CHAPTER

1

General Pharmacology

Shyamalendu Tripathy

Introduction and scope of Pharmacology

1.1. WHAT IS PHARMACOLOGY?

Pharmacology comes from the Greek words "pharmakon" (drug) and "logos" (study), so it literally translates to the "study of drugs". Encompassing a vast range of knowledge about drugs, it primarily focuses on their safe and effective use for medicinal purposes.

A. **Key Areas of Pharmacology:** Two fundamental, interrelated areas are:
   - **Pharmacodynamics:** Examines how drugs affect the body at the molecular, biochemical, and physiological levels. This includes exploring a drug's mechanism of action, which is how it produces its intended effects.
   - **Pharmacokinetics:** Tracks what the body does to a drug. This involves studying how a drug is Absorbed, Distributed, Metabolized (broken down), and Eliminated from the body.

B. **The Broader Scope of Pharmacology:** Pharmacology reaches far beyond these two core areas. Here are some additional aspects it covers:
   - **Drug Discovery and Development:** This exciting field involves researching, creating, and testing new drugs for various diseases.
   - **Toxicology:** Explores the adverse effects of drugs and chemicals on living organisms.
   - **Pharmacogenomics:** Investigates how a person's genes influence their response to medications.
   - **Clinical Pharmacology:** Applies pharmacological principles to patient care, ensuring safe and effective drug use in humans.
   - **Pharmacovigilance:** Monitors the safety of drugs after they are marketed, identifying and reporting any potential adverse effects.

C. **The Importance of Pharmacology:** Pharmacology plays a vital role in modern medicine. By understanding how drugs interact with the body, we can develop effective treatments for a wide range of diseases and improve patient health outcomes. The field is constantly evolving as new discoveries are made, leading to the development of more targeted and personalized therapies.

1.2. COMMON ROUTES OF DRUG ADMINISTRATION

Drugs can enter the body through various routes, each with its own set of pros and cons. Here are some major ones:

- **Oral Route (PO):** This is the most common route, involving swallowing pills, capsules, or liquids.
  - **Advantages:** Convenient, inexpensive, and self-administered by most patients.
  - **Disadvantages:** Slow and unpredictable absorption; may be broken down by the digestive system (first-pass effect); not suitable for patients with swallowing difficulties, nausea, or vomiting.
- **Sublingual and Buccal Routes:** Medications are placed under the tongue (sublingual) or between the cheek and gum (buccal) for rapid absorption through the mucous membranes.
  - **Advantages:** Bypasses the digestive system and first-pass effect, leading to a faster onset of action. Convenient for some patients.
  - **Disadvantages:** Limited to drugs that are absorbed well through these membranes; may have an unpleasant taste.
- **Enteral Routes (Other):** Rectal suppositories or enemas are used when oral administration is not feasible.
  - **Advantages:** Useful for patients who cannot swallow or are nauseated. Rectal route offers faster absorption than oral in some cases.
  - **Disadvantages:** Can be uncomfortable or inconvenient for patients; rectal route may irritate the lining of the rectum.
- **Parenteral Routes:** These routes involve injections to deliver drugs directly into the body tissues, bypassing the digestive system.
  - **Subcutaneous (SC):** Injected under the skin.
  - **Intramuscular (IM):** Injected into a muscle.
  - **Intravenous (IV):** Injected directly into a vein.
  - **Advantages:** Rapid and predictable onset of action; avoids the digestive system and first-pass effect; useful for unconscious patients or those who cannot absorb drugs orally.
  - **Disadvantages:** Requires a healthcare professional for administration; can be painful; risk of infection at the injection site.
- **Inhalation Route:** Drugs are delivered as a mist or aerosol for direct absorption into the lungs.
  - **Advantages:** Rapid onset of action for some medications; useful for respiratory conditions.
  - **Disadvantages:** Can irritate the respiratory tract; may require special equipment for proper administration.
- **Topical Route:** Creams, ointments, gels, or patches are applied to the skin or mucous membranes for localized or systemic effects.

  - **Advantages:** Convenient and non-invasive; useful for localized treatment of skin conditions. Some topical medications can provide systemic effects.
  - **Disadvantages:** Limited systemic absorption for some drugs; may irritate the application site.
- **Choosing the Right Route:** The selection of the most suitable route for drug administration depends on various factors, including:
  - The desired speed of action
  - The properties of the drug (absorption, stability)
  - The patient's condition and ability to take medication orally
  - The intended site of action

Ultimately, healthcare professionals consider all these aspects to determine the safest and most effective route for administering a particular drug to a specific patient.

