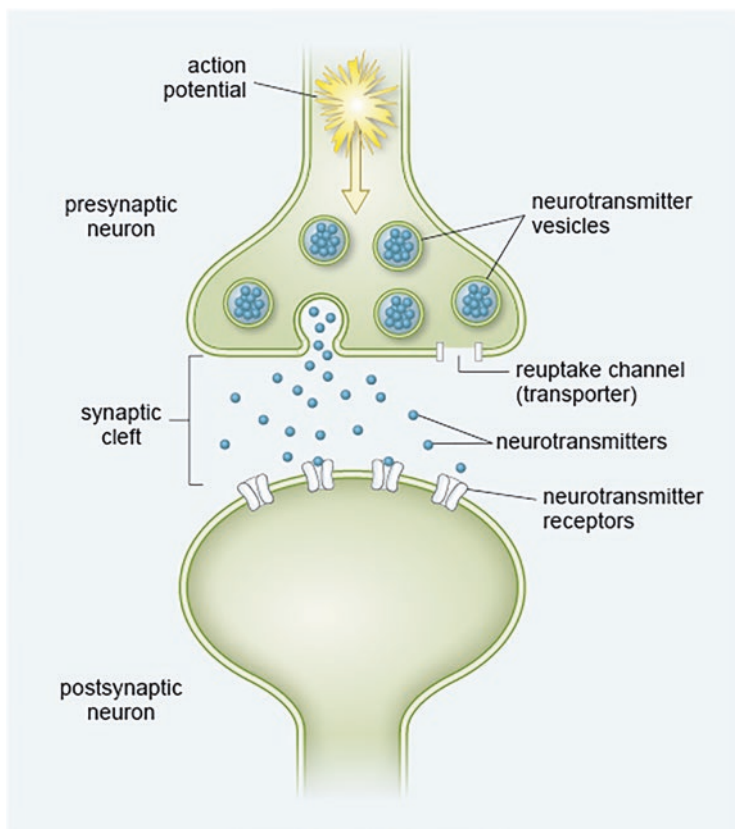


Fig. 5.9 Release of neurotransmitter at the synaptic cleft (McKechnie et al. 2023)

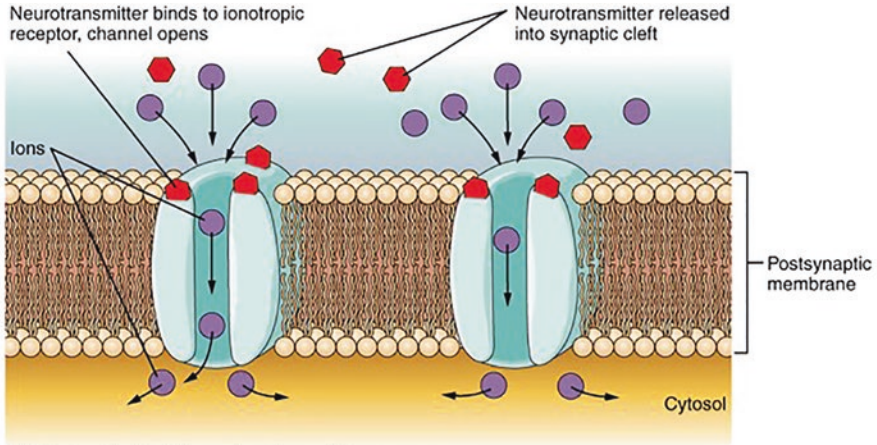
neurotransmitter to be taken up and reabsorbed into the presynaptic cell in order to be released later on. Enzymes that break down neurotransmitters can also eliminate them. Ultimately, neurotransmitters have the ability to disperse from synapses and move away from receptors (McKechnie et al. 2023).

5.4.4 Action of Neurotransmitter through Receptor

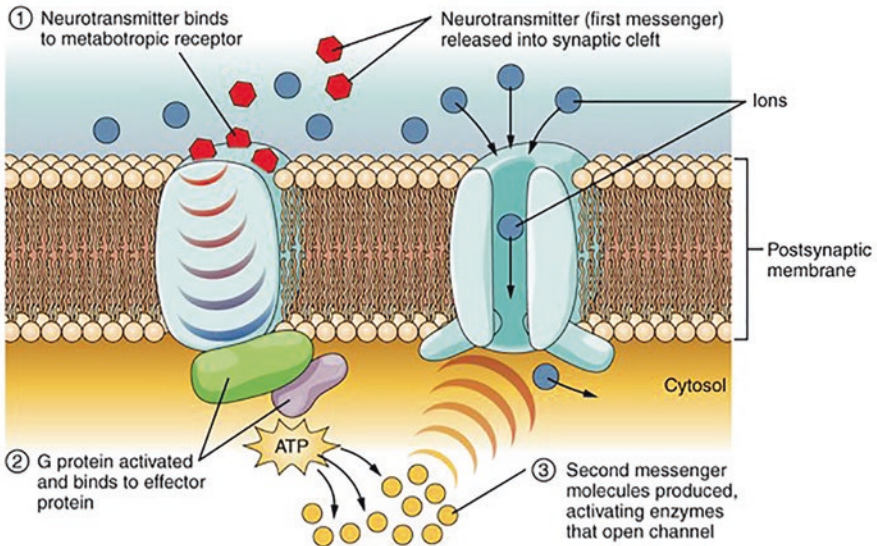
By attaching to members of the broad protein family known as neurotransmitter receptors, neurotransmitters elicit postsynaptic electrical reactions. The postsynaptic membrane's ion channels are then opened or closed by the receptors to produce electrical impulses. A neurotransmitter's excitatory or inhibitory postsynaptic activities depend on the type of ion channel it affects as well as the number of ions that permeate both inside and outside of the cell. The receptor molecule can be classified into two main classes: those where it is an ion channel as well, and those where it is an independent molecule from the ion channel. The former produces quick

postsynaptic responses that usually last a few milliseconds; they are known as ligand-gated ion channels or ionotropic receptors. Those that produce slower postsynaptic actions and potentially longer half-lives are known as metabotropic receptors (as depicted in Fig. 5.10).

Ligand-gated ion channels (LGICs) are membrane proteins that are integral to the cell membrane. They have a hole that permits the controlled passage of specific ions across the plasma membrane. The permanent ions' electrochemical gradient drives the passive ion flux. Neurotransmitters attach to one or more orthosteric sites



(a) Direct activation brings about immediate response



(b) Indirect activation involves a prolonged response, amplified over time

Fig. 5.10 Action of neurotransmitter through receptor (Engidawork et al. 2016)

to open, or gate, the channels by causing a conformational shift that leads to the conducting state. The binding of endogenous or foreign modulators to allosteric sites can modify gating. Within the neurological system and at the muscular neuromuscular junction, LGICs mediate rapid synaptic transmission on a millisecond's time scale. This type of transmission occurs when a presynaptic neuron releases a neurotransmitter, which then triggers the activation of receptors situated postsynaptically, which in turn produces a fast, phasic electrical signal known as the excitatory or inhibitory postsynaptic potential (Alexander et al. 2011).

The fourth-largest superfamily in the human genome is made up of essential membrane proteins called G protein-coupled receptors, or GPCRs. The naming of GPCRs was based on their shared capacity to bind with heterotrimeric G proteins ($G\alpha\beta\gamma$). By causing conformational changes in the receptor that support heterotrimeric GTP-binding protein (G protein) activation, the binding of extracellular ligands starts the signal transduction cascade. The G protein links the GPCR to ion channels or enzymes by attaching itself to the cytoplasmic side of the plasma membrane. Sometimes G proteins engage in interactions with GPCRs prior to the activation of the receptor, while in other situations G proteins only engage in interactions with GPCRs following ligand stimulation. There are three subunits in G proteins: α , β , and γ .

G protein α subunit binds to guanosine diphosphate (GDP) while it is inactive. When a GPCR is triggered, the α subunit releases GDP and binds to guanosine triphosphate (GTP). GPCR functions as a GEF (guanine nucleotide exchange factor) as a result of this. G protein shape changes as a result of GDP and GTP exchanging, activating the protein. Once GTP is hydrolyzed to GDP, the G protein's α subunit loses its GTPase activity. The interaction of the G protein α subunit with a particular regulator of G protein signaling (RGS) greatly increases its GTPase activity. Receptor-gathering GTPase-activating proteins (GAPs) are mediated by RGS proteins (Rehman et al. 2023).

5.4.5 Inactivation of Neurotransmitters

It is imperative to deactivate neurotransmitters to enable synapses to react swiftly to fluctuations in the presynaptic neuron's firing frequency. Enzymatic breakdown, transportation out of the cleft of the synaptic to return to neurons or glia, or passive dispersion away from the synapse are the three potential methods of inactivating a transmitter, and they are not complementary. Synapse transmission can be affected by the pharmacological modification of certain enzymes that are involved in the degradation of both conventional and peptide transmitters. Choline and acetate are produced when acetylcholinesterase hydrolyzes acetylcholine, cleaving the transmitter molecule. When amines are carried only into neurons, amino acid transmitters can be delivered into glia or neurons (shown in Fig. 5.11) (Rehman et al. 2023).

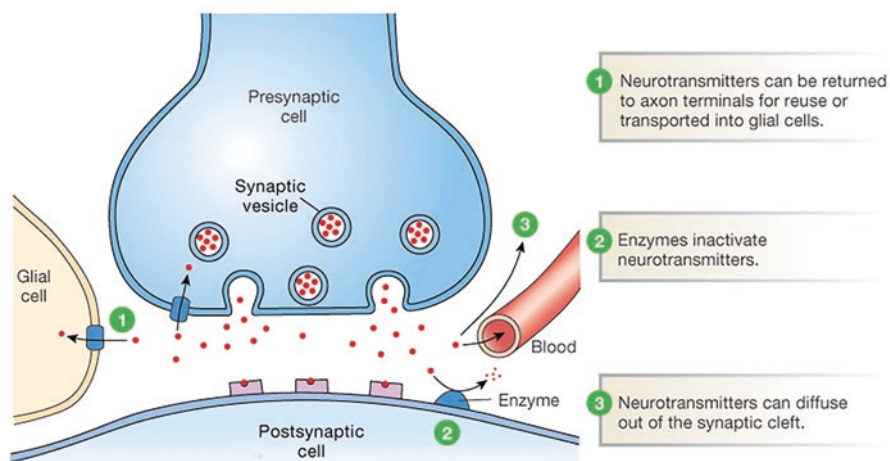


Fig. 5.11 Inactivation of neurotransmitter via different methods Psychologybank (2021)

5.5 Approaches for Diseases

Epilepsy A seizure refers to a momentary clinical occurrence that can be triggered by various extrinsic or intrinsic variables. It is characterized by an excessive and hypersynchronous discharge of cortical neuronal glial cells, which can present in a localized or widespread fashion inside the brain. Seizures are the outcome of this aberrant activity taking over any or all of the brain networks' regular functioning (Jenrow and Elisevich 2019).

This neurological illness known as epilepsy is complex. Epileptic seizures can cause harm to the brain or various parts of the body because they cause jerky or quivering responses in the body caused by aberrant neuronal activity. Alterations in brain development, as well as behavioral and cognitive alterations, can result from as little as one seizure. Patients with epileptic seizures experience behavioral, emotional, and neurological abnormalities. Different parts of the brain can experience seizures, and the effectiveness of a seizure depends on its characteristic area, kind, and location of aberrant neuronal activity (Giourou et al. 2015; Stafstrom and Carmant 2015; Anwar et al. 2020).

Based on its etiology, epilepsy is divided into three groups: acquired, idiopathic, and epilepsy of developmental or hereditary origin. The identifiable structural aberrations in our brains cause acquired epilepsy. Cerebrovascular diseases, cerebral immunological disorders, hippocampal sclerosis, cerebral trauma, cerebral tumors, cerebral infections, and prenatal and infantile causes are responsible for acquired epilepsy. Meningioma, cerebral infarction, viral meningitis, and epilepsy resulting from open head surgery are a few instances. The majority of cases of idiopathic epilepsy occur in childhood and are asymptomatic. Childhood absence epilepsy and juvenile myoclonic epilepsy are examples of idiopathic epilepsies.

Antiepileptic medicines (AEDs) or anticonvulsive pharmaceuticals are considered to be the most essential therapy choice for epileptic seizures. There are numerous established AEDs in use, and experimental research is also being conducted on more recent AEDs to ascertain their effectiveness. When administered at the earliest stage of the illness, AEDs have been shown to totally treat about 65% of youngsters. Many people require alternate treatments since they are resistant to AEDs. Particular care must be exercised when taking AEDs to prevent interactions with potentially dangerous medications. While these medications combat seizures through a variety of ways, the majority of them function as ion channels (sodium or calcium) or neurotransmitter (GABA) inhibitors (Table 5.2 shows drugs used in the treatment of epilepsy) (Anwar et al. 2020; Valton et al. 2020; Fisher et al. 2017).

Parkinson's Disease People with Parkinson's disease (PD) lose their dopaminergic function due to progressive degradation of dopaminergic neurons in the substantia nigra pars compacta (SNpc) that branch out to the striatum (the nigrostriatal pathway). Patients typically do not get the motor symptoms of Parkinson's disease (PD) until between 50% and 80% of their dopaminergic neurons have been destroyed. This suggests that a compensatory mechanism may be involved in the disease's early stages. D₁ (excitatory type) and D₂ (inhibitory type) dopamine receptors affect motor activity in the extrapyramidal system. This system consists of the pars reticulata section of the substantia nigra (SNpr) and the basal ganglia, which includes the internal globus pallidus segment (GPi) of the ventral striatum. These elements are a part of bigger circuits found in the cortex and thalamus. Patients with Parkinson's disease (PD) have dopamine depletion in the striatum, which causes the GPi/SNpr circuits to become more active. This leads to gamma-aminobutyric acid (GABA) malfunction, which in turn inhibits the thalamus. The ultimate consequence is a reduction in the thalamus's capacity to stimulate the frontal cortex, which leads to the diminished motor activity that is indicative of Parkinson's disease. Therefore, clinical improvement in the motor symptoms of Parkinson's disease (PD) is mediated by restoring activity of dopamine in the striatum through D₂ and D₁ activation of receptors with dopaminergic treatments. Furthermore, because dopamine no longer has the same inhibitory effect, dopaminergic depletion increases cholinergic activity and decreases thalamic activation (Table 5.3 shows drugs used in Parkinson's disease) (Beaulieu and Gainetdinov 2011; Galvan and Wichmann 2007; Chu et al. 2009; DeMaagd and Philip 2015).

Psychotic Disorder The neurotransmitter dopamine is most closely associated with the pathogenesis of psychotic illnesses. One theory is that too much dopamine in the mesolimbic tract is the source of positive symptoms in psychotic illnesses. Additionally, implicated is glutamate, an excitatory neurotransmitter. Reduced N-methyl-D-aspartate (NMDA) glutamate receptor function has been reported in a number of investigations. A significant inhibitory neurotransmitter that has also been mentioned in studies is gamma-aminobutyric acid (GABA). Research has indicated that patients with schizophrenia exhibit signs of malfunction. Finally, the consequences suggest a cholinergic irregularity (Table 5.4 shows drugs used in the

Table 5.2 Drugs used in the treatment of epilepsy (Anwar et al. 2020; Ambrósio et al. 1998; Thom et al. 2011; Aurora et al. 2012; Harrison and Keating 2006; Zhao et al. 2017; Barrons and Roberts 2010; Nohria and Giller 2007; Monaghan et al. 1997; Beletti and Lambert 2005; De 2024; Lamb 2022; Patel 2015)

Name of the drug	Mechanism of action	Importance	probable ADRs
Bumetanide	Blocks the Na-K-Cl channel	Support for infantile seizures AEDs work best for those having epilepsy associated with temporal lobe	Nausea, dizziness, and disorientation
Carbamazepine	Carbamazepine treats seizure activity by blocking the firing of sodium channels	Carbamazepine is recommended to be used to treat seizures and discomfort related to genuine trigeminal neuralgia, mixed and partial seizures accompanied by intricate symptoms, and generalized tonic-clonic seizures, bipolar I disorder-related manic and mixed manic-depressive episodes	Aggression, anxiety, and disorientation
Felbamate	Targets GABA and calcium channels	Specific to the treatment of epilepsy. Only to be used in patients with severe epilepsy with significant risk of aplastic anemia and/or liver failure	Anger and alterations in behavior
Ganaxolone	Ganaxolone belongs to a new class of neuroactive steroids known as “epalons,” including ganaxolone are strong and selective positive allosteric agonists of γ -aminobutyric acid type A (GABA-A) receptors in the CNS. Endogenous and exogenous neurosteroids are linked, among other things, to anxiolytic, sedative, and anticonvulsant actions via amplifying the inhibitory effects of GABA-A receptors	The FDA has approved the use of ganaxolone in patients ≥ 2 years old to treat seizures linked to cyclin-dependent kinase-like 5 (CDKL5) deficient disorder (CDD). For the same problem, the EMA has also approved it as an additional therapy for patients 2–17 years of age, with the possibility of continuation for patients 18 years of age or beyond	Weariness and dizziness
Perampanel	Perampanel inhibits the AMPA receptor noncompetitively, which lowers neuronal excitement	In children with epilepsy, perampanel is used to treat seizures as a supplement to treat primary generalized tonic-clonic seizures	Anger, agitation, and hostility
Retigabine	GABA receptors and potassium channels are activated	Adjunctive care for seizures with partial onset	Aggressive conduct limited to overdose situations

Table 5.3 Drugs used in the treatment of Parkinson’s disease (Mittur et al. 2017; Gilbert et al. 2000; Rang and Dale 2012; Baslam et al. 2023; Giachetti et al. 1986; Downs et al. 2019; Grimes et al. 2019)

Name of drug	Mechanism of action	Importance	Probable ADRs
Levodopa	In the brain, levodopa is converted to dopamine by decarboxylation. A drop in natural concentrations, this additional dopamine stimulates dopaminergic receptors to fill the function that endogenous dopamine cannot	Levodopa in conjunction with carbidopa and other medications is used to treat Parkinson’s patients on an infrequent basis. Most frequently, levodopa supplement includes a peripheral dopa decarboxylase (DDC) inhibitor which is intended to treat PD	Postural hypotension, cardiac arrhythmia, exacerbation of angina existing heart disease, alteration in taste sensation
Carbidopa	Carbidopa inhibits the DDC, which in turn prevents levodopa from being metabolized peripherally. The conversion of L-DOPA to dopamine and the production of L-tryptophan to serotonin both depend heavily on DDC. DDC is present in the blood–brain barrier as well as the periphery of the body. Since carbidopa cannot cross the blood–brain barrier, its activity is limited to peripheral DDC. As a result, it will inhibit levodopa metabolism in the peripheral but have no effect on dopamine synthesis in the central nervous system	In addition to levodopa, carbamazepine is recommended for the treatment of Parkinson disease symptoms, to lessen nausea and vomiting caused by levodopa. When the daily dosage of levodopa and carbidopa combination therapy is insufficient for a patient, the carbidopa product should be utilized	Fatiness, decrease in appetite, diarrhea, parched mouth, throat and mouth ache, regurgitation, shift in flavor perception, disorientation, or forgetfulness
Bromocriptine	The 7-transmembrane G protein-coupled dopamine D2 receptor is connected to Gi proteins. Inducing inhibition of adenylyl cyclase in lactotrophs via activation of the dopamine D2 receptor lowers cAMP concentrations and prevents release of Ca ²⁺	Monotherapy in the early stages of Parkinson’s disease or as a supplement to levodopa in more advanced instances with motor problems	Nausea, headache, dizziness, lightheadedness, constipation, cramping in the abdomen, diarrhea, nasal congestion, and hypotension

(continued)

Table 5.3 (continued)

Name of drug	Mechanism of action	Importance	Probable ADRs
Selegiline	In the brain, dopamine undergoes oxidative deamination through the involvement of MAO-B to which selegiline binds in the nigrostriatal pathways, inhibiting dopamine's microsomal metabolism and boosting the activity of dopamine in the significant nigra. Apart from inhibiting MAO-B, selegiline may potentially raise dopaminergic activity by additional means	Both monotherapy and adjunct therapy are options for treating Parkinson's disease in people who are not responding well to levodopa/carbidopa	Abrupt episodes of sleep, dyskinesia, arrhythmias, extrapyramidal symptoms, mental status changes, hallucinations, and serotonin syndrome
Amantadine	Along with stimulating the norepinephrine response, it seems to be generating dopamine from the brain cells' nerve ends. Its effects on NMDA receptors are also antagonistic	For the management of extrapyramidal responses brought on by drugs and parkinsonism	Symptoms such as headaches, lightheadedness, nausea, constipation, sleepiness, headaches, blurred vision, and difficulty sleeping
Trihexyphenidyl	Trihexyphenidyl binds more strongly to the M1 subtype while being a non-selective antagonist of the muscarinic acetylcholine receptor	Recommended as an adjuvant for treating parkinsonism in conjunction with levodopa, an adjunct for treating parkinsonism itself, and a means of managing extrapyramidal diseases brought on by medications that affect the CNS	Illusions of being persecuted, distrusted, wary, or aggressive Very parched mouth feeling Erroneous beliefs that the facts cannot refute Seeing, perceiving, or feeling unreal phenomena

Table 5.4 Drugs used in the treatment of psychotic disorder (Seeman 2002; Hyttel 1981; Golden and Honigfeld 2008)

Name of drug	Mechanism of action	Importance	Probable ADRs
Chlorpromazine	Several postsynaptic receptors are blocked by chlorpromazine, which functions as an antagonist (blocking agent). These include serotonergic receptors, dopaminergic receptors, and serotonergic receptors	For the short-term management of hyperactive children exhibiting: impulsiveness, difficulty maintaining attention, aggression, mood instability, and low frustration tolerance	Dry tongue, hazy vision, constipation, trouble urinating, and sinus tachycardia
Thioridazine	The effects of thioridazine include blocking postsynaptic mesolimbic dopaminergic in the brain, inhibiting the α -adrenergic effect, lowering the release of hormones from hypothalamus and pituitary gland	For the management of generalized anxiety disorder and schizophrenia.	Agitation, disorientation, coma, and impaired vision
Fluphenazine	Fluphenazine inhibits the release of hormones from hypothalamus and pituitary gland, blocks postsynaptic D1 and D2 receptors in the brain, and is thought to inhibit the reticular activating system	Treatment of psychotic illness symptoms	Sluggishness, headache, nausea, lightheadedness, dizziness, constipation, perspiration, a dry mouth, vision impairment, and loss of appetite
Haloperidol	Haloperidol selectively blocks the brain's postsynaptic dopamine (D2) receptors, preventing dopamine neurotransmission and relieving the hallucinations and delusions that are frequently connected to psychosis	Haloperidol is an antipsychotic medication used to treat agitation, frustration, and delirium symptoms in addition to schizophrenia and other psychoses	Headache, anxiety, difficulty urinating, lightheadedness, sleepiness, or difficulties in sleep
Flupentixol	Inhibitor of D2 receptors	For patients with schizophrenia who do not exhibit excitement, agitation, or hyperactivity as their primary symptoms, flupentixol is recommended as maintenance medication. It can be used to treat depression who may or may not be exhibiting anxiety symptoms as well. Adults with anxiety, depression, and asthenia symptoms can benefit from taking flupentixol along with melitracen	Severe anxiety, excitation, disorientation, drowsiness, seizures, coma, and either hyperthermia or hyperthermia

(continued)

Table 5.4 (continued)

Name of drug	Mechanism of action	Importance	Probable ADRs
Pimozide	Pimozide binds to the CNS dopamine D2 receptor and inhibits it	An antipsychotic called pimozide is used to treat severe motor and phonic tics	Blood dyscrasias, comatose states, hepatic diseases, renal insufficiency, NS depression, and in people who have previously shown signs of medication hypersensitivity
Clozapine	Antagonistic interactions between the serotonin type 2A (5-HT _{2A}) and dopamine type 2 (D ₂) receptors. In addition, clozapine functions as an antagonist at serotonergic and dopaminergic receptors as well as adrenergic, cholinergic, and histaminergic receptors	Patients with severe schizophrenia who do not react well to normal antipsychotic medication should be treated with clozapine. Only patients who have not responded well to normal antipsychotic medication should be prescribed clozapine due to the risks of severe neutropenia and seizure associated with its use	Tachycardia, hypotension, sedation, delirium, coma, respiratory depression or failure, and hypersalivation. Seizures, cardiac arrhythmias, and aspiration pneumonia have all been reported

Table 5.5 Drugs used in the treatment of depression (Bymaster et al. 2001; Sansone and Sansone 2014; Shelton 2022; Mandrioli et al. 2018; Shin Abdolreza 2019)

Name of drug	Mechanism of action	Importance	Probable ADRs
Moclobemide	The selective, reversible suppression of MAO-A is part of the moclobemide mode of action which results in degradation in the neurotransmitters. Monoamine levels rise as a result, reducing the symptoms of depression	For the management of bipolar disorder and serious depressive illness	Fast or pounding heart rate, thumping or erratic heartbeat, stiff neck feeling, intense, forward-radiating headache that begins at the rear of the head
Amitriptyline	Blocks the membrane pump mechanism that allows transmitter amines like norepinephrine and serotonin to be reabsorbed, which raises the concentration of these chemicals in the brain's synaptic clefts	Amitriptyline (tricyclic antidepressants) is prescribed to treat endogenous or psychotic depression and to reduce anxiety related to depression	Lowered body temperature, stupor, unresponsiveness or coma, abnormally low blood pressure, disorientation, seizures, dilated pupils and other eye issues, impairing heart function, drowsiness, hallucinations, and altered focus
Desipramine	Prevents the specific reuptake of noradrenaline, or norepinephrine, from the synapses between neurons. Moreover, it prevents serotonin reuptake	To alleviate symptoms in different depression syndromes, particularly internal depression	Anxiousness, restlessness, trepidation, headache, and malaise
Fluoxetine	It works as a therapeutic agent by preventing serotonin from being reabsorbed presynaptically	Obsessive compulsive disorder, bulimia nervosa, and major depressive disorder can all be treated with fluoxetine, both acutely and over time	Tachycardia, tremor, and sleepiness
Venlafaxine	Inhibits serotonin and norepinephrine reuptake at the presynaptic terminal both potently and selectively.	Major depressive illness (MDD), panic disorder, social anxiety disorder (SAD), and generalized anxiety disorder (GAD) can all be treated with venlafaxine	Mild vertigo, paresthesia in the limbs, and altered consciousness
Trazodone	Impede serotonin reuptake and block alpha-1-adrenergic and histamine receptors	To treat the symptoms of eating disorders, fibromyalgia, dementia, Alzheimer's disease, and schizophrenia	Dyspnea, bradycardia, hypotension, altered mental status, comatose state, and unconsciousness

treatment of psychotic disorder) (Geddes et al. 2011; Kehrer et al. 2008; Kinon et al. 2011; Ortega et al. 2023).

Depression It is believed that neurotransmitters are important in the etiology of depression. Since serotonin (5-HT) is extensively distributed throughout the neural systems, a shortage in it can cause anxiety, phobias, depression, and other mental health disorders in vertebrates. The 5-HT theory has fueled research into the fundamental causes of depression over the past few decades. It has been reported that patients with depression may have changed 5-HT receptors, such as downregulated 5-HT_{1A} and upregulated 5-HT₂ receptors, and low brain 5-HT levels. Social isolation reduces 5-HT₁ neurotransmission; 5-HT₂ receptors inhibit 5-HT₁ neurotransmission; and hypercortisolemia inhibits 5-HT₁ neurotransmission are the three potential mechanisms causing reduced 5-HT_{1A} function in depression. The development and functionality of 5-HT neurons in adult brains are correlated with endogenous proteins including neurotrophin-3 and BDNF (Table 5.5 shows drugs used in the treatment of depression) (Holtzheimer III and Nemeroff 2006; Li et al. 2021; De-Miguel and Trueta 2005; Maes et al. 2009; Deakin and Graeff 1991; Xue et al. 2021; Tian et al. 2022).

Anxiety Norepinephrine, serotonin, dopamine, and gamma-aminobutyric acid (GABA) are considered to be the principal arbitrators of anxiety in the CNS. A majority of the symptoms are mediated by the autonomic nervous system, specifically the sympathetic nervous system. Diminishing fear and anxiety is mostly dependent on the amygdala. Higher amygdala response to anxiety stimuli has been shown in patients with anxiety disorders. Prefrontal-limbic activation imbalances can be corrected with pharmacological or psychological therapies, as the components of the limbic system and the amygdala are linked to prefrontal cortex areas (as shown in Table 5.6) (Garcia-Garcia et al. 2014).

Treatment Using Opioid Analgesics Medication used to relieve pain that acts on opioid receptors is referred to as an opioid analgesic. While these drugs have also historically been referred to as narcotics, the preferred word at this time is opioid analgesic. It has been suggested that opioids be classified according to how they work on receptors (full, partial, or mixed agonists) or how they originate (endogenous, opium alkaloids, semi-synthetic, totally synthetic). Based on equivalency dosage estimates, tables can be utilized to compare opioids based on their relative strength, independent of their classification (Table 5.7 shows drugs of opioid analgesics) (Schofferman and Mazanec 2012).

Table 5.6 Drugs used in the treatment of anxiety (Yocca 1990; Altamura et al. 2013; Dooley 2015)

Name of drug	Mechanism of action	Importance	Probable ADRs
Diazepam	In the brain and spinal cord, benzodiazepines (diazepam) bind to receptors in different areas inhibiting GABA (gamma-aminobutyric acid) that induces sleep, regulates neural excitability, hypnosis, memory, anxiety, and epilepsy	Diazepam is generally helpful in the symptomatic treatment of mild to moderate anxiety in situations where tension, excitement, agitation, fear, or aggression predominate, such as in case of psychoneurosis, anxiety responses brought on by stressful situations, and anxiety states manifested somatically	Apnea, coma, areflexia, and cardio-respiratory depression, necessitating the use of suitable countermeasures
Buspirone	Buspirone functions as a partial agonist at postsynaptic 5-HT1A receptors and as a full agonist at dorsal raphe-expressed presynaptic 5-HT1A receptors, also known as 5-HT1A autoreceptors	Suitable for treating anxiety disorders or providing momentary respite from anxiety symptoms	Lightheadedness, sleepiness, miosis, and upset stomach
Hydroxyzine	The histamine H1-receptors are powerfully inversely agonistic by hydroxyzine	Hydroxyzine is prescribed to treat the symptoms of tension and anxiety related to psychoneuroses and as a supportive treatment for organic disease states where anxiety is present	Excessive sedation

Table 5.7 Drugs of opioid analgesics (Pacifci [2016](#); Kim et al. [2016](#); Florvaag and Johansson [2012](#))

Name of drug	Mechanism of action	Importance	Probable ADRs
Morphine (natural analgesic)	The opioid receptors kappa and mu are agonistically activated by morphine and its metabolites	Chronic, moderate-to-severe pain is treated with morphine Morphine is one of the opioids that are useful for treating pain in the short term	Respiratory depression, mydriasis, miosis, skeletal muscular flaccidity, chilly and clammy skin
Pholcodine (semi-synthetic analgesic)	Pholcodine's acts as an analgesic on the periphery reflexogenic receptors in the medulla oblongata which is referred to as "cough center"	The reduction of ineffective coughing is pholcodine activity. It also has a slight hypnotic effect and negligible or no analgesic effects	Respiratory depression impact
Meperidine (synthetic analgesic)	Meperidine possesses both local anesthetic and kappa-opiate receptor agonist properties	An opioid agonist having sedative and analgesic effects, meperidine is used to treat extreme pain	Seizures, syncope, shock, and hallucinations

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Drugs Acting on Renal and Cardiovascular Function

6

Raja Chakraverty and Tatini Debnath

Abstract

Cardiovascular medications play a crucial role in medical practice by influencing the functionality of the heart and blood vessels. These medications are employed to address a range of conditions such as hypertension and angina pectoris. Hypertension denotes elevated blood pressure levels, while angina pectoris manifests as chest discomfort due to insufficient blood supply to the heart muscle through the coronary arteries. Furthermore, cardiovascular drugs are instrumental in managing heart failure, characterized by insufficient cardiac output relative to the body's demands, and arrhythmias, which represent irregularities in heart rhythm. This chapter delves into the significance and effects of cardiovascular drugs, as well as medications impacting renal functions, within the medical realm. A comprehensive understanding of how these drugs influence the cardiovascular system enables healthcare practitioners to offer more efficacious treatment modalities for patients grappling with cardiovascular ailments.

Keywords

Heart function · Renal function · Diuretics · Cardiovascular drugs

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6.1 Introduction

This chapter delves into the various classes of medications utilized for managing cardiovascular and renal conditions. It commences by examining diuretics, including thiazides and loop diuretics, and their application in addressing conditions such as hypertension and heart failure. Subsequently, it explores antiplatelet, anticoagulant, and fibrinolytic agents. Antiplatelet medications like aspirin and clopidogrel serve to mitigate the risk of myocardial infarction and ischemic stroke, while anticoagulants such as heparin and warfarin prevent thrombus formation, and fibrinolytics like streptokinase dissolve existing thrombi. This chapter then delves into the elevated risks of stroke, coronary artery disease with myocardial infarction, and sudden death correlated with systemic hypertension. It discusses medications that either elevate or lower blood pressure, with a predominant focus on those that reduce systemic blood pressure, such as renin–angiotensin system inhibitors, calcium channel blockers, and β -adrenoceptor blockers. Additionally, it briefly addresses the management of renal and pulmonary hypertension. The text also covers pharmacotherapies for treating and preventing angina pectoris attacks, including the use of nitrates. Medications like cardiac glycosides, β -adrenoceptor antagonists, ACE inhibitors, AT1-receptor antagonists, and aldosterone receptor antagonists are elucidated, as they play integral roles in heart failure management. Following a concise consideration of cardiac arrhythmia mechanisms, it delves into the classes of antiarrhythmic drugs, providing exemplars for each class (e.g., lignocaine, atenolol, (+)-sotalol, calcium channel blockers, adenosine), and includes medications with multiple actions such as amiodarone. Finally, this chapter explores medications employed in managing hyperlipidemia to forestall atherosclerosis, specifically mentioning statins and fibrates (Cardiovascular Consultants 2006).

6.2 Overview of Renal Function (Shown in Fig. 6.1)

The kidneys play a pivotal role in regulating the composition and volume of the extracellular fluid (ECF). Their primary function involves maintaining a consistent internal environment by excreting appropriate amounts of various substances through urine. These substances include waste products, foreign compounds, and excess beneficial substances obtained from diet, beverages, or metabolic processes. This chapter delves into the fundamental renal mechanisms responsible for eliminating a wide array of substances.

The kidneys perform numerous essential functions (Cleveland Clinic 2009):

The kidneys perform a multitude of vital functions:

1. **Osmotic Pressure Regulation:** They maintain the osmolality of body fluids by excreting urine that can be either dilute or concentrated, based on the body's requirements.

