Pharmacodynamics –(Part I)

If **Pharmacokinetics (PK)** is "what the body does to the drug," **Pharmacodynamics (PD)** is **"what the drug does to the body."**

1. Concept of Pharmacodynamic Effect

A **pharmacodynamic effect** is defined as a measurable and reproducible modification—whether functional or organic—induced by a drug within a biological system referred to as an **'effector'**.

A drug induces one or more **pharmacodynamic effects** at varying doses. A drug is characterized by:

- A **primary therapeutic effect**, which is the intended clinical response.
- **Side effects**, which may be beneficial, indifferent, or lead to **adverse drug reactions (ADRs)**.

Different drugs can elicit the same pharmacodynamic effect; such agents are grouped into a **pharmacological class**. A pharmacological class consists of all medications sharing a common **Mechanism of Action (MoA)**.

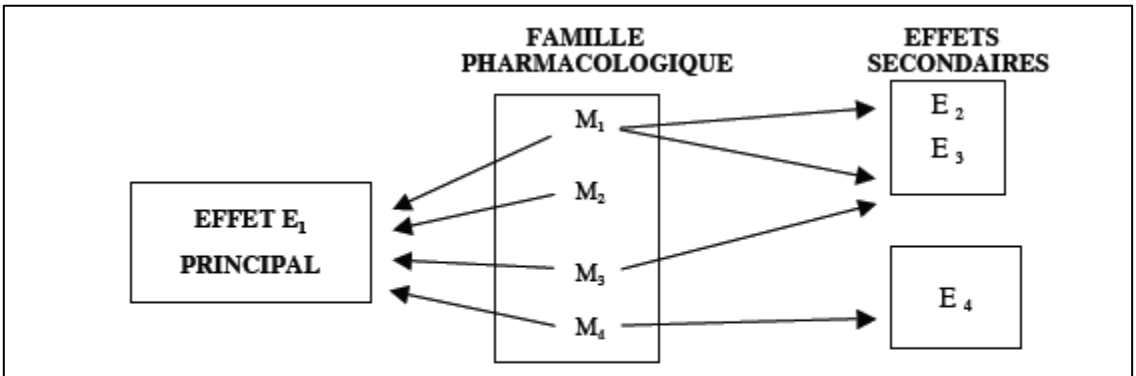

figure 2.1.-1 : familles pharmacologiques - Les membres d'une famille pharmacologique ont en commun l'effet principal tandis que les effets secondaires peuvent différer selon les substances. M_1... médicaments, E_1... effets pharmacodynamiques.

2. MECHANISMS OF ACTION

Drugs can act in three different ways: by binding to a target within the body, by binding to a target foreign to the body (e.g., pathogens), or without binding (non-specific action).

2-1- Action via specific binding

Drugs generally act by binding to structures within the body. This binding is specific to the drug and its resulting effect. It is highly dependent on the drug's structure and chemical properties. The molecular structure to which the drug binds is called a "target".

2-1-1- Binding to a protein

In most cases, binding occurs on a protein. These can include:

- **Receptors:** Receptors are specific proteins that are part of the physiological systems of intercellular communication (signal transmission).
- **Enzymes:** Drugs can act on enzymes through inhibition, activation, or diversion of the enzymatic reaction (e.g., Angiotensin-Converting Enzyme (ACE) inhibitors like captopril...).
- **Transporters:** Transporters are proteins that facilitate the passage of ions and small physiological molecules across cell membranes.
- **Ion channels:** Channels are transmembrane proteins that allow the selective passage of certain ions (Na+, K+, Ca^{2+}$, Cl^-) according to their electrochemical gradient. They can be either in an open or closed state.
- **Structural cellular proteins:** Such as tubulin, though this is less common.

