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Essentials of Pharmacodynamics and Drug Action

Springer

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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
Kolkata, West Bengal, India

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 — Raja Chakraverty
New Delhi, Delhi, India — Rajani Mathur
Kolkata, West Bengal, India — Pranabesh Chakraborty

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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.

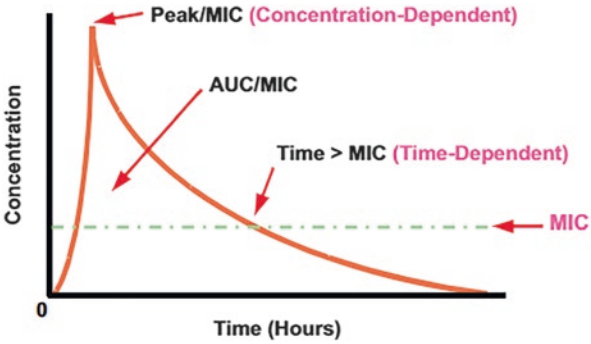

Fig. 1.1 Pharmacokinetic plasma drug concentration profile

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	IκB 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 α1-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

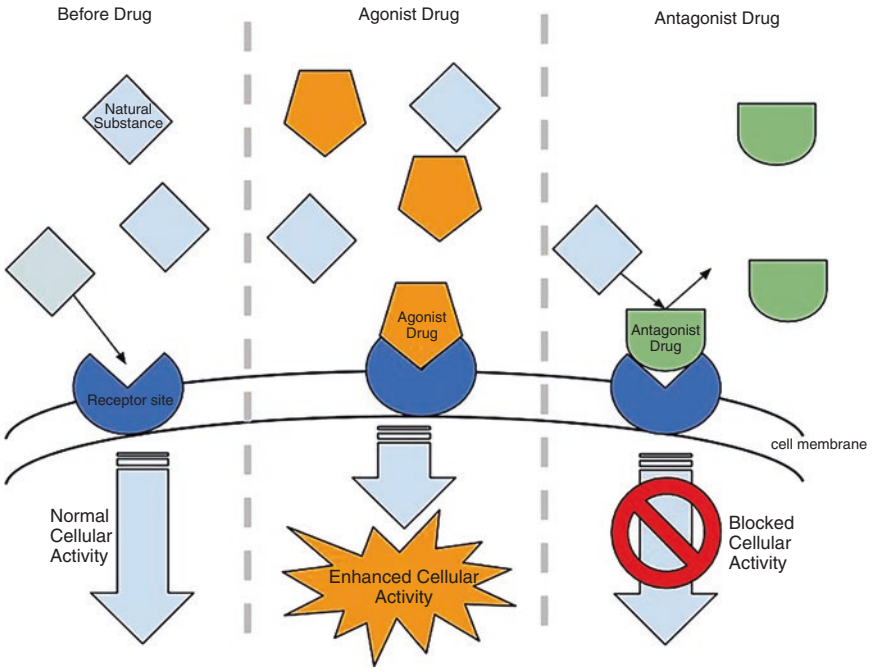

Fig. 2.1 Activity of agonist and antagonist (https://en.wikipedia.org/wiki/Agonist-antagonist)

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:

(a) Lipid-soluble ligands can cross the membrane and act on intracellular receptors.
(b) 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.
(c) Few receptors are present that work through the activation of tyrosine kinase.
(d) Transmembrane protein corridors that are permeable to specific ions are called an ion channel.
(e) 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.

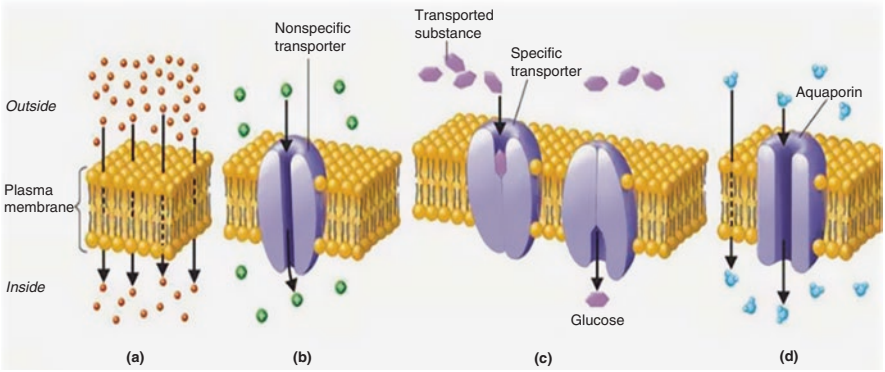

Fig. 2.2 Different types of passive transports (https://microbenotes.com/passive-transport/). (**a**) Simple diffusion through the lipid bilayer. (**b**) Facilitated diffusion through a nonspecific transporter. (**c**) Facilitated diffusion through a specific transporter. (**d**) Osmosis through the 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 ATPases[2], 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 subclasses 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 mammalians, 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-

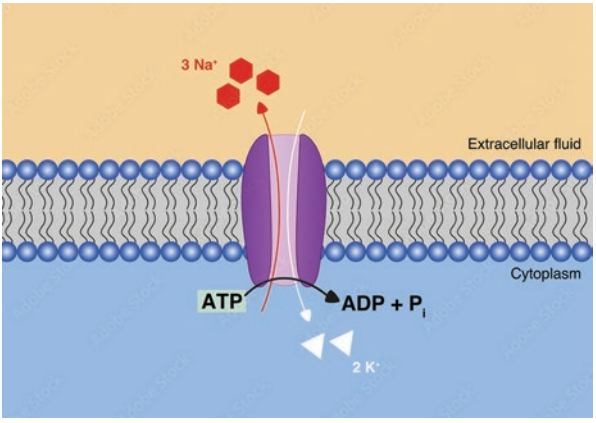

Fig. 2.3 Na^+K^+ATPase pump mediated transportation of Na^+ and K^+ ion across the cell membrane (Skaliora et al. 2015; Williams et al. 2014)