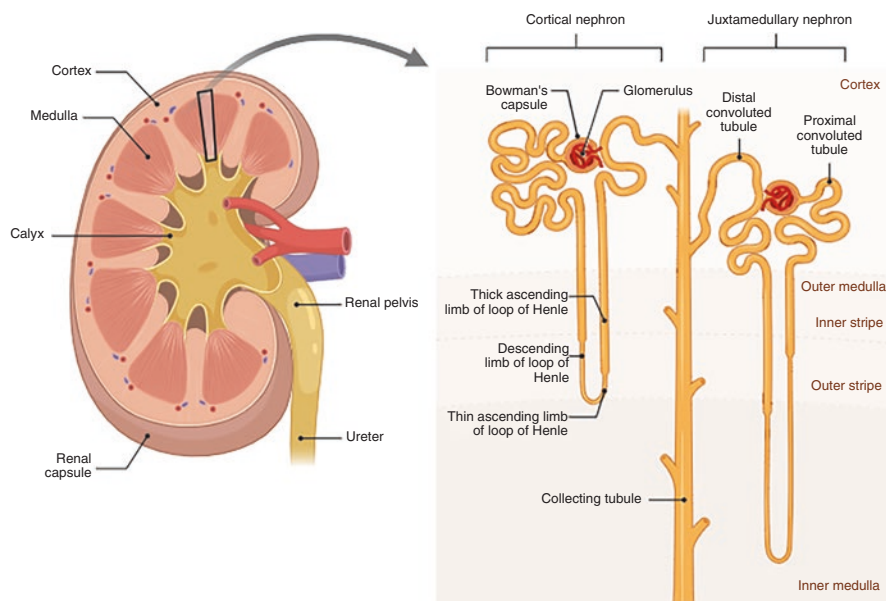


Fig. 6.1 Structure showing parts of kidney

2. **Ion Concentration Regulation:** They regulate the concentrations of various ions in blood plasma, including sodium (Na^+), potassium (K^+), calcium (Ca^{2+}), magnesium (Mg^{2+}), chloride (Cl^-), bicarbonate (HCO_3^-), phosphate, and sulfate.
3. **Acid–Base Balance:** They play a central role in the body's acid–base balance by eliminating excess hydrogen ions (H^+) in cases of acid surplus or excess bicarbonate (HCO_3^-) in cases of base surplus.
4. **Extracellular Fluid (ECF) Volume Control:** They manage the excretion of sodium (Na^+) and water to control the volume of extracellular fluid.
5. **Blood Pressure Regulation:** They contribute to the regulation of arterial blood pressure by adjusting sodium (Na^+) excretion and producing substances like renin, which can impact blood pressure.
6. **Metabolic Waste Removal:** They eliminate metabolic waste products such as urea (from protein metabolism), uric acid (from purine metabolism), and creatinine (from muscle metabolism).
7. **Drug and Toxin Excretion:** They remove various drugs (e.g., penicillin) and foreign or toxic compounds from the body.
8. **Hormone Production:** They are major sites for the production of specific hormones, including erythropoietin (important for red blood cell production) and 1,25-dihydroxy vitamin D3 (important for calcium regulation).
9. **Polypeptide Hormone Breakdown:** They break down several polypeptide hormones, including insulin, glucagon, and parathyroid hormone.
10. **Ammonia Synthesis:** They synthesize ammonia, which contributes to acid–base balance.

11. **Regulation of Renal Blood Flow:** They produce substances like arachidonic acid derivatives (prostaglandins, thromboxane A₂) and kallikrein, which influence renal blood flow and sodium (Na⁺) excretion.

6.3 Overview of the Heart (Jowett and Thompson 2007)

The heart, a muscular organ, serves as a continuous pump responsible for circulating blood throughout the body. Situated at the center of the circulatory system, this system comprises a network of blood vessels, including arteries, veins, and capillaries, which facilitate the transportation of blood to and from all body regions. An electrical system governs the heart's activity, utilizing electrical signals to initiate contractions of the heart's walls, thereby facilitating the pumping of blood into the circulatory system. To ensure the correct direction of blood flow, the heart chambers are equipped with inlet and outlet valves. The heart is vital for overall health, as it plays an essential role in virtually all bodily functions. Without the heart's pumping action, blood circulation within the body would be impossible. Blood acts as a carrier of essential oxygen and nutrients required by the body's organs to function efficiently. Additionally, it transports carbon dioxide, a waste product, to the lungs for elimination from the body into the air. A healthy heart ensures that the body's various regions receive an adequate volume of blood at the necessary rate for normal functioning. However, in cases where disease or injury weakens the heart, the body's organs do not receive a sufficient blood supply to function properly (shown in Fig. 6.2).

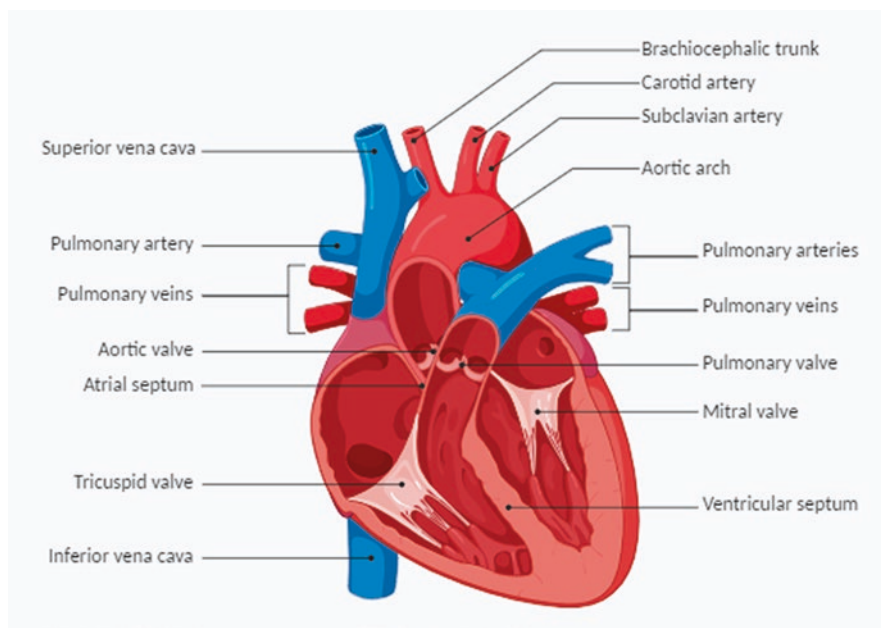


Fig. 6.2 Various parts of heart

6.4 Impacts on Cardiac Performance (Miller and Froelicher 2004)

Medications exert their influence on heart function through three primary mechanisms. They have the ability to modify the strength of the heart muscle's contractions, known as inotropic effects, thereby affecting the force with which the heart pumps blood. Additionally, medications can impact the heart rate or rhythm, referred to as chronotropic effects, either by increasing or decreasing the rate at which the heartbeats. Furthermore, certain medications can disrupt the regularity of the heartbeat, causing arrhythmias or irregular heart rhythms, termed rhythmic effects.

6.5 Alteration in Heart Contraction

Inotropic agents are substances that affect the strength of contractions in the cardiac muscle, thereby influencing cardiac output. These agents exert a positive inotropic effect when they enhance the force of the heart's contractions. Among these agents, cardiac glycosides stand out as a significant group, with compounds naturally found in plants like foxglove (*Digitalis purpurea*). The efficacy of cardiac glycosides in treating heart disease was established by English physician William Withering in 1785, who successfully used an extract from foxglove leaves to address heart failure. The two most commonly used glycosides for therapeutic purposes are digoxin and digitoxin.

However, it is important to note that cardiac glycosides come with undesirable side effects. These side effects include a tendency to obstruct the conduction of electrical impulses responsible for contractions as they travel from the atria to the ventricles of the heart, a condition known as heart block. Additionally, cardiac glycosides may provoke irregular cardiac rhythms by triggering electrical impulses in regions of the heart other than the usual pacemaker site, leading to ectopic heartbeats. While occasional ectopic beats are generally harmless, if they progress to ventricular fibrillation, the heart's pumping action ceases, potentially resulting in death within minutes. Due to the narrow safety margin between therapeutic and toxic doses of glycosides, their use must be approached with caution.

Cardiac glycosides enhance the force of cardiac muscle contractions by binding to and inhibiting a membrane enzyme responsible for expelling sodium ions from within the cell. Additionally, these drugs promote the release of calcium from internal cellular stores, resulting in an elevation of intracellular calcium levels. This increase in intracellular calcium is the key factor behind the heightened strength of contractions, as these calcium ions initiate the shortening of muscle cells. Disruptions in heart rhythm induced by cardiac glycosides are partly attributable to cell depolarization and partly to the elevation in intracellular calcium levels. Given that these rhythm disturbances stem from the same underlying mechanism responsible for their beneficial effects, finding a cardiac glycoside with a significantly improved safety margin is unlikely.

In addition to their cardiac effects, cardiac glycosides tend to lead to symptoms like nausea and loss of appetite. Furthermore, due to the extended plasma half-lives of digoxin and digitoxin (2 and 7 days, respectively), they have the potential to accumulate within the body. Consequently, the use of these drugs requires vigilant monitoring to prevent adverse effects resulting from their gradual buildup in the system. Another category of inotropic agents, which enhance the force of cardiac muscle contractions, includes dobutamine. When administered intravenously in moderate doses, dobutamine can increase contractility without affecting blood pressure or heart rate.

6.6 Regulation of Heart Rate

The heart rate is regulated by the antagonistic effects of the sympathetic and parasympathetic nervous systems, as well as the influence of epinephrine released from the adrenal gland. Activation of sympathetic nerves in the heart leads to the release of norepinephrine, while the adrenal gland releases epinephrine, both resulting in an increase in heart rate. Conversely, acetylcholine released by parasympathetic nerves decreases the heart rate. Propranolol, a competitive antagonist, acts to inhibit the stimulatory effects of norepinephrine on the heart. By doing so, it slows down the heart rate, making it a common treatment for anginal attacks and cardiac rhythm disturbances. Conversely, atropine blocks acetylcholine receptors, and it is administered during anesthesia to prevent excessive slowing of the heart.

6.7 Antiarrhythmic Medications and their Effects

Procainamide, quinidine, phenytoin, and lidocaine exert their antiarrhythmic effects by reducing electrical excitability. However, quinidine and procainamide have the disadvantage of also diminishing the heart's contractile force, which may potentially lower blood pressure. Additionally, they carry the risk of side effects such as nausea and skin rashes.

Lidocaine, commonly employed as a local anesthetic, exhibits a brief duration of action and is typically administered intravenously. Its primary role is to prevent ventricular arrhythmias that may arise following the acute blockage of a coronary artery. One significant factor exacerbating the development of ectopic pacemakers is the release of norepinephrine from sympathetic nerves. Norepinephrine stimulates beta-adrenoceptors in the heart, resulting in an increased heart rate and a greater propensity for ectopic pacemakers to emerge. Beta-adrenoceptor-blocking drugs, commonly known as beta-blockers (e.g., propranolol), are extensively utilized to manage such arrhythmias as they slow down heart activity. However, they also possess the potential to diminish the heart's contractile force, which could be disadvantageous and may lead to various other undesired effects.

6.8 Calcium Channel Blockers in the Mid-1970s

During the mid-1970s, a new category of antiarrhythmic drugs emerged, known as calcium channel blockers. Notable examples of these drugs include verapamil and diltiazem. Their primary mechanism of action involves reducing the influx of calcium ions through the cell membrane, a process that typically occurs during cell depolarization. This movement of calcium ions across the membrane is believed to play a crucial role in the development of reentrant rhythms and ectopic heartbeats. Inhibiting the entry of calcium ions has proven effective in managing various forms of arrhythmia. However, it is important to note that because calcium entry is essential for initiating the contraction of heart muscle cells, calcium channel blockers tend to diminish muscle contractility. Additionally, since calcium entry also contributes to the contraction of smooth muscle in blood vessels, these drugs induce vasodilation and consequently tend to lower arterial blood pressure.

6.9 Effects of Antiarrhythmic Drugs and Management of Heart Block

All the antiarrhythmic medications mentioned earlier have the potential to disrupt the conduction of impulses for heart muscle contraction, which can lead to heart block. As a result, the use of antiarrhythmic drugs requires careful management to mitigate the various risks and side effects they may present. Heart block results in an abnormal slowing of the heart rate and is typically not addressed with medications. In emergency situations, beta-adrenoceptor agonists such as isoproterenol are occasionally utilized. However, for sustained and effective control, the standard approach is to implant an artificial electrical pacemaker device.

6.10 Classification of Drugs (Roden 2006)

6.10.1 Anti-Anginal Drugs

Anti-anginal medications are pharmaceutical compounds used in the management of angina pectoris, a condition affecting the coronary arteries. These arteries are responsible for delivering oxygen-rich blood from the left ventricle to all regions of the heart, including the heart muscles within the ventricles themselves. The coronary arteries play a crucial role in sustaining cardiac function and are expected to adapt to sudden increases in demand brought about by heightened physical activity. Typically, these arteries respond to such demands by dilating or expanding. However, they may develop atherosclerotic deposits that impede the normal flow of blood, particularly during strenuous activity. As a result, the heart has to work harder to push blood through these narrowed, atherosclerotic arteries. This leads to the heart being deprived of oxygen, resulting in a condition known as ischemia. Angina serves as the primary symptom of ischemic heart disease, manifesting as sudden

and intense chest pain that can radiate from the chest to the left shoulder and down the arm.

6.10.2 Types of Anti-Anginal Drugs

The article discusses the three categories of drugs used to alleviate anginal pain: organic nitrates, calcium channel blockers, and beta-adrenergic blockers. Each category is suitable for different types of angina: organic nitrates and calcium channel blockers are used for spastic and chronic stable angina, while beta-adrenergic blockers are primarily used for angina triggered by physical exertion. These anti-anginal medications work by reducing the heart's oxygen demands, thereby decreasing anginal discomfort. Each class of medication utilizes a distinct mechanism to reduce the heart's workload, and they can be used in combination to enhance therapeutic effectiveness.

Organic nitrates, also known as nitrovasodilators, were discovered in 1867 with amyl nitrite being the pioneer antianginal agent. Today, various organic nitrates are available for clinical use, each with different levels of potency. Despite the emergence of newer agents like calcium channel blockers and beta-adrenergic blockers, organic nitrates continue to be the preferred choice for managing episodes of spastic angina. This suggests the enduring efficacy and relevance of organic nitrates in the treatment of spastic angina. It is vital for healthcare professionals to consider the specific characteristics of each anti-anginal medication and their respective mechanisms of action in order to tailor the treatment to the individual patient's needs. Understanding the distinct mechanisms of action of these drugs can help optimize their use and achieve better outcomes for patients suffering from angina.

6.10.3 Pharmacokinetics

This chapter investigates the effectiveness and duration of action of organic nitrates, focusing on how their molecular structure influences their pharmacokinetics and biochemical mechanism of action. This study finds that the size and steric hindrance of the nitrate group in the molecule affect the onset and duration of action, with smaller molecules having a quicker onset (around 30 s) and shorter duration (30–60 min) compared to larger molecules (15–30 min onset and 3–5 h duration). Metabolism, primarily through first-pass metabolism in the liver and extra-hepatic tissues, plays a crucial role in the antianginal effects of organic nitrates. These compounds release nitric oxide (NO) during metabolism, which is responsible for the vasodilating effect on the arteries. This chapter also details the chemical and enzymatic processes involved in releasing NO from the nitrovasodilators. Furthermore, the biochemical mechanism of action is explored, highlighting how nitric oxide released by nitrovasodilators leads to muscle relaxation through the activation of guanylate cyclase and subsequent increase in cGMP concentration, which in turn activates protein kinases that prevent the phosphorylation of myosin, leading to

muscle relaxation and vasodilation. Overall, this chapter provides detailed insights into the pharmacokinetics and biochemical mechanism of action of organic nitrates, shedding light on their role in alleviating anginal pain.

6.10.4 Calcium Channel Antagonists

This chapter discusses the role of free Ca^{2+} ions in muscle contraction and the potential of molecules to block the passage of these ions into muscle cells, thereby inhibiting muscle contraction. The L-type calcium channel, responsible for allowing calcium ions to enter various types of muscle cells, is highlighted as a target for calcium channel antagonists, which can effectively block these channels and impact muscle contraction. It is explained that these antagonists do not physically obstruct the channel but instead bind to specific sites in the open state of the channel. The potential of these agents as anti-anginal agents is also mentioned, emphasizing their ability to reduce the workload on the heart and lower the oxygen requirement. This information suggests the potential of targeting calcium channels to develop therapeutic interventions for conditions related to muscle contraction and heart workload.

6.11 Metabolism

6.11.1 Pharmacokinetics of Calcium Channel Blockers (CCBs)

This research discusses the properties and pharmacokinetics of calcium channel blockers (CCBs). It highlights that CCBs contain an amine group, allowing for the preparation of their hydrochloride salts for oral administration. Due to their hydrophobic structure, these agents are rapidly and completely absorbed after oral ingestion, with a significant portion (75–95%) present in the bloodstream. The majority of CCBs are primarily found in a protein-bound state (80–95%) in the plasma, although they remain active in their free form. The duration of action for most CCBs ranges from 4 to 8 h, except for amlodipine, which has an extended 24-h duration of action due to the presence of a chlorine atom.

6.11.2 Metabolic Pathways of Specific CCBs

This chapter also emphasizes the metabolic pathways of specific CCBs. Verapamil, diltiazem, and nifedipine undergo extensive first-pass metabolism, resulting in low bioavailability. Verapamil is converted into norverapamil, which is only about 20% as active as the parent molecule. Diltiazem is metabolized through esterases, yielding its desacetyl derivative, with only about 50% of its activity. Both verapamil and diltiazem also undergo N- and O-demethylations, producing inactive metabolites. Dihydropyridines are predominantly metabolized into inactive species with extensive hydroxylation of the phenyl group.

6.11.3 Summary and Implications

In summary, this study provides insights into the pharmacokinetic properties of CCBs, emphasizing their absorption, plasma binding, duration of action, and metabolic pathways. The findings underscore the importance of understanding these properties for the effective and safe clinical use of CCBs.

6.12 β -Adrenergic Antagonists

6.12.1 Propranolol's Role in Exertion-Induced Angina

This chapter discusses the wide use of propranolol, a nonselective β -blocker that affects both cardiac and bronchial adrenergic receptors, in the treatment of exertion-induced angina. Exertion-induced angina often stems from coronary atherosclerosis. β -blockers like propranolol reduce heart rate and the force of muscle contractions, making them useful in managing conditions such as hypertension, cardiac arrhythmias, and angina. Propranolol is frequently used in combination with organic nitrates or calcium channel blockers to enhance its anti-anginal effectiveness.

6.12.2 Propranolol's Broader Efficacy in Cardiovascular Conditions

This chapter highlights propranolol's effectiveness in managing exertion-induced angina, especially in the context of coronary atherosclerosis. It also emphasizes the broader utility of β -blockers in treating conditions like hypertension and cardiac arrhythmias due to their heart rate-reducing and muscle contraction-diminishing effects. Additionally, this chapter stresses the value of combining propranolol with organic nitrates or calcium channel blockers to enhance its anti-anginal efficacy.

6.12.3 Conclusion: The Significance of Propranolol

In conclusion, this chapter underscores the significance of propranolol, a nonselective β -blocker, in managing exertion-induced angina associated with coronary atherosclerosis. It also emphasizes the broader application of β -blockers in treating conditions such as hypertension and cardiac arrhythmias. The combination of propranolol with organic nitrates or calcium channel blockers is noted as a valuable approach to augment its effectiveness in managing angina.

6.12.4 Anti-Arrhythmic Agents

This chapter provides an overview of arrhythmia, a condition characterized by irregular or altered heart contractions. It explains that these contractions are regulated by pacemaker cells, known as the S-A node, and occur as a result of electrical

activities spreading through the myocardial tissue. The propagation of impulses throughout the myocardium generates the distinctive electrocardiogram (ECG) pattern, which reflects variations in membrane action potentials due to changes in the concentrations of specific ions within the heart muscle cells. This chapter highlights the significance of understanding the electrical activities and ion concentrations involved in cardiac contractions and their implications for arrhythmia.

6.12.5 Mechanism of Arrhythmias

This chapter explores the various origins of cardiac arrhythmias, focusing on disturbances in the electrical impulse's origin, particularly from pacemaker cells. It highlights that altered automaticity in pacemaker cells, resulting from conditions like hypertension, atherosclerosis, hyperthyroidism, or lung disease, can lead to arrhythmias. Additionally, this chapter discusses ectopic arrhythmias, where impulses originate from cells other than pacemaker cells, often caused by myocardial ischemia, excessive catecholamine release, or toxic effects of cardiac glycosides. This chapter also delves into premature heartbeats, where the electrical impulse does not fully dissipate before the start of a new cycle, leading to asynchronous depolarization. Finally, it addresses re-entrant arrhythmias, common in individuals with coronary atherosclerosis, caused by electrical impulses circulating in a loop within the heart tissue. Overall, this article provides a comprehensive overview of the different sources and mechanisms underlying cardiac arrhythmias, shedding light on the diverse factors contributing to these abnormal heart rhythms.

6.13 Classes of Anti-Arrhythmic Drugs

6.13.1 Classification of Anti-Arrhythmic Agents

This chapter discusses the classification of anti-arrhythmic agents based on their mode of action or impact on the electrocardiogram. Class I drugs act as local anesthetics and affect cell membranes to slow down the maximum rate of depolarization, thereby reducing the conduction of electrical impulses. They are further subdivided into three groups based on their effect on the duration of the action potential (QT interval): Class IA drugs increase the duration, class IB decreases it, and class IC drugs do not significantly alter the action potential's length. All class I agents bind to the fast Na⁺ channel and interfere with the depolarization process. The affinity of class I agents for the three distinct states of the Na⁺ channel varies, resulting in different effects on the action potential duration.

6.13.2 Mode of Action of Anti-Arrhythmic Agents

Class II drugs are beta-adrenergic blocking agents that stabilize the cell membrane or block the adrenergic-enhanced phase 4 depolarization. These drugs decrease neurologically initiated automaticity, leading to a depression of the effects of ectopic

pacemaker cells and a reduction in heart rate. Class III drugs prolong the duration of the action potential without altering the maximal rate of depolarization or the resting potential. These drugs act through various mechanisms that involve the transport of ions like Ca^{2+} , K^+ , and Cl^- . Class IV drugs, which are calcium channel blockers, inhibit the slow movement of Ca^{2+} ions during phase 2, resulting in a prolongation of the action potential's duration.

A detailed overview of different classes of anti-arrhythmic agents and their mechanisms of action, including their effects on the duration of the action potential and their interactions with ion channels are described. This classification is crucial for understanding the diverse pharmacological properties of anti-arrhythmic agents and their potential applications in the treatment of cardiac arrhythmias.

6.14 Drugs Belonging to Class IA

6.14.1 Overview of Quinidine

This chapter discusses the properties and medical uses of quinidine, a dextrorotatory diastereoisomer of quinine derived from the Cinchona plant. Quinidine functions as a classic anti-arrhythmic drug by reducing the sodium ion current through binding to open ion channels. It is utilized in the treatment of various arrhythmias, including supraventricular and ventricular ectopic arrhythmias, atrial and ventricular tachycardia, atrial flutter, and atrial fibrillation. The drug is available in different formulations such as sulfate, gluconate, and polygalacturonate, each with distinct physical and bio-absorption properties. Quinidine sulfate is administered orally and intramuscularly, with rapid absorption from the gastrointestinal tract and an onset of action in about 30 minutes. Quinidine gluconate, however, is water-soluble and used for emergency situations requiring a rapid response. Finally, quinidine polygalacturonate provides more stable and consistent blood levels of the drug.

In summary, this chapter provides an overview of the properties and medical uses of quinidine, highlighting its role as an anti-arrhythmic drug for various types of arrhythmias. It also discusses the different formulations of quinidine and their respective administration routes and absorption properties, emphasizing their roles in different clinical situations.

6.14.2 Procainamide

This chapter discusses the significance of procainamide hydrochloride as an anti-arrhythmic drug for managing cardiac arrhythmias. One of its key features is its stability in water across a broad pH range (pH 2–7), setting it apart from other amide bond-containing molecules. When metabolized, procainamide forms N-acetylprocainamide, which is only a quarter as effective as the parent drug. In contrast to quinidine, procainamide has a lower binding affinity to serum albumin.

Despite this, it is rapidly absorbed, with a high absorption rate of 75–95% from the gastrointestinal tract. This information sheds light on the pharmacological properties of procainamide, including its stability, metabolism, and absorption characteristics. Understanding these attributes is crucial for its effective use in managing cardiac arrhythmias.

6.14.3 Pharmacokinetic and Pharmacodynamic Properties of Disopyramide and Lidocaine

This examines the pharmacokinetic and pharmacodynamic properties of disopyramide and lidocaine as anti-arrhythmic drugs. Disopyramide is available for oral and intravenous use and reaches peak concentrations in the bloodstream within about 2 h when taken orally. Approximately 50% of disopyramide is bound to serum proteins, distinguishing it from other anti-arrhythmic medications in terms of protein binding.

6.14.4 Mechanisms of Action of Lidocaine

Lidocaine, originally introduced as a local anesthetic, is now commonly administered intravenously to treat arrhythmias stemming from acute myocardial infarction and cardiac surgery. It exerts its effects by binding to both active and inactive sodium channels with nearly equal affinity, resulting in a reduction of diastolic depolarization and automaticity. Due to its significant positive charge at physiological pH, lidocaine does not extensively bind to serum proteins. It undergoes rapid metabolism during first-pass metabolism, forming the metabolite monoethylglycinexylyl-dide, which is an effective anti-arrhythmic agent. The half-life of lidocaine ranges from 15 to 30 min, and lidocaine solutions containing epinephrine are exclusively used for local anesthetic purposes.

In conclusion, this chapter provides valuable insights into the pharmacokinetic and pharmacodynamic characteristics of disopyramide and lidocaine, highlighting their distinct properties and mechanisms of action as anti-arrhythmic drugs.

6.14.5 Drug Classification and Clinical Applications

This chapter discusses various anti-arrhythmic drugs, their structures, modes of action, and clinical applications. It begins by examining phenytoin, commonly used to manage grand mal type epileptic seizures. Phenytoin's structural similarity to barbiturates, but without their sedative effects, is highlighted. The drug is also found to be effective in treating arrhythmias induced by digitalis, sharing similarities in action with lidocaine. The next drug discussed is mexiletine, which belongs to the class IB of anti-arrhythmic drugs and shares properties similar to lidocaine. Mexiletine's stability as an ether and prolonged half-life of nearly 10 h when

administered orally are highlighted, along with its metabolism producing inactive derivatives.

6.14.6 Structures and Properties of Specific Drugs

Tocainide, another drug examined, is found to be analogous to lidocaine and used for ventricular ectopy and tachycardia. It is noted for its low pK_a and the advantage of not being significantly subject to first-pass metabolism. Finally, it covers encainide and flecainide, both class IC anti-arrhythmic agents with local anesthetic properties. Encainide's extensive metabolism in the body leads to the formation of active products, with one metabolite nearly as potent as the parent drug. In contrast, flecainide's metabolism results in a meta-O-dealkylated product with approximately 50% less activity than the parent drug. This provides a comprehensive overview of these anti-arrhythmic drugs, their structures, metabolism, and clinical applications.

The antiarrhythmic properties of five different drugs: flecainide, moricizine, propafenone, sotalol, and amiodarone. Flecainide is administered orally to manage various irregular heart rhythms, providing an effective therapeutic option. Moricizine, belonging to the phenothiazine derivative class, acts by blocking sodium channels and is used to treat life-threatening ventricular arrhythmias. Propafenone, sold as a racemic mixture, exhibits a stronger antiarrhythmic effect when the (S)-enantiomer is present. Sotalol, also sold as a racemic mixture, possesses both class II and class III activities, impacting heart rate by β -adrenergic blockade and K^+ channel blockade. Amiodarone, known for its pronounced antiarrhythmic action, has a very slow onset of action and elimination rate, with potential side effects including hypothyroidism and drug interactions due to its inhibitory effect on the oxidative system enzymes. This chapter provides valuable insights into the mechanisms of action, pharmacokinetics, and potential side effects of these antiarrhythmic drugs, highlighting their distinct characteristics and therapeutic applications.

This chapter discusses the characteristics and mechanisms of action of three types of cardiovascular drugs: Bretylium tosylate, verapamil, and diltiazem, as well as the impact of anti-hypertensive agents on hypertension. Bretylium tosylate, a quaternary ammonium salt, functions as an adrenergic neuronal blocking agent and was initially used as an antihypertensive agent. However, its use was discontinued due to tolerance development and pain-related side effects. It prolongs the effective refractory period in cardiac tissue, qualifying it as a class III antiarrhythmic agent. Verapamil and diltiazem are calcium channel blockers, used to control atrial arrhythmias and paroxysmal tachycardias. They are both extensively bound to plasma proteins and classified as class IV antiarrhythmic agents. This chapter also addresses hypertension, its prevalence, and impacts on the body. It distinguishes essential and secondary hypertension, pointing out that the former is influenced by genetic factors, while the latter has identifiable underlying causes. Additionally, it discusses the temporary factors contributing to hypertension, including certain medical conditions, medications, alcohol consumption, coffee consumption, stress, and exercise.

This chapter discusses the various classes of anti-hypertensive drugs and their mechanisms of action. The main classes of anti-hypertensive drugs include diuretics, beta-blockers, ACE inhibitors, ARBs, calcium channel blockers, alpha-blockers, central adrenergic inhibitors, direct vasodilators, renin inhibitors, and combination medications. It emphasizes that the choice of anti-hypertensive medication depends on the patient's specific condition, age, and concurrent health issues. This suggests that treatment often involves a combination of drugs from different classes to achieve the best blood pressure control and that patients should work closely with their healthcare providers to determine the most suitable medication or combination for their individual needs.

6.14.7 The Renin–Angiotensin System

The renin–angiotensin system is a hormonal regulatory mechanism that plays a key role in controlling the excretion of sodium and maintaining body fluid balance. It is closely intertwined with the sympathetic nervous system and the biosynthesis of aldosterone, which is a hormone that regulates sodium retention by the kidneys.

6.14.8 Renin–Angiotensin System and Blood Pressure Regulation

The renin–angiotensin system (RAS) plays a crucial role in regulating blood pressure. When blood pressure drops, the kidneys release renin, which acts on angiotensinogen to produce angiotensin-I. This is then converted to angiotensin-II by angiotensin-converting enzyme (ACE), leading to vasoconstriction and an increase in blood pressure. Angiotensin-II can also be further processed to form angiotensin-III, which influences sodium excretion and aldosterone release, further impacting blood pressure regulation.

6.14.9 Function of Angiotensin-Converting Enzyme (ACE)

Angiotensin-converting enzyme (ACE) is essential for the conversion of angiotensin-I to angiotensin-II and requires zinc for its activity. ACE cleaves the second peptide bond from the carboxyl terminus of a polypeptide. Peptides with a penultimate prolyl residue are typically not cleaved by ACE, contributing to the stability of angiotensin-II.

6.14.10 Role of ACE Inhibitors in Blood Pressure Management

Inhibitors of ACE, known as ACE inhibitors, reduce the synthesis of vasoconstrictors like angiotensin-II, thereby lowering blood pressure. ACE inhibitors are commonly used as antihypertensive medications to manage high blood pressure and its

cardiovascular effects. Understanding the mechanisms of the renin–angiotensin system and the role of ACE inhibitors provides insights into potential therapeutic targets for managing hypertension and related cardiovascular conditions.

6.15 Angiotensin-Converting Enzyme (ACE) Inhibitors: Captopril and Lisinopril

6.15.1 Captopril and Lisinopril: Mechanism of Action

This chapter discusses two angiotensin-converting enzyme (ACE) inhibitors: captopril and lisinopril. Captopril contains a carboxylate group that interacts with the cationic site in the enzyme's active site, inhibiting its ability to convert angiotensin-I to angiotensin-II. Additionally, it contains a thiol group to potentially enhance its binding to zinc in the enzyme, but this has been associated with side effects like rashes and loss of taste. Captopril is considered a stoichiometric inhibitor, forming a one-to-one complex with the enzyme. Lisinopril, derived structurally from lysine, also inhibits ACE, blocking the conversion of angiotensin-I to angiotensin-II. Both drugs are used to treat high blood pressure by interfering with the renin-angiotensin system, and they are part of a class of antihypertensive medications effective in reducing blood pressure.

6.15.2 Captopril and Lisinopril

In summary, captopril and lisinopril are ACE inhibitors used for treating high blood pressure. They both inhibit ACE by interfering with the conversion of angiotensin-I to angiotensin-II. Captopril's structure includes a carboxylate group interacting with the enzyme's active site and a thiol group potentially enhancing its binding to zinc, but with associated side effects. Lisinopril, structurally derived from lysine, also inhibits ACE and is utilized for its antihypertensive effects, along with interfering with the renin–angiotensin system.

6.15.3 Enalapril, Benazepril, Quinapril, and Ramipril

This chapter discusses ACE (angiotensin-converting enzyme) inhibitor prodrugs, which are compounds that need to be converted within the body to their active forms. These prodrugs contain a common structural element, a 2-(S)-aminophenylbutyric acid ethyl ester moiety, which undergoes metabolic activation to become active ACE inhibitors. The ester moiety typically needs to be hydrolyzed by nonspecific esterases in the liver and intestines, contributing to their prolonged duration of action. This outlines three specific ACE inhibitors within this category: enalapril, benazepril, and quinapril. Enalapril is converted into its active form, enalaprilat, and is available as an enalapril maleate salt. Benazepril undergoes metabolic activation to benazeprilat and is available as benazepril hydrochloride. Quinapril is transformed

into its active metabolite, quinaprilat, and is available as quinapril hydrochloride. These ACE inhibitors are used in the treatment of mild to moderate hypertension, either as monotherapy or in combination with diuretics or calcium channel blockers. The extended duration of action of these inhibitors is due to their prodrug form, which requires metabolic conversion within the body to become effective. Additionally, fosinopril, another ACE inhibitor containing a phosphorus atom, is mentioned in this chapter and is used in the management of hypertension. This sheds light on the structural and metabolic aspects of ACE inhibitor prodrugs and their relevance in the treatment of hypertension.

6.15.4 Direct-Acting Vasodilatory Drugs

This discusses the role of drugs that induce dilation of smooth muscle cells in the treatment of hypertension. These drugs are valuable in reducing peripheral vascular resistance and blood pressure. The first drug highlighted is hydralazine, a vasodilator that directly acts on the smooth muscle in blood vessels, causing relaxation and dilation, leading to reduced resistance to blood flow and a drop in blood pressure. The second drug is sodium nitroprusside, a potent vasodilator that rapidly dilates arteries and veins. It is often used in acute settings, such as in hypertensive emergencies, to quickly lower blood pressure. The third class of drugs discussed is calcium channel blockers, which inhibit the entry of calcium into smooth muscle cells, leading to relaxation and dilation of blood vessels, thus decreasing blood pressure. Common examples include amlodipine, nifedipine, and verapamil. Finally, the potassium channel openers, which can cause smooth muscle cells to hyperpolarize and relax, resulting in vasodilation and lowering of blood pressure. These medications are valuable tools in managing hypertension, as they help reduce the resistance in blood vessels, ultimately resulting in improved blood flow and lower blood pressure.