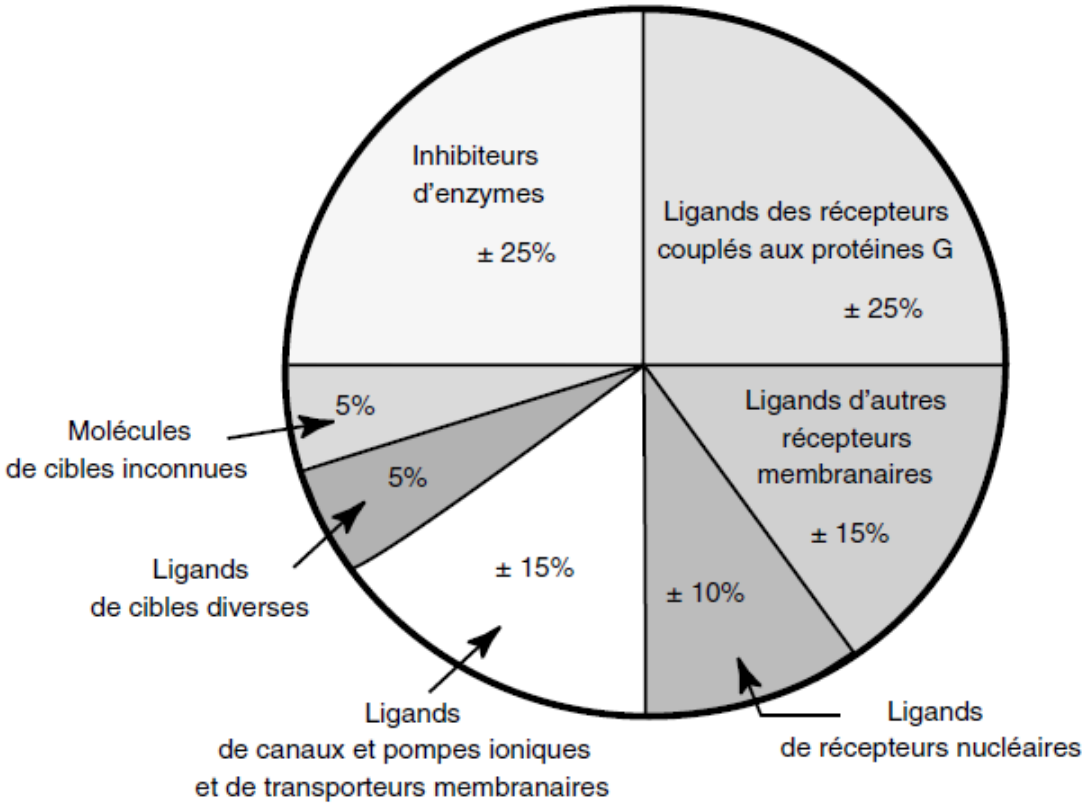

Figure 1.2 – **Répartition des molécules utilisées actuellement comme médicament en fonction de la nature de leurs cibles.**

2-1-2- Binding to the genome

Drugs can bind to the genome (DNA, RNA, associated proteins). They can modulate gene expression. Some can prevent cell proliferation. This binding can also be responsible for the mutagenic or carcinogenic effects of certain drugs.

2-1-3- Other binding sites

A few rare drugs bind to sites other than proteins or nucleotides, such as membrane lipids or calcium salts within the bone matrix.

2.2. Non-specific action (Without binding in the body)

These drugs act through their physical properties (bulk/volume: bulk-forming laxatives like mucilages and seed bran) or by modifying the properties of the extracellular environment (osmotic pressure: mannitol in the nephron tubule, lactulose "DUPHALAC"; acid-base balance: $NaHCO_3$ and NH_4Cl; electrolyte balance, etc.). *See inset below.*

Limitations of the drug-target binding dogma

Some drugs do not interact strictly with a molecular target or macromolecules of the cells of the organism to which they are administered. A few examples:

- drugs intended to destroy pathogenic organisms bind mostly to a target within these organisms agents modifying blood pH or stomach pH, such as sodium bicarbonate;
- pulmonary surfactant administered to compensate for lung immaturity in newborns;
- osmotic laxatives and bulk-forming laxatives, which lead to the hydration of the fecal bolus and thus facilitate its evacuation;
- cholestyramine, a bile acid-chelating resin (or bile acid sequestrant) with a lipid-lowering effect;
- chelating agents for di- and trivalent ions, such as EDTA used in lead poisoning, or penicillamine used for these poisonings and in Wilson's disease (caused by an excess of copper in the body); although ions are not macromolecules, there is still a principle of recognition and selective interaction between the administered drug and a component of the body.

2-3- Action on foreign organisms

Some drugs act on pathogenic organisms (bacteria, viruses, parasites, fungi). The mechanisms of action are similar to those listed above.