1.3. DRUG ABSORPTION: DEFINITION AND IMPORTANCE

Drug absorption is the critical first step in a drug's journey to reach its site of action in the body. It refers to the process by which a drug enters the bloodstream from its administration site. Once absorbed, the drug can then be distributed throughout the body to exert its therapeutic effect.

A. **Types of Drug Absorption:** There are two main mechanisms by which drugs traverse cell membranes for absorption:
   - **Passive Diffusion:** The most common type. Here, drug molecules move from an area of higher concentration (administration site) to an area of lower concentration (bloodstream) driven by a natural tendency to achieve equilibrium. There are two subtypes:
     - **Simple Diffusion:** Unaided passage of small, non-ionic lipophilic (fat-soluble) drugs through the cell membrane.
     - **Facilitated Diffusion:** Passive transport with the help of carrier molecules that ferry drugs across the membrane.
   - **Active Transport:** An energy-dependent process that utilizes carrier proteins to move drugs against a concentration gradient (from low to high concentration). This method is less common for drug absorption.

B. **Factors Affecting Drug Absorption:** Several factors can influence how readily a drug is absorbed into the bloodstream. Here are some key ones:
   - **Properties of the Drug:**
     - **Solubility:** Lipophilic drugs dissolve more easily in fats and readily pass through cell membranes for absorption.
     - **Ionization:** The charged state of a drug can affect absorption. Generally, non-ionized forms penetrate membranes better.
     - **Particle Size:** Smaller drug particles have a larger surface area for absorption, leading to faster and more complete absorption.

- **Routes of Administration:**
  - **Oral route:** Absorption can be slow and variable due to factors like digestion and first-pass effect (partial breakdown by the liver).
  - **Parenteral routes (injection):** Generally lead to faster and more predictable absorption.
  - **Other routes:** Absorption rates vary depending on the route (e.g., topical route may have slow systemic absorption).
- **Physiological Factors:**
  - **Gastrointestinal (GI) Tract Function:** Conditions like vomiting, diarrhea, or altered stomach emptying can affect drug absorption from the oral route.
  - **Blood Flow:** Increased blood flow to the administration site can enhance drug absorption.
  - **Presence of Food:** Food can interact with some drugs, delaying or reducing their absorption.
- **Other Factors:**
  - **Age:** Absorption may be slower in infants and older adults due to physiological changes.
  - **Disease State:** Certain diseases can alter absorption, like liver or kidney dysfunction.

Understanding these factors is crucial for optimizing drug therapy. By considering them, healthcare professionals can select the most appropriate route of administration and dosage to ensure effective drug absorption and achieve the desired therapeutic outcome.

1.4. BIOAVAILABILITY: UNDERSTANDING HOW MUCH DRUG REACHES ITS TARGET

Bioavailability refers to the "**Proportion of an administered drug that reaches its site of action in the body in its unmodified, active form**". It essentially reflects how much of the drug is available to exert its intended effect.

A. **Why is Bioavailability Important?:** Bioavailability is a critical concept in pharmacology because it directly impacts a drug's effectiveness and safety. A drug with high bioavailability will have a greater therapeutic effect at a lower dose compared to a drug with low bioavailability that requires a higher dose to achieve the same effect. Higher doses can increase the risk of side effects.

B. **Factors Affecting Bioavailability:** Several factors can influence how much of a drug becomes available at its site of action. Here's a breakdown of some key players:

C. **Physicochemical Properties of the Drug:**
- **Solubility:** Drugs that are more soluble (dissolve easily) are generally better absorbed and have higher bioavailability.
- **Ionization:** The charged state of a drug affects its ability to pass through cell membranes. Non-ionized forms typically penetrate membranes better.

- **Particle Size:** Smaller drug particles have a larger surface area for absorption, leading to potentially higher bioavailability.

D. **Route of Administration:**
- **Oral Route:** Absorption can be slow and variable due to factors like digestion and first-pass effect (partial breakdown by the liver before reaching systemic circulation). This can lead to lower bioavailability for some drugs.
- **Parenteral Routes (injection):** Generally lead to faster and more predictable absorption, often resulting in higher bioavailability.
- **Other Routes:** Absorption rates and bioavailability vary depending on the route (e.g., topical medications may have low systemic bioavailability).

E. **Physiological Factors:**
- **Gastrointestinal (GI) Tract Function:** Conditions like vomiting, diarrhoea, or altered stomach emptying can affect drug absorption from the oral route, impacting bioavailability.
- **Blood Flow:** Increased blood flow to the administration site can enhance drug absorption and potentially improve bioavailability.
- **Presence of Food:** Food can interact with some drugs, delaying or reducing their absorption, thereby affecting bioavailability.

F. **Formulation of the Drug:**
- Dosage forms like tablets, capsules, or liquids can influence drug release and absorption rates. Special formulations may be designed to improve a drug's bioavailability.