6.15.5 Hydralazine

The described drug is hydralazine, used to treat moderate to severe hypertension, often in combination with other antihypertensive medications. It functions by dilating vascular smooth muscle fibers, reducing resistance in blood vessels and subsequently lowering blood pressure. The drug is particularly beneficial for patients with renal dysfunction, as it enhances renal blood flow. Although the specific mechanism through which hydralazine induces vasodilation is not fully comprehended, it is available in its hydrochloride form and is a stable yellow solid with low water solubility. It achieves peak plasma concentration around 1 h post-administration and undergoes rapid metabolism through processes like benzylic oxidation, glucuronidation, and N-acetylation. This makes it an integral part of comprehensive antihypertensive regimens for individuals with elevated blood pressure. This summary highlights hydralazine's significance in managing hypertension and its potential as part of an overall treatment plan for high blood pressure.

6.16 Sodium Nitroprusside

6.16.1 Sodium Nitroprusside for Hypertension Management

This chapter discusses the pharmacological properties of three drugs used for the management of hypertension: sodium nitroprusside, diazoxide, and minoxidil. Sodium nitroprusside, known for its rapid onset of action, is a potent blood pressure-lowering drug used in emergency situations such as hypertensive crises. Its mechanism of action involves the release of nitric oxide, leading to vasodilation of arterial and venous smooth muscle cells. However, its short duration of action and potential for toxicity limit its use to emergency situations.

6.16.2 Diazoxide and Minoxidil for Hypertension Management

Diazoxide and minoxidil, both potassium channel agonists, also contribute to vasodilation and are used in managing hypertension. Diazoxide reduces peripheral vascular resistance when administered intravenously, and its highly protein-bound nature can displace other drugs bound to proteins. Minoxidil, however, requires activation to its functionally active form and is particularly useful in severe hypertension cases that are difficult to control with other medications. These drugs play a crucial role in the treatment of high blood pressure, especially when other antihypertensive agents may not effectively achieve blood pressure control.

In summary, this highlights the pharmacological properties and mechanisms of action of sodium nitroprusside, diazoxide, and minoxidil for blood pressure management, emphasizing their value in emergency situations and cases of difficult-to-control hypertension.

6.16.3 Diuretics (Roden 2006)

This chapter discusses diuretics, a class of drugs that enhance urine excretion by the kidneys. These drugs primarily work by inhibiting sodium transport at various sites along the nephron, where sodium reabsorption occurs. Consequently, the inhibition of sodium reabsorption leads to increased excretion of water and electrolytes by the kidneys. The three main processes involved in the action of diuretics are glomerular filtration, tubular reabsorption, and tubular secretion. Diuretics interfere with tubular reabsorption, leading to increased excretion of water and electrolytes in the urine.

This chapter highlights the wide-ranging medical applications of diuretics in treating conditions and disorders such as congestive heart failure, nephritic syndrome, diabetes insipidus, nutritional edema, cirrhosis of the liver, hypertension, edema of pregnancy, and ocular and cerebrospinal fluid pressure. In congestive heart failure, diuretics are effective in treating cardiac edema, while in nephritic syndrome, they help manage fluid retention. They are also used to combat excessive urination and thirst in diabetes insipidus and reduce fluid retention in cases of malnutrition. Additionally, in cirrhosis of the liver, diuretics manage fluid accumulation

in the abdomen, while they are commonly prescribed to lower blood pressure in hypertension.

Moreover, diuretics may be used to manage edema during pregnancy in specific cases and employed to lower intraocular pressure in conditions like glaucoma or cerebrospinal fluid pressure in cases of increased intracranial pressure. Overall, this chapter emphasizes the vital role of diuretics in managing these conditions by promoting diuresis, which helps reduce excess fluid and alleviate related symptoms.

This chapter discusses the various therapeutic uses of diuretics in different medical conditions. Diuretics are commonly used in the management of congestive heart failure, essential hypertension, hepatic cirrhosis, and nephrotic syndrome. In congestive heart failure, the choice of diuretic depends on the severity of the condition, with options ranging from milder diuretics like hydrochlorothiazide to more potent ones like furosemide in emergency situations. Furthermore, potassium-sparing diuretics like spironolactone may be added to thiazide therapy to help maintain potassium levels. For essential hypertension, thiazide diuretics are commonly used as primary antihypertensive agents, either alone for milder cases or in combination with other antihypertensive medications for more severe conditions. In the management of hepatic cirrhosis, spironolactone is often employed, and if insufficient, a thiazide diuretic can be cautiously added to the treatment regimen. In cases of refractory edema, more potent diuretics like furosemide may be used in combination with spironolactone. For nephrotic syndrome, a low-sodium diet may be recommended along with the administration of a thiazide diuretic, and spironolactone may be added to help control secondary hyperaldosteronism. The choice of diuretic and its dosage will depend on the individual patient’s condition and response to treatment. It is emphasized that diuretics should be used under the guidance of a healthcare provider, as they can affect electrolyte balance and other aspects of health. Regular monitoring of serum potassium levels is essential due to the risk of potassium disturbances. Overall, this chapter provides valuable insights into the diverse therapeutic uses of diuretics and highlights the importance of personalized treatment based on individual patient characteristics and response (Tables 6.1 and 6.2 show classification of diuretics and therapeutic uses).

6.16.4 Classification of Diuretics

Table 6.1 Classification of diuretics (Roden 2006)

Diuretics				
Carbonic anhydrase inhibitors	Thiazides	Loop diuretics or high ceiling diuretics	Osmotic diuretics	Potassium sparing diuretics
Acetazolamide	Chlorothiazide		Isosorbide	
Methazolamide	Hydrochlorothiazide	Bumetanide	Glycerol	Spironolactone
Dichlorphenamide	Hydroflumethiazide	Ethacrynic acid	Urea	Triamterene
	Cyclothiazide	Furosemide	Mannitol	Amiloride
	Bendrofluazide			
	Polythiazide			
	Indapamide			
	Chlorthalidone			
	Quinethazone			

Table 6.2 Representation of diuretics and their therapeutic uses (Anon n.d.-b)

Drug	Mechanism of action	Pharmacokinetics	Therapeutic uses	Adverse effects
Carbonic anhydrase inhibitors				
Dorzolamide or Acetazolamide	Its acts at the proximal convoluted tubules inhibiting the enzyme, sodium bicarbonate re-absorption causing diuresis	Once a day give orally Onset of action 30 min $t_{1/2} = (6-9)$ h Duration of action (12 h approx.) Excreted by active secretion from proximal tubules Hence produces Alkaline urine	Reduces intracranial pressure Reduces formation of CSF (cerebrospinal fluid) in management of benign intracranial hypertension Epilepsy (decreases cerebrospinal fluid) Metabolic alkalosis Hyperphosphatemia	Metabolic acidosis Hypokalemia
Loop diuretics				
The most potent and effective diuretic is high ceiling diuretics	To inhibit the co-transporter responsible for sodium, potassium, and chloride in the thick ascending limb of the Henle loop's luminal membrane	Administered either orally or intravenously Fast onset of action Short duration of action Excreted through active tubular secretion of weak acids into the urine via an acid carrier, with strong binding to plasma proteins	Increases urinary excretion of sodium and potassium Drug of choice in emergency situations Used to treat severe edema associated with conditions such as congestive heart failure and nephrotic syndrome, treatment for oliguric ARF	Hypovolemia Hyponatremia Hypokalemia Postural hypotension
Thiazide diuretics				
Low ceiling diuretics	Operates by inhibiting the sodium/chloride co-transporter located on the luminal membrane of the distal convoluted tubules	Administered orally, it is effectively absorbed from the gastrointestinal tract, has a slow onset of action, and is lipid-soluble. It exhibits a prolonged duration of action, lasting approximately 40 h, and is subject to secretion by the active tubular secretory system of the kidney. It is eliminated through a combination of glomerular filtration, tubular secretion, with some reabsorption	Utilized for the treatment of essential hypertension due to its cost-effectiveness and good tolerability. Its efficacy is limited when the glomerular filtration rate (GFR) is less than 30–40 ml/min, except in the case of metolazone and indapamide Used in the management of mild heart failure to help reduce extracellular volume	May lead to fluid and electrolyte imbalances, potentially resulting in metabolic alkalosis

Potassium sparing diuretics				
	Operate in the collecting tubules and ducts by inhibiting the reabsorption of sodium and reducing the excretion of potassium and hydrogen ions, exhibiting a potassium-sparing effect. This can be achieved through various mechanisms	Easily absorbed from the gastrointestinal tract with a half-life of approximately 1.6 h. It is highly protein-bound and subject to enterohepatic recycling. The onset of its action is delayed, as it acts on nuclear receptors, with the maximum diuretic effect occurring around 4 days after administration. In the gut and liver, it undergoes conversion to canrenone, an active metabolite with a half-life of approximately 16 h	Augments the excretion of sodium induced by other diuretics Helps prevent or alleviate hypokalemia (low potassium levels) Hence, it is often used in conjunction with loop and thiazide diuretics	Hyperkalemia Metabolic acidosis in cirrhotic patients
Osmotic diuretics				
Mannitol	Mannitol enhances urine production through osmosis, prompting the movement of water from cells into the bloodstream Exerts its influence within the proximal tubules and descending limb of the Henle loop via its osmotic impact	When administered orally, it is poorly absorbed When administered intravenously Eliminated through glomerular filtration within 30–60 min, without undergoing reabsorption or secretion	Acute kidney injury resulting from shock or traumatic events In cases of acute drug overdose Reduction in intracranial and intraocular pressure prior to ophthalmic or neurosurgical procedures, particularly in cases of cerebral edema	Expansion of extracellular volume, which can complicate heart failure and lead to pulmonary edema Excessive use causing dehydration

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Drugs Affecting Gastrointestinal Functions

7

Moitreyee Chattopadhyay and Sweety Gupta

Abstract

The digestive system in humans is the mechanism that the body uses to carry out digestion. Food is ingested by the digestive system, which is intended to break it down both physically and enzymatically. The breakdown products are subsequently absorbed and sent to the liver. One of the major areas of exposure to the external environment is the gastrointestinal system. The gut barrier refers to the gastrointestinal tract's ability to monitor and protect the host's interior from outside invaders. Following damage from a variety of sources, such as oxidative stress and nonsteroidal anti-inflammatory medication usage, disruptions in the gut barrier occur that involve processes. Furthermore, the chapter's focus is on the developing concept that gastrointestinal dysfunction contributes to gastrointestinal disease. For this reason, it is critical to understand the pathophysiology of the many digestive diseases, including gastric ulcers, chronic constipation, gastroesophageal reflux diseases, gallstones, and diarrhoea, as well as the role that medications play in gastrointestinal functions.

Keywords

Gastrointestinal tract · Ulcer · GERD · Emesis · Diarrhoea · Constipation

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145

7.1 Gastrointestinal Tract Anatomy and Physiology

Anatomy of Gastrointestinal Tract The mouth's buccal cavity is where the gastrointestinal (GI) tract, sometimes referred to as the alimentary canal, begins, and it ends at the anus. It is separated into two sections: the small and large intestines in the lower GI tract and the mouth, throat, oesophagus, and stomach in the upper GI tract. Alongside the basic activities of the digestive system are the auxiliary organs, such as the pancreas, liver, gallbladder, and salivary glands (Fig. 7.1).

Physiological Function of the Gastrointestinal Tract The three primary functions of the GI tract are food and drink ingestion, waste removal, and nutrient absorption through digestion (Belleza 2017). Schematic explanations of the digestive system's physiology have been provided in Fig. 7.2.

Digestive juices, hormones, and enzymes are secreted from the gastrointestinal tract as in Table 7.1.

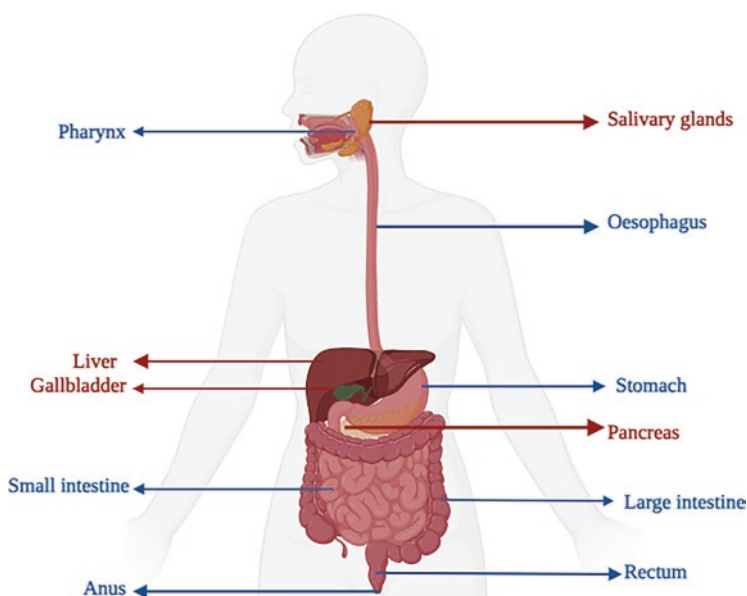


Fig. 7.1 Anatomy of human gastrointestinal tract; Blue colour arrow indicates primary organs of GIT; Brown colour arrow indicates auxiliary organs

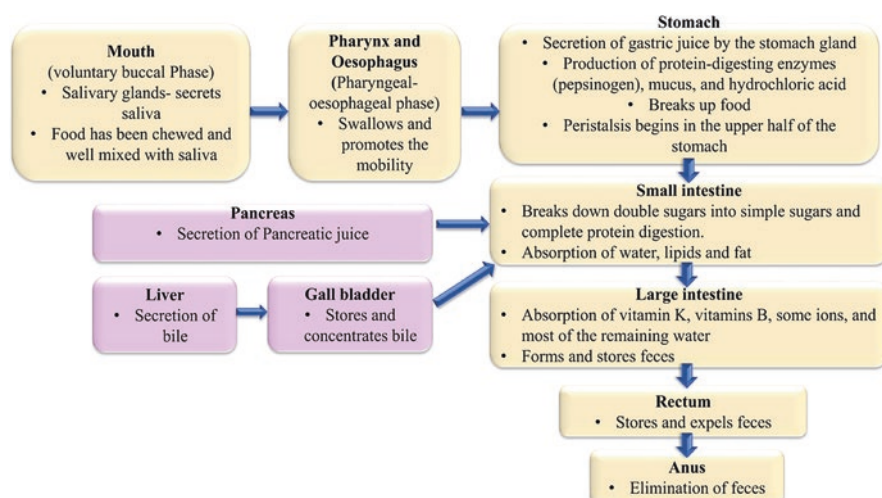


Fig. 7.2 Schematic representation of physiological function of gastrointestinal tract

Table 7.1 Digestive juices, hormones, and enzymes (Belleza 2017)

Organ	Secretion
Salivary glands	Amylase, mucus, sodium bicarbonate, water
Stomach	Pepsin, hydrochloric acid, mucus, water, gastrin
Pancreas	Proteases, trypsin, chymotrypsin, elastase, collagenase, amylase, lipase, sodium-bicarbonate, mucus, and water
Intestinal mucosa	Cholecystokinin, gastric inhibitory peptide and secretin, mucus, water, sodium-bicarbonate

7.2 Drugs for Ulcer

7.2.1 Pathophysiology of Gastric Ulcer

To start with, *Helicobacter pylori* is a kind of bacterium that inhabits between 45 and 50 percent of the stomach mucosa globally. Early childhood vaccination campaigns against these bacteria are common in developing nations with poor socioeconomic status and congested families. Gastritis is the result of the host's inflammatory reaction to these bacteria, which causes degradation, damage, and an epithelial response. Pan-gastritis is usually the outcome for people with this illness. This impairs the release of antral somatostatin, which increases gastrin secretion and

subsequently triggers the formation of more acid. It is noteworthy that not every patient suffering from this infection exhibits symptoms; this varies based on the virulence of the bacteria and additional risk factors associated with the host. The generation of *cagA*, which increases cytokine cell death and mucosal injury, is a frequent virulence factor in bacteria.

The second most frequent cause of stomach ulcers is NSAID (non-steroidal anti-inflammatory drug) drugs. When exposed to stomach acid, the medications themselves turn into weak acids. They stay within the epithelial cells and cause a rise in cellular permeability, which damages the cells physically. The main way that NSAIDs cause ulcers is by reducing the production of prostaglandins. NSAIDs work by inhibiting the cyclooxygenase-1 enzyme, which typically increases prostaglandin production. Prostaglandin promotes the creation of mucus barriers, improves mucosal blood flow, and speeds up the restoration and repair of damaged or dead epithelial cells, as well as the release of gastric bicarbonate. The stomach mucosa is more susceptible to injury from gastric acid and pepsin while using NSAIDs. All things considered, the most harmful physiological damage is caused by the decrease in stomach blood flow and the mild ischemia in the stomach mucosa (Fig. 7.3) (Woolf and Rose 2019).

Classification of Antiulcer Drugs Antiulcer drugs have been categorized in Table 7.2.

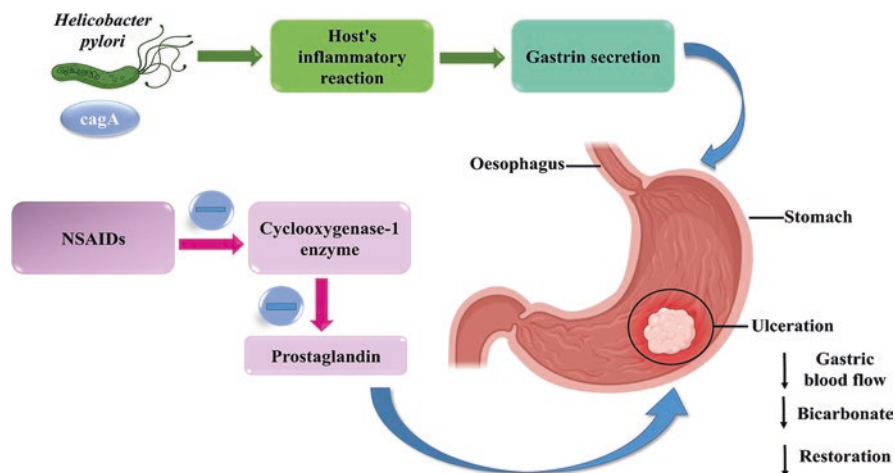


Fig. 7.3 Pathophysiology of gastric ulcer

Table 7.2 Classification of antiulcer drugs (<https://www.ncbi.nlm.nih.gov/books/NBK548007/2019>; Bethesda 2012a)

Category	Name of drugs
Proton pump inhibitor	Pantoprazole, lansoprazole, esomeprazole, dexlansoprazole, omeprazole, rabeprazole
Selective Histamine Type 2 Receptor Antagonists/Blockers	Famotidine, cimetidine, ranitidine, nizatidine

7.2.2 Pharmacological Actions of Antiulcer Drugs

7.2.2.1 Proton Pump Inhibitors (PPIs)

PPIs are prodrugs that need to be activated by stomach acid. Once absorbed, they spread throughout the stomach's parietal cells and gather in the acidic secretory canaliculi. The PPIs' active version inactivates the pump molecule that carries protons (H^+ molecules) into the stomach lumen by binding covalently to the acid-producing parietal cell's $H^+/K^+-ATPase$. Although PPIs have an hourly half-life, their active form remains retained in the parietal cell, resulting in a 24–48 h blockage of the proton pump. The oral PPIs reduce stomach acidity by 80–95% and are quickly absorbed (Bethesda 2012b).

Adverse Effects In addition to nausea, stomach discomfort, flatulence, constipation, diarrhoea, and rash, other gastrointestinal symptoms include headache, dizziness, and rash (Yibirin et al. 2021).

7.2.2.2 The H2 Receptor Blockers

H2 receptor blockers attach to histamine type 2 receptors on the basolateral (antiluminal) surface of the stomach parietal cells, obstructing the processes involved in the secretion and generation of gastric acid. The histamine type 1 receptors have minimal influence on stomach acid production. Despite being less effective in suppressing acid production compared to the PPIs, the H2 blockers are 70% effective for 24 h. Their night time effectiveness is prominent affecting the baseline acid secretion (<https://www.ncbi.nlm.nih.gov/books/NBK547929/2018>).

Adverse Effects Headache, tiredness, constipation, diarrhoea, or stomach discomfort. The use of H2RAs has been associated with negative effects on the central nervous system, including delirium, disorientation, hallucinations, and slurred speech, in individuals with renal impairment, hepatic impairment, or who are older than 50. It is generally accepted that cimetidine is the most common source of these symptoms; however, famotidine has also been shown to have comparable effects (Nugent and Terrell 2019).

Therapeutic Action of Antiulcer Drugs Table 7.3 provides an overview of the antiulcer medication's therapeutic effects.

Table 7.3 Therapeutic action of antiulcer drugs (Bethesda 2012a)

Drugs	Used for/therapeutic duration
Lansoprazole/ dexlansoprazole	Peptic ulcer disease and gastrointestinal reflux, 15 mg daily for 4–8 weeks, then continue at a similar dose over time
Omeprazole/ esomeprazole	Severe instances of peptic ulcer disease and gastrointestinal reflux, omeprazole is often used once day at a dose of 20 mg
Pantoprazole	Peptic ulcer illness, 40 mg once day for 4–8 weeks is the usual dose of pantoprazole, with similar long-term maintenance doses
Rabeprazole	4–8 weeks, the usual dosage for duodenal ulcer disease is 20 mg once day; comparable dosages are recommended for long-term maintenance therapy
Cimetidine	Up to 8 weeks, persons with peptic ulcer disease should take 300–400 mg of cimetidine twice day or 800 mg at night, with maintenance doses of 400 mg once day
Famotidine	People with peptic ulcer disease, a common suggested dose is 40 mg once day for 4–8 weeks, maintained by 20 mg daily
Ranitidine	Peptic ulcer disease in adults, 150 mg twice day or 300 mg once overnight is the usual prescribed ranitidine dosage for 4–8 weeks

7.3 Drugs for Gastro-oesophageal Reflux Disease (GERD)

7.3.1 Pathophysiology for GERD

Regurgitation and heartburn are common events of gastro-oesophageal reflux disease, but it has also been linked to extra-oesophageal manifestations including asthma, a persistent cough, and laryngitis. Variations in lower oesophageal sphincter pressure and temporary relaxations are part of the complex pathophysiology of gastro-oesophageal reflux disease. This leads to damage to the mucosa of the oesophagus due to reflux of acid, bile, pepsin, and pancreatic enzymes. Hiatal hernia, decreased oesophageal clearance, delayed stomach emptying, and compromised mucosal defence mechanisms are additional aspects that contribute to the pathophysiology of gastro-oesophageal reflux disease. Because hiatal hernias promote lower oesophageal sphincter dysfunction, they can aggravate gastro-oesophageal reflux disease (Fig. 7.4). The mucosa's extended exposure to acid is caused by impaired oesophageal clearance (De Giorgi et al. 2006).

7.3.2 Classification of Drugs Used in GERD (Savarino et al. 2021)

*Similar as classification of antiulcer drugs.

a. Pharmacological actions of drugs used in GERD:

*Similar as pharmacological actions of drugs used in ulcer.

b. Therapeutic action of drugs used in GERD:

*Similar as therapeutic action of antiulcer drugs.

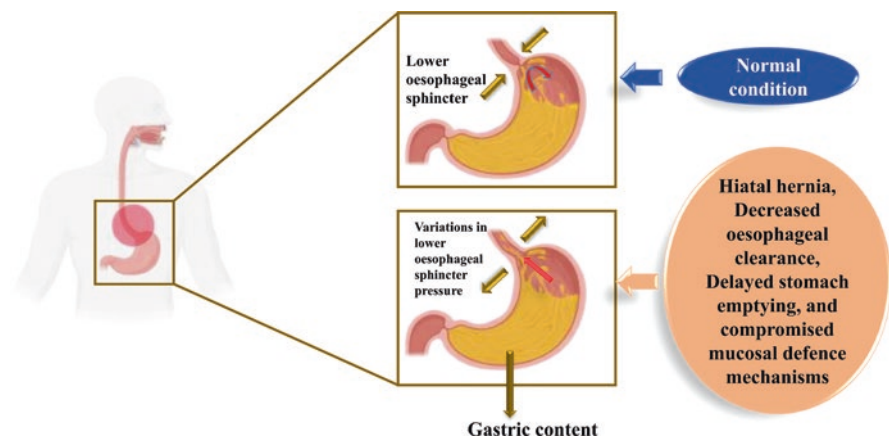


Fig. 7.4 Pathophysiology of GERD

7.4 Drugs Acting as Emetic and Antiemetic

An agent's tendency to induce nausea or vomiting is referred to as its "emetogenicity." The Hesketh or emetogenicity scale was first introduced in 1997 and classified chemotherapy drugs and dosages into five levels according to how likely they were to produce chemotherapy-induced nausea and vomiting (CINV). Since then, this scale has been amended by the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) to be separated into the following four sections:

Highly emetogenic: Drugs or dosages that result in CINV in more than 90% of patients.

Moderately emetogenic: Drugs that cause 30–90% of people to get CINV.

Low emetogenic: Drugs that are connected to 10–30% CINV rates.

Minimally emetogenic: Drugs that, in less than 10% of individuals, result in CINV.

Emetogenic chemotherapy drugs are classified in Table 7.4.

7.4.1 Mechanistic Pathway for Emesis

The emetic centre, located in the brain stem's reticular formation, has primary control over the vomiting reaction. Three sources provide information to the emetic centre: the chemoreceptor trigger zone, the brain, and the periphery. Neurokinin (NK) and serotonin (5-hydroxytryptamine₃ [5-HT₃]) are the primary mediators of peripheral pathways. The dopamine and histamine-mediated cortical circuit is the cause of anticipatory emesis. Following the activation of the emetic centre, signals are sent to the salivatory, respiratory, vasomotor, and cranial

Table 7.4 Emetogenic chemotherapy drugs by risk factor (Gupta et al. 2021)

Emetogenicity of chemotherapy	Intravenous drugs	Oral drugs
HEC (>90%)	Combination Anthracycline/cyclophosphamide Carmustine, dacarbazine, cyclophosphamide, cisplatin Mechlorethamine, dactinomycin Streptozotocin, carboplatin, doxorubicin	Procarbazine Hexamethylmelamine
MEC (30–90%)	Carboplatin, arsenic trioxide, amifostine, bendamustine, aldesleukin, busulfan, cyclophosphamide, actinomycin, cytarabine, clofarabine, azacitidine, daunorubicin, carmustine, alemtuzumab, doxorubicin, cytarabine, epirubicin, interferon alfa, idarubicin, methotrexate, ifosfamide, romidepsin, melphalan, temozolomide, thiotepa, oxaliplatin, trabectedin, irinotecan	Crizotinib Cyclophosphamide Imatinib Vinorelbine Ceritinib Bosutinib Temozolomide
LEC (10–30%)	Cytarabine, etoposide, carfilzomib, blinatumomab, brentuximab, ixabepilone, aflibercept, cabazitaxel, cetuximab, docetaxel, ipilimumab, eribulin, bortezomib, gemcitabine, catumaxomab, methotrexate, temsirolimus, mitoxantrone, trastuzumab-entansine, nab-paclitaxel, topotecan, panitumumab, paclitaxel, 5-fluorouracil, trastuzumab, belinostat, mitomycin, pemetrexed, pegylated, liposomal doxorubicin, pertuzumab, vinflunine	Dabrafenib, fludarabine, capecitabine, axitinib, everolimus, ibrutinib, lapatinib, afatinib, dasatinib, lenalidomide, olaparib, sunitinib, etoposide, nilotinib, vorinostat, pazopanib, tegafur uracil, ponatinib, idelalisib, thalidomide, regorafenib, vandetanib
Minimal (<10%)	Busulfan, bleomycin, cetuximab 2-Chlorodeoxyadenosine, bevacizumab, cladribine, ofatumumab, pixantrone, nivolumab, trastuzumab, vinblastine, vinorelbine Fludarabine, rituximab Pembrolizumab, vincristine Pralatrexate	Hydroxyurea, erlotinib, gefitinib, chlorambucil, melphalan, L-phenylalanine mustard, ruxolitinib, vemurafenib, methotrexate, vismodegib, pomalidomide, sorafenib, 6-thioguanine

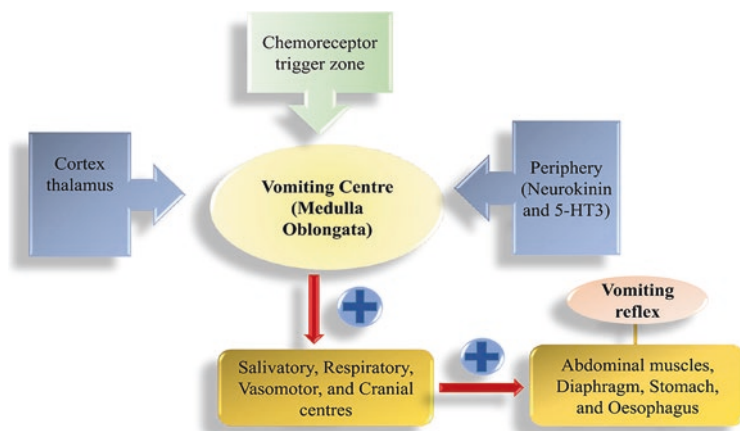


Fig. 7.5 Mechanistic pathway for emesis

Table 7.5 Classification of antiemetic drugs (Bethesda 2012a)

Category	Name of drugs
Anticholinergic Agents	Methscopolamine, Hyoscyamine, Scopolamine
Antihistamines	Dimenhydrinate, Cyclizine, Hydroxyzine, Promethazine, Meclizine
Cannabinoid receptor agonists	Dronabinol, Tetrahydrocannabinol, Nabilone
Phenothiazines	Prochlorperazine, Chlorpromazine
Serotonin 5-HT ₃ Receptor Antagonists	Palonosetron, Alosetron, Granisetron, Dolasetron, Ondansetron,
Neurokinin 1 receptor antagonists/ substance P	Aprepitant, Fosaprepitant, Rolapitant

centres, which in turn activate the abdominal muscles, diaphragm, stomach, and oesophagus—the organs implicated in the vomiting reflex (Becker 2010) (Fig. 7.5).

Classification of Antiemetic Drugs Antiemetic medication classification is provided in Table 7.5.

7.4.2 Pharmacological Actions of Antiemetics

7.4.2.1 Anticholinergic Agents

Natural, synthetic, and semisynthetic substances with a variety of effects on the parasympathetic nervous system and smooth muscle cells are the anticholinergics used in therapeutic use. Anticholinergics have antisecretory properties and reduce salivation, lacrimation, sweating, gastric acid production, and nasal and bronchial secretions. By inhibiting cholinergic transmission from the vestibular nucleus to the

centre of vomiting and blocking muscarinic receptors, the anticholinergics are applied to reduce nausea or vomiting due to motion sickness or in the perioperative phase (Bethesda [2012a](#)).

Adverse Effects Central effects: Headache, memory loss, diminished cognitive function, behavioural abnormalities, anxiety, and sleeplessness at modest doses. Symptoms of agitation, disorientation, delirium, and seizures are core adverse effects that occur at high doses and are on the verge of anticholinergic toxicity.

Peripheral effects: Inhibition of muscular contraction, end-organ targeting, and exocrine glandular secretion by the peripheral parasympathetic neural system (Ghossein et al. [2023](#)).

7.4.2.2 Antihistamines

The area postrema and vomiting centre in the vestibular nucleus are two regions of the central nervous system that contain H1 receptors. Additionally, muscarinic receptors are blocked at the same locations by the anticholinergic properties of a number of antihistamines. The blood–brain barrier is the challenge for antihistamines (Schaefer and Zito [2020](#)).

Adverse Effects It is possible to see gastrointestinal abnormalities, such as constipation and diarrhoea. There are reports of confusion, tiredness, and dizziness. Cimetidine is one particular medication in this class that has a wide variety of potential side effects. Its antiandrogenic properties are correlated with a higher risk of male gynecomastia. It may result in galactorrhea in females (Farzam and O'Rourke [2022](#)).

7.4.2.3 Cannabinoid Receptor Agonists

The cannabinoid receptors CB1 (centrally) and CB2 (peripherally) are involved with antiemesis. It has been demonstrated that dronabinol medication reduces nausea and vomiting induced on by cancer chemotherapy (Bethesda [2012c](#)).

Adverse Effects Unlike the natural cannabinoid, the synthetic agonists of the receptors are frequently linked to serious toxicities, including immunotoxicity, cardiotoxicity, and even mortality (Chung et al. [2021](#)).

7.4.2.4 Phenothiazines

Phenothiazine, a tricyclic aliphatic, functions via postsynaptic inhibition of dopamine receptors. It also produces alpha-adrenergic stimulation and inhibits the effects of histamine and serotonin on the peripheral and central nervous systems. Phenothiazine is prescribed to treat nausea, persistent hiccups, and both acute and chronic psychosis.

7.4.2.5 The Most Common Adverse Reactions Include

Extrapyramidal symptoms, such as tardive dyskinesia, akathisia, dystonia, and parkinsonism, gaining weight, prolonged QTc.

7.4.2.6 Rare Adverse Events

Malignant neuroleptic syndrome, pigmentosa retina, phenotypic and agranulocytosis.

7.4.2.7 Common Less Severe Adverse Events

Urinary retention and reluctance, chapped lips, swollen eyes, constipation, photosensitivity, pruritus, and sedation (Kidron and Nguyen 2021).

7.4.3 5HT₃ Receptor Antagonists

This inhibitory activity of the antagonists causing central and peripheral suppression of serotonin activity, together with a reduction in vagal activity and disruption of pathways in the brain stem's solitary tract nucleus and chemoreceptor trigger zone, appears to be responsible for the antiemetic effects.

Adverse Effects Headache, exhaustion, diarrhoea, and lightheadedness. Dolasetron is prone to drug–drug interactions and has the ability to extend the QTc interval (Bethesda 2012d).

7.4.4 Substance P/Neurokinin 1 Receptor Antagonists

The vomiting reflex is triggered with activation of the neurokinin 1 (NK1) receptor through substance P which is blocked by a substance P antagonist (Bethesda 2012a).

7.4.5 Severe Adverse Reactions

Hives and rash, Stevens–Johnson syndrome

7.4.6 Mild Adverse Reactions

Constipation, fatigue, weakness, sleepiness, diarrhoea, heartburn, gas, nausea, hiccups, stomach discomfort decrease in appetite, itching, fever, headache, hair loss (Bethesda 2012d).

Therapeutic Action of Antiemetic Table 7.6 lists the antiemetic's therapeutic activity.