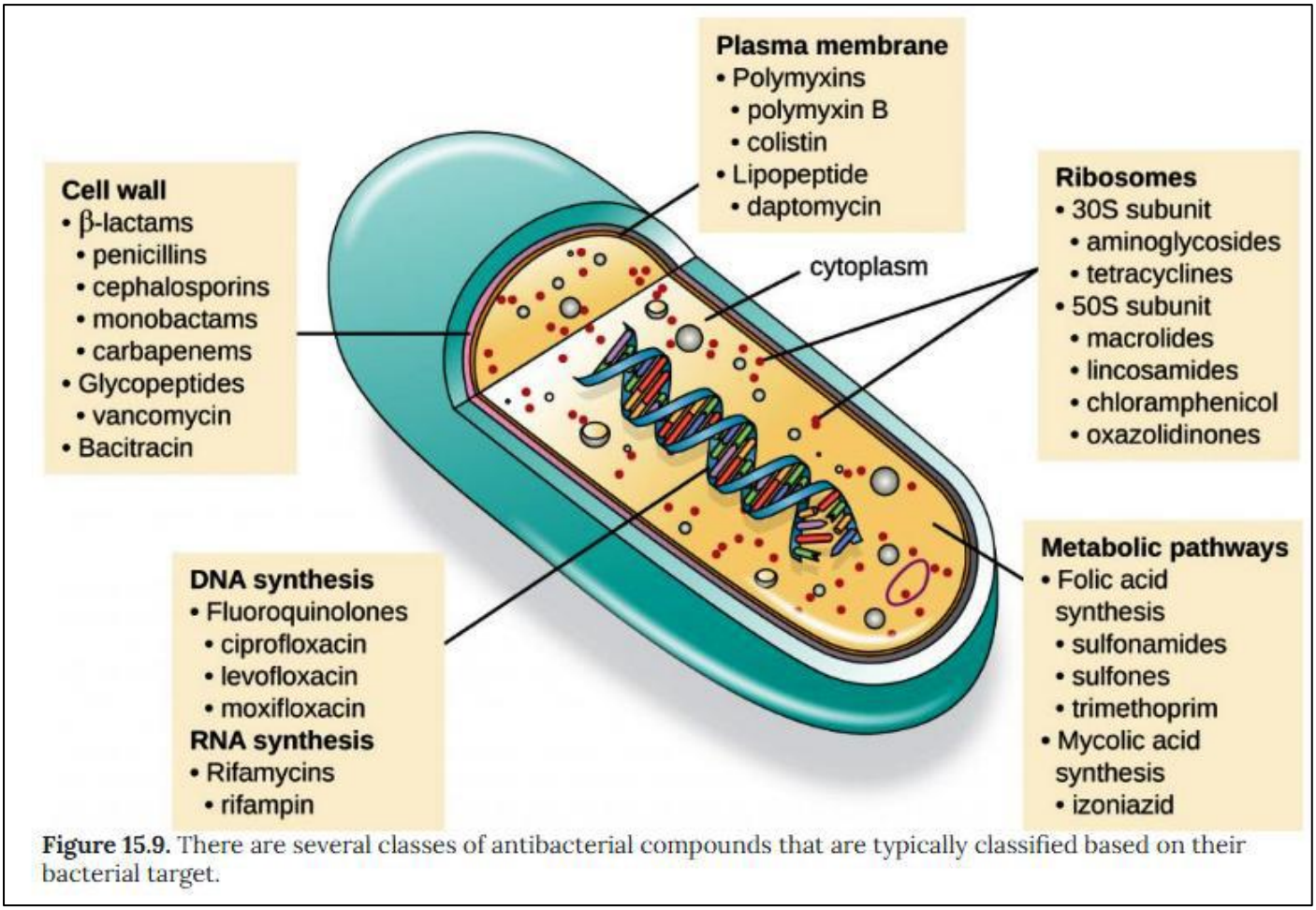

Figure 15.9. There are several classes of antibacterial compounds that are typically classified based on their bacterial target.

3- RECEPTOR THEORY

3-1- Definition

A "pharmacological receptor" is defined as a functional biochemical structure (proteins that play a physiological role in the body's communication systems) to which the **specific binding** of a drug molecule induces a stimulus that originates the pharmacodynamic effect. However, this concept can be generalized to other "receptor" proteins (enzymes, transporters, channels). In all cases, the drug carries information that it transmits to the receptor. The latter will then trigger the **cellular effect** (or cellular response).

3-2- Properties required for the biochemical definition of a receptor

- **It must accept a specific ligand;** example: histamine is the specific ligand for histamine receptors, adrenaline for β-adrenergic receptors,...
- **The binding of this specific ligand to its receptor must trigger a characteristic physiological response,** proportional to the amount of bound ligand;
- **This receptor must exhibit a characteristic regional distribution** within the body;
- **It must be saturable** in the presence of an excess of ligand;

- **It must be subject to displacement phenomena** by ligands with similar chemical structures but different affinities: **the phenomenon of competition**.

These properties distinguish a receptor from a simple **acceptor** (a molecule that non-specifically binds any drug) which does not elicit any biological response. Examples of acceptors: serum albumin, lipids...

A receptor is a molecular structure that receives, processes, and transmits information.