Court 09: Biological consequences of drug-target interaction

1. Introduction:

Drug interactions are classified into two main types:

— Pharmacokinetics

Pharmacokinetic interactions lead to changes in the blood concentration of the target drug. An increase in concentration amplifies the effects and can cause adverse events. A decrease in concentration results in a loss of therapeutic efficacy. Interactions can occur at several stages: absorption, distribution, metabolism, or elimination of the drug. Different mechanisms are involved at each stage. For example, absorption can be impaired due to complexation with another drug, changes in gastric pH, delayed gastric emptying, or accelerated intestinal transit .

Pharmacokinetic interactions will have clinical implications for drugs with a narrow therapeutic index.

— Pharmacodynamics

Pharmacodynamic interactions result from interference at the drug's site of action. These mechanisms can be direct (same site of action) or indirect, leading to a loss of drug efficacy, an increase in therapeutic effects, and/or adverse effects. For example, the combination of an antagonist and an agonist, or the combination of two agonists, are pharmacodynamic interactions. Unlike pharmacokinetic interactions, pharmacodynamic interactions involve specific drug classes.

Many contextual elements can modify the risk of developing a drug interaction. These can be related to the drug itself, such as dosage, duration of administration, and route of administration, or related to the patient's pathophysiological characteristics, such as age (elderly), sex, pathologies (severe renal or hepatic insufficiency), and pharmacogenomics (slow or rapid metabolizer).

2. Mechanisms of action of a drug

This results in a reaction, or response, from the cell. This response can be more specifically contractile (skeletal muscles, cardiac muscle, smooth muscles), secretory (exocrine and endocrine secretory cells, neurons, immune cells), or metabolic (modification of lipid or carbohydrate reserves…).

Understanding a drug's mechanism of action is crucial for its rational use. The mechanism of action is a common thread among many drugs, as it allows us to classify a drug within a pharmacological class or subclass, and to logically deduce its indications, contraindications, precautions for use, and adverse effects.

Understanding the mechanism of action of drugs opens the way to the analysis and understanding of the pathophysiology of diseases, and guides the development of new drugs.

It is crucial to distinguish between mechanism of action, pharmacological effect, and therapeutic effect:

• **The mechanism of action** : this is the set of phenomena that modify cell functions in a localized or generalized way. This results in chemical, biochemical, or biophysical changes that a living organism undergoes following the introduction of a drug.

• **the pharmacological effect** : this is the biological consequence of the prior binding of the active drug molecule to a target in the body.

• **The therapeutic effect** : this is the improvement in the state of health or well-being of a subject related to the use of a drug and a priori explainable by one of its pharmacological properties.

Target drug → Pharmacological effect → Therapeutic effect

- **Concepts of selectivity and specificity:**

Selectivity : preferential interaction with a particular target; we will speak of interaction selectivity.

Specificity : action limited to a precise biological mechanism; we will speak of specificity of effect.

• Selectivity and specificity are as important as the potency of the drug.

• Absolute selectivity does not exist.

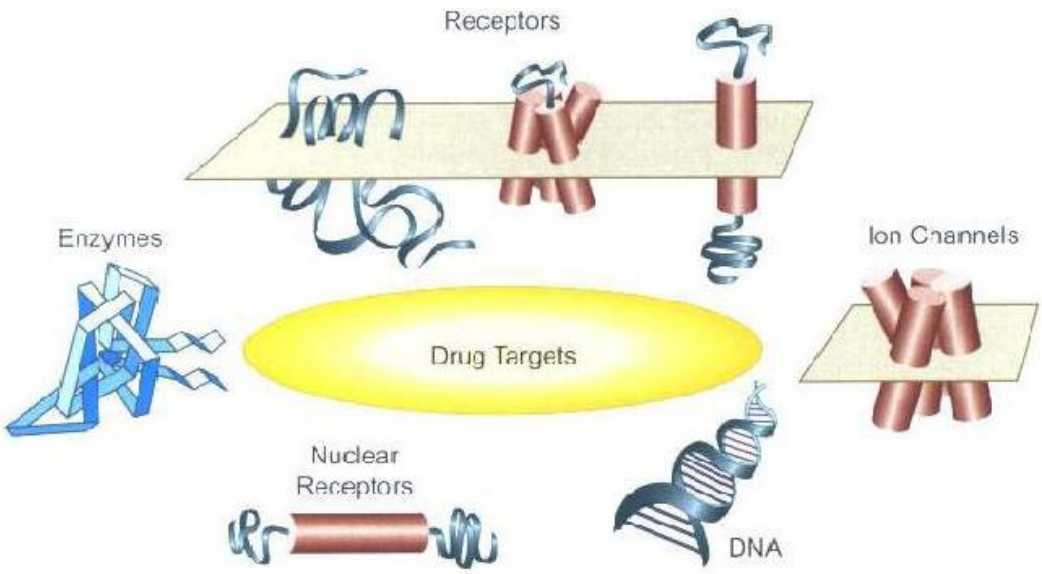
Selectivity is a fundamental concept in drug knowledge. It determines the reliability of its therapeutic use. Indeed, no drug is specific to a single biological target. Simply increasing the administered dose will lead to binding to other targets and, consequently, other effects, which may include side effects, adverse effects, or toxic effects.