Table 7.6 Therapeutic action of antiemetic (Bethesda 2012a)

Drugs	Used for
Hyoscyamine	Nausea and antiemetic, functional bowel syndrome, motion sickness, gastrointestinal spasm, and hypermotility
Scopolamine	Antiemetic, antisecretory, and antispasmodic medication to treat gastrointestinal disturbances and spasms, functional bowel syndrome, nausea, motion sickness, duodenal ulcer disease
Cyclizine	The most popular medications for treating motion sickness (nausea, vomiting, and dizziness)
Dimenhydrinate	Used to avoid motion sickness and nausea
Hydroxyzine	Used for nausea and anxiety
Meclizine	Meclizine is generally used to treat vertigo and motion sickness symptoms such as nausea, vomiting, and dizziness
Promethazine	It is extensively used to cure and prevent nausea
Dronabinol	Dronabinol medication has been demonstrated to reduce nausea and vomiting due to cancer chemotherapy
Nabilone	Patients receiving chemotherapy for cancer have demonstrated reduced nausea and vomiting when on nabilone medication
Chlorpromazine	Chlorpromazine is prescribed to treat nausea, persistent hiccups
Prochlorperazine	The main indication for prochlorperazine is the treatment of nausea and vomiting
5-HT3 antagonists	Used off-label occasionally to treat severe vomiting and nausea, especially those caused by acute gastroenteritis and hyperemesis gravidarum
Aprepitant	Used for postoperative nausea and vomiting

Table 7.7 Classification of prokinetic agents, appetite stimulants and digestants

Category	Name of Drugs
Prokinetic agents (serotonin 5-HT ₄ receptor agonists)	Cisapride, alosetron, prucalopride, lubiprostone, domperidone, linaclotide, metoclopramide, plecanatide, tegaserod
Appetite stimulant	Megestrol acetate, oxandrolone, dronabinol
Digestant	Hydrochloric acid, pepsin, papain, pancreatin, diastase, and takadiastase

7.5 Drugs Acting as Prokinetic, Appetizers, and Digestant (RxList 2022; pharmacy180.com n.d.; Bethesda 2012e)

Classification of Prokinetic Agents, Appetite Stimulants and Digestants Table 7.7 classifies prokinetic agents, appetite stimulants, and digestants.

7.5.1 Pharmacological Actions of Prokinetic Agents, Appetizers, and Digestant

7.5.1.1 Serotonin 5-HT₄ Receptor Agonists

The production of serotonin by specialised enterochromaffin cells in the gut mucosa is crucial for the intestine's regular motility and secretory function. Potent prokinetic drugs known as serotonin type 4 (5-HT₄) receptor agonists enhance gastric emptying, minimise oesophageal reflux, and stimulate intestinal peristalsis.

Adverse Effects Nausea, vomiting, vertigo, drowsiness, headache getting worse, stiffness or discomfort in the chest, throat, or jaw, chest pain, flushing, chills, stomach ache, dysphagia, dyspepsia, asthenia, and back discomfort.

7.5.1.2 Appetite Stimulant

Medication known as appetite stimulants is administered to enhance the nutritional status and boost appetite. Neuropeptide Y is a peptide that stimulates hunger in the brain and is produced, released, and transported by appetite stimulants.

Adverse Effects Elevated blood pressure, mood alteration, rash, sweating, and hot flashes, amenorrhea, menstrual disturbances, impotence, bloating, flatulence, regurgitation, emesis, spitting, gaining weight, deep vein thrombosis, pulmonary embolism, thrombophlebitis, low RBC count, asthenia, and adrenal insufficiency.

Overdose May Cause Cough, shortness of breath, unsteady gait, chest pain.

7.5.1.3 Digestants

These compounds assist in the process of food digestion. Many combination formulations of proteolytic, amylolytic, and lipolytic enzymes are available. They are useful frequently, but only when their GIT elaboration is inadequate.

Adverse Effects Pancreatin side effects include nausea, diarrhoea, and hyperuricaemia.

Therapeutic Action of Prokinetic Agents, Appetite Stimulants, and Digestants Table 7.8 describes the prokinetic drugs, appetite stimulants, and digestants' therapeutic actions.

Table 7.8 Therapeutic action of prokinetic agents, appetite stimulants, and digestants

Drugs	Used for
Cisapride	Increases peristalsis and intestinal tone (withdrawn from market)
Tegaserod	Prokinetic agent
Megestrol acetate	Stimulate appetite (Manikkuttiyl and Nguyen 2021)
Oxandrolone	Use for weight gain
Digestants (Bestozyme: Alfa-amylase, papain, dimethicone Alvizyme: Pancreatin, simethicone Lupizyme: Pepsin, diastase, vit B1, B2, B6, B12, pantothenol, nicotinamide Digiplex: Diastaseg, pepsin, vit B1, vit B2, vit B6, nicotinamide, pantothenyl alcohol, vit B12 Takadiastase: Takadiastase Digenzymes: Pepsin, diastase, papain Dizec: Pancreatin, sodium tauroglycocholate, methylpolysiloxane Ralcrizyme: Pancreatin, pepsin, bile extract, diastase, methylpolysiloxane Pepsinozyme: Diastase, pepsin, papain, vit B1, vit B2, niacinamide, activated charcoal)	Used for digestion of food

7.6 Drugs for Diarrhoea

Diarrhoea In children under five, diarrhoea is the second cause of worldwide mortality, according to the Centres for Disease Control and Prevention, characterised by loose stool, cramping in the abdomen, frequent bowel movements, nausea, and dehydration (The Health Site 2022).

7.6.1 Cause for Diarrhoea (National Institute of Diabetes and Digestive and Kidney Diseases n.d.-a)

- Infections
 - Infectious viruses
 - Bacterial infections
 - Parasitic infections
- Travelers' diarrhoea (caused by consuming food or water that has been infected by bacteria)
- Food allergies and intolerances
- Side effects of medicines
- Digestive system issues: Celiac disease, functional gastrointestinal (GI) diseases, overgrowth of bacteria in small intestine, Crohn's disease, ulcerative colitis
- Surgical procedures for the abdomen

7.6.2 Types of Diarrhoea (The Health Site 2022)

There are three main classifications for diarrhoea. They consist of:

- **Acute diarrhoea:** Defined by loose, watery stools which fade away on its own when enough fluids are replaced.
- **Persistent diarrhoea:** The diarrhoea lasts for 2–4 weeks.
- **Chronic diarrhoea:** This type of diarrhoea lasts for more than 4 weeks.

Classification of Antidiarrheal Agents Table 7.9 lists antidiarrheal agents according to their classification.

7.6.3 Pharmacological Actions of Antidiarrheal Agents

7.6.3.1 Opiates and Opioids

By lowering neuronal excitability, mu and delta opioid agonists prevent the myenteric plexus from releasing acetylcholine and prevent peristaltic contractions produced on by distention. Nonpropulsive movement patterns become more prevalent and muscle tone is changed. Human studies indicate that the upper intestine's capacity to hold onto fluid may have increased due to relaxation of circular muscle as a result, transit is delayed, and the absorption of fluid via intestinal transport mechanisms takes prolonged. Delta opiate agonists have the potential to suppress mucosal secretion and alleviate diarrhoea (Schiller 2017).

Adverse Effects Respiratory depression, physical dependency, nausea, vomiting, constipation, sedation, and dizziness (Benyamin et al. 2008).

Table 7.9 Classification of antidiarrheal agents (Bethesda2012a; Schiller 2017)

Category	Name of drugs
Opiates	Opium, eluxadolone, difenoxin, codeine, paregoric, morphine, loperamide, diphenoxylate
5-HT ₃ antagonist	Alosetron
α 2-Adrenergic agonist	Clonidine
Enkephalinase inhibitor	Racecadotril
Enterocyte apical membrane chloride channel inhibitors	Crofelemer
Somatostatin and analogs	Octreotide, pasireotide, lanreotide
Intraluminal agents	Clays, kolin
Fiber	Psyllium
Bile acid-binding resins	Cholestyramine
Oral rehydration solutions	

7.6.3.2 5-HT₃ Antagonists

A particular neurotransmitter that contributes to intestinal peristalsis through 5-HT₃ receptor on the afferent neurons in the enteric nervous system. Alosetron treats irritable bowel syndrome with diarrhoea, targets this receptor (Schiller 2017).

Adverse Effects Headache, exhaustion, diarrhoea, and lightheadedness (Bethesda 2012d).

7.6.3.3 Alpha-Adrenergic Agonists

The intestinal mucosa's absorption of salt and chloride is improved by catecholamines and motility is interfered through α_2 receptors on enterocytes and the enteric nervous system (Schiller 2017).

Adverse Effects Reduced venous compliance, increased cardiac afterload, and decreased renal perfusion. Renal failure has been reported in particular in events of phenylephrine (Dean II and Reddivari 2020).

7.6.3.4 Somatostatin and Somatostatin Analogues

The endocrine cells when release somatostatin which has paracrine actions suppress gastrointestinal function. Somatostatin acts on the digestive system and it has been tested for numerous different diarrheal illnesses (Schiller 2017).

Adverse Effects Discomfort and erythema at the injection site, gastrointestinal (GI) abnormalities, including gallstones or biliary sludge, diarrhoea, abdominal pain, nausea, and vomiting, and altered glucose metabolism (Grasso et al. 2015).

7.6.3.5 Enterocyte Apical Membrane Chloride Channel Inhibitors

The chloride ion is secreted through apical channels of enterocytes which is controlled by cystic fibrosis transmembrane conductance regulator (CFTR). Additionally, enterotoxins, peptides, and neurotransmitters promote the release of second messengers into the cytoplasm of the enterocyte, such as calcium and cyclic AMP, these channels open.

7.6.3.6 Intraluminal Agents

Minerals with fine grains called clays frequently include silicates. Kaolin and activated attapulgite are such examples. The attapulgite has the ability to absorb approximately eight times of water of its own weight. Diasorb composition contains attapulgite.

7.6.3.7 Bile Acid-Binding Resins

Constipation is a common side effect of bile acid-binding resins for people receiving hypercholesterolemia treatment. As a result, various substances have been attempted

to treat diarrhoea. It was thought that intraluminal bile acid or bacterial toxins bound to resin might lessen diarrhoea. Bile acid binders have been the subject of increasing research as a therapy for chronic idiopathic diarrhoea. Patients with chronic *C. difficile* diarrhoea are treated with these drugs (Schiller 2017). Bile acids and cholestyramine bond to form an insoluble substance that is eliminated in the stools and cannot be reabsorbed (<https://www.ncbi.nlm.nih.gov/books/NBK548431/> 2017).

Adverse Effects Bile acid sequestrants have few systemic side effects since they are not absorbed in the gastrointestinal system. Constipation, bloating, stomach pain, vomiting, heartburn, indigestion, loss of appetite, and upset stomach are among the most frequent gastrointestinal side effects (Lent-Schochet and Jialal 2022).

7.6.3.8 Fiber

It has been suggested that psyllium and other medical fibre supplements are the remedies that stiffen loose stools and soften hard ones (Schiller 2017).

Adverse Effects Bloating, gas, feeling overly full, cramping in the stomach, constipation or diarrhoea, dehydration, inadequate absorption of some essential nutrients, weight gain or loss, nausea, and in rare instances, intestinal blockage (Medical News Today 2022).

7.6.3.9 Oral Rehydration Solutions

Since most cases do not alter nutrient-linked salt absorption, sodium and water losses can be compensated for by enhancing amino acid-sodium or glucose-sodium cotransport by giving nutrients, fluid, and electrolytes orally. While this method can rectify fluid and electrolyte depletion, it may not decrease the amount of faeces produced (Schiller 2017).

Therapeutic Action of Antidiarrheal Agents Table 7.10 provides the therapeutic activity of antidiarrheal drugs.

Table 7.10 Therapeutic action of antidiarrheal agents (Bethesda 2012a)

Drugs	Used for
Loperamide	Treat acute diarrhoea
Morphine	Used with deodorised opium tincture for chronic diarrhoea
Cholestyramine	Not formally approved for treating diarrhoea
Crofelemer	Treat non-infectious diarrhoea in patients receiving antiretroviral therapy for HIV/AIDS
Psyllium	Watery diarrhoea
Oral rehydration solution	Maintain stool losses and replace dehydration

Table 7.11 Classification of laxatives and purgatives (Bashir and Sizar 2019)

Category	Name of drugs
Bulk-forming laxatives	Psyllium, dietary fibre, methylcellulose
Osmotic agents	Milk of magnesia, sorbitol, polyethylene glycol, lactulose
Lubricants	Mineral oil
Prokinetic agents	Cisapride, tegaserod
Stimulants	Cascara, senna, sodium picosulfate, Bisacodyl
Surface active agents	Docusate
Guanylate cyclase agonist	Linacotide
Chloride channel activator	Lubiprostone

7.7 Drugs for Constipation

7.7.1 Laxatives and Purgatives

Patient education, behaviour modification, dietary adjustments, and laxative medication are all part of the treatment plan for a patient suffering from persistent constipation (Bashir and Sizar 2019). A class of medications known as laxatives either reduces the consistency of the faeces or speeds up their passage. While purgatives cause a more fluid evacuation, they are mostly used to relieve constipation.

Classification of Laxatives and Purgatives Table 7.11 provides an appropriate classification of laxatives and purgatives.

7.7.2 Pharmacological Actions of Laxatives and Purgatives (Bashir and Sizar 2019)

Bulk-forming laxatives: These substances make stools heavier and more uniform while retaining fluid. For bulk-forming agents to function, it is crucial to consume sufficient amounts of water. In turn, dehydration causes bloating and may result in intestinal blockage.

Osmotic agents: This class of medications attracts water into the colon's lumen and is poorly absorbed.

Adverse Effects Vomiting, diarrhoea, bloating, and nausea. Osmotic agents, such as magnesium, can lead to disruptions in metabolism, particularly when there is renal involvement. Magnesium excretion is also dependent on renal function; therefore, when renal function is compromised, magnesium should be used with caution.

Prokinetic agents: Prokinetic substances function as 5-hydroxytryptamine receptor agonists. They function by activating intrinsic neurons, causing mucosal secretion, and releasing acetylcholine.

Adverse effects: Headache, nausea, and diarrhoea.

Lubricants: Mineral oil lubricates the whole gut, facilitating the transit of faeces.

Table 7.12 Therapeutic action of laxatives and purgatives (Bashir and Sizar 2019)

Drugs	Used for/therapeutic duration
Psyllium	Up to three times a day, one tablespoon can be taken orally
Methylcellulose	For bulk formation, one tablespoon powder or 2000 mg fibre caplets can be administered three times a day
Lactulose	One dose per day of 10–20 g (15–30 mL) is recommended for constipation; this can be raised to 40 g (60 mL) if necessary. For hepatic encephalopathy, take 30–40 g (30–45 mL) orally every hour to cause a rapid bowel movement
Tegaserod	Prior to its withdrawal from the market, the usual suggested dosage was 2–6 mg twice day; for the treatment purpose of irritable bowel syndrome and constipation
Mineral oil	Used as a lubricant; administered orally in single or split doses up to 45 mL in a 24-h period and rectally up to 118 mL in a single dosage
Linacotide	It comes in oral capsule form in dosages of 72, 145, and 290 mcg. Patients with idiopathic constipation that is chronic are administered 72–145 mcg once a day. 290 mcg is used orally once daily for individuals with constipation and IBS
Lubiprostone	For constipation brought on by opioids, 24 mcg is taken twice a day orally

Adverse effects: Mineral oil can lead to lipoid pneumonia and aspiration.

Stimulants: They promote intestinal secretions and motility by activating the myenteric and Auerbach plexuses and lessen the amount of water absorbed from the colon's lumen. Sodium picosulfate (SPS), cascara, senna, and bisacodyl are typical examples. Herbal drinks and treatments often contain cascara and senna.

Adverse effects: Abdominal pain is a known side effect of stimulant laxatives.

Surface active agents: Water and lipids can enter the stool because docusate reduces surface tension.

Guanylate cyclase agonist: By inducing cGMP, linacotide triggers the release of water and electrolytes into the lumen through CFTR.

Adverse effects: On rare occasions, secretagogues such as linacotide might induce diarrhoea.

Chloride channel activator: The chloride channel activator lubiprostone causes the secretion of water and chlorides into the stool, resulting in a softer consistency.

Therapeutic action of laxatives and purgatives: Table 7.12 provides a summary of the laxative and purgative therapeutic actions.

7.8 Drugs Used as Liver Protective and in Gallstones

7.8.1 Hepatoprotective Agents

The largest and most intricate internal organ in living systems is the liver. It is essential for the excretion of numerous endogenous and foreign substances during detoxification. One of the most common and deadly causes of illness and death is liver disease. Because they actively participate in the supplementary therapy of liver disease, hepatoprotective drugs have received attention (Maqbool et al. 2019).

Table 7.13 Classification of liver protective agents (Li et al. 2022)

Category	Name of drugs
Antioxidant	Silymarin, bicyclol
Diet supplement (amino acid derivative)	L-carnitine
Detoxification drugs	GSH (glutathione), N-acetylcysteine
Anti-inflammatory drugs	Glycyrrhizic acid preparation

Table 7.14 Classification of gallstone dissolution agents ([https://www.niddk.nih.gov/health-information/digestive-diseases/gallstones/treatment#:~:text=Ursodiol%20link%20\(Actigall\)%20and%20chenodiol](https://www.niddk.nih.gov/health-information/digestive-diseases/gallstones/treatment#:~:text=Ursodiol%20link%20(Actigall)%20and%20chenodiol) 2017; Guarino et al. 2013)

Category	Name of drugs
Gallstone dissolution agents	Chenodiol, ursodiol

Classification of Liver Protective Agents Table 7.13 provides a classification of liver protecting agents.

Gallstones Gallstones are tough, pebble-like deposits that form in the gallbladder and are typically composed of bilirubin or cholesterol. A person may experience abrupt discomfort when gallstones obstruct bile ducts; in this case, immediate medical assistance is required. They may lead to complications if untreated (National Institute of Diabetes and Digestive and Kidney Diseases 2017).

Classification of Gallstone Dissolution Agents Table 7.14 provides a classification of agents that dissolve gallstones.

7.8.2 Pharmacological Actions of Hepatoprotective Agents

7.8.2.1 Detoxification Agents

N-acetylated derivative of L-cysteine (L-Cys) (NAC) is a precursor of glutathione. Its helps in DNA molecule protection, micro-vessel dilatation, anti-oxidation, and anti-inflammation.

Adverse Effects Mood changes such as mood swings, depression, anxiety, and agitation, body changes such as flu-like symptoms, nausea, shaking, headaches, craving (American Addiction Centers 2019).

7.8.2.2 Anti-inflammatory Drugs

Glycyrrhizin acid (produced from glycyrrhiza glabra plant roots) is a triterpenoid chemical which is broken down into glucuronic acid and glycyrrhizin acid in vivo by the enzyme glucuronidase. It helps treat drug-induced liver injury (DILI) by acting as an antioxidant, an anti-inflammatory, and a hormone substitute while shielding the liver from inflammatory damage.

Adverse Effects Its high consumption results in hypermineralocorticoidism, characterised by potassium loss and salt retention, elevated blood pressure, oedema, and renin-angiotensin-aldosterone system depression (Størmer et al. [1993](#)).

7.8.2.3 Antioxidant

Bicyclol Bicyclol's pharmacological action is primarily attributed to its suppression of inflammatory regulatory factors induced by liver injury, including NF- κ B, IL-1 β , IL-18, TNF- α , TGF- β 1, and others. It also decreases the generation of reactive oxygen species (ROS) which in turn reduces the consumption of antioxidants like GSH.

Silymarin Initially identified in 1968, silymarin is a flavonoid generated mostly from flavonols derived from lignin, such as silydianin, silychristin, silybin, and isosilybin, with silybin being the most active component. Silymarin has the ability to bind iron a little bit, which prevents human hepatocyte glutathione decrease (Karimi et al. [2011](#)).

Adverse Effects Gastrointestinal problems (e.g., diarrhoea, nausea, abdominal bloating, dyspepsia, abdominal bloating, flatulence, abdominal fullness or pain, anorexia, and changes in bowel habits), skin reactions (rash, urticaria, eczema and pruritus), neuropsychological conditions (e.g., insomnia, asthenia, and malaise), arthralgia, rhinoconjunctivitis, impotence, headache, anaphylaxis (Mulrow et al. [2000](#)).

7.8.2.4 Pharmacological Action of Gallstone Dissolution Agents

The chemical is known as ursodeoxycholic acid (UDCA) or ursodiol. By inhibiting cholesterol absorption in the intestine and cholesterol release into bile, UDCA, in therapeutic doses, significantly lowers biliary cholesterol saturation by 40–60%. UDCA reduces the toxicity of bile acids, which results in cholestasis through the reduction of the small intestine's ability to absorb hydrophobic endogenous bile acids, the exertion of a choleric function that causes the bile ducts to dilute endogenous bile salts, and the protection of hepatocytes against toxic bile acids.

Adverse Effects Bloody or cloudy urine, chest pain, bladder pain, skin rash or itching all over the body, rapid heartbeat, burning or painful urination, frequent urinal urges, dizziness, indigestion, severe nausea, lower back or side pain, stomach pain, black, tarry stools, chills or fever, pinpoint red spots on the skin, cough, vomiting, unusual bleeding or bruising, ulceration, or white patches within the mouth or on the lips, weakness or unusual tiredness, sore throat, or swollen glands sores (Mayo Clinic [2023](#)).

7.9 Conclusions

This chapter includes the pharmacology of the gastrointestinal tract enlisting the different category of drugs that are used in the diseases affecting the GI tract along with their mechanism of action, pharmacological actions, uses, and adverse effects. This chapter has summarized the facts about the diseases altering the gastrointestinal tract.

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Pharmacotherapy of Microbial Diseases

8

Pranabesh Chakraborty and Dipesh Chakraborty

Abstract

Microbial diseases comprise a significant portion of the global disease burden. Starting from moderate flulike condition to serious life-threatening conditions can be resulted due to microbial infection. Very evidently so it is a great matter of interest for the pharmaceutical scientists. Microbial diseases involve a large number of drugs as depending upon the nature of disease and the causative organisms. The drugs which target the microbes vary largely in chemical structure, mechanism of action, spectrum of activity, or specificity toward specific microorganisms. This chapter will build a strong foundation of the basic biomolecular mechanism followed by drugs to counter the microbial diseases as well as the pathway by which the microbes cause diseases in body.

Keywords

Pharmacotherapy · Antibiotics · Microbial diseases · Side effects

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Abbreviations

Ala	Alanine
ART	Antiretroviral therapy
BT	Borderline tuberculoid
CCR5	C-C chemokine receptor type 5
CD4	Clusters of differentiation 4
Cys	Cysteine
DDS	Sulfones-dapsone
DHFR	Dihydrofolate reductase
DNA	Deoxyribonucleic acid
DNA	Deoxyribonucleic acid
EF-G	Elongation factor G
ENL	Erythema nodosum leprosum (ENL)
FA	Folic acid
GABA	Gamma-aminobutyric acid (GABA)
HIV	Human immunodeficiency virus
HSV	Herpes simplex virus
IRIS	Immune reconstitution inflammatory syndrome
KatG	Catalase-peroxidase
LDL	Low-density lipoprotein
MBL	Multibacillary leprosy
MDR	Multidrug resistant
mRNA	Messenger RNA
NAD	Nicotinamide adenine dinucleotide
NADP	Nicotinamide adenine dinucleotide phosphate
PABA	Para-aminobenzoic acid
PAS	Para-aminosalicylic acid
PBL	Paucibacillary leprosy
PBPs	Penicillin-binding proteins
PfEMP1	<i>P. falciparum</i> erythrocyte membrane protein 1
PFOR	Pyruvate:ferredoxin oxidoreductase
PTC	Peptidyl transferase center
RNA	Ribonucleic acid
RNAP	DNA-dependent RNA polymerase
rRNA	Ribosomal RNA
SOS	Son of Sevenless
TB	Tuberculosis
tRNA	Transfer RNA
TT	Tuberculoid
VLDL	Very low-density lipoprotein

8.1 Introduction to Pharmacotherapy in Microbial Diseases

Pharmacotherapy or drug therapy can be defined as the treatment approach involving one or more pharmaceutical drug compound for both the prevention and cure of diseases.

The term “chemotherapy,” which refers to the administration of particular medications that specifically inhibit or eliminate the pathogenic microbe, is often used to describe this kind of therapy, working against a specific target without affecting the host as such.

The principle lying underneath the medication’s effect on a crucial cell component of any microorganism is known as selective microbial toxicity. Now that component can be anything but has to be is a must for the bacteria to maintain its cellular integrity and functionality. The few best targets against bacteria are bacterial cell walls and different metabolic processes like folate synthesis, etc. While targeting the different proteins or pathways or may be any structural feature of microbes, it should be kept in mind that none of them should be found in the host; otherwise, it can seriously affect the host.

Antibiotics are substances produced by microorganisms that, when present in extremely low concentrations, have the specific ability to either stop the growth of other microorganisms or kill them but not the parent microorganism. The definition is not inclusive of the biological molecules produced by the body’s immune system inside the body.

8.2 Classification of Antimicrobial Medication

Numerous attributes can be used to categorize antimicrobial medications:

8.2.1 Classification on the Basis of Chemical Nature and Their Mechanism of Action

8.2.1.1 Sulfonamides and Related Drugs

Many bacteria generate folic acid (FA) on their own, incorporating para-aminobenzoic acid (PABA) that they take up from the media. Sulfonamides, which resemble PABA structurally, prevent bacterial folate synthase from working, preventing the synthesis of folic acid and impairing a number of vital metabolic processes. In order to create dihydropteroic acid, which subsequently joins with glutamic acid to make dihydrofolic acid, sulfonamides competitively prevent the combining of PABA and pteridine residue. Furthermore, because the sulfonamide shares chemical properties with PABA, it may combine with it to create a modified form of folate that is harmful to the metabolism. Examples: Sulfadiazine, sulfones-dapsone, and para-aminosalicylic acid.

8.2.1.2 Diaminopyrimidine Class of Drugs

A pyrimidine ring is replaced by two amine groups in the diaminopyrimidine class of organic compounds. They work as inhibitors against the enzyme dihydrofolate reductase, which is essential for the synthesis of DNA (Baccanari and Kuyper 1993). Examples: Trimethoprim, pyrimethamine.

8.2.1.3 Quinolones

These are active against type II topoisomerases, preventing synthesis, cell division, and DNA replication (Fàbrega et al. 2009). Examples: Norfloxacin, nalidixic acid, ciprofloxacin, etc.

8.2.1.4 β -Lactam Antibiotics

In case of β -lactam antibiotics, these are bactericidal agents that work by covalently attaching to penicillin-binding proteins (PBPs) of bacteria to stop them from forming cell walls. Penicillin-binding proteins (PBPs) are essential enzymes which essentially contribute to the last phases of peptidoglycan crosslinking in bacteria, both Gram-positive and Gram-negative (Bush and Bradford 2016). Examples: Penicillins, cephalosporins, monobactams, and carbapenems.

8.2.1.5 Tetracyclines

In order to stop aminoacyl-tRNA from attaching to the acceptor domain of the mRNA-ribosome complex, tetracyclines specifically inhibit the 30S ribosomal subunit. If this mechanism is interrupted, a cell cannot continue to operate normally and cannot divide or proliferate further. This kind of tetracycline impairment is what characterizes them as “bacteriostatic” (Nazarian and Akhondi 2023). Examples: Oxytetracycline, doxycycline, etc.

8.2.1.6 Nitrobenzene Derivative

Although it is bacteriostatic, high concentrations of chloramphenicol have the potential to be bactericidal. This antibiotic exhibits broad-spectrum of action and is effective against both anaerobic and Gram-positive/Gram-negative bacteria, by attaching to the 50S ribosomal subunit and obstructing the bacterial protein from being formed, chloramphenicol inhibits the synthesis of proteins. Chloramphenicol inhibits tRNA's ability to connect to the A-site on the 50S ribosome.

8.2.1.7 Aminoglycosides

Aminoglycosides bind to the A-site on the 30S ribosome's 16S ribosomal RNA to prevent synthesis of proteins. All members of the aminoglycoside class alter the conformation of the A-site, despite having varying specificities for various A-site regions. Because of this interaction, when the aminoacyl transfer RNA is delivered, the antibiotic causes codon misreading, which in turn promotes mistranslation. This leads to error-prone protein synthesis, which makes it possible for the wrong amino acids to combine to form a polypeptide that is then released to harm other parts of the cell, including the membrane (Krause et al. 2016). Examples: Streptomycin, gentamicin, amikacin, etc.

8.2.1.8 Macrolide Antibiotics

Protein synthesis by bacteria is inhibited by macrolides by binding the bacterial 50S ribosomal subunit (Krause et al. 2016), macrolides stop the synthesis of new proteins. The medication prevents the peptidyl transferase enzyme from binding to the tRNA and adding the subsequent amino acid, which stops mRNA translation and, more precisely, the peptide chain from growing. Since most, if not all, bacterial species share a high degree of conservation in their ribosomal structure, bacteria are thought to have broad-spectrum structures (Vázquez-Laslop and Mankin 2018). Examples: Erythromycin, clarithromycin, azithromycin, etc.

8.2.1.9 Lincosamide Antibiotics

When lincosamides attach to the 50S ribosome, they prevent the synthesis of new proteins. Combination therapy should be avoided because the binding sites of these antimicrobials are similar to those of chloramphenicol and macrolides, which reduce the overall efficacy when used concurrently. Examples: Lincomycin, clindamycin.

8.2.1.10 Glycopeptide Antibiotics

Glycopeptide antibiotics target lipid II to prevent Gram-positive bacteria from producing peptidoglycans. This stops the lipid transporter bactoprenol phosphate, necessary for both wall teichoic acid synthesis and peptidoglycan biosynthesis (Singh et al. 2017). Examples: Vancomycin, teicoplanin.

8.2.1.11 Oxazolidinone

By attaching to the P-site of ribosomal 50S subunit, oxazolidinones prevent the formation of new proteins. Oxazolidinone activity is unaffected by resistance to other protein synthesis inhibitors; however, there have been isolated reports of oxazolidinone resistance cases that are linked to 23S rRNA changes during treatment (Bozdogan and Appelbaum 2004). Examples: Linezolid, posizolid, radezolid, etc.

8.2.1.12 Polypeptide Antibiotics

The negatively charged bacterial membrane is contacted by the cationic antimicrobial peptides (AMPs) which increase permeability of membrane and cause cell membrane breakage and release of content. This results in antibacterial activity. When AMPs approach the cytoplasmic membrane via the microbial membrane's electrostatic interaction, they attach to it and engage with the plasma membrane's anionic constituents. In order to enhance the interaction between the anionic lipid membrane and an aqueous solution, the α -helical AMPs cling to the membrane and transform its disordered structure into an amphiphilic α -helical structure. Examples: Polymyxin B, colistin, bacitracin, tyrothricin (Zhang et al. 2021).

8.2.1.13 Nitrofurantoin Derivatives

By reducing unstable metabolites via the flavoprotein nitrofurantoin reductase, nitrofurantoin is activated inside bacteria and causes disruption of ribosomal RNA, DNA, and other intracellular components. It has bactericidal properties, particularly

against bacteria found in acidic urine (Hamoonga [n.d.](#)). Examples: Nitrofurantoin and furazolidone.

8.2.1.14 Nitroimidazoles

They are thought to prevent DNA synthesis and have bactericidal properties. Intestinal and extraintestinal amoebiasis, bacterial vaginosis, intestinal and extraintestinal amoebiasis, protozoal infections (e.g., trichomoniasis and giardiasis), and surgical prophylaxis are among the conditions for which they are indicated for treatment (Zaidi and Weier [n.d.](#)). Examples: Metronidazole, tinidazole, etc.

8.2.1.15 Nicotinic Acid Derivatives

The hepatocyte enzyme diacylglycerol acyltransferase-2, which is necessary for the synthesis of triglycerides, is directly and non-competitively inhibited by niacin. Niacin-induced inhibition of triglyceride synthesis causes a decrease in LDL and VLDL particle secretion as well as an acceleration of intracellular hepatic apo B degradation. According to recent in vitro cell culture research and previous human kinetic studies, niacin mainly prevents apo A-I (as opposed to apo A-II) from being catabolized in the liver, but it has no effect on scavenger receptor BI-mediated cholesterol esters (Kamanna and Kashyap [2008](#)). Examples: Isoniazid, pyrazinamide.

8.2.1.16 Polyene Antibiotics

It binds to ergosterol in fungal cell membranes to create aqueous pores that encourage intracellular ion leakage and interfere with membrane-potential-dependent active transport processes. Examples: Nystatin, amphotericin-8, hamycin.

8.2.1.17 Azole Derivatives

The ergosterol biosynthesis pathway requires the essential enzyme 14 α -demethylase, which is dependent on cytochrome P450 and is inhibited by azole antifungal drugs like ketoconazole, fluconazole, and itraconazole (Renau et al. [1998](#)). Examples: Fluconazole, ketoconazole, miconazole, and clotrimazole.

8.2.1.18 Other Drugs

Spectinomycin, rifampin, cycloserine, viomycin, ethambutol, clofazimine, griseofulvin, sodium fusidate (Table [8.1](#) shows classification of antimicrobial drugs).

8.2.2 Classification on the Basis of the Primary Activity of the Drugs on Different Pathogens

Drugs which mainly functional as **antibacterial** are penicillins, erythromycin, aminoglycosides, fluoroquinolones, etc., as **antifungals** are amphotericin B, griseofulvin, ketoconazole, etc., and **antiviral** drugs such as acyclovir, zidovudine, etc., antiprotozoal drugs such as metronidazole, chloroquine, etc., anthelmintics such as diethylcarbamazine, pyrantel, mebendazole, etc.

Table 8.1 Classification of antimicrobial drugs based on chemical nature (Khan [n.d.](#))

Chemical nature	Drugs	Mechanism of action
Sulfonamides and related drugs	Sulfadiazine, dapsone, Para-aminosalicylic acid	Inhibits bacterial folate synthase and prevents folic acid formation
Diaminopyrimidines	Trimethoprim, pyrimethamine	Inhibits dihydrofolate reductase
Quinolones	Nalidixic acid, norfloxacin, ciprofloxacin	Inhibits topoisomerases II
Beta-lactam antibiotics	Penicillins, cephalosporins, monobactams, and carbapenems	Binds to proteins called penicillin-binding proteins (PBPs), which stop the formation of bacterial cell walls
Tetracyclines	Oxytetracycline, doxycycline	Suppresses the production of new proteins by binding to the 30S ribosomal subunit
Nitrobenzene derivative	Chloramphenicol	Suppresses the production of new proteins by binding to the 50S ribosomal subunit
Aminoglycosides	Streptomycin, gentamicin, amikacin, etc.	Binds A-site on the 30S ribosome's 16S ribosomal RNA to prevent protein synthesis
Macrolide antibiotics	Erythromycin, clarithromycin, Azithromycin, etc.	Suppresses the production of new proteins by binding to the 50S ribosomal subunit
Lincosamide antibiotics	Lincomycin, Clindamycin, etc.	Suppresses the production of new proteins by binding to the 50S ribosomal subunit
Glycopeptide antibiotics	Vancomycin, teicoplanin	Stops lipid transporter bactoprenol phosphate, thus preventing cell wall teichoic acid and peptidoglycan biosynthesis
Oxazolidinone	Linezolid, posizolid, radezolid, etc.	Binds to the 50S ribosomal subunit's P-site and prevents the production of new proteins
Polypeptide antibiotics	Polymyxin B, colistin, etc.	Increases membrane permeability and causes cell membrane lysis
Nitrofurantoin derivatives	Nitrofurantoin and furazolidone	Causes disruption of ribosomal RNA, DNA, proteins, and other intracellular components
Nitroimidazoles	Metronidazole, tinidazole, etc.	Prevents DNA synthesis
Nicotinic acid derivatives	Isoniazid, pyrazinamide, etc.	Inhibition of diacylglycerol acyltransferase-2
Polyene antibiotics	Nystatin, amphotericin-8, etc.	Binds ergosterol in fungal cell membranes to create aqueous pores
Azole derivatives	Miconazole, clotrimazole, etc.	Inhibits cytochrome P450-dependent 14 α -demethylase and prevents ergosterol synthesis
Others	Rifampin, spectinomycin, sodium fusidate, etc.	Miscellaneous mechanisms are followed

8.2.3 On the Basis of the Spectrum of Activity

It can again be classified into broad-spectrum antibiotics (tetracyclines, chloramphenicol) and narrow-spectrum antibiotics (penicillin G, streptomycin, erythromycin, etc.).