G. **Individual Variability:**
- **Genetics:** Genetic variations can influence how individuals metabolize drugs, potentially affecting bioavailability.
- **Age:** Absorption and metabolism may be slower in infants and older adults, impacting bioavailability.
- **Disease State:** Certain diseases can alter absorption or metabolism, affecting bioavailability (e.g., liver or kidney dysfunction).

1.5. DRUG DISTRIBUTION—DEFINITION, FACTORS AFFECTING DRUG DISTRIBUTION

Drug distribution is the phase after a drug enters the bloodstream, where it travels throughout the body and reaches its target sites. It essentially describes how a drug moves from the bloodstream and distributes itself into various tissues and organs.

A. **Factors Affecting Drug Distribution:** Several factors influence how a drug is distributed within the body. Here's a look at some key players:
- **Blood Flow:** Drugs are carried throughout the body by blood. Tissues with higher blood flow (like the heart, liver, and kidneys) will generally receive the drug faster and in higher concentrations compared to tissues with lower blood flow (like fat or muscle).

- **Plasma Protein Binding:** Many drugs bind to proteins in the blood plasma, particularly albumin. Only the unbound, free fraction of the drug is pharmacologically active and can diffuse out of the bloodstream into tissues. The extent of protein binding can affect how much drug is available to exert its effect.
- **Lipophilicity (Fat Solubility):** Lipophilic drugs dissolve more easily in fats and readily pass through cell membranes to enter tissues. Highly lipophilic drugs may accumulate in fat tissues, affecting their distribution and potentially prolonging their effects.
- **Tissue Permeability:** The permeability of tissue barriers, like the blood-brain barrier, can influence drug distribution. The blood-brain barrier restricts the passage of many drugs into the brain, limiting their access to the central nervous system.
- **pH:** The acidity (pH) of tissues and blood can affect drug distribution. For example, acidic drugs may accumulate more in acidic compartments like the stomach.
- **Disease State:** Certain diseases can alter tissue blood flow, protein binding, or other factors, impacting drug distribution. For instance, liver disease can affect protein binding, potentially leading to increased free drug levels.

1.6. BIOTRANSFORMATION OF DRUGS: THE BODY'S CHEMICAL MAKEOVER FOR MEDS

Biotransformation, also known as drug metabolism, is the process by which the body chemically modifies drugs into different compounds. These altered forms, called metabolites, can be:

- **More water-soluble:** This facilitates easier excretion of the drug from the body through urine or bile.
- **More or less active:** Sometimes, biotransformation can activate an inactive prodrug (a medication designed to become active in the body) or convert an active drug to a less active or inactive metabolite.
- **Toxic:** In some cases, biotransformation can generate toxic metabolites that may contribute to side effects.

A. **Types of Biotransformation Reactions:** There are two main phases involved in biotransformation, often referred to as Phase I and Phase II reactions:

- **Phase I Reactions:** These reactions typically involve adding a functional group (like a hydroxyl or methyl group) to the drug molecule, making it more polar (water-soluble). Common Phase I reactions include oxidation, reduction, and hydrolysis.
- **Phase II Reactions:** These reactions involve conjugation, where the modified drug molecule (from Phase I or the parent drug itself) is linked with another molecule (like glucuronic acid or sulfate) to further increase its water solubility and facilitate excretion.

B. **Factors Influencing Drug Metabolism:** Several factors can influence how quickly and extensively a drug undergoes biotransformation:
   - **Intrinsic Factors:** These are inherent to the individual and can vary considerably.
     - **Genetics:** Gene variations (polymorphisms) in enzymes responsible for metabolism can significantly affect how quickly a drug is broken down. This can lead to some individuals being "poor metabolizers" or "extensive metabolizers," which can impact drug efficacy and safety.
     - **Age:** Newborns and older adults often have reduced metabolic activity, which can affect drug metabolism.
     - **Gender:** There can be some gender-based differences in drug metabolism due to hormonal variations.
   - **Extrinsic Factors:** These are external factors that can influence drug metabolism.
     - **Other Medications:** Certain medications can induce (increase) or inhibit (decrease) the activity of drug-metabolizing enzymes, potentially affecting the metabolism of other concurrently used drugs. This can lead to drug interactions.
     - **Diet:** Some dietary components can induce or inhibit drug-metabolizing enzymes, influencing drug metabolism.
     - **Smoking:** Smoking can induce the activity of certain drug-metabolizing enzymes, leading to faster drug breakdown and potentially reduced effectiveness.

1.7. DRUG EXCRETION: SAYING GOODBYE TO MEDICATIONS

Drug excretion is the final stage of a drug's journey in the body. It refers to the process by which the body eliminates a drug and its metabolites from the bloodstream. This elimination is crucial for preventing drug accumulation and potential toxicity.