8.2.4 On the Basis of the Fate of the Microorganism After the Action of Drugs

Bacteriostatic are those who inhibit the growth of bacteria and **Bactericidal** are those who can kill the bacteria and get rid of the disease. Examples include sulfonamides, erythromycin, tetracyclines, etc. as bacteriostatic and penicillins, cephalosporins, aminoglycosides as bactericidal.

Certain mainly bacteriostatic medications, such as erythromycin and nitrofurantoin, in higher concentrations (as obtained in the urinary tract) may become bactericidal. However, in some situations, certain bactericidal medications—like streptomycin and cotrimoxazole—may just be static.

Natural sources yielded antibiotics: Fungi, Bacitracin, Penicillin, Cephalosporin, Bacteria, Polymyxin B, etc.

8.2.5 Classification on the Basis of Mechanism of Action of Antibacterial Drug

8.2.5.1 Inhibit Cell Wall Synthesis

Stage I of Cell Wall Synthesis (Cytoplasmic Stage) Targeting Molecules

Both Gram-positive and Gram-negative the bacteria require alanine racemase as a very important component for the biosynthesis of cell wall peptidoglycan (Wei et al. 2016), and d-alanine-d-alanine ligase helps forming the peptidoglycan precursor UDP-N-acetylmuramoyl pentapeptide (Trivedi et al. 2018). Compound that act as inhibitor of d-Ala racemase and d-Alanine-d-Alanine ligase, like d-cycloserine (seromycin, 1). It is a cyclic small molecule that resembles d-alanine and can inhibit alanine racemase and d-Ala-d-Alanine ligase (Lambert and Neuhaus 1972).

Fosfomycin inhibits enzyme MurA. It can inhibit the initial stage of cell wall biosynthesis by binding to UDP-N-acetylglucosamine-3-enolpyruvyl transferase (MurA) and imitating the specific substrate phosphoenolpyruvate. By forming a thioether bond with the crucial residue Cys115 in the active site of MurA, the antibiotic inhibits the enzyme. *Enterococcus faecalis* and *Escherichia coli* urinary tract infections are the main conditions for which oral fosfomycin is used (Sarkar et al. 2017).

Stage II (Membrane-Associated Stage) Targeting Molecules

Numerous **uridyl peptides** have been identified as competitive inhibitors of **MraY**, e.g., tunicamycin (targets bacterial translocase I) (Zhang et al. 2021), liposidomycins, and mureidomycin (Brandish et al. 1996). Comprising the entire peptidoglycan precursor subunit, **Lipid II** is a crucial constituent of the cell wall biosynthesis pathway. Nisin and ramoplanin are two examples of medications that function by preventing lipid II.

Molecules Aimed at Stage III

β -lactam rings imitate the pentapeptide terminal's d-Ala-d-Ala moiety, leading PBPs to mistake them for their substrate. The PBPs active site's serine residue targets the carbonyl of the β -lactam ring, thus causing cleaving of the ring and creating an inactivated acyl-enzyme with a protracted half-life. The β -lactam entirely prevents a subsequent nucleophilic attack on the active site because it lacks a leaving group. This prevents these enzymes from initiating the process of peptidoglycan layer crosslinking. Even though the cell wall's biosynthesis is stopped, the murein sacculus's autolysis proceeds, compromising this element and eventually lysing the cell (Walsh 2003).

8.2.5.2 Cause a Change in Bulk Property of the Cell Membrane

Agents that target phospholipids can change the properties of membranes in a number of ways. Changing the bulk physical properties is one such method. Agents that modify the bulk properties of the membrane impact one or more of the bulk properties rather than binding to a particular membrane component.

Biological membranes contain lipids that are enriched in specific domains rather than being evenly distributed throughout the membrane. For instance, this distribution can be altered by combining cationic peptides with multiple positive charges with anionic lipids. For the bacteria, this could be detrimental because it inhibits the lipids' ability to interact with other molecules in the cell membrane. We call this clustering.

When biological membranes bend from a flat position, they can acquire a physical curvature. Since the membrane is made up of two layers, for it to bend, each monolayer would need to take on an opposing type of curvature. The intrinsic curvature of each monolayer in the bilayer exists in addition to the physical curvature. It can be a good example of mechanism changing the bulk properties. The lipid composition of bacterial membranes varies significantly among different species. The three primary classes of phospholipids are cardiolipin, phosphatidylglycerol, and phosphatidylethanolamine. There are antibiotics that can affect different phospholipids like cardiolipins that separate into a domain when specific cationic antimicrobial peptides are present. There is evidence that the antibiotic daptomycin redistributes cardiolipin on the membrane surface as part of its mechanism of action. The first peptides to be proposed as phosphatidylethanolamine receptors included cinnamycin and duramycin, two members of class I, type B antibiotics.

Menaquinones and other isoprenoid quinones are found in the cytoplasmic membrane of cyanobacteria, mycoplasma, Gram-positive, and Gram-negative organisms (Epanand et al. 2016). They play a crucial part in active transport, endospore formation, and electron transport chain as well as being an essential component of the cytoplasmic membrane. Lysocin E was more potent than other widely used antibiotics like vancomycin, and it rapidly induced bacteriolysis in *S. aureus*. It was discovered that lysocin E directly binds to menaquinone in the bacterial membrane (Hamamoto et al. 2015).

8.2.5.3 Inhibit Protein Synthesis

Antibacterial drugs frequently target the bacterial ribosome due to its crucial function. In fact, a sizable number of antibiotics that are clinically beneficial explicitly target this intricate translational ribonucleoprotein machinery. The majority of these compounds, which are mostly of natural origin, bind to three significant ribosomal sites: the 50S peptide escape tunnel, the 30S decoding (or A-site), and the 50S peptidyl transferase center (PTC). Codon identification and translocation are impeded by antibiotics that bind to the A-site, including aminoglycosides. The binding of tiny compounds, such as oxazolidinones, to the PTC inhibits the formation of peptide bonds. Finally, near the peptide exit tunnel, macrolides typically prevent the development of the amino acid chain (McCoy et al. 2011).

The 30S or 50S ribosomal subunits of bacteria are bound by aminoglycosides, which then inhibit peptidyl-tRNA from translocating from the A-site to the P-site and misinterpret mRNA, among other processes by which they act as bactericidal agents. These actions are caused by strong antibiotics that impede bacterial protein synthesis.

8.2.5.4 Inhibit DNA Gyrase

The quinolone and coumarin classes of antibiotics are two examples of drugs that prevent DNA replication. The quinolones have the ability to bind specifically to the A subunit of DNA gyrase, also known as topoisomerase II, at the exposed ends of the chain of cut DNA strands. As a result, the freshly created DNA cannot be sealed by DNA gyrase, leading to severely broken chromosomes. DNA experiences multiple double-strand breaks as a result of quinolone-induced topoisomerase inhibition, which can set off the DNA stress response (SOS response). When DNA is damaged during this process, RecA is activated, which makes it easier for the LexA repressor protein to auto-cleave. Following auto-cleavage, the expression of SOS response genes, which include DNA repair enzymes, is induced (Kohanski et al. 2010).

8.2.5.5 Inhibit Intermediate Metabolism

Antibiotic efficacy in the context of bacterial metabolism is defined by these three postulates taken together.

(1) The metabolic state of bacteria is altered by antibiotics, which affects the bacteria's susceptibility to antibiotics. (2) This influence increases the death or

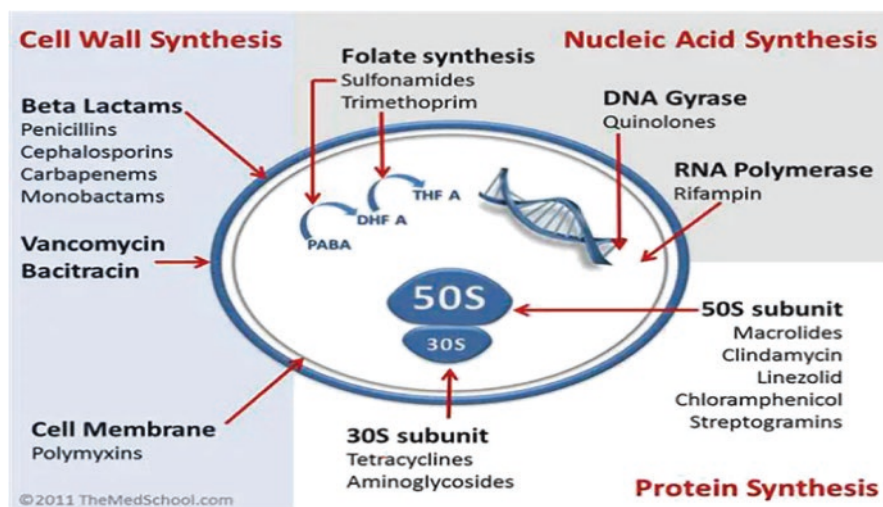


Fig. 8.1 Diagram showing how antibiotics affect several bacterial cell locations (Dijmărescu et al. 2022)

stasis that results from the antibiotics. (3) By changing the metabolic state of bacteria, antibiotic efficacy can be increased (Stokes et al. 2019) (Fig. 8.1 shows how antibiotics affect bacterial cell wall).

In summary, antibiotics that work against the bacterial cell wall include phosphomycin, vancomycin, isoniazid, cycloserine, ethionamide, B-lactams, and ristocetin. Polymyxin B and E (colistin) are two antibiotics that can actively penetrate the bacterial cytoplasmic membrane. The quinolone antibiotics, which include ciprofloxacin, norfloxacin, and nalidixic acid, block DNA gyrase, whereas metronidazole breaks down DNA and works well against bacteria. Rifampin and actinomycin D are two antibiotics that prevent transcription in bacteria. The antibiotics aminoglycosides, nitrofurans, spectinomycin, and tetracyclines bind to the 30S ribosome of bacteria to prevent translation. Chloramphenicol, erythromycin, clarithromycin, lincomycin, clindamycin, puromycin, and fusidic acid are among the antibiotics that bind to the 50S ribosome and prevent translation.

Sulfonamides and trimethoprim are two antibiotics that work by preventing folic acid biosynthesis. Penicillins, cephalosporins, monobactams, and thienamycins are examples of B-lactam antibiotics that share a structure because they all include a B-lactam ring. They are all d-alanyl-d-alanine analogs. The structural similarity among the aminoglycoside antibiotics is attributed to the presence of a common aminocyclitol ring structure. Among them are tobramycin, gentamycin, kanamycin, neomycin, amikacin, and streptomycin. One structural similarity among the macrolide antibiotics is the macrocyclic lactone ring. This is connected to one or more sugars and contains 12–22 carbon atoms. Among them are clarithromycin and erythromycin.

8.3 Pharmacotherapy Against Specific Diseases

8.3.1 Antitubercular Drugs

Multi-systemic in nature, tuberculosis manifests itself in different ways. The disease is spread through inhalation of infected aerosolized droplets. The primary factors determining the spread and severity of an organism are its genetic makeup, the body's immunity, and whether an organism is exposed to it initially or subsequently. *M. tuberculosis* normally possesses several virulence factors that increase the pathogenic potential to cause damage and stands tough for alveolar macrophages to get rid of that.

Virulence factors involve:

- (a) Alveolar macrophages face difficulty in phagocytosing bacteria in the outer capsule due to their high mycolic acid content.
- (b) Few constituents of cell wall, like cord factor or trehalose dimycolate, are critical in survival inside the host cell and cause direct damage to alveolar macrophages.
- (c) *Mycobacteria tuberculosis* has the capacity to prevent the formation of a phagolysosome which can inhibit the growth of an organism by reducing the pH and making it acidic.

Initial contact with the host cell of *Mycobacterium tuberculosis* can cause symptoms that are referred to as primary tuberculosis. The Ghon focus of primary TB is the area of the lungs where this infection is localized. The Ghon focus usually enters a latent stage for most of the patients which is known as latent tuberculosis. This mostly happens to the nonimmune host who does not have the proper cover of the immune system against the pathogen, again this latent TB can also get active to the host cell where immunosuppression has taken place.

First-time cases of the disease are uncommon; when they do occur, it is known as primary progressive tuberculosis and is typically seen in children, immunocompromised individuals, and individuals taking steroids and immunosuppressants.

Tuberculosis patients generally develop the disease after a prolonged period of latency (which may take several years), this event is known as secondary tuberculosis. Reactivation of latent tuberculosis in the absence of immunity is the main cause of secondary TB and the lesions are visible in lung apices. A very small number of patients are there who develop secondary tuberculosis due to reinfection. Lesions are visible in the apices of the lungs in both cases of secondary tuberculosis (reactivation and reinfection), and the presence of cavitation sets it apart from primary progressive tuberculosis, which typically affects the middle lung zones.

Tuberculosis is one well-known instance of a cell-mediated delayed-type IV hypersensitivity reaction. *Mycobacterium tuberculosis* stimulates the immune system, the helper T-lymphocytes, or CD4+ cells. This stimulation results in the recruitment and activation of tissue macrophages as well as the production of cytokines, particularly interferon-gamma, which keeps the process going. The two primary changes involving macrophages that occur during this process are the development of multinucleated giant cells and the emergence of epithelioid cells. Giant cells are

groups of merging macrophages that are intended to improve phagocytosis. A granuloma is an accumulation of massive cells that includes the lymphocytes and other cells that surround the mycobacterium particle.

Macrophages that have changed in shape and acquired the capacity to produce cytokines are known as epithelioid cells. Instead of the globular shape that is typical of normal macrophages in contrary epithelioid cells have a flat (spindle-like) shape. In a tuberculoid granuloma, epithelioid cells frequently coalesce to form giant cells. The cytokines tumor necrosis factor-alpha (TNF-alpha), interleukin-6 (IL-6), and interleukin-4 (IL-4) are essential for the development of a tuberculosis granuloma in addition to interferon-gamma (IFN-gamma).

The granuloma in tuberculosis appears caseous or cheese-like upon gross examination, primarily explained by the mycobacterium cell wall's high mycolic acid content. Granulomatous necrosis brought on by *Mycobacterium tuberculosis* has been referred to as caseous or caseating necrosis because of this distinct characteristic(as shown in Table 8.2).

Screening tests for TB:

1. Tuberculin skin testing also known as Mantoux test.
2. Interferon release assays.

Combination medications are necessary for the treatment of confirmed TB. It is always recommended to use combination therapy rather than monotherapy when treating tuberculosis. The following anti-TB medications are part of the most typical TB treatment regimen.

8.3.1.1 Multidrug-Resistant TB

These days, multidrug-resistant tuberculosis is common. High doses of combination therapy, which combines first- and second-line medications, are used to treat this illness.

Bedaquiline, a drug for the treatment of MDR-TB received FDA approval on December 28, 2012, in the USA. This is the first anti-TB medication to receive FDA approval in 40 years. All patients taking isoniazid must undergo liver function tests. Monitoring for retinopathies in patients taking ethambutol is another form of TB monitoring.

8.3.1.2 Treatment of TB Patients Having HIV

Patients with severe level of immunosuppression (CD4+ 60/microliter) who have both active TB and HIV should begin antitubercular therapy immediately. After 2–4 weeks, antiretroviral therapy should be started. Immune reconstitution inflammatory syndrome (IRIS) cannot develop if antiretroviral therapy is postponed. This syndrome is characterized by a paradoxical worsening of primary disease symptoms following the start of antiretroviral treatment. Retroviral therapy should begin no earlier than 2 weeks after the initial treatment for the presenting infection. The likelihood of IRIS increases with the timing of the start of antiretroviral therapy. Antiretroviral therapy that is delayed unnecessarily increases the risk of AIDS-related death.

Table 8.2 Drugs used for the treatment of tuberculosis and their mechanism of action (Schmitz et al. 2019)

Class of drug	Subclass	Name of drugs	Mechanism of action
First-line medications, group 1		Isoniazid, rifampicin, rifabutin, and rifapentine	<p>Isoniazid is activated peroxidatively by a mycobacterial enzyme reactive species produced by KatG combined with NAD(+) and NADP(+) to form adducts that are strong inhibitors of the enzymes responsible for the biosynthesis of lipids and nucleic acids and prevent the formation of cell walls (Timmins and Deretic 2006)</p> <p>Rifampin demonstrates bactericidal antimicrobial activity by inhibiting DNA-dependent RNA polymerase (RNAP) and either sterically restricting the elongating RNA's route at the 5' end or by lowering RNAP's affinity for short RNA transcripts. It stops additional RNA synthesis by specifically inhibiting the microbial RNAP (Alnewais et al. 2023)</p> <p>Rifabutin works by preventing prokaryotic cells from synthesizing DNA-dependent RNA. Rifabutin is widely distributed, concentrates in the lungs, and has a high level of intracellular penetration. 25-O-desacetyl rifabutin (des-rifabutin) is one of its active metabolites. Des-rifabutin has significantly fewer significant drug–drug interactions than rifampicin because it significantly less strongly induces CYP3A and glucuronosyltransferases (Rockwood et al. 2019). It causes neutropenia, uveitis (0.01%), polyarthralgias, hepatotoxicity. DNA-dependent RNA polymerase activity is inhibited by rifapentine. In susceptible cells both rifampin and rifapentine produce side effects like pruritis, flulike symptoms, hepatotoxicity, orange discoloration of body fluid</p> <p>The <i>pncA</i> gene-encoded pyrazinamidase enzyme converts pyrazinamide within the mycobacterial cell to the active metabolite pyrazinoic acid. This metabolite builds up in an acidic environment and probably prevents the production of mycolic acid. If used alone, resistance emerges quickly and is primarily brought on by <i>pncA</i> gene mutation. It causes polyarthralgia, acute gouty arthritis, rash, and photosensitive dermatitis (Hussain et al. 2021).</p> <p>Ethambutol blocks the production of arabinogalactan by inhibiting the arabinosyl transferases (encoded by the <i>embAB</i> genes), which prevents the incorporation of mycolic acid into the cell wall of mycobacteria. It causes retrobulbar neuritis (Chamberlain et al. 2017)</p>

Second-line anti-tuberculosis drugs, group 2	Injectable aminoglycosides	Amikacin, kanamycin, streptomycin	Amikacin's resistance to bacterial enzymes that modify aminoglycosides is an exceptional quality. It is a derivative of kanamycin that is semisynthetic. In cases of high gentamicin/tobramycin resistance, it is advised to use it as a backup medication for empirical treatment of hospital-acquired gram-negative bacillary infections They all follow almost same mechanism in antitubercular action
	Injectable polypeptides	Capreomycin, viomycin	Capreomycin has a similar mycobactericidal activity to aminoglycoside Viomycin prevents messenger mRNA from being translocated on the ribosome by elongation factor G (EF-G), which is what causes the bacterial protein to be produced They follow the basic working mechanism of quinolones
Group 3 Oral and injectable fluoroquinolones	Fluoroquinolones	Levofloxacin, moxifloxacin, ofloxacin, gatifloxacin	
		Para-aminosalicylic acid, cycloserine, terizidone, ethionamide, prothionamide, thioacetazone, linezolid	Similar to sulfonamides, Para-aminosalicylic acid inhibits folate synthase, potentially through a similar mechanism. Its selectivity might result from <i>M. tuberculosis</i> 's higher affinity for folate synthase than other bacteria Cycloserine is an analogue of D-alanine, derived from <i>S. Orhidaceus</i> . Consequently, it stops the enzymes that racemize L-alanine and link two D-alanine residues from doing their jobs, preventing the synthesis of bacterial cell walls. It is TB-static, the cycloserine
Group 5		Clofazimine, linezolid, amoxicillin/clavulanic acid, imipenem/cilastatin, and clarithromycin	These drugs may or may not be effective against tuberculosis. As last resort treatments for completely drug-resistant TB

Monitoring closely for these side effects is one of the most crucial parts of treating tuberculosis. The majority of these side effects are controllable with dose adjustments or careful observation. Sometimes the drug needs to be stopped, and if there are no other options, second-line therapy should be explored (Khan [n.d.](#)).

8.3.2 Antileprotic Drugs

Mycobacterium leprae (*M. leprae*) is a rod-shaped, aerobic, slow-growing, acid-fast bacteria that causes leprosy. The highest risk of contracting *M. leprae* infection is among those who live in endemic areas with substandard conditions, such as dirty water, inadequate bedding, and inadequate diet, or with other illnesses that impair immune function. It has been speculated that co-existing HIV infection may worsen the pathogenesis of leprosy lesions and/or increase susceptibility to leprosy, similar to the effects of tuberculosis.

By infecting Schwann cells (SCs), *M. leprae* can cause demyelination, which damages the nerve and results in disability (Rambukkana et al. [2002](#)). *M. leprae* binding to SCs causes demyelination and axonal conductance loss as it results in addition of PGL-1 (Marques et al. [2001](#)). Moreover, *M. leprae* can infiltrate SCs by means of a particular 21 kDa laminin-binding protein. PGL-1, the primary unique glycoconjugate on the surface of *M. leprae*, binds laminin-2, which explains why the bacteria prefers peripheral nerves (Ng et al. [2000](#)). Dystroglycan (DG), a molecule that targets the SC receptor of *M. leprae*, may play a part in the early stages of nerve degeneration. The direct bacterial ligation of the neuregulin receptor by *Mycobacterium leprae* causes the activation of Erk1/2 and ErbB2, which leads to signaling and proliferation of MAP kinase (Tapinos et al. [2006](#)). A delayed-type hypersensitivity reaction to *M. leprae* occurs naturally and is referred to as a type I reaction. Clinically speaking, it is identified by a reduction in bacillary load and a “upgrading” of the clinical picture toward the tuberculoid pole. It exhibits a predominantly Th1 response, strong development of skin test reactivity, and lymphocyte responsiveness immunologically. Immune complex deposition is thought to be connected to type II reaction pathogenesis. Increased cytokine levels, including TNF- α , IL-1, and IFN- γ , are indicative of type II reactions. Furthermore, increased levels of alpha-1-antitrypsin, amyloid A protein, and C-reactive protein have been found in the sera of ENL patients.

4,4'-diamino diphenyl sulfone (DDS, dapsone), rifampicin, and clofazimine are the three main antileprosy medications currently in use. Rifampicin, a potent antibiotic, induces the metabolism of dapsone during multidrug therapy, which reduces the plasma half-life of dapsone and its metabolites (Table [8.3](#) shows drugs used in the treatment of leprosy).

For ease of use, the WHO classified leprosy as follows:

1. Paucibacillary leprosy (PBL): The patient is non-infectious and has few bacilli. Both the tuberculoid (TT) and borderline tuberculoid (BT) types are included.
2. Multibacillary leprosy (MBL): The patient is contagious and has a high bacillary load. The LL, BL, and BB types are among them.

Table 8.3 List of drugs used in the treatment of leprosy and their mechanism of action (Onifade and Ojo 2024)

Types of drugs	Example	Mechanism of action
Sulfone	Dapsone-diamino diphenyl sulfone (DDS)	Dapsone inhibits folate synthase's ability of bacteria to incorporate PABA into folic acid. The folate synthase enzyme of <i>M. Leprae</i> may have a different affinity, which accounts for its specificity
Phenazine derivative	Clofazimine	Mechanism of action of clofazimine is due to the following: <ul style="list-style-type: none"> – In <i>M. leprae</i>, interference with the DNA template function – The transport function of the membrane structure is altered – Interference with the electron transport chain in the mitochondria
Antitubercular drugs	Rifampin, ethionamide	Because of the possibility of rapid bacillary killing, this medication should not be administered to patients who have liver or renal dysfunction, or who have “erythema nodosum leprosum” (ENL) or “reversal reaction” in leprosy patients
Other antibiotics	Ofloxacin, moxifloxacin, minocycline, and clarithromycin	Ofloxacin monotherapy, administered for 22 days, was found to be cidal to <i>M. Leprae</i> , killing over 99.9% of bacilli in one study. When used as an alternative to rifampin in the course of avoiding chances of drug resistance Minocycline is effective against <i>M. Leprae</i> because of its high lipophilicity, which allows it to enter their bodies. Only major side effect from using it frequently is vertigo

8.3.3 Antimalarial Drugs

An infection may be suspected when the first liver schizont bursts and motile merozoites are sent into the peripheral circulation to enter red blood cells. Most infected patients experience a silent initial invasion and rupture; however, over the next 24–48 h, as the asexual cycle repeats itself, parasitaemia increases and the immune system fortifies in response. Other inflammatory markers in the cascade that are usually elevated in conjunction with TNF-alpha include interleukin 10 (IL-10) and interferon-gamma (IFN-gamma). A more severe clinical presentation is generally associated with higher parasitaemia's, though there is significant variation in this relationship (Onifade and Ojo 2024).

The capacity of *P. falciparum* infections to alter the surface of infected red blood cells and produce an adhesive phenotype is the primary factor influencing their virulence. The *P. falciparum* erythrocyte membrane protein 1 (PfEMP1) family, which is generated via var. gene transcription, mediates the cytoadhesion. Owing to a possible link between the start of severe malaria and enhanced transcription of some var. genes, the enormous diversity of var. genes present in the parasite population

has received significant attention lately. The sequestration of infected red blood cells in the microvasculature of multiple organs due to mature-staged cytoadherence to endothelium, platelets, and uninfected red blood cells compromises tissue perfusion, lactic acidosis, microcirculation obstruction, and end-organ damage.

During pregnancy, prominent sequestration takes place in the placenta, leading to congenital malaria, anemia, low birth weight, and miscarriage.

To summarize, the main characteristics that make the illness lethal are *P. falciparum*'s tissue sequestration, along with the overexpression of cytokines and other harmful compounds and the lack or delayed administration of an efficient antimalarial treatment (Zekar and Sharman *n.d.*) (Table 8.4 shows classification of antimalarial drugs and mechanisms).

Table 8.4 Classification of antimalarial drugs and mechanism of action (Tapinos et al. 2006)

Class of drug	Example	Mechanism of action
4-Aminoquinolines	Chloroquine, amodiaquine	The acidic vacuoles of plasmodia break down hemoglobin to get nutrition. It works quickly to kill all plasmodia species, with the exception of <i>P. Falciparum</i> , which is resistant to chloroquine. It is weakly basic in nature and increases the pH of the vacuolar solution, preventing hemoglobin degradation by parasitic lysosomes because it accumulates in the parasite's acidic vacuoles. Chloroquine also exhibits activity against <i>Giardia lamblia</i> and <i>Entamoeba histolytica</i> . Pregnant women who have malaria can take chloroquine; no teratogenic or abortifacient side effects have been documented. When liver damage is present, caution should be taken
Quinoline-methanol	Mefloquine	Efficient against plasmodia that are resistant to and sensitive to chloroquine. Its mechanism of action resembles chloroquine but rather than in the acidic vacuole, the parasitic cytosol is where mefloquine acts. Toxic effect includes sinus bradycardia and Q-T prolongation
Cinchona alkaloid	Quinine, quinidine	Prevent heme from polymerizing into hemozoin; free heme or heme–quinine complex ruins and kills parasite membranes
Biguanide	Proguanil	Body cyclizes proguanil to cycloguanil, a triazine derivative that inhibits plasmodial DHFRase-thymidylate synthase
Diaminopyrimidine	Pyrimethamine	Pyrimethamine inhibits plasmodial DHFRase directly; unlike proguanil, it does not need to be converted into a cyclic triazole. The high affinity of pyrimethamine for the plasmodial enzyme is necessary for its selective antimalarial action
8-Aminoquinoline	Primaquine, tafenoquine	It is thought that primaquine's reactive intermediate metabolites produce intraparasitic toxic oxidative species that impair plasmodial mitochondria's ability to transport electrons

Table 8.4 (continued)

Class of drug	Example	Mechanism of action
Sulfonamide	Dapsone, sulfadoxine	The mechanism of action has already been discussed earlier
Antibiotics	Doxycycline, clindamycin	For the treatment of chloroquine-resistant malaria, doxycycline must always be used in conjunction with quinine. It is never used alone to treat malaria
Sesquiterpene-lactones	Artesunate, artemether	For severe malaria, the first-choice medication is intravenous artesunate. Artesunate induces CYP2B6 and CYP3A4 to auto-induce its own metabolism following repeated dosage. Artemether is second choice of drug if artesunate is not available
Amino alcohol	Halofantrine	Although halofantrine is not authorized in India, it has been used in other nations to treat multiresistant falciparum malaria in cases where there is no other viable treatment option
Naphthoquinone	Atovaquone	Atovaquone causes plasmodial mitochondrial membranes to collapse and obstructs the synthesis of ATP. Proguanil inhibits the development of resistance and strengthens its antimalarial effect
Naphthyridine	Pyronaridine	Pyronaridine is the water-soluble Mannich base, pyronaridine shares structural similarities with amodiaquine. It is an erythrocytic schizonticide that functions similarly to chloroquine and has a high efficacy

8.3.4 Antifungal Drugs

Fungi are eukaryotic, unicellular or multicellular organisms that can be found in all types of environments across the globe. They can take many different forms, ranging from microscopic yeasts and molds to fungi that are visible to the unaided eye, like mushrooms. A number of medical conditions, such as asthma, AIDS, cancer, organ transplantation, and corticosteroid therapy, can lead to serious fungal infections (Table 8.5 shows classification of antifungal drugs).

8.3.4.1 Some Major Fungal Diseases Are

Candidiasis

Yeasts called *Candida* are present in the intestinal tract, mucous membranes, and skin. If these yeasts proliferate too much, symptoms may appear. Oropharyngeal candidiasis, or “thrush,” is the term for candidiasis that appears in the mouth or throat. Usually, vaginal candidiasis is described as a “yeast infection.” Overgrowth of these fungi can lead to invasive candidiasis, a dangerous infection that can affect the bones, brain, eyes, blood vessels, heart, and other parts of the body in people who have certain risk factors. The most common type of invasive candidiasis, known as candidemia, is a bloodstream infection caused by *Candida albicans* that often affects hospitalized patients.

Table 8.5 Classification of antifungal drugs and their mechanism of action (Ng et al. 2000).

Types of drugs	Subtype	Example	Mechanism of action
Antibiotics	Polyene	Amphotericin B Nystatin	Both amphotericin B and nystatin attach themselves to the ergosterol found in the fungal cell membrane, causing pores to open, ions to leak out, and eventually fungal cell death (Waugh n.d.)
	Heterocyclic benzofuran	Griseofulvin	Enters the dermatophyte by energy-dependent transport mechanisms, attaches itself to the fungal microtubules, and interferes with their function to prevent mitosis (Gull and Trinci 1973)
	Echinocandins	Caspofungin Anidulafungin	The fungal cell wall formation is disrupted due to the inhibition of β -1,3-D-glucan synthase (Schmitz et al. 2019)
Antimetabolites		Flucytosine	Taken up by cytosine permease of fungus, converted into 5-fluorouracil by cytosine deaminase, this competitively inhibits uracil and results in disrupted RNA synthesis and impairment of protein
Azole	Imidazole	Clotrimazole (topical)	Clotrimazole blocks the demethylation of 14 α -lanosterol, which prevents the biosynthesis of ergosterol in a concentration-dependent manner
		Ketoconazole (systemic)	Causes lanosterol 14 α -demethylase, an enzyme dependent on cytochrome P-450 that changes lanosterol in fungal cell membrane into ergosterol, to be inhibited
	Triazole	Fluconazole, itraconazole	Works same way as imidazoles
Topical agents		Benzoic acid Butenafine	Buildup of benzoate at low external pH, which prompts phosphofructokinase sensitivity by lowering intracellular pH. Growth is hampered by the subsequent inhibition of glycolysis, which lowers ATP (Krebs et al. 1983) Butenafine prevents the squalene epoxidation stage in fungi, which inhibits the synthesis of sterols (Syed and Maibach 2000)

Cryptococcosis

Bird droppings are frequently linked to cryptococcus fungus, which are ubiquitous in soil across the globe. *Cryptococcus neoformans* and *C. gattii* are the two primary species that cause illness. For those with weakened immune systems, like those with HIV/AIDS, these fungi can pose a serious risk, even though they hardly ever infect healthy people. Most often, the fungus is inhaled and results in illness. Infections most frequently occur in the nervous system and lungs. As a primary cause of death for HIV/AIDS patients, cryptococcal meningitis is the most common type of meningitis in sub-Saharan population.

Aspergillosis

One type of fungus that is frequently found both indoors and outdoors is *Aspergillus*. Every day, people inhale a lot of *Aspergillus* spores without getting sick. However, *Aspergillus*-related health issues are more likely to affect those with compromised immune systems or lung conditions. *Aspergillosis* comes in a variety of forms, from mild to extremely dangerous. *Aspergillus*, for instance, can inflame the sinuses (allergic *Aspergillus sinusitis*) or lungs (allergic bronchopulmonary aspergillosis) without causing an infection. For those whose immune systems are weakened, invasive aspergillosis—a common and deadly infection of the lung or other body systems—is the primary cause of death.

Coccidioidomycosis (Valley Fever)

Coccidioides immitis and *C. posadasii* are the fungi that cause coccidioidomycosis, which is also referred to as valley fever. These soil-dwelling fungi inhabit dry, desert-like environments. Unlike most severe fungal infections, *Coccidioides* infection is typically caused by breathing spores into the lungs. Healthy individuals are susceptible to contracting *Coccidioides* infection. Valley fever is a complex disease that can range in severity from a mild, self-limiting flu-like illness to even a severe one, widespread infection that may require lifelong care.

Histoplasmosis

The fungus *Histoplasma capsulatum* is the cause of histoplasmosis. This fungus grows in soil that has been exposed to a lot of bat or bird droppings. Inhaling microscopic fungal spores can cause infections in humans, especially when contaminated soil is disturbed. The illness typically resolves on its own in healthy individuals and is characterized by mild flu-like symptoms. Histoplasmosis can be severe in those with compromised immune systems, necessitating long-term antifungal therapy to treat the illness.

Blastomycosis

The fungus *Blastomyces dermatitidis* is the source of the infection known as blastomycosis. This fungus grows in moist soil and on decaying materials like leaves and wood. In individuals with weakened immune systems, *Blastomyces* can result in severe infections that travel from the lungs to the skin, bones, and central nervous system.