A. **Routes of Drug Excretion:** The body primarily eliminates drugs and their metabolites through several major routes:
   - **Kidneys:** This is the major route of excretion for most water-soluble drugs and metabolites. The kidneys filter the blood and eliminate drugs and metabolites in the urine.
   - **Liver:** The liver plays a key role in drug biotransformation. After metabolizing drugs, the liver excretes some metabolites directly into the bile. These metabolites may then be eliminated in the feces or reabsorbed back into the bloodstream (enterohepatic circulation) for further metabolism and excretion.
   - **Other Routes:** Small amounts of drugs and metabolites may also be excreted through:
     - **Lungs:** Certain inhaled or volatile drugs can be eliminated through exhalation.

  - **Sweat:** Some lipophilic drugs can be excreted in sweat, though this is usually a minor route.
  - **Saliva and Tears:** Excretion through saliva and tears is typically minimal for most drugs.
  - **Breast Milk:** Lipophilic drugs can pass into breast milk, which is a concern for nursing mothers and their infants.

B. **Factors Affecting Drug Excretion:** Several factors can influence how quickly a drug is eliminated from the body:

- **Kidney Function:** Reduced kidney function can lead to slower excretion of drugs and metabolites, potentially increasing the risk of accumulation and side effects.
- **Liver Function:** Liver impairment can affect drug metabolism and excretion, potentially leading to prolonged drug action and toxicity.
- **Urine pH:** Highly acidic or alkaline urine pH can alter the excretion of certain drugs.
- **Age:** Kidney and liver function generally decline with age, which can slow down drug excretion in older adults.

1.8. GENERAL MECHANISMS OF DRUG ACTION AND FACTORS MODIFYING DRUG ACTION

Drugs exert their effects by interacting with specific molecules in the body, primarily targeting proteins. Here's a breakdown of some common mechanisms:

- **Receptor Binding:** Many drugs act by binding to specific receptors on cell surfaces. These receptors act like molecular locks, and the drug acts like a key. When the drug binds to the receptor, it triggers a cellular response that produces the desired therapeutic effect.
  - **Agonists:** Mimic the natural signalling molecule (ligand) that binds to the receptor, activating it and producing a similar response (e.g., adrenaline mimicking the effects of the fight-or-flight response).
  - **Antagonists:** Block the binding of the natural ligand to the receptor, preventing its activation and its associated effects (e.g., some heartburn medications block histamine receptors in the stomach).
- **Enzyme Inhibition:** Some drugs act by inhibiting enzymes, which are proteins that accelerate biochemical reactions in the body. By inhibiting an enzyme, the drug can disrupt a specific pathway and alter a cellular process. (e.g., some cholesterol-lowering drugs inhibit enzymes involved in cholesterol synthesis).
- **Ion Channel Modulation:** Certain drugs interact with ion channels, which are protein pores in cell membranes that regulate the flow of charged ions (like sodium, potassium) across the membrane. This can alter the electrical activity of cells and influence functions like nerve impulse transmission or muscle contraction.
- **Carrier Protein Inhibition/Enhancement:** Some drugs can inhibit or enhance the function of carrier proteins, which are responsible for transporting molecules

across cell membranes. This can affect the uptake or efflux of essential nutrients or signalling molecules.

A. **Factors Modifying Drug Action: Why One Size Doesn't Always Fit All:** The way a drug affects an individual can vary depending on several factors:

Physiological Factors:

- **Age:** Children and older adults may have different drug absorption, distribution, metabolism, and excretion (ADME) profiles compared to young adults. This can necessitate adjustments in dosage.
- **Genetics:** Genetic variations can influence how individuals metabolize drugs, affecting their effectiveness and potentially leading to side effects.
- **Gender:** Gender-based differences in hormones, body composition, and enzyme activity can sometimes influence drug response.
- **Body Weight:** Drug dosages often need to be adjusted based on body weight to ensure safe and effective effects.
- **Pregnancy:** Certain drugs can be harmful to the developing fetus, so pregnant women may require alternative medications.

B. **Pathological Factors (Diseases):**

- **Liver Disease:** Liver impairment can affect drug metabolism and excretion, potentially leading to drug accumulation and toxicity.
- **Kidney Disease:** Reduced kidney function can slow down drug excretion, requiring dosage adjustments.

C. **Other Factors:**

- **Drug Interactions:** Concurrent use of other medications can interact with a drug, affecting its absorption, metabolism, or excretion. This can lead to altered effectiveness or increased side effects.
- **Diet:** Certain foods or beverages can interact with some drugs, impacting their absorption or metabolism.