8.3.5 Antiviral Drugs (Non-retroviral)

Antiviral drugs (non-retroviral) drugs mainly include medications against herpes, hepatitis, and influenza. Herpes, also known as herpes simplex virus (HSV), is a common infection that can result in excruciating blisters or ulcers. The main way it spreads is through skin-to-skin contact. Herpes comes in two varieties. HSV-1 can affect face and mouth. HSV-2 affects the vaginal region. Herpes is a chronic illness that a person can never fully recover from. The term “hepatitis” refers to liver inflammation. The liver is a vital organ that processes nutrients, fights infections, and filters blood. The liver’s ability to function can be impacted by inflammation or damage. Hepatitis can be brought on by toxins, heavy alcohol consumption, certain medications, and specific medical conditions. Hepatitis, however, is frequently brought on by a virus. Hepatitis A is highly transmissible. It can be acquired by accidentally ingesting even trace amounts of the virus, coming into close contact with an infected person, or accidentally consuming tainted food or drink. Hepatitis A symptoms, which include fatigue, nausea, stomach pain, and jaundice, can linger for up to 2 months. The majority of hepatitis A patients do not experience chronic illness. Vaccination is the most effective way to avoid contracting hepatitis A. Hepatitis B can spread when blood, semen, or other bodily fluids from an infected person come into contact with an uninfected person’s body. Sexual contact, sharing syringes, needles, or other injection supplies, as well as pregnancy or childbirth, can all lead to this. While not everyone newly infected with HBV experiences symptoms, those who do may experience nausea, vomiting, lethargy, poor appetite, and jaundice. Hepatitis B is frequently a transient illness for many people. Influenza viruses come in four different varieties: A, B, C, and D. Almost every winter in the United States, seasonal epidemics of disease in humans, commonly referred to as flu season, are caused by the influenza A and B viruses. The only influenza viruses that are known to cause pandemics, or widespread outbreaks of the flu, are influenza A viruses. A pandemic can happen when a novel strain of the influenza A virus surfaces, one that is highly contagious, capable of infecting large numbers of people, and to which most people have little to no immunity. Infections with the influenza C virus typically result in mild illness and are not believed to be the cause of human epidemics. Influenza D viruses do not currently know how to infect humans and cause illness; they primarily affect cattle and can spread to other animals (as shown in Table 8.6).

8.3.6 Antiviral Drugs (Anti-Retrovirus)

Antiretroviral therapy is the term for HIV treatment (ART). With antiretroviral therapy (ART), a daily regimen of HIV medications is taken. ART is advised for all HIV-positive individuals. While HIV cannot be cured, medications can help infected individuals live longer, healthier lives. Additionally, ART lowers the chance of HIV transmission. HIV targets and eliminates the immune system’s CD4 cells, or CD4 T-lymphocytes, which fight infection. The body finds it more difficult to fight off

Table 8.6 Classification of antiviral (non-retroviral) drugs and their mechanism of action (Marques et al. 2001)

Types of drug	Subtype	Example	Mechanism of action
Anti-herpes virus drugs		Acyclovir, ganciclovir	The main way that ganciclovir works against cytomegalovirus is by preventing viral DNA replication. A particular and strong inhibition of the viral DNA polymerase is part of this inhibition
Anti-hepatitis virus drugs	Used against hepatitis B	Lamivudine, entecavir	Lamivudine is nucleoside reverse transcriptase inhibitor Entecavir was created to specifically impede the three stages of the hepatitis B virus's replication Entecavir
	Used against hepatitis C	Ribavirin, velpatasvir	A protein called HCV NS5A is inhibited by velpatasvir and is necessary for the virus to replicate. The HCV NS5A protein, which is necessary for viral replication, is inhibited by velpatasvir
Anti-influenza virus drugs		Amantadine Zanamivir	Among the ion channel blocker class of anti-influenza medications is amantadine. Influenza A has been treated and prevented with it. Neuraminic acid's sialic acid component is broken down by the viral enzyme zanamivir, also referred to as a neuraminidase inhibitor, in the respiratory epithelial cells' hemagglutinin receptors (Stiver 2003)

infections and some HIV-related cancers when CD4 cells are lost. HIV medications lessen the quantity of HIV in the body, also known as the viral load, by preventing HIV from proliferating (producing copies of itself). Reducing the amount of HIV in the body allows the immune system to heal and generate more CD4 cells. The body still contains some HIV, but the immune system is capable of fending off infections and some HIV-related cancers (depicted in Table 8.7).

8.3.7 Antiamoebic and Other Antiprotozoal Drugs

Amoeba and other few protozoa are also responsible for causing diseases and it also requires application of drugs which work through many different mechanisms. Drugs are mainly targeting tissue amoebocyte and luminal amoebocytes (Table 8.8 shows classification of antiamoebic and antiprotozoal drugs).

8.3.8 Anthelmintic Drugs

A wide variety of parasitic worms, such as nematodes (roundworms), trematodes (flat worms), and cestodes (tapeworms), make up helminths. The species and worm burden have an impact on the pathogenesis of the disease. The most prevalent

Table 8.7 Classification of antiviral drugs (anti-retrovirus) and their mechanism of action

Types of drugs	Example	Mechanism of action
Nucleoside reverse transcriptase inhibitors	Zidovudine, Lamivudine	The pharmacologic action of these medications depends on intracellular phosphorylation to the triphosphate anabolite. Drug-triphosphate lacks the 3' hydroxyl on the deoxyribose ring required for the sugar-phosphate linking reaction; therefore, it competes with natural nucleotides for inclusion into the growing HIV DNA chain, limiting HIV DNA chain elongation and blocking HIV reverse transcriptase
Non-nucleoside reverse transcriptase inhibitors	Nevirapine, Efavirenz	These directly bind to reverse transcriptase (RT), disrupting the catalytic site of the enzyme to prevent both DNA-dependent and RNA-dependent DNA polymerase activities
Protease inhibitors	Ritonavir, Indinavir	Protease breaks down protein precursors to create new viral particles. By preventing this cleavage process, protease inhibitors prevent the virus from creating new particles. The liver enzyme cytochrome P450 3A4 (CYP450-3A4) is inhibited by ritonavir, which is an important mechanism of action for the treatment of HIV and HCV. Other protease inhibitors are metabolized by this cytochrome pathway. The bioavailability of other antiretroviral medications rises when ritonavir inhibits CYP450-3A4. Furthermore, inhibiting this CYP450 pathway lowers the rate at which ARVs are broken down, increasing serum drug levels (Igho-Osagie et al. 2023)
Entry inhibitor	Enfuvirtide	It shows strong and targeted suppression of the viral and cell membrane. It specifically blocks the HIV-1 transmembrane glycoprotein gp41 from functioning (Kapić et al. 2005)
CCR-5 receptor inhibitor	Maraviroc	Interferes with the CCR5 coreceptor's function to target the HIV entry process (Ray 2009)
Integrase inhibitor	Raltegravir, dolutegravir	Prevents HIV-1 DNA from being inserted into the genome of the host cell by inhibiting the activity of HIV-1 integrase

helminth infections worldwide are those of the gastrointestinal system (pinworms, hookworms, *Ascaris*, *Trichuris*). Other nematodes have phases that are muscle (*Trichinella* sp.), skin (*Onchocerca*), or blood (*Filaria* sp.). Schistosomes, or blood-stream parasites, are the most common trematode (flake) infection worldwide. A few species of trematodes cause infections in the gastrointestinal or biliary tract, as well as in the lungs (*Paragonimus* sp.). Infections with tapeworms can occur in two stages in humans. The larval stage of the tapeworm is what causes illness, even though the adult stage is located in the intestine. Therefore, *Taenia solium* larval cysts are located in the brain, whereas *Echinococcus* larval cysts are located in the liver or lungs.

Sometimes drugs, also written as anthelmintics, are a class of pharmaceuticals and chemical compounds, used to treat a variety of parasite illnesses. Although their modes of action differ, they usually paralyze the parasitic worm, which allows it to be released and expelled. Agents are unique to their respective parasite categories,

Table 8.8 Classification of antiamoebic and other antiprotozoal Drugs (Rambukkana et al. 2002)

Types of drugs	Subclass	Example	Mechanism of action
Tissue amoebocytes	For intestinal and extraintestinal amoebiasis	Metronidazole Emetine (alkaloid)	Emetine works by preventing the intraribosomal translocation of the tRNA–amino acid complex, which prevents amoebae from synthesizing proteins
	Extraintestinal amoebiasis	Chloroquine	Already discussed before
Luminal amoebicides	Amides	Nitazoxanide	Nitazoxanide, a prodrug that, upon absorption, transforms into the active form tizoxanide, which inhibits the PFOR enzyme, a crucial pathway involved in the electron transport energy metabolism of anaerobic organisms
	Antibiotics	Tetracycline, paromomycin	Paromomycin is an aminoglycoside antibiotic
	8-Hydroxyquinolines	Quiniodochlor, diiodohydroxyquin	They do not have tissue amoebicidal activity, but they do destroy the amoebic trophozoites that form cysts in the intestine

with a few notable exceptions. For instance, ivermectin is used to treat nematodes, while praziquantel is used to treat trematodes. For numerous nematodes, as well as many trematodes and protozoa, albendazole is generally effective. The recommended medication for chronic fascioliasis is carbendazole, which has been in use for many years throughout much of the world. Crucially, depending on the indication, anthelmintic therapy's dosage and duration vary significantly. When treating gastrointestinal infestations, a single dose of a poorly absorbed anthelmintic usually works well; however, for trichuriasis, dosages may need to be repeated once or twice or given for a period of 1–3 days. Multiple courses or a longer course may be required for systemic infections; these courses can range from 1 or 2 doses to daily doses for several months or years. Rarely, suppressive therapy requires ongoing care.

Benzimidazoles, such as mebendazole, albendazole, and thiabendazole (since removed), are anthelmintics connected to hepatotoxicity. Rare instances of cholestatic liver injury—which can be severe and chronic—have been linked to these medications. The other anthelmintics don't appear to have a lot of hepatotoxic potential.

These medicines are often administered for brief periods of time, and many of them are not fully absorbed (LiverTox 2012) (as shown in Table 8.9).

Table 8.9 Classification of anthelmintic drugs and their mechanism of action (Ray 2009)

Types of drugs	Example	Mechanism of action
For roundworm, hookworm, pinworm	Mebendazole, albendazole	Mebendazole's primary site of action seems to be the parasite's "P-tubulin" microtubular protein. It has a strong affinity for P-tubulin in vulnerable worms and prevents its polymerization. Within the worm's cells, intracellular microtubules gradually disappear. In addition, it prevents the parasite from taking glucose, inhibits a few mitochondrial enzymes, and depletes its glycogen reserves. I-latching is another term for eggs and larvae of inhibited nematodes
For whipworm	Albendazole, mebendazole	Ascariasis, hookworm, and enterobiasis have shown cure rates after a single dose of medication of albendazole that are comparable to those of a three-day mebendazole treatment. In cases of trichuriasis, mebendazole has shown better results. The mechanism of action is quite similar to mebendazole
For threadworm	Ivermectin, albendazole	<i>Streptomyces avermitilis</i> is the source of ivermectin, it is highly recommended for treating strongyloidiasis and onchocerciasis with a single dose. Ivermectin functions via a unique kind of Cl^- -channel, which is only present in invertebrates and is gated by glutamate. It has also been noted that GABAergic transmission in the worm is amplified. The only oral medication that effectively treats pediculosis and scabies is ivermectin
For filariasis	Diethylcarbamazine, ivermectin, and albendazole	The modification of the microfilariae organelle membranes, which promotes cell death, seems to be the primary function of diethylcarbamazine. Additionally, it has been hypothesized that adult worms and microfilariae are dislodged due to altered muscular activity
For tapeworm	Praziquantel, niclosamide	The presence of a particular Ca^{2+} channel variant that is praziquantel-sensitive in tapeworms and flukes may be necessary for the drug's selective action against these worms. The intestinal mucosa gives way and the tapeworms are ejected The medication with niclosamide seems to work by preventing mitochondrial oxidative phosphorylation and interfering with the tapeworm's anaerobic ATP synthesis. The tapeworms that are harmed by niclosamide undergo partial digestion in the intestine
For hydatid disease	Albendazole, mebendazole	Already discussed before

Table 8.10 Antibiotics and their adverse effects (LiverTox 2012)

Classification	Drugs	Adverse effect
Aminoglycoside	Neomycin, tobramycin, amikacin, gentamicin	Ototoxicity, renal toxicity, hypersensitivity reaction
Cephalosporin	Cephalexin, cefazolin, ceftriaxone, cefepime	Nephrotoxicity, gastrointestinal disturbance
Quinolone (fluroquinolone)	Ciprofloxacin, levofloxacin	Photosensitivity, bone marrow depression, tendonitis
Macrolides	Erythromycin, azithromycin	Hypersensitivity reactions, gastrointestinal disturbances
Penicillins	Amoxicillin, ampicillin, penicillin G, dicloxacillin	Anaphylaxis, superinfection
Sulfonamides	Sulfamethoxazole/trimethoprim	Bone marrow suppression, Steven-Johnson syndrome
Lincosamide	Clindamycin	Neutropenia, thrombocytopenia, jaundice
Tetracycline	Doxycycline, minocycline, oxytetracycline	Discoloration of teeth, intracranial hypertension
Chloramphenicol		Bone marrow toxicity, gray baby syndrome

8.4 Antibiotics and Their Adverse Effects

Antibiotics are in real terms a very effective medication but regular use or irrational use of it can cause adverse effect. Nowadays, the antimicrobial resistance has been a real threat to the modern pharmaceutical world but even if it is not resistant antibiotics can cause real damage in many ways. Here we will know some antibiotics and their specific adverse effects (Table 8.10 shows antibiotics and their adverse effect).

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Hormones and Hormones Antagonists

9

Arshvir Kaur, Raja Chakraverty, and Rajani Mathur

Abstract

Diabetes mellitus (DM) encompasses a group of metabolic disorders characterized by persistent elevation of blood sugar levels. This condition arises when the pancreas fails to produce sufficient insulin from β -cells or when insulin is ineffective in binding to its receptors, resulting in hyperglycemia. Recent surveys indicate a projected increase in the prevalence of diabetes among adults, rising from 4% in 1995 to an estimated 6.4% by 2025. Globally, it was anticipated that 537 million individuals would have diabetes in 2021, with a projected surge of 46% to 783 million by 2045. Additionally, it was forecasted that 541 million people would experience impaired glucose tolerance in 2021, with over 90% of diabetes cases being classified as type 2 diabetes (T2D). Prediabetes, a precursor to T2D, can progress by 5–10% annually. Current treatments for DM include medications such as metformin, sulfonylurea, thiazolidinedione, or DPP-4 inhibitors, although these options only offer partial control over the condition, leaving room for further advancements in treatment modalities.

Keywords

Antidiabetics · Insulin secretagogues · Insulin sensitizers

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199

9.1 Introduction

In biological systems, receptors serve as protein-based structures responsible for receiving and transmitting signals (Pasquier and Andersson 2018). These medications and receptors are currently utilized in the treatment of diabetes. Examples include insulin, GLP-1, PPARs, biguanides, sulfonylureas, glinides, thiazolidinediones, gliptins, α -glucosidase inhibitors, amylin analogs, SGLT-2 inhibitors, and dopamine D-2 agonists. When blood glucose levels are elevated, the pancreas plays an active role by releasing insulin, which subsequently binds to its receptor, initiating its activation. Insulin is synthesized from proinsulin through the action of exoprotease carboxypeptidase and prohormone convertases (PC I and PC 2), leading to the production of insulin and C-peptide. In response to insulin, adipose and skeletal muscle cells (as well as other cells) in the body enhance glucose absorption by facilitating the translocation of GLUT4 to the cell membrane. Insulin plays a crucial role in regulating blood glucose levels and is indispensable in type 1 diabetes (T1D), also known as insulin-dependent diabetes mellitus (IDDM) or juvenile onset diabetes mellitus, and remains effective in all cases of diabetes mellitus (DM) (Tripathi 2018). New potential targets for diabetes management comprise GPCR 119 (Roshanzamir et al. 2018), GPER (Arterburn et al. 2023), 11-hydroxysteroid dehydrogenase 1, vaspin (Weiner et al. 2019), metrn1 (Miao et al. 2020), PEDF, fetuin-A, ACRP30 (AdipoQ) (Parida et al. 2019), visfatin, melatonin (Mok et al. 2019), GIP (Bailey et al. 2020), and GPCR (Hauser et al. 2021) among others. These represent emerging avenues for diabetic treatment in the future.

Traditional targets refer to medications that have been long used in the market for treating diabetes, yet they are limited and come with various drawbacks such as weight gain and hypoglycemia. Moreover, they merely provide control over the condition and delay complications. For instance, biguanides work by decreasing glucose production and enhancing glucose utilization in the liver and skeletal muscles, thereby regulating blood glucose levels. SGLT-2 inhibitors facilitate increased glucose excretion through the kidneys. α -glucosidase inhibitors assist in decreasing the intestinal absorption of glucose and free fatty acids. Sulfonylureas enhance insulin release and pancreatic sensitivity. Thiazolidinediones (2,4-T) mitigate free fatty acid production from fat cells (Fig. 9.1).

Recent targets in the quest for new diabetes therapy drugs encompass receptors and mediators. Extensive research efforts, including *in silico*, *in vitro*, *in vivo*, and clinical studies, have been dedicated to exploring these targets.

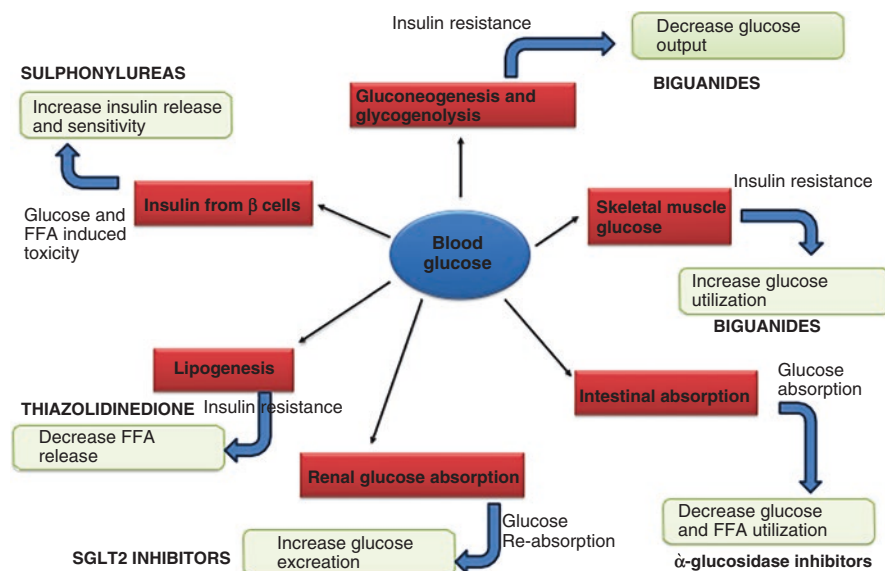


Fig. 9.1 Conventional targets in diabetes mellitus. *FFA* free fatty acid, *SGLT2* sodium glucose cotransporter-2

9.2 Antidiabetic Drugs

Antidiabetic medications are pharmaceuticals utilized to stabilize and regulate blood glucose levels in individuals with diabetes. These medications play a crucial role in the management of diabetes, helping individuals maintain optimal blood sugar levels.

1. Cardio-renal protective glucose-lowering medications.
 - (a) Sodium-glucose cotransporter-2 inhibitors: Canagliflozin, dapagliflozin, empagliflozin and ertugliflozin.
 - (b) Glucagon-like peptide-1 receptor agonist (GLP-1 RA):
 - Short-acting GLP-RAs (injectable drugs): Exenatide and lixisenatide.
 - Long-acting GLP-RAs: Liraglutide, dulaglutide, and semaglutide (albiglutide*¹).
2. Other glucose-lowering medications.
 - (a) Biguanides (AMPK activator): Metformin
 - (b) Sulphonylureas (SUs; ATP-sensitive potassium channel blockers)
 - First-generation SUs: Tolbutamide and chlorpropamide.
 - Second-generation SUs: Glyburide (or glibenclamide)², glipizide, gliclazide and glimepiride.

- (c) Meglitinides/glinides (phenylalanine analogs): Repaglinide and nateglinide.
 - (d) Dipeptidyl peptidase-4 inhibitors (DPP-4 Is):
 - Short-acting DPP-4 Is: Alogliptin, linagliptin, saxagliptin, sitagliptin and vildagliptin
 - Long-acting DPP-4 Is: Omarigliptin and trelagliptin.
 - (e) Dopamine (D2) agonist: Bromocriptine (QR).
 - (f) Glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist: Tirzepatide.
 - (g) Thiazolidinediones/glitazones (PPAR γ activator): Pioglitazone and rosiglitazone.
 - (h) Amylin analogs: Pramlintide.
3. Less commonly used glucose-lowering medications.
 - (a) Alpha-glucosidase inhibitors: Acarbose.
 4. Insulin therapy.
 - (a) Basal insulin.
 - Human insulin: Neutral protamine Hagedorn.
 - First-generation basal analogs: Insulin glargine (Gla-100).
 - Second-generation basal analogs: Insulin glargine (Gla-300), ultra-long-acting insulin degludec (IDeg-100 or IDeg-200).
 - (b) Prandial insulin: Regular human insulin, rapid-acting insulin analog, ultra-fast acting insulin analog and inhaled insulin.
 - (c) Premixed insulin combinations: Premixed human insulin and premixed analog insulin.
 - (d) Other insulin options: Fixed-ratio combination of basal insulin and GLP-I receptor agonist, regular insulin U-500.
 5. Antidiabetic combinations.

9.3 Cardio-Renal Protective Glucose-Lowering Medications

9.3.1 Sodium-Glucose Cotransporter-2 Inhibitors

This class of drugs carries a relatively low risk of hypoglycemia due to the increased glycosuria, which also slows down as blood sugar levels decrease (Janssen Pharmaceuticals Inc. [n.d.](#)). However, heightened glycosuria is associated with caloric loss, osmotic diuresis, and natriuresis, leading to decreased blood pressure, weight loss, reduced plasma volume, and decreased cardiac preload (Abd El Aziz et al. [2020](#)). SGLT2 inhibitors (SGLT2i) have been found to enhance cardiovascular (CV) and renal outcomes by promoting uric acid excretion (Abdelaziz et al. [2020](#)).

Approximately 97% of glucose reabsorption in the proximal convoluted tubule is facilitated by the high-capacity, membrane-bound SGLT2 receptors (Ferrannini and Solini [2012](#)). By lowering the renal threshold for glycosuria, SGLT2 receptor inhibitors (SGLT2i) decrease renal glucose reabsorption and renal gluconeogenesis (DeFronzo et al. [2012](#)).

9.3.1.1 Mechanism of Action

Increased plasma volume, hemoglobin, and hematocrit levels observed in patients with type 2 diabetes mellitus (Zinman et al. 2015) may be linked to reduced cardiovascular (CV) mortality, likely due to heightened erythropoietin production induced by SGLT2 inhibitors (SGLT2i). Additionally, SGLT2i may lead to elevated calcium levels in mitochondria and improved cardiac contractility (Packer et al. 2017). Notably, SGLT2i inhibits sodium-hydrogen (Na^+/H^+) exchange (NHE), a precursor to cardiomyocyte damage and ultimately CV mortality (Lytvyn and Bjornstad 2017), particularly in failing myocardium via overexpression of NHE1 (Batzias et al. 2018). In a study involving patients with type 2 diabetes mellitus and stable atherosclerotic disease without heart failure, treatment with either empagliflozin 10 mg daily or a placebo for three months resulted in a significant reduction in left ventricular mass observed on imaging in the empagliflozin group (Heerspink et al. 2016).

SGLT2 inhibitors (SGLT2i) have been shown to enhance endothelial function and reduce arterial stiffness, resulting in decreased afterload (Batzias et al. 2018). Particularly in individuals with diabetes mellitus (DM), they reduce the accumulation of epicardial fat, which has been associated with the development of cardiac fibrosis, heart failure (HF), and impaired cardiac contractility. SGLT2i also significantly impacts systemic inflammation, a critical pathway in the development of atherosclerosis and ventricular remodeling. Numerous studies have highlighted the anti-inflammatory, antioxidant, and anti-apoptotic properties of SGLT2i, achieved through modulation of mediators such as interleukins (IL) [IL-6, IL-10, IL-1b], nucleotide-binding oligomerization domain-like receptor 3 (NLRP-3), TNF- α , cyclo-oxygenase 2 (COX-2), and signal transducer and activator of transcription 3 (STAT3) (Lahnwong et al. 2018).

Furthermore, SGLT2 inhibitors (SGLT2i) stimulate the release of glucagon while inhibiting the release of insulin, leading to a shift in the body's preferred energy source from free fatty acids and glucose to ketone bodies, primarily β -hydroxybutyrate. Another proposed mechanism of action for this drug class involves altering cardiac substrate utilization to a more energy-efficient mode, favoring fatty acids and ketones. There is emerging evidence suggesting that SGLT2i may also improve the characteristics of non-alcoholic fatty liver disease (NAFLD), which has been linked to increased cardiovascular morbidity and mortality (Wei et al. 2021).

9.3.1.2 Dosing, Indications, and Contraindications

As per the latest ADA guidelines (Alshnbari et al. 2020), the currently available SGLT2 inhibitors (SGLT2i) include canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin.

1. *Canagliflozin*: The initial dose of canagliflozin is 100 mg, to be taken orally once daily, preferably before the first meal of the day. If necessary, the dose can be increased to 300 mg. However, canagliflozin should not be prescribed to patients with severe hepatic impairment. In type 2 diabetes (T2D) patients, canagliflozin

should not be used if the estimated glomerular filtration rate (eGFR) falls below 30 mL/min/1.73 m². It is important to note that there have been reports of canagliflozin-associated acute kidney injury, prompting a warning from the U.S. Food and Drug Administration in 2016 regarding the risk of acute renal function impairment.

2. *Dapagliflozin*: For patients with heart failure and reduced ejection fraction, dapagliflozin may be administered orally at a dose of 10 mg once daily, with or without meals, at any time of the day. However, in type 2 diabetes (T2D) patients, dapagliflozin should not be used if the estimated glomerular filtration rate (eGFR) falls below 25 mL/min/1.73 m². It is important to be aware that there have been reports of dapagliflozin-associated acute kidney injury, leading to a warning from the U.S. Food and Drug Administration in 2016 regarding the risk of acute renal function impairment. Notably, a significantly lower number of cases with dapagliflozin were reported in a trial investigating cardiovascular outcomes in patients with type 2 diabetes (Draznin et al. 2022).
3. *Empagliflozin*: Empagliflozin can be administered orally up to a dose of 25 mg once daily to establish glycemic control in heart failure trials due to its cardio-renal protective actions. Unlike some other SGLT2 inhibitors, empagliflozin does not require dose adjustment in patients with severe hepatic impairment (American Diabetes Association Professional Practice Committee 2022a). However, in type 2 diabetes (T2D) patients, empagliflozin should not be used if the estimated glomerular filtration rate (eGFR) falls below 25 mL/min/1.73 m². It is worth noting that empagliflozin can be administered at lower eGFR values (i.e., ≥ 20 mL/min/1.73 m²) in the presence of heart failure (with or without T2D).
4. *Ertugliflozin*: Ertugliflozin is administered once daily in the morning, with or without food, starting at a dose of 5 mg. If glucose control remains unsatisfactory, the dose may be increased to 15 mg. However, in type 2 diabetes (T2D) patients, ertugliflozin should not be used if the estimated glomerular filtration rate (eGFR) is less than 60 mL/min/1.73 m².

9.3.2 Glucagon-Like Peptide –1 Receptor Agonist (GLP-1 RA)

The GLP-1R, or glucagon-like peptide-1 receptor, is a type of G-protein coupled receptor predominantly located in pancreatic beta-cells. However, it is also expressed in various other tissues including the skin, immune cells, renal tissue, gastric mucosa, and hypothalamus. This receptor is believed to play a key role in the appetite-suppressing effects associated with this class of drugs. GLP-1 receptor agonists (GLP-1 RAs) are a specific subclass of “incretin-based therapies (IBTs),” which are widely used in the treatment of type 2 diabetes (Holst 2019).

9.3.2.1 Mechanism of Action

GLP-1, or glucagon-like peptide-1, exerts several beneficial effects in the body, including suppressing glucagon secretion, inhibiting appetite, slowing stomach emptying, and stimulating insulin secretion in a glucose-dependent manner. However, in patients with type 2 diabetes (T2D), these incretin actions are compromised, and GLP-1 levels are relatively low. Due to these characteristics, GLP-1 has emerged as a promising target for the treatment of T2D. However, its effectiveness is hindered by the enzyme DPP-4, or dipeptidyl peptidase-4, which is expressed on various cell surfaces and circulates in the bloodstream, rapidly inactivating native GLP-1 (American Diabetes Association Professional Practice Committee 2022b) (Rizzo et al. 2021).

As detailed earlier, both the central hypothalamus and gastrointestinal systems contribute to the overall beneficial effects of weight loss attributed to GLP-1. Alongside its role in promoting weight loss, there is evidence supporting the notion that increased GLP-1 concentrations enhance insulin sensitivity. Additionally, endoplasmic reticulum (ER) stress has been implicated in insulin resistance, and GLP-1 is believed to mitigate this association (Hare et al. 2010). Multiple molecular pathways are thought to be involved in this mechanism, including the reduction of TNF- α and nuclear factor-kappa B (NF- κ B) levels in endothelial cells, modulation of inflammatory responses by altering microRNAs (miRNAs) associated with lipid metabolism, and attenuation of oxidative stress through the enhancement of the antioxidant defense system (Capuani et al. 2018).

By stimulating GLP-1 receptors, both semaglutide and liraglutide enhance incretin function effectiveness. They achieve this by increasing glucose-dependent insulin secretion, suppressing glucagon release, and inhibiting hepatic gluconeogenesis, thereby lowering both fasting and postprandial glucose levels. Semaglutide has demonstrated a favorable proinsulin to insulin ratio, indicating improved beta-cell functioning efficiency and increased insulin production. Additionally, it has shown to enhance insulin sensitivity, likely mediated by a reduction in body weight. Furthermore, semaglutide, a short-acting GLP-1 receptor agonist, promotes weight loss by inducing satiety, suppressing appetite, decreasing post-meal glucose values, and delaying stomach motility, leading to reduced caloric intake. These medications also stimulate the proliferation of pancreatic beta-cells. Importantly, their mechanism of action renders them less prone to causing hypoglycemia, except when used in combination with insulin-enhancing drugs or insulin, which increases the risk (Wronka 2023).

Liraglutide has been shown to alleviate hyperglycemia-induced endothelial dysfunction. It exhibits antioxidant properties by reducing reactive oxygen species (ROS), lipid hydroperoxides, and heme oxygenase-1 levels while also preventing apoptosis through an increase in the concentration of anti-apoptotic protein Bcl-2 and a decrease in the level of pro-apoptotic protein Bax. Additionally, liraglutide decreases the concentration of MCP-1, indicating a reduction in inflammation. Furthermore, it restores GLP-1R/PKA and GTPCH1/eNOS pathway signaling and appears to restore calcium homeostasis through the PI3K/Akt/survivin pathway. Importantly, these antioxidant and anti-inflammatory properties of liraglutide are independent of glycemic control or weight (Wronka 2023).

9.3.2.2 Dosing, Indications and Contraindications

GLP-1 receptor agonists (GLP-1 RAs) are classified into two classes based on their molecular structure: those derived from the exendin-4 molecule and those derived from human GLP-1. Exenatide and lixisenatide are examples of GLP-1 RAs derived from Gila monster venom, representing synthetic forms of exendin-4. Animal studies have suggested that exenatide may promote beta-cell regeneration, although this finding has not been replicated in human studies. Conversely, liraglutide, dulaglutide, and semaglutide are GLP-1 RAs modified from human endogenous GLP-1. These GLP-1 RAs are administered via subcutaneous injection, except for oral semaglutide, which was FDA approved based on efficacy results from the “Peptide InnOvation for Early diabEtestReatment (PIONEER)” and “Evaluate Cardiovascular and Other Long-Term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN)” trials (Nauck et al. 2021).

Several studies have demonstrated that GLP-1 RAs effectively lower HbA1c levels with minimal risk of hypoglycemia when used alone or in combination with other medications. They are resistant to degradation by dipeptidyl peptidase-4 (DPP-4) and increase the half-life of GLP-1, providing sustained stimulation of the GLP-1 receptor (GLP-1R) and supra-physiologic GLP-1 levels. Indeed, GLP-1 receptor agonists (GLP-1 RAs) are classified into short-acting and long-acting categories based on their pharmacokinetic and pharmacodynamic properties. Short-acting GLP-1 RAs, such as exenatide and lixisenatide, are typically administered twice daily and have a relatively short half-life of 2–4 h. These agents primarily target and reduce postprandial hyperglycemia. The increased secretion of insulin and delayed gastric emptying are believed to contribute to this effect (Amin 2018).

1. *Exenatide*: Exenatide, a short-acting GLP-1 receptor agonist, is typically administered subcutaneously twice daily, either immediately before or within 1 hour prior to the morning and evening meals. The initial dose is 5 mg twice daily, which may be increased to 10 mg twice daily after approximately 1 month if necessary (Amori et al. 2007). However, it is important to note that this medication is contraindicated in patients with a history of severe hypersensitivity reactions to exenatide or related products (Anon n.d.). Additionally, it should not be used in individuals with advanced renal failure, defined as an estimated glomerular filtration rate (eGFR) ≤ 30 mL/min/1.73 m², as well as patients with severe gastrointestinal pathology such as gastroparesis.

2. *Lixisenatide*:

Lixisenatide, another short-acting GLP-1 receptor agonist, can be used in combination with oral agents as well as with basal insulin. The medication is administered as a subcutaneous injection approximately 1 h prior to any meal, starting at an initial dose of 10 µg. This dose may be increased to 20 µg after 2 weeks if glucose control remains suboptimal. Similar to exenatide, lixisenatide is indicated as an adjunct to diet and exercise in patients with type 2 diabetes (T2D) and is contraindicated in patients with a history of hypersensitivity reactions to the drug. Additionally, it is not recommended for use in individuals with advanced renal failure or in patients with gastroparesis (Collins and Costello 2022).

Long-acting GLP-1 receptor agonists (GLP-1 RAs) such as liraglutide, semaglutide, and dulaglutide primarily target and improve basal hyperglycemia. These medications are designed to provide sustained and continuous stimulation of the GLP-1 receptor throughout the day, leading to enhanced glucose control, particularly in fasting and between-meal periods. By increasing insulin secretion in a glucose-dependent manner and suppressing glucagon release, they help regulate blood sugar levels more effectively, thereby addressing basal hyperglycemia, which is often a key feature in the management of type 2 diabetes.

1. *Liraglutide*: It is a prolonged-acting GLP-1 receptor agonist (RA), synthesized through recombinant DNA technology, fused with a 16-carbon fatty acid compound that binds to albumin, thereby extending the drug's half-life to 13 h by hindering degradation by DPP4. Administered via daily subcutaneous injections due to poor oral bioavailability, facilitating once daily dosing. The initial dosage commences at 0.6 mg daily for the first week, progressing to 1.2 mg daily in the subsequent week, with a maximum dosage potentially titrated up to 1.8 mg daily, primarily guided by basal glucose levels. Liraglutide, akin to other prolonged-acting GLP-1 RAs, is contraindicated in individuals with a history of medullary thyroid cancer, multiple endocrine neoplasia IIA or IIB, predominantly influenced by certain rodent studies. Nevertheless, clinical trials have yet to report any instances of medullary thyroid carcinoma associated with liraglutide treatment, with sustained low levels of calcitonin post-treatment. The rarity and gradual clinical development of medullary thyroid carcinoma pose challenges in assessing potential risks associated with this complication. Indicated for glycemic control in type 2 diabetes mellitus (T2DM) patients, alongside a healthy lifestyle, either independently or in combination with other glucose-lowering medications. While metformin remains the primary treatment for T2DM, GLP-1 analogs, including liraglutide, serve as alternatives when metformin is intolerable or contraindicated, or when target HbA1c levels are not met within 3 months or exceed the threshold by over 1.5%. Large liraglutide doses have gained approval for managing obesity or overweight with comorbidities, yielding up to 2.9 kg of weight loss. Its versatility in timing, once daily subcutaneous administration, irrespective of meal intake, enhances its appeal. Notably, liraglutide's efficacy in mitigating microvascular complications is not significantly superior to other agents like glargine, glimepiride, or sitagliptin. However, liraglutide therapy has demonstrated efficacy in reducing nephropathy incidence and progression. Liraglutide emerges as a promising predictor of cardiovascular events, manifesting in reduced cardiovascular and all-cause mortality rates, alongside prevention of non-fatal strokes and myocardial infarctions. Furthermore, this drug category exerts favorable effects on systolic blood pressure and lipid profile, decreasing total cholesterol, triglycerides, and low-density lipoprotein cholesterol while elevating high-density lipoprotein cholesterol. Intriguingly, individuals at higher cardiovascular risk may derive greater benefits from liraglutide therapy (Novo Nordisk Inc. n.d.).
2. *Dulaglutide*: This is another extended-release GLP-1 receptor agonist (RA) with a half-life lasting approximately 5 days. The initial prescribed dosage is

0.75 mg administered subcutaneously once weekly. If blood glucose levels persist uncontrolled, the dosage can be escalated to 1.5 mg administered subcutaneously once weekly. For patients diagnosed with type 2 diabetes (T2D) and confirmed atherosclerotic cardiovascular disease (ASCVD), or displaying indicators of high ASCVD risk, such as individuals aged 55 years or older with left ventricular hypertrophy (LVH), carotid, coronary, or lower-extremity artery stenosis exceeding 50%, or those with chronic kidney disease (CKD), the American Diabetes Association (ADA) guidelines recommend considering liraglutide, semaglutide, or dulaglutide, regardless of baseline HbA1c levels, HbA1c target, or metformin usage. Conversely, for patients lacking clinical ASCVD, the choice between prolonged- and short-acting agents is typically made to suit patient convenience (Ludvik et al. 2018).

3. *Semaglutide*: This marks the debut of the initial oral medication within the GLP-1 RA category for managing type 2 diabetes (T2D). Findings from the PIONEER trial series reveal that semaglutide significantly reduces HbA1c levels and body weight compared to other antidiabetic agents. Presently, oral semaglutide is available in three doses: 3 mg, 7 mg, and 14 mg (marketed as Rybelsus; 3, 7, 14 mg), all administered once daily. The starting dose is 3 mg once daily for 30 days, which may then be increased to 7 mg daily. Should glycemic control remain insufficient after 30 days, the dosage can be further escalated to 14 mg daily. Oral semaglutide includes a co-formulation with a fatty acid derivative called SNAC (sodium-N-[8-(2-hydroxybenzoyl) amino] caprylate; utilizing Eligen® Technology by Emisphere Technologies), acting as a permeation enhancer. SNAC enhances semaglutide's solubility by raising the local pH, allowing passive transcellular transport across cell membranes, and safeguarding semaglutide from proteolytic degradation in the stomach's acidic environment. The tablet should be ingested on an empty stomach, preferably 30 min prior to a meal. Injectable formulations are also available (marketed as Ozempic; 0.5, 1.0 mg). The initial dosage is 0.25 mg once weekly for 4 weeks, followed by an increase to 0.5 mg once weekly. The Ozempic pen (available in red and blue) contains a strength of 1.34 mg/mL. The red pen delivers the initiation dose of 0.25 mg and the maintenance dose of 0.5 mg, while the blue pen is intended for the 1.0 mg (maximum maintenance dose). The dose can be titrated up to a maximum FDA-approved dose of 2 mg weekly as of March 2022. In June 2021, the FDA approved semaglutide 2.4 mg once weekly (marketed as Wegovy) for chronic weight management in individuals with obesity or overweight accompanied by additional cardiovascular risk factors. Transitioning between injectable and oral formulations is feasible. Notably, a randomized, double-blinded phase II clinical trial demonstrated significant reductions in HbA1c levels and body weight with both oral and subcutaneous semaglutide compared to placebo, with no notable disparities between the available formulations. Semaglutide is indicated as an adjunct therapy to diet and exercise for improving glycemic control in patients with T2D and to reduce cardiovascular events in adults with T2D at high cardiovascular disease (CVD) risk. The American Diabetes Association in 2020 suggests semaglutide use when greater glycemic control and weight reduction are imperative, and before insulin initiation. Semaglutide is par-

ticularly recommended for cardiovascular diseases of atherosclerotic nature and in cases of SGLT-2 inhibitor intolerance. Studies report semaglutide's ability to reduce atherosclerosis by negatively regulating multiple inflammatory pathways in proatherogenic animal models. Furthermore, GLP-1 agonists have been found to exhibit cardioprotective effects by reducing apoptosis in rat cardiac cells. It has also received approval for use in liver and kidney impairment, without necessitating dose adjustment (Collins and Costello 2022).

9.4 Other Glucose-Lowering Medications

9.4.1 Biguanides: Metformin

Metformin, one of the earliest medications utilized in the treatment of diabetes, traces its origins back to the 1920s with the identification of the anti-hyperglycemic properties found in the active components of the French lilac plant, *Galega officinalis*. Following its initial introduction in Europe, metformin gained approval for usage in the USA in 1995 (Triggle et al. 2022).

9.4.1.1 Mechanism of Action

Today, metformin is acknowledged as a versatile medication with a plethora of intricate mechanisms of action. This hydrophilic cation not only activates cellular AMP kinase but also impedes hepatic gluconeogenesis through modifications in mitochondrial enzymes and the hepatic redox state. Moreover, it facilitates the restoration of insulin secretion, elevates endogenous GLP-1 levels via mechanisms distinct from DPP-4 inhibition, and safeguards pancreatic cells against glucotoxicity and lipotoxicity (Yang et al. 2017). The efficacy of delayed-release metformin highlights its capacity to enhance glucose utilization in the gastrointestinal (GI) tract. While metformin primarily reduces post-meal blood sugar levels, it also decreases postprandial blood sugar in a manner resembling that of a prandial insulin secretagogue. Metformin not only enhances glycemic management but also exhibits a range of pleiotropic effects on other organs such as the heart and nervous system. According to U.S. FDA recommendations, metformin should be discontinued if the estimated glomerular filtration rate (eGFR) falls below 30 mL/min/1.73 m². Safe and effective metformin doses for stages 3A (eGFR 45-59 mL/min/1.73 m²), 3B (eGFR 30-44 mL/min/1.73 m²), and 4 (eGFR 15-29 mL/min/1.73 m²) of chronic kidney disease (CKD) have been reported as 1500 mg/day, 1000 mg/day, and 500 mg/day, respectively. According to the FDA, metformin use may be deemed safe in CKD stage 4 at its lowest dose (500 mg/day). It's noteworthy that for individuals with CKD stage 3 and above, eGFR should be reassessed every 3–6 months. Additionally, metformin should be discontinued if a single blood lactate level exceeds 5 mmol/L or if two levels exceed 2.5 mmol/L, as a small percentage of asymptomatic individuals may experience a modest increase in lactate levels (American Diabetes Association Professional Practice Committee 2022b).

9.4.2 Sulfonylureas (SUs)

Sulfonylureas (SUs) gained FDA approval in the 1950s as the first oral antidiabetic medications, originating from discoveries made in the 1940s when it was observed that patients treated with sulfonamides for typhoid fever experienced severe hypoglycemia. First-generation SUs, like tolbutamide and chlorpropamide, are now rarely prescribed. However, second—and third-generation SUs, such as glyburide (also known as glibenclamide), glipizide, gliclazide (not available in the USA), and glimepiride, continue to be utilized in contemporary clinical practice (Lavabre-Bertrand and Faillie 2021).

9.4.2.1 Mechanism of Action

When sulfonylureas (SUs) bind to the sulfonylurea receptor 1 (SUR-1) subunit of the ATP-sensitive potassium (K-ATP) channels, insulin secretion occurs independently of blood glucose levels. This binding leads to channel closure, membrane depolarization, intracellular calcium influx, and subsequent insulin secretion. Apart from pancreatic beta-cells, SUR isoforms (SUR-2A and SUR-2B) exist in other tissues like neurons, myocardium, and vascular smooth muscle cells. These isoforms possess different binding affinities for SUR-1, which harbors two distinct binding sites: the SU site and the meglitinide site. Consequently, each drug in this class exhibits varied pharmacodynamic and pharmacokinetic properties due to these differences (Gribble et al. 1998).

9.4.2.2 Dosing, Indications, and Contraindications

To attain glycemic control, it is essential to titrate sulfonylurea (SU) dosages, gradually increasing them starting from a low dose and continuing every 2 weeks. Rarely do doses exceeding the half-maximum contribute to improved glycemic control; instead, they elevate the risk of hypoglycemia (Costello et al. 2022).

1. *Glyburide*: Glyburide should be taken with meals at dosages ranging from 2.5 to 15 mg once or twice a day. It is important to note that the metabolites of glyburide possess hypoglycemic properties.
2. *Gliclazide*: It should be taken with meals at dosages ranging from 40 to 320 mg. Instant-release formulations are typically taken 30 min before a meal once or twice a day.
3. *Glimepiride*: It should be taken with meals at dosages ranging from 1 to 6 mg once or twice a day. Additionally, it is worth noting that the metabolites of glyburide and glimepiride possess hypoglycemic properties.
4. *Glipizide*: The instant-release formulation is typically taken at dosages ranging from 2.5 to 20 mg, 30 min before a meal, once or twice a day.

9.4.3 Meglitinides/Glinides

Decades ago, it was discovered that glibenclamide's non-sulfonylurea (non-SU) component possesses insulintropic properties. This revelation led to the

introduction of three medications in this therapeutic class, known as meglitinides: nateglinide, repaglinide, and mitiglinide. Repaglinide was first granted FDA approval in 1997 and is available in the USA, Europe, and Japan, along with nateglinide and mitiglinide (Dornhorst 2001).

9.4.3.1 Mechanism of Action

Meglitinides are insulin secretagogues that bind to SUR-1 on islet beta-cells at a site distinct from the sulfonylurea (SU) site in the pancreas. This binding causes the closure of K-ATP channels and subsequent insulin release (Guardado-Mendoza et al. 2013). Meglitinides are particularly effective in controlling postprandial glucose excursions due to their ability to induce early-phase postprandial insulin secretion, which peaks at 1–2 h and has a short half-life of 1–1.5 h. Insulin concentrations return to fasting levels within 6 h. Compared to SUs, meglitinides work more rapidly and for a shorter duration, resulting in improved postprandial glucose management and reduced risk of late-onset hypoglycemia. Although not definitively proven, nateglinide is believed to lower DPP-4 levels, thereby increasing incretin hormone levels. Both repaglinide and nateglinide undergo extensive metabolism primarily by the hepatic cytochrome P450 enzyme system, including CYP3A4 and CYP2C9 isoenzymes. Approximately 90% of repaglinide is eliminated via the gastrointestinal tract, with the remainder excreted in the urine. Nateglinide, however, is primarily eliminated through urinary excretion.

9.4.3.2 Dosing, Indications, and Contraindications

1. *Repaglinide*: The dose range for repaglinide is typically 0.5–4.0 mg orally, administered three times daily with meals or up to 30 min before eating. Repaglinide offers the advantage of not requiring dose adjustments when administered to individuals with mild to moderate renal insufficiency (eGFR 40 mL/min/1.73 m²) because its metabolism is primarily hepatic. For patients with an eGFR of 20–40 mL/min/1.73 m², the initial dose of repaglinide should be 0.5 mg before the largest meal, with additional doses administered before other meals as needed. Unlike sulfonylureas (SUs), repaglinide does not necessitate a snack between meals to prevent hypoglycemia due to its rapid onset, allowing for variable mealtime dosing. However, repaglinide is contraindicated in certain situations. For instance, co-administration with clopidogrel and gemfibrozil can inhibit hepatic excretion, increasing the risk of hypoglycemia. Additionally, combining repaglinide with specific antibiotics such as cefditoren, levofloxacin, and clarithromycin has been associated with an elevated risk of hypoglycemia. Therefore, caution should be exercised when prescribing repaglinide in these scenarios.
2. *Nateglinide*: The dose range for repaglinide is typically 60–120 mg orally, administered three times daily with meals or up to 30 min before eating. It is important to note that active metabolites are excreted through the kidneys, which can lead to hypoglycemia in patients with impaired renal function. Therefore, meticulous monitoring of blood glucose levels is essential in such patients to ensure appropriate management and prevent hypoglycemic episodes.

Meglitinides present several challenges in terms of adherence due to their various daily dose schedules. Additionally, they have the potential to induce weight gain and may interact with other drugs due to their hepatic metabolic pathway. It is important to exercise caution when prescribing meglitinides in patients with moderate to severe liver disease, as their metabolism may be affected. Therefore, careful monitoring and consideration of potential drug interactions are essential when using meglitinides in such patients (Blickl'e 2006)

9.4.4 Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

The incretin effect refers to the phenomenon where the human insulin response is observed to be higher following oral glucose administration compared to intravenous glucose infusion. This effect is mediated by the release of incretin hormones, particularly GLP-1 (glucagon-like peptide-1) and GIP (glucose-dependent insulinotropic peptide), which are rapidly degraded by the enzyme DPP-4 (dipeptidyl peptidase-4). GLP-1 stimulation and the inhibition of its degradation lead to several beneficial effects, including glucose-dependent insulin secretion, promotion of pancreatic beta-cell proliferation, reduction of food intake and glucagon secretion, and delay in gastric emptying. Since 2006, a class of oral medications known as DPP-4 inhibitors or gliptins has been approved for the treatment of type 2 diabetes (T2D). There are 11 DPP-4 inhibitors approved worldwide (Deacon 2020). Among the most widely used are sitagliptin, linagliptin, vildagliptin, saxagliptin, and alogliptin. These medications are available in the USA except for vildagliptin.

9.4.4.1 Mechanism of Action

DPP-4 (dipeptidyl peptidase-4) is a serine protease enzyme widely expressed in various organs, including the uterus, enterohepatic system, and kidneys. In type 2 diabetes (T2D), decreased post-prandial incretin levels lead to reduced insulin secretion and hyperglycemia. The enzyme DPP-4 breaks down incretin hormones like GLP-1 and GIP, which have short half-lives (1–2 min and 7 min, respectively). DPP-4 inhibitors block this enzyme by more than 80–90%, resulting in a 2–3-fold increase in GLP-1 (mainly) and GIP levels. Elevated GLP-1 levels in the presence of glucose stimulate higher insulin secretion and reduced glucagon concentrations, ultimately lowering blood glucose levels. Research is ongoing regarding dihydropyrimidine phthalimide hybrids as potential new, potent, and selective DPP-4 inhibitors (Holst 2019).

9.4.4.2 Dosing, Indications and Contraindications

Individuals with renal disease, including those with end-stage renal disease (ESRD), can safely use DPP-4 inhibitors. However, except for linagliptin, the doses of these medications need to be adjusted according to the degree of renal impairment. DPP-4 inhibitors are considered a preferable treatment option for patients who face challenges with polypharmacy due to their minimal drug-drug interactions. In addition to metformin, DPP-4 inhibitors are recommended as second-line treatment for

patients with T2D. According to the ADA (American Diabetes Association) and EASD (European Association for the Study of Diabetes) guidelines, in the absence of chronic kidney disease (CKD), significant cardiovascular (CV) risk, or known CV disease (in which case GLP-1 receptor agonists and/or SGLT2 inhibitors are preferred), DPP-4 inhibitors should be considered, especially when there is a need to reduce hypoglycemia. This recommendation is particularly relevant for weak and elderly patients (>75 years) with multiple comorbidities and organ dysfunction. Due to their favorable side effect profile (e.g., no weight gain or hypoglycemia), durability, and comparable efficacy, DPP-4 inhibitors are preferred over sulfonylureas (SU). Evidence suggests that these medications are safe and effective for treating post-kidney transplant diabetic mellitus (PTDM) (Gallwitz 2019).

9.4.5 Dopamine D-2 Agonists

The D2 receptor (D2R) agonist bromocriptine has been approved by the Food and Drug Administration (FDA) since 2009 for the treatment of type 2 diabetes mellitus. It has demonstrated efficacy in reducing glycated hemoglobin (HbA1c), fasting plasma glucose levels, and body weight. Cycloset, an enantiomer of bromocriptine, was specifically approved by the FDA in 2010 as a glucose-lowering medication. Since then, it has been widely utilized in the management of type 2 diabetes mellitus across the USA.

9.4.5.1 Mechanism of Action

Bromocriptine is a selective D2 dopamine receptor agonist that also exhibits some antagonist properties for D1 dopamine receptors. In individuals with type 2 diabetes, bromocriptine influences the levels of monoamine neurotransmitters in specific brain regions such as the suprachiasmatic and ventromedial nuclei of the hypothalamus. This leads to a sympatholytic effect, slowing down metabolic activity and potentially increasing the risk of glucose intolerance and insulin resistance. Bromocriptine regulates prolactin secretion and hypothalamic sympathetic output. Recent discoveries indicate that peripheral dopamine plays a role in stimulating glucose uptake *in vivo* within insulin-sensitive tissues such as adipose tissue, the liver, and skeletal muscle. Bromocriptine directly influences glucose uptake, insulin sensitivity, and metabolic function in these tissues. Treatment with bromocriptine increases levels of D1 dopamine receptors (D1R) and tyrosine hydroxylase (TH) in adipose tissue and the liver, leading to enhanced insulin sensitivity and increased catabolic activity. Furthermore, bromocriptine acts on pancreatic beta-cells to reduce glucose-stimulated insulin secretion (GSIS). This mechanism helps prevent long-term beta-cell depletion, contributing to the overall management of glucose levels in individuals with type 2 diabetes (Tavares et al. 2021).

Additionally, bromocriptine has been found to increase the levels of GLUT4 (glucose transporter 4) and the insulin receptor (InsR) gene in the peri-epididymal adipose tissue (pEWAT), as well as enhance the activation of the InsR following a mixed meal. Administration of bromocriptine also resulted in rapid potentiation of

insulin-mediated glucose uptake in adipose tissue explants through activation of the D2 dopamine receptor (D2R). The significant expression of the D1 dopamine receptor (D1R) in response to bromocriptine, linked to the Gs protein-cAMP signaling pathway, suggests its involvement in the regulation of catabolic pathways in pEWAT. Increased levels of AMPK-Thr172 and ACL-Ser455 during fasting in pEWAT indicate heightened fasting catabolic activity directed toward lipid oxidation. Dopamine receptor agonists that act at the pituitary to reduce serum prolactin levels are expected to impair glucose tolerance. Bromocriptine, commonly used to treat prolactinoma, reduces prolactin levels, inhibits insulin production, and decreases insulin sensitivity. Central insulin in the mesolimbic pathway has been shown to decrease dopamine levels, creating a feedback regulatory loop. The regulation of glucose homeostasis relies on appropriate levels of central dopamine and prolactin, as dysregulation of these levels could lead to central insulin resistance.

9.4.5.2 Dosing, Indications, and Contraindications

For the treatment of type 2 diabetes mellitus, bromocriptine is available in tablet or capsule form for oral administration, typically starting at a dose of 0.8 mg. Once the target level of glycemic control is achieved, the dose is gradually increased weekly by 0.8 mg, up to a maximum daily dose of 4.80 mg. Bromocriptine is available in two formulations: a quicker release (QR) formulation of 0.8 mg, which reaches peak blood concentrations in about 45–60 min and has a bioavailability of 65–95%, and a standard release formulation of 2.5–5 mg, which reaches peak blood concentrations after about 3 h with a bioavailability of 28%. Common side effects of bromocriptine include fatigue, nausea, vomiting, lightheadedness, low blood pressure, and hypotension. More serious side effects may include psychosis, fibrosis (cardiac valve, pleural, and retroperitoneal), and cardiovascular events such as myocardial infarction, stroke, and valvular damage. Bromocriptine treatment is not recommended for individuals with type 1 diabetes, syncope, or psychosis. It should also be avoided by individuals with syncopal migraines due to the risk of hypotensive episodes, as well as by breastfeeding individuals because it inhibits lactation. Additionally, caution is advised when administering bromocriptine in conjunction with inducers or inhibitors of CYP3A4, as well as in patients with hepatic impairment. The QR formulation can be used in patients with compromised renal function, as 98% of its metabolites are eliminated into bile acid. Clinical studies have shown that bromocriptine QR alone can decrease HbA1c levels by 0.65% without increasing the risk of hypoglycemia. Furthermore, the QR formulation has been shown to significantly reduce cardiovascular outcomes in patients with type 2 diabetes mellitus in randomized clinical trials (Tavares et al. [2021](#)).

9.4.5.3 Safety and Tolerability

Bromocriptine-QR presents itself as a promising insulin sensitizing therapy with a favorable safety profile, minimal side effects, and no risk of weight gain or hypoglycemia. It also holds the potential to reduce unfavorable cardiovascular risk and promote strong treatment adherence. However, caution is advised regarding its use in pregnancy, as decreased prolactin release in the fetus may occur with prolonged use,

necessitating a pregnancy test if amenorrhea develops. Before initiating bromocriptine therapy, patients should undergo a cardiovascular evaluation and liver function tests (LFTs) to assess for elevated liver enzymes, as its metabolism primarily occurs in the liver via the cytochrome P450 3A4 enzymes. Individuals with hepatic impairment should avoid bromocriptine use. Accidental overdoses of bromocriptine, predominantly affecting children, have been reported. These overdoses may result in various dopaminergic effects, notably hypotension. Management of overdose typically involves the administration of activated charcoal to prevent systemic absorption, nasogastric administration of magnesium citrate, and intravenous saline to increase blood pressure. While bromocriptine-QR shows promise as an alternative for managing type 2 diabetes mellitus, especially in challenging cases, long-term safety and efficacy data are lacking, and it has not yet received approval in Japan. Further research is needed to fully understand its benefits and risks in the treatment of diabetes (Gibson et al. [2012](#)).

9.4.6 Glucose-Dependent Insulinotropic Polypeptide (GIP) and Glucagon-Like Peptide-1 Receptor Mono/Dual Agonist

GIP, one of the incretin hormones, is distributed in various tissues such as the brain, adipose tissue, and pancreatic β -cells. Its primary role lies in enhancing the insulin response triggered by the postprandial rise in blood sugar levels, making it a key player in type 2 diabetes mellitus and other metabolic disorders. Tirzepatide, a newly approved medication, has demonstrated significant efficacy in reducing both body weight and HbA1c levels in individuals with obesity and diabetes. Unlike GLP-1R mono-agonists such as semaglutide and liraglutide, tirzepatide acts as a dual agonist for two GPCRs: the GLP-1 and GIP receptors. This dual action confers tirzepatide with superior ability to lower blood glucose levels and promote weight loss. As a first-in-class agent for the treatment of type 2 diabetes, tirzepatide is administered once weekly via injection and targets both the glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 receptor (GLP-1RA). It has received approval for use in various countries including Australia, Canada, the European Union, the UK, and the USA. The optimal place for tirzepatide in diabetes therapy is still being determined as ongoing research investigates its effects on major adverse cardiovascular events (MACE), diabetic kidney disease, and heart failure. Nevertheless, its high efficacy in controlling blood sugar levels and inducing weight loss makes it an appealing option for the management of type 2 diabetes (Mounjaro (tirzepatide), package insert [2023](#)).

9.4.6.1 Mechanism of Action

GIP exerts its insulinotropic effects by interacting with the GIP receptor (GIPR), leading to an increase in intracellular levels of cyclic adenosine monophosphate (cAMP). This increase in cAMP levels activates protein kinase-A (PKA) and exchange protein activated by cAMP 2 (EPAC2). Subsequently, voltage-gated

calcium channels depolarize, causing an influx of intracellular calcium ions (Ca^{2+}), which in turn activates Ca^{2+} from intracellular stores through PKA and EPAC2 pathways. The elevated Ca^{2+} concentration promotes the transcription of the proinsulin gene, thereby facilitating increased insulin production from β -cells. Tirzepatide is a 39-amino-acid modified peptide with a C20 fatty diacid moiety, allowing it to bind to albumin and extend its half-life for once-weekly dosing. This compound selectively binds to and activates both the GIP and GLP1 receptors, which are the targets for native GIP and GLP1, respectively. This unique mechanism of action makes tirzepatide the first-in-class dual GIP/GLP1 receptor agonist.

9.4.6.2 Dosing, Indications, and Contraindications

Tirzepatide recommended dose is 2.5 mg s.c. with once-weekly titration to max 15mg/week. It contributes to weight loss and have neutral effects on CVS. GIT effects like nausea, decreased appetite, diarrhoea, constipation, vomiting, dyspepsia and abdominal pain were observed with its use. Pancreatitis may be seen infrequently, but it can prevent chronic kidney disease and reduce eGFR decline. Its use is contraindicated in thyriod C cell tumors. Personal or familial history of medullary thyroid carcinoma, Multiple endocrine neoplasia syndrome type 2 (MEN-2) and known hypersensitivity to tirzepatide (Mounjario (tirzepatide), package insert [2023](#)).

9.4.7 Thiazolidinediones/Glitazones

Thiazolidinediones (TZDs), also known as glitazones, were serendipitously discovered in the 1980s during efforts by Japanese researchers to synthesize more potent fibrates. It was found that some of these compounds, in addition to their lipid-modifying properties, also exhibited hypoglycemic effects in diabetic mice. Following this discovery, rosiglitazone and pioglitazone were approved for use in the USA in 1999, and they remain the only two glitazones currently in use (Lalloyer and Staels [2010](#)).

9.4.7.1 Mechanism of Action

Thiazolidinediones (TZDs), acting as insulin sensitizers, selectively activate peroxisome proliferator-activated receptor-gamma (PPAR-gamma), a member of the nuclear hormone receptor family involved in regulating energy metabolism. Upon activation, PPAR-gamma agonists such as TZDs enhance the secretion of adiponectin, a protein derived from adipocytes that possesses insulin-sensitizing properties. Additionally, they increase the expression of glucose transporter type 4 (GLUT-4) in both muscle and adipose tissue. Furthermore, TZDs inhibit the effect of tumor necrosis factor-alpha (TNF-alpha) in adipocytes. PPAR-gamma is prominently expressed in adipose tissue compared to skeletal muscle. The primary effect of TZDs occurs in adipose tissue, where they facilitate the uptake and storage of fatty acids, consequently reducing fat accumulation in the liver, muscle, and pancreas. This mechanism leads to improvements in both insulin action and secretion (Tyagi et al. [2018](#)).

9.4.7.2 Dosing, Indications, and Contraindications

1. The initial recommended dosage of pioglitazone is 15 mg taken orally once daily. This dosage can be adjusted based on individual patient response and tolerability. The maximum recommended dose of pioglitazone is 45 mg taken once daily.
2. The recommended starting dose of rosiglitazone is 4 mg taken orally once daily. The maximum recommended dose of rosiglitazone is 8 mg daily, which can be administered either as 4 mg twice daily or as a single dose of 8 mg once daily.

The maximum glycemic effect of TZDs, such as pioglitazone and rosiglitazone, may take up to 10–14 weeks to manifest fully. Therefore, adjustments to the dosage should not be considered before a minimum of 12 weeks of treatment. It's important to monitor liver function tests and HbA1c periodically during TZD therapy. TZDs are typically administered once daily regardless of food intake. They undergo hepatic metabolism and do not require dosage adjustments for any degree of renal impairment, including end-stage renal disease (ESRD) (Wang et al. 2017).

9.4.8 Amylin Analogs

Amylin is a neuroendocrine hormone that is co-secreted with insulin by pancreatic beta-cells in an equimolar manner. Its primary function is to regulate postprandial glucose levels by slowing gastric emptying, suppressing glucagon secretion, and reducing food intake. Amylin deficiency is observed in patients with type 1 diabetes (T1D) and late-stage type 2 diabetes (T2D). Pramlintide (Symlin) is a synthetic analog of amylin that mimics its physiological actions. It was approved by the FDA in 2005 for use in both types of diabetes. Pramlintide is administered subcutaneously before meals to help control postprandial glucose excursions. It can be used as an adjunct to insulin therapy in patients with T1D or T2D who have failed to achieve glycemic control with insulin alone (Lee and Norris 2010).

9.4.8.1 Mechanism of Action

Indeed, amylin, through its various mechanisms of action, plays a crucial role in regulating postprandial glucose concentrations and overall glucose homeostasis. By inhibiting gastric emptying, enhancing satiety, suppressing glucagon secretion, and reducing hepatic glucose production, amylin helps to control blood sugar levels after meals. The combination of insulin and amylin replacement therapy is considered more physiological than insulin alone, particularly in insulin-requiring patients such as those with type 1 diabetes or advanced type 2 diabetes. Pramlintide, as a synthetic amylin analogue, provides an adjunctive treatment option to insulin therapy, aiming to mimic the physiological effects of amylin and improve overall glycemic control, especially in the postprandial period (Uwaifo and Ratner 2005).

9.5 Less Commonly Used Glucose-Lowering Medications

9.5.1 Alpha-Glucosidase Inhibitors

Among the four alpha-glucosidase inhibitors (AGIs) you mentioned—acarbose, miglitol, voglibose, and emiglitate—only acarbose and miglitol are approved by the FDA and available for use in the United States. Acarbose and miglitol work by inhibiting the enzymes in the small intestine responsible for breaking down carbohydrates into simple sugars, thus slowing down the absorption of glucose after meals. This mechanism helps to reduce postprandial blood sugar spikes in individuals with type 2 diabetes (Pishdad et al. [2020](#)).

9.5.1.1 Mechanism of action

Exactly. Alpha-glucosidase inhibitors (AGIs) such as acarbose, voglibose, and miglitol work as reversible inhibitors of the enzyme alpha-glucosidase, which is present in the brush border of the small intestine. By inhibiting this enzyme, they slow down the breakdown of complex carbohydrates into simple sugars, thus reducing the absorption of glucose from the gut into the bloodstream. This leads to lower postprandial glucose and insulin levels after meals. Acarbose and voglibose are minimally absorbed from the gut and are primarily excreted in the stool, while miglitol is absorbed systemically and excreted through the kidneys. Additionally, recent research suggests that AGIs may also increase gut incretin levels, further contributing to their glucose-lowering effects (Kalra [2014](#)).

9.6 Insulin Therapy

Insulin plays a crucial role in regulating glucose metabolism by facilitating the uptake of glucose into cells, thereby lowering blood glucose levels. Here are some differences between insulins derived from different sources:

Species Source: Insulin can be obtained from various sources, including pigs, cattle, and humans.

Amino Acid Sequence: While the overall structure of insulin is similar across species, there are differences in the amino acid sequence, particularly in the A and B chains. These differences can affect the pharmacokinetics and immunogenicity of the insulin.

Immunogenicity: Insulins derived from non-human sources, such as pigs and cattle, may be more immunogenic in humans compared to human insulin. This can lead to immune reactions and antibody formation against the insulin, potentially affecting its efficacy over time.

Purity: Human insulin produced using recombinant DNA technology (rDNA) tends to be purer and more consistent in its composition compared to insulin obtained from animal sources. This can result in more predictable pharmacokinetics and reduced risk of adverse reactions.

Formulations: Insulin formulations vary based on their onset, peak, and duration of action. These formulations include basal insulins (long-acting), prandial

insulins (rapid-acting), and premixed insulins (combination of rapid-acting and intermediate-acting insulins). Each type of insulin formulation serves a specific purpose in managing blood glucose levels throughout the day.

Route of Administration: Insulin is commonly administered via subcutaneous injection, but advancements have led to the development of alternative delivery methods, such as inhaled insulin. These alternative routes of administration offer convenience and may improve patient adherence to insulin therapy (DeMarsilis and Mantzoros 2022).

Overall, the development of various types of insulin over the past century has revolutionized the management of diabetes, providing patients with more options for effectively controlling their blood glucose levels and improving their quality of life. (Table 9.1):

Indeed, pig insulin is more structurally similar to human insulin compared to beef insulin. Here is a breakdown of the insulin synthesis process and the role of the C-peptide:

1. **Preproinsulin:** Insulin is initially synthesized in pancreatic beta-cells as a precursor molecule called preproinsulin. Preproinsulin consists of 110 amino acids (AA) and contains a signal peptide that targets it to the endoplasmic reticulum.
2. **Proinsulin:** The signal peptide is cleaved off, resulting in proinsulin, which consists of 86 amino acids. Proinsulin contains three regions: the A-chain (21 AA), the B-chain (30 AA), and the connecting peptide or C-peptide (35 AA).
3. **Insulin and C-peptide Formation:** Within the Golgi apparatus, proinsulin undergoes proteolytic cleavage, leading to the formation of insulin and the C-peptide. The A and B chains of insulin are held together by two disulfide bonds, while the C-peptide is separated from insulin during this processing.
4. **Storage and Secretion:** Both insulin and the C-peptide are packaged into secretory granules within the pancreatic beta-cells. Upon stimulation by glucose or other stimuli, these granules release insulin and the C-peptide into the bloodstream in equimolar amounts.
5. **C-Peptide in the Blood:** While insulin is responsible for regulating blood glucose levels by promoting glucose uptake into cells, the C-peptide serves no known physiological function. However, because insulin and the C-peptide are secreted in equimolar amounts, the measurement of C-peptide levels in the blood can serve as a marker of endogenous insulin secretion (Tripathi 2018).

Overall, the synthesis and processing of insulin involve the formation of proinsulin, which is then cleaved to generate insulin and the C-peptide. Both insulin and the

Table 9.1 Differences between human, pork, and beef insulins

Species	A-chain		B-chain
	8th AA	10th AA	30th AA
Human	THR	ILEU	THR
Pork	THR	ILEU	ALA
Beef	ALA	VAL	ALA

C-peptide play important roles in glucose metabolism and can serve as important markers in the diagnosis and management of diabetes.

9.6.1 Mechanism of Action

Insulin exerts its effects on various tissues and organs in the body through its interaction with insulin receptors. Here is how insulin functions at the cellular level:

1. **Glucose Uptake:** Insulin binds to its receptor on the cell membrane of target cells, such as skeletal muscle and adipose tissue. This binding activates intracellular signaling pathways that promote the translocation of glucose transporter proteins, particularly GLUT4, to the cell membrane. As a result, there is an increased uptake of glucose into the cells, leading to a decrease in blood glucose levels.
2. **Glucose Metabolism:** Once inside the cell, glucose is phosphorylated to glucose-6-phosphate by the enzyme glucokinase. This step is crucial for further metabolism of glucose, including glycolysis and glycogen synthesis, which are stimulated by insulin. By promoting these pathways, insulin facilitates the utilization and storage of glucose as glycogen in muscle and liver cells.
3. **Protein Synthesis:** Insulin plays a role in promoting protein synthesis by facilitating the entry of amino acids into cells, particularly muscle cells. It inhibits the breakdown of muscle protein (proteolysis) and enhances the uptake of amino acids, which are essential for protein synthesis and tissue repair.
4. **Lipid Metabolism:** Insulin inhibits lipolysis, the breakdown of triglycerides into fatty acids and glycerol, in adipose tissue. This leads to a decrease in circulating fatty acids. Additionally, insulin promotes lipid synthesis (lipogenesis) in the liver and adipose tissue, contributing to fat storage.
5. **Glycogenolysis and Gluconeogenesis:** Insulin suppresses the breakdown of glycogen (glycogenolysis) in the liver, reducing the release of glucose into the bloodstream. It also inhibits gluconeogenesis, the synthesis of glucose from non-carbohydrate sources, by decreasing the activity of key enzymes involved in this process.
6. **Receptor Structure and Signaling:** The insulin receptor is a tetrameric protein composed of two extracellular α subunits and two transmembrane β subunits linked by disulfide bonds. Upon insulin binding, the receptor undergoes autophosphorylation of tyrosine residues in the β subunits, activating intracellular signaling cascades such as the PI3K/Akt pathway and the MAPK pathway. These signaling pathways mediate the metabolic effects of insulin on glucose uptake, metabolism, and gene expression (Thota and Akbar 2022).

Overall, insulin plays a central role in regulating glucose and energy metabolism in the body, coordinating various cellular responses to maintain glucose homeostasis (Fig. 9.2).

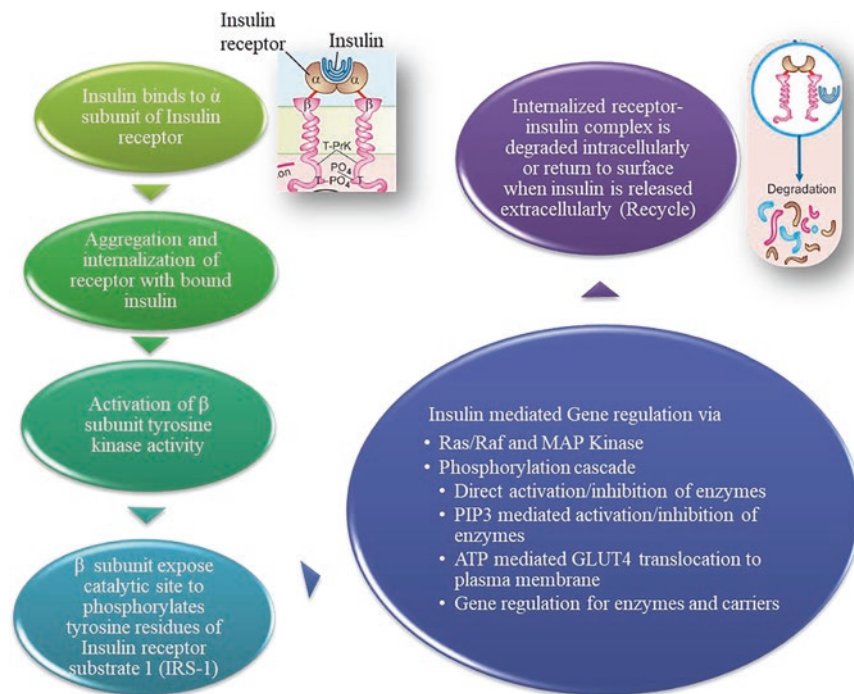


Fig. 9.2 Mechanism of action of insulin. *T* tyrosine residue, *GLUT4* insulin-dependent glucose transporter, *IRS* insulin receptor substrate proteins, *PIP3* phosphatidyl inositol trisphosphate, *MAP kinase* mitogen-activated protein kinase, *T-PrK* tyrosine protein kinase, *Ras* regulator of cell division and differentiation (protooncogene product)

9.6.2 Regular Insulin U-500

U-500 regular insulin, which is five times more concentrated than standard U-100 insulin, was approved for use in 1994 for individuals requiring high doses of insulin, typically exceeding 200 units per day. Its higher concentration allows for the delivery of larger doses of insulin in a smaller volume, which can be beneficial for those with severe insulin resistance who require large amounts of insulin to control their blood sugar levels.

Due to its increased concentration, U-500 regular insulin has a longer duration of action, altered time to reach maximum effect, and a different peak concentration compared to standard U-100 insulin. This altered pharmacokinetic profile may result in improved glycemic control without the need to increase the total number of insulin units injected. However, the use of U-500 regular insulin is associated with some drawbacks. It is linked to an increased risk of hypoglycemia (low blood sugar levels) and weight gain, which are common side effects of insulin therapy. Therefore, close monitoring of blood sugar levels and adjustment of insulin doses are necessary to minimize these risks. The typical dosing regimen for U-500 regular insulin

involves administration 2–3 times per day, serving as both basal and prandial insulin to manage blood sugar levels throughout the day. Despite its challenges, U-500 regular insulin remains a valuable option for individuals with severe insulin resistance who require high doses of insulin to achieve glycemic control (shown in Fig. 9.3).

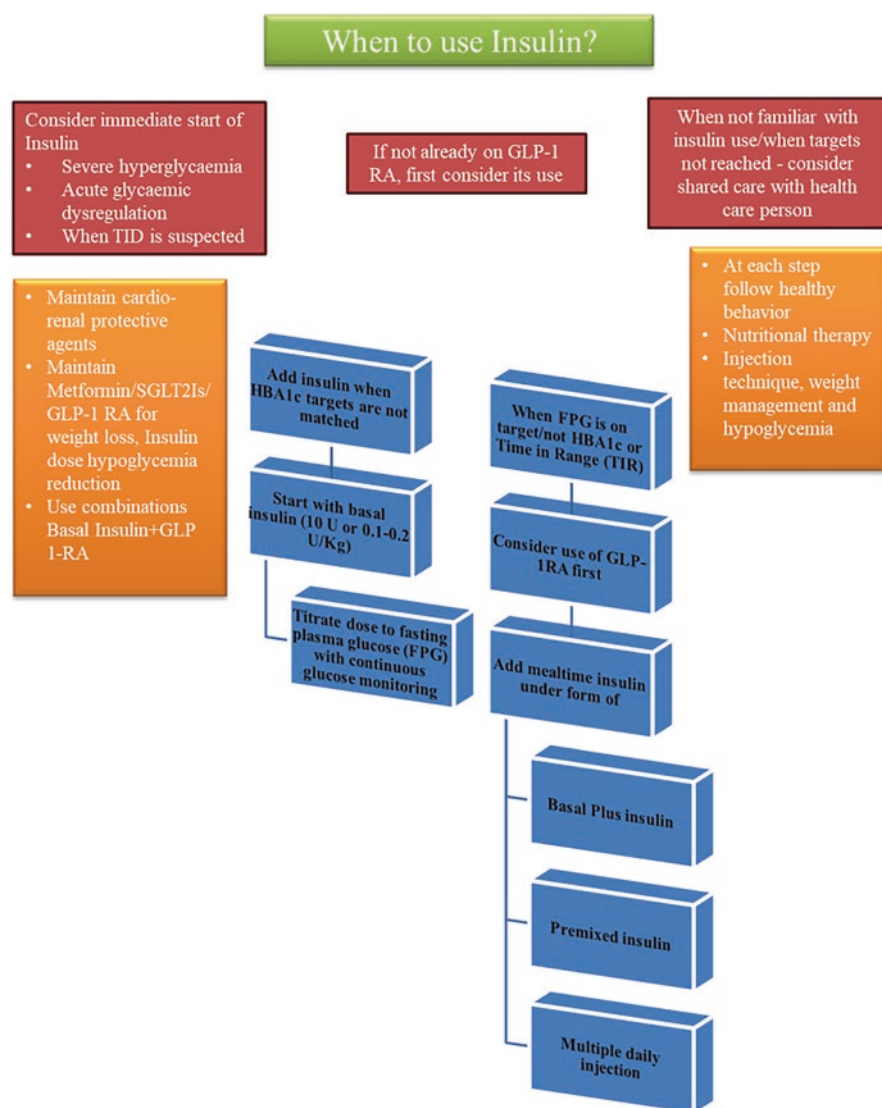


Fig. 9.3 When to use insulin for treatment of diabetes? *T1D* Type 1 Diabetes; *SGLT2Is* Sodium-Glucose Co-transporter 2 Inhibitors; *GLP-1RA* Glucagon Like Peptide 1 Receptor Agonists; *HbA1c* Glycated haemoglobin;

9.7 Novel Targets for T2D Treatment

Some of the promising novel targets being under clinical development include the following. The sequence of their clinical evaluation in different phases is elucidated in Fig. 9.4.

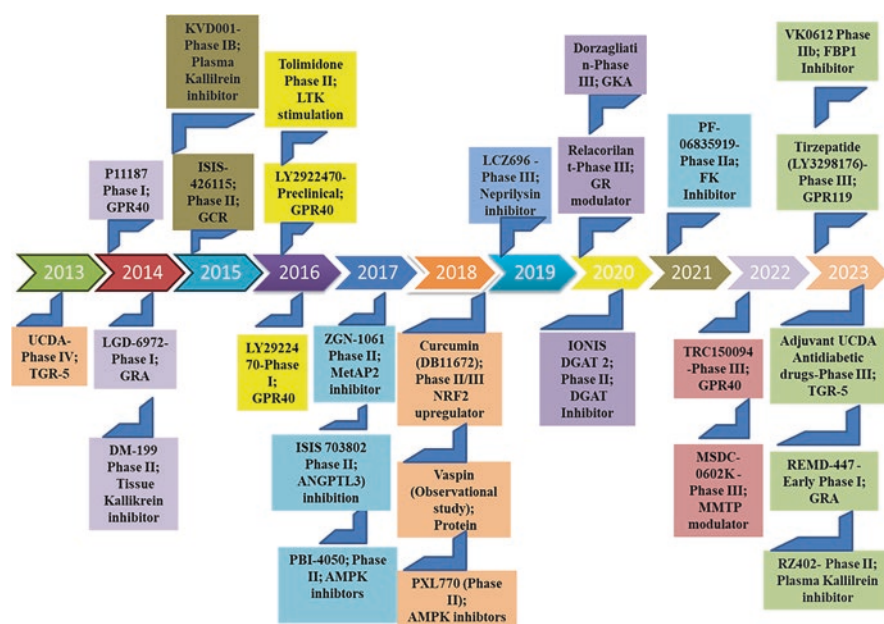


Fig. 9.4 The sequential clinical evaluation of the novel drug targets as antidiabetics. *GPR40* G-protein-coupled receptor 40; *GCR* Glucagon receptors; *GKA* Glucokinase activators; *GR* Glucocorticoid receptor; *FK* Fructokinase; *FBPI* Fructose-1,6-bisphosphatase-1; *GPR-119* G-protein-coupled receptor-119; *TGR-5* Takeda G protein-coupled receptor 5; *MetAP2* Methionine aminopeptidase 2; *ANGPTL3* Angiopoietin-related protein 3; *AMPK* AMP-activated protein kinase; *NRF2* Nuclear Factor (Erythroid-Derived 2)-Like 2; *DGAT* Diacylglycerol acyltransferase;

9.8 Conclusions

The landscape of pharmacotherapy for type 2 diabetes mellitus (T2D) is continually evolving, with a wide array of established and cutting-edge treatments available to patients. As our understanding of each agent and their benefits grows, there is increasing emphasis on personalized treatment approaches tailored to individual patients' needs. This involves considering both clinical factors such as body weight, current HbA1c levels, and comorbidities, as well as non-clinical factors like cost, health literacy, and patient preferences. Shared decision-making between healthcare providers and patients plays a crucial role in maximizing treatment adherence and success. Despite the availability of various treatment options, there is still a need for further research to deepen our understanding of precision medicine in diabetes care. This includes gaining insights into new therapeutic targets and advancing the discipline from basic research to implementation science. Given the significant impact of diabetes on public health and healthcare costs, individualizing care while addressing social determinants of health remains essential. Many conventional methods for treating T2D, such as insulin therapy, biguanides, sulfonylureas, and others, have been used for decades. However, these treatments often come with side effects such as weight gain, hypoglycemia, and gastrointestinal issues. Moreover, they primarily focus on managing symptoms and delaying disease progression rather than providing a long-term solution. To address these challenges, researchers are exploring novel therapeutic targets for diabetes medication. Over the years, various receptors and molecules involved in insulin regulation, such as GPCRs, 11-hydroxysteroid dehydrogenase 1, and others, have emerged as potential targets for drug development. Additionally, advancements in gene therapy and stem cell research hold promise for future diabetes treatments with improved efficacy and fewer adverse effects. Continued research in these areas is crucial for developing better therapies for managing diabetes and its complications.

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Drugs Used for Immunomodulation

10

Subarna Ganguli and Tatini Debnath

Abstract

Immunomodulators are substances that can modify the body's immune response. The human immune system comprises a variety of components, including organs, white blood cells (WBCs), proteins, and other chemical elements that serve to safeguard the body from the threats posed by diseased cells and toxins. When the immune system is compromised, individuals may require immunomodulators to enhance its effectiveness. The immune system consists of both cellular and humoral components. Cellular components encompass macrophages, dendritic cells, NK cells, T-cells, and B-cells, while humoral components include antibodies and cytokines. One critical function of the immune system is to prevent the development of cancer by eliminating or suppressing oncogenic viral infections. Immunomodulators can alter the inflammatory environment, which plays a significant role in tumor formation. Additionally, the immune system conducts immune surveillance, identifying and eliminating transformed cells before they can inflict harm on the body.

Keywords

Immunosuppressants · Immunotherapy · Corticosteroids · DMARDs

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229

10.1 Introduction

Immunomodulators are medications designed to alter the way your body's immune system responds. The immune system is a complex network comprising organs, white blood cells, proteins, and various chemicals that function collectively to shield the body from threats, including germs and diseased cells like cancer cells, prompting a robust immune response to combat them. There are various conditions that can impede the proper functioning of your immune system, preventing it from effectively safeguarding your health. In such situations, immunomodulators may be necessary to enhance the immune system's functionality and help it better protect the body. Hence, immunomodulation refers to a therapeutic approach wherein efforts are made to intervene in the natural self-regulating processes of the body's defense system. Immunomodulation acts in two ways, i.e., immunosuppression and immunostimulation (Bascones-Martinez et al. [2014](#)).

10.2 Immune System

The immune system is composed of various elements that work together to protect the body from infections, diseases, and other threats. These elements include

1. **White Blood Cells (Leukocytes):** White blood cells are a crucial component of the immune system. They are divided into several types, including:
 - (a) **Neutrophils:** These are the most abundant white blood cells and play a key role in fighting bacterial infections.
 - (b) **Lymphocytes:** These include T-cells, B-cells, and natural killer (NK) cells. They are responsible for specific immune responses and antibody production.
 - (c) **Monocytes:** These cells can differentiate into macrophages and dendritic cells, which are important for phagocytosis and antigen presentation.
 - (d) **Eosinophils:** Primarily involved in combating parasitic infections and allergic responses.
 - (e) **Basophils:** Release histamine and other mediators during allergic reactions.
2. **Lymphatic System:** The lymphatic system consists of lymph nodes, lymph vessels, and lymphatic organs. It plays a critical role in filtering and transporting lymph (a clear fluid), which contains immune cells and removes pathogens and waste products from the body.
3. **Bone Marrow:** This is where blood cells, including white blood cells, are produced and mature.
4. **Thymus:** The thymus gland is vital for the maturation and development of T lymphocytes (T-cells), which are essential for cell-mediated immunity.
5. **Spleen:** The spleen acts as a blood filter and is involved in the production of antibodies, removal of damaged blood cells, and storage of platelets.
6. **Lymph Nodes:** Lymph nodes are small, bean-shaped structures that filter lymph and contain immune cells. They help identify and combat infections.

7. **Antibodies (Immunoglobulins):** Antibodies are proteins produced by B-cells. They recognize and bind to specific pathogens, marking them for destruction by other immune cells.
8. **Complement System:** The complement system consists of proteins that help the immune system clear pathogens through various mechanisms, including cell lysis and opsonization.
9. **Phagocytes:** These are specialized white blood cells that engulf and digest pathogens. They include macrophages, neutrophils, and dendritic cells.
10. **Cytokines:** Cytokines are signaling molecules that regulate immune responses, including inflammation, cell communication, and cell differentiation.
11. **Antigen-Presenting Cells (APCs):** These cells, such as dendritic cells and macrophages, capture and present antigens to T-cells, initiating immune responses.
12. **Immune Memory:** The immune system has the capacity to remember previous encounters with pathogens, enabling faster and more effective responses upon re-exposure.

These elements work together to recognize, respond to, and eliminate pathogens and foreign substances, thereby maintaining the body's health and protecting it from infections.

10.3 Function of Immunomodulators

Immunomodulators can be categorized into two general categories based on how they work. They may:

1. **Immunosuppressors (Immunosuppressive Agents):**
 - (a) **Suppress the Immune Response:** Immunosuppressors are used to dampen or suppress the activity of the immune system. They are commonly employed in autoimmune diseases or conditions where the immune system is overactive and causes harm to the body.
 - (b) **Examples:** Corticosteroids, calcineurin inhibitors (cyclosporine, tacrolimus), and various chemotherapy drugs.
2. **Immunostimulants (Immunostimulatory Agents):**
 - (a) **Enhance the Immune Response:** Immunostimulants are substances that boost or stimulate the immune system's activity. They are used to improve the body's defense mechanisms against infections or diseases.
 - (b) **Examples:** Interferons, interleukins, and certain vaccines.

These two categories represent the dual role of immunomodulators in either dampening or enhancing the immune response, depending on the specific medical condition or therapeutic goal.

Immunomodulators, as the name suggests, are substances that can modify or regulate the immune response in the body. In the context of treating cancer, immunomodulators are utilized to enhance the immune system's ability to recognize

and destroy cancer cells effectively (Pelletier-Dattu 2015). These treatments aim to boost the body's natural defenses against cancer by activating immune cells and signaling pathways that target and eliminate malignant cells. For instance, immunomodulatory therapies like immune checkpoint inhibitors work by blocking certain proteins on the surface of immune cells, allowing them to recognize and attack cancer cells more effectively. Other immunotherapies involve the use of genetically engineered immune cells, such as CAR-T cells, which are designed to specifically target cancer cells in the body. By increasing the immune response in this manner, immunomodulators play a vital role in the evolving field of cancer immunotherapy, offering new and promising avenues for the treatment of various types of cancer.

Immunosuppressants are a class of immunomodulators that are specifically designed to reduce or suppress the activity of the immune system. These medications are commonly used when there is a need to decrease the body's immune response, and they are particularly important in the following scenarios:

1. **Autoimmune Diseases:** In autoimmune diseases, the immune system mistakenly targets and attacks healthy cells and tissues within the body. Immunosuppressants are prescribed to help mitigate this harmful immune response, preventing or slowing down the attack on healthy tissues.
2. **Transplants (Organ or Stem Cell):** After procedures like organ transplants or allogeneic stem cell transplants, there is a risk of the recipient's immune system recognizing and attacking the newly transplanted tissue or cells as foreign invaders. Immunosuppressants are used in these cases to suppress the immune response and prevent rejection of the transplanted material.

These immunosuppressant drugs work by interfering with various components of the immune system, reducing its activity and its ability to attack healthy tissues or transplanted organs. While they are valuable in managing autoimmune diseases and preventing transplant rejection, they also come with potential side effects and risks, as they lower the body's defenses against infections and other threats. Therefore, their use is carefully monitored and tailored to each individual's specific medical condition and needs.

Immunomodulators treat the following condition as enumerated below:

1. Ulcerative colitis.
2. Sjogren's syndrome.
3. Rheumatoid vasculitis.
4. Rheumatoid arthritis.
5. Psoriasis.
6. Plaque psoriasis.
7. Pericarditis.
8. Multiple sclerosis.
9. Myositis.
10. Lupus erythematosus.

11. Juvenile idiopathic arthritis.
12. Irritable bowel syndrome.

There are many more conditions which are encompassed under the immunomodulators.

10.4 Immunotherapy

Immunotherapy is a type of medical treatment that works by educating and enhancing the immune system's ability to identify and combat cancer cells. Cancer cells often possess mechanisms to evade the body's standard immune defenses. Immunotherapy is designed to bolster the immune response, making it more effective in detecting and eliminating cancer cells. This treatment approach makes it challenging for cancer cells to proliferate and evade the immune system's surveillance, ultimately contributing to the fight against cancer.

- Checkpoint inhibitors are a class of immunotherapy drugs used to treat cancer. Cancer cells can employ a strategy to evade the body's immune system by deactivating the signals that typically instruct T-cells (a type of immune cell) to attack and eliminate them. Checkpoint inhibitors work by preventing cancer cells from turning off these important signals. In essence, they "keep the signals turned on" and enable the immune system to recognize and target cancer cells, enhancing the body's natural ability to combat the disease. This approach has shown promise in improving the outcomes for some cancer patients by bolstering the immune response against the malignancy.
- Adoptive cell therapy, often referred to as T-cell transfer therapy, is a specialized cancer treatment that involves the removal of T-cells (a type of immune cell) from a patient's body. These harvested T-cells are then modified and enhanced in a laboratory setting to make them more effective at recognizing and attacking cancer cells. Once these T-cells have been reprogrammed to target cancer, they are reintroduced into the patient's body. The modified T-cells are better equipped to locate and destroy cancer cells, providing a targeted and potent approach to treating certain types of cancer. This innovative therapy has shown significant promise in the field of cancer immunotherapy.
- Monoclonal antibody therapy is a medical approach that harnesses the power of antibodies, which are proteins naturally present in the body and used to combat various threats. In this therapy, laboratory-generated replicas of the body's own antibodies, known as monoclonal antibodies, are employed to target and combat cancer. These synthetic antibodies are designed to specifically recognize and bind to cancer cells or other molecules involved in the growth and spread of cancer. By using monoclonal antibody therapy, medical professionals can enhance the body's natural immune response against cancer and disrupt the cancer's progression. This treatment has proven to be effective in certain cases and is part of the broader field of cancer immunotherapy.

- Cancer vaccines are a form of immunotherapy that functions by instructing the immune system to identify and target cancer cells. These vaccines are designed to “train” the immune system to recognize specific markers or antigens found on cancer cells. By introducing these markers to the immune system through vaccination, the body’s immune cells learn to identify cancer cells as threats. As a result, if cancer cells develop, the immune system is better equipped to recognize and attack them, which can help prevent or control the growth of cancer. Cancer vaccines are a promising area of research and treatment in the field of oncology, aiming to stimulate the body’s natural defenses against cancer.
- Immune system modulators represent a category of cancer treatments designed to disrupt the processes that cancer cells employ to multiply and spread. These treatments encompass various approaches, including the use of cytokines, Bacillus Calmette-Guerin (BCG), and biologic response modifiers. Biologic response modifiers are substances that modify the body’s response to diseases, and in the context of cancer, they can help regulate the immune system to combat the disease more effectively.

Examples of biologic response modifiers used in cancer treatment include:

- Thalidomide.
- Lenalidomide.
- Pomalidomide.
- Imiquimod.

These substances can have various effects on the immune system and may enhance the body’s ability to recognize and attack cancer cells, contributing to the management of the disease. Immune system modulators are an important part of the arsenal of treatments available for cancer.

10.5 Corticosteroids

Corticosteroids are a class of medications that have immunosuppressive properties and are often used to reduce inflammation in the body. These drugs are among the most frequently prescribed immunosuppressants. Corticosteroids work by dampening the body’s immune response and suppressing inflammation. They are utilized in the treatment of various conditions, including:

- **Autoimmune Conditions:** Corticosteroids are commonly prescribed to manage autoimmune diseases, where the immune system mistakenly attacks the body’s own tissues. These drugs help reduce the immune response, alleviating symptoms and controlling the disease.
- **Allergies:** Corticosteroids are used to alleviate allergic reactions and conditions, such as allergic rhinitis and asthma, by reducing inflammation in the airways and other affected areas.

- **Some Cancers:** In certain situations, corticosteroids may be part of the treatment plan for specific types of cancer, where they help manage inflammation and symptoms associated with the disease.

While corticosteroids can be effective in treating these conditions, they also come with potential side effects, especially when used long term. Their use is typically carefully monitored by healthcare professionals to balance the benefits of reducing inflammation and suppressing the immune response with the potential risks and side effects. Examples of corticosteroids are prednisolone, dexamethasone, prednisone, etc.

10.6 Disease-Modifying Antirheumatic Drugs (DMARDs)

Disease-modifying antirheumatic drugs (DMARDs) encompass a range of medications that have the capacity to reduce the immune response in the body. By decreasing the immune response, DMARDs can alleviate pain and inflammation, making them a valuable treatment for various medical conditions.

DMARDs are commonly used in the management of rheumatoid arthritis, where they work to modify the course of the disease, slow its progression, and alleviate symptoms. In addition to rheumatoid arthritis, certain forms of DMARDs are also employed to treat other autoimmune conditions, allergies, skin conditions, and some types of cancer. Furthermore, some traditional DMARDs may serve to prevent the body from rejecting a transplanted organ following an organ transplant procedure.

The specific DMARD prescribed and its application depend on the particular medical condition and the patient's individual needs and medical history. These drugs are an important component of treatment plans for various immune-related and inflammatory conditions. The medicines are methotrexate, hydroxychloroquine, sulfasalazine, etc.

10.7 Biologics

Biologics represent a more recent category of disease-modifying antirheumatic drugs (DMARDs). Unlike traditional DMARDs, which are typically chemical compounds, biologics are composed of proteins that are manufactured in a laboratory. These proteins are specifically designed to target and interfere with the activities of specific cells and pathways in the immune system that are responsible for causing inflammation.

One of the distinguishing features of biologics is their precision in targeting the immune system. They are capable of targeting very specific components involved in the inflammatory response. This targeted approach can make biologics more potent and effective in managing inflammatory conditions, such as rheumatoid arthritis, psoriasis, and inflammatory bowel disease, compared to traditional DMARDs.

Biologics have been a significant advancement in the field of immunology and have provided new and powerful treatment options for individuals with autoimmune and inflammatory disorders. However, it is important to note that they are typically more expensive and may carry different side effect profiles compared to traditional DMARDs, and their use should be carefully monitored and tailored to the patient's specific needs.

The various types of biologics are as follows:

Tumor necrosis factor (TNF) inhibitors are a class of medications that work by reducing the effects of TNF, a substance in the body that plays a significant role in causing inflammation. These drugs are used to manage inflammatory conditions, particularly autoimmune diseases like rheumatoid arthritis, psoriasis, and inflammatory bowel disease, where excessive TNF can contribute to chronic inflammation and tissue damage (Sausville and Longo 2015).

Some common TNF inhibitors include:

- Adalimumab.
- Infliximab.
- Etanercept.

Interleukin-1 (IL-1) inhibitors are medications designed to block the effects of IL-1, a protein known for its role in promoting inflammation in the body. These drugs are used to manage inflammatory conditions where excess IL-1 activity contributes to chronic inflammation and tissue damage. An example of an IL-1 inhibitor is anakinra, which is sold under the brand name Kineret®. By blocking IL-1, these medications help reduce inflammation and alleviate symptoms associated with conditions such as rheumatoid arthritis and other autoimmune diseases. IL-1 inhibitors have proven to be effective in treating a range of inflammatory disorders, providing relief to individuals suffering from these conditions. However, like other immunomodulatory drugs, their use should be closely monitored by healthcare professionals due to potential side effects and individualized treatment considerations.

Interleukin-6 (IL-6) inhibitors are a class of medications designed to block the effects of IL-6, a protein that plays a key role in promoting inflammation within the body. These drugs are used to manage inflammatory conditions where excessive IL-6 activity contributes to chronic inflammation and related symptoms. An example of an IL-6 inhibitor is tocilizumab, which is marketed under the brand name Actemra®. By inhibiting the action of IL-6, these drugs help reduce inflammation and alleviate symptoms associated with various autoimmune diseases, including rheumatoid arthritis and certain systemic inflammatory conditions. IL-6 inhibitors have proven to be effective in addressing these conditions and providing relief to affected individuals. Nonetheless, similar to other immunomodulatory medications, their usage should be carefully supervised by healthcare professionals to account for potential side effects and individualized treatment considerations.

T-cell inhibitors are a class of medications designed to prevent T-cells, a type of immune cell, from mistakenly attacking and killing healthy cells in the body. These drugs are used to manage autoimmune conditions where the immune

system's T-cells become overactive and attack the body's own tissues. An example of a T-cell inhibitor is abatacept, which is sold under the brand name Orencia®. By inhibiting T-cell activity, these medications help reduce the immune response and alleviate the symptoms associated with autoimmune diseases like rheumatoid arthritis. T-cell inhibitors are an important component of treatment for these conditions, as they help to modulate the immune system and prevent the ongoing damage caused by misguided T-cell attacks. However, their use is typically monitored by healthcare professionals due to potential side effects and individual patient needs.

B-cell inhibitors are a class of medications designed to prevent B-cells, a type of immune cell, from releasing antibodies that attack the body's own healthy cells. These drugs are used to manage autoimmune conditions and certain diseases where the immune system's B-cells produce antibodies that target and harm healthy tissues. An example of a B-cell inhibitor is rituximab, marketed under the brand name Rituxan®. By inhibiting B-cell activity, these medications help reduce the production of autoantibodies, which can lead to the relief of symptoms associated with autoimmune diseases such as rheumatoid arthritis, lupus, and certain types of vasculitis. B-cell inhibitors are an important part of the treatment strategy for these conditions, as they help regulate the immune response and mitigate the damage caused by autoantibodies. However, the use of these drugs is typically closely monitored by healthcare professionals due to potential side effects and individualized treatment considerations.

Administration of immunomodulators

1. Parenterally.
2. By injection.
3. Orally.
4. Topical application.

Immunomodulators, which are medications that modify or regulate the immune system, can have various side effects. The specific side effects can vary depending on the type of immunomodulator, the individual's response to the medication, and the underlying medical condition being treated. Common side effects associated with immunomodulators may include:

1. **Suppressed Immune Response:** Many immunomodulators, especially immunosuppressants, can weaken the immune system's ability to defend against infections. This may increase the risk of infections and make it harder for the body to fight off illnesses.
2. **Allergic Reactions:** Some individuals may experience allergic reactions to immunomodulators, which can range from mild skin rashes to severe allergic responses.
3. **Gastrointestinal Issues:** Nausea, diarrhea, vomiting, and abdominal discomfort are common gastrointestinal side effects associated with some immunomodulators.

4. **Skin Reactions:** Skin problems, including rashes, hives, and skin discoloration, can occur as side effects.
5. **Fatigue:** Many people may experience fatigue or increased tiredness as a side effect of immunomodulators.
6. **Liver and Kidney Problems:** Some immunomodulators can affect liver and kidney function, leading to abnormal liver enzyme levels or kidney dysfunction.
7. **Mood Changes:** Mood swings, depression, and anxiety are reported side effects of some immunomodulators.
8. **Bone Marrow Suppression:** Certain immunomodulators can affect the bone marrow's ability to produce blood cells, potentially leading to anemia, thrombocytopenia, or leukopenia.
9. **Increased Blood Pressure:** Some immunomodulators may lead to elevated blood pressure.
10. **Hair Loss:** Hair loss or thinning can be a side effect of certain immunomodulators.
11. **Respiratory Issues:** Breathing problems, including shortness of breath and cough, can occur in some cases.

It is important to note that these side effects can vary widely from person to person. Not everyone will experience all of these side effects, and some individuals may experience side effects not listed here. Additionally, the severity of side effects can differ, and some may be mild and manageable while others are more severe and require medical attention. Patients prescribed immunomodulators should be closely monitored by healthcare providers, and any concerns or side effects should be promptly discussed with a medical professional to determine the appropriate course of action, including potential adjustments to the treatment plan.

10.8 Risk of Immunomodulators

Immunomodulators, like many medications, carry certain risks and considerations. These risks can vary depending on the specific immunomodulator used, the individual's health, and the underlying medical condition being treated. Here are some of the common risks associated with immunomodulators:

1. **Infection Risk:** Many immunomodulators suppress the immune system, which can increase the susceptibility to infections. This includes bacterial, viral, and fungal infections. In some cases, these infections can be severe or difficult to treat.
2. **Allergic Reactions:** Some individuals may have allergic reactions to immunomodulators, which can range from mild skin rashes to severe anaphylactic reactions.
3. **Cancer Risk:** Certain immunomodulators have been associated with an increased risk of developing certain types of cancer, particularly lymphomas and skin cancers.

4. **Autoimmune Reactions:** In some cases, immunomodulators can paradoxically lead to autoimmune reactions, where the immune system attacks the body's own tissues.
5. **Organ Toxicity:** Some immunomodulators can have toxic effects on specific organs, such as the liver or kidneys, which may require regular monitoring.
6. **Blood Disorders:** Bone marrow suppression is a risk with some immunomodulators, which can lead to conditions like anemia, thrombocytopenia, or leukopenia.
7. **Cardiovascular Effects:** Some immunomodulators can impact blood pressure and cardiovascular health.
8. **Psychiatric Effects:** Mood changes, including depression and anxiety, have been reported as side effects of certain immunomodulators.
9. **Gastrointestinal Issues:** Digestive problems, including nausea, vomiting, and diarrhea, can occur with some immunomodulators.
10. **Bone Health:** Osteoporosis and bone fractures are potential risks associated with long-term use of certain immunomodulators.
11. **Pregnancy and Fertility:** Some immunomodulators can affect pregnancy and fertility. Women of childbearing age should discuss these risks with their healthcare provider.

It is essential for individuals considering or prescribed immunomodulators to have a thorough discussion with their healthcare provider about the potential risks and benefits. In many cases, the decision to use immunomodulators is carefully weighed against the severity of the underlying condition and the patient's overall health. Regular monitoring and follow-up with a healthcare provider are typically necessary to manage and mitigate these risks effectively. Patients should always report any concerning symptoms or side effects to their healthcare team.

10.9 The Effectiveness of Immunomodulators

It indeed varies depending on the specific medical condition being treated, the type of immunomodulator used, and the individual's response to the treatment. Immunomodulators are prescribed with the goal of achieving various outcomes, which can include (Wiseman 2016):

1. **Symptom Management:** In many cases, immunomodulators are used to alleviate symptoms associated with autoimmune diseases and inflammatory conditions. This can lead to improved quality of life for individuals dealing with these conditions.
2. **Disease Control:** For certain conditions, immunomodulators are employed to control the progression of the disease, prevent flare-ups, or maintain the condition in a stable state.
3. **Prevention:** In some instances, immunomodulators are used to prevent the recurrence of specific conditions or to reduce the risk of complications.

4. **Organ Transplantation:** Immunomodulators are critical in organ transplantation to prevent the body from rejecting the transplanted organ, improving the chances of a successful transplant.

The effectiveness of immunomodulators is typically assessed on an individual basis, and treatment plans are tailored to each patient's specific needs. Regular monitoring by healthcare professionals is essential to ensure that the treatment is working as intended and to make any necessary adjustments. Patients should communicate openly with their healthcare team to discuss treatment goals and expectations while also reporting any side effects or concerns.

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