• **Adverse effects** : any adverse and unwanted reaction occurring when taking medication at the recommended dose or resulting from misuse of the medication or product.

• **Toxic effects** : harmful manifestations resulting from an excess of medication.

3. Drug targets

Drug action is often linked to a direct effect on cellular function. From a chemical perspective, a drug is a molecule, sometimes an ion, that interacts with a molecular target. These interactions require mutual recognition of the two partners, which can then interact and form one or more chemical bonds. Drug binding modifies the properties of the target, inducing a cellular response. This is the source of a drug's beneficial effects, but also, in some cases, its side effects. From a biological perspective, the two most important classes of targets are membrane receptors for neurotransmitters (45% of targets) and enzymes (28%). Ion channels (5%) and nuclear receptors (2%) are other potential drug targets.



3.1. The targets are proteins

Cellular proteins represent almost all the targets of specific-action drugs, depending on their role in the cell. Target proteins act as receptors for the body's neurotransmitters/hormones and as molecular receptors for drugs (agonists/antagonists). These receptors can be:

- Located at the level of the cell membrane: membrane receptor.

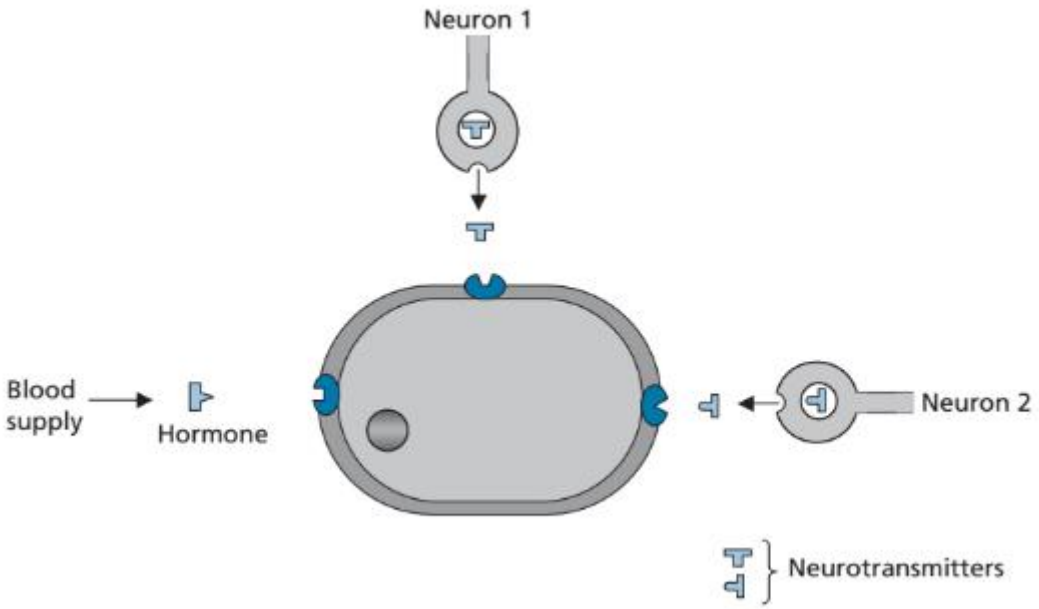
- Located inside the cell: nuclear (cytoplasmic) receptor.

■ The mediators

The body's mediators ensure interactions between different cell types for the proper functioning of its various systems. They regulate the characteristic properties of each cell type by binding to its receptor. These mediators are either neurotransmitters or hormones.

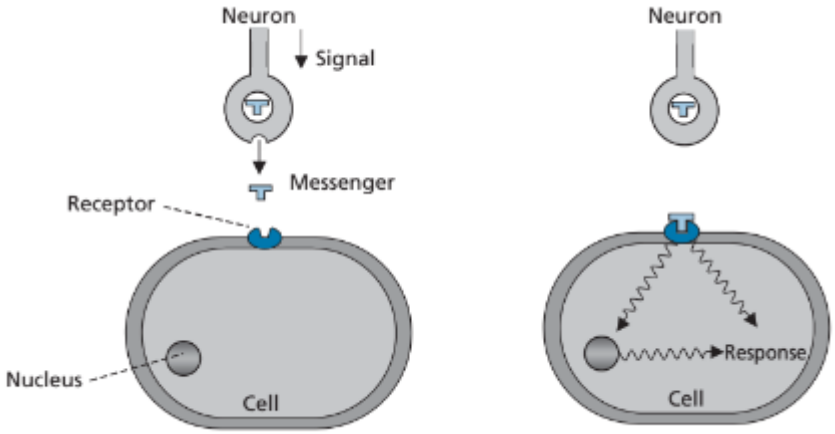
• Neuromediators or neurotransmitters secreted by central or peripheral neurons. Action: they act in the short term on cells very close to the originating neurons.

• Hormones secreted by endocrine cells circulating in the blood. Action: they act for a ±long time and ±far from the site of secretion.



Various specific receptors for each type of messenger.

Mediators trigger a cellular response via a signaling pathway (a set of intracellular biochemical processes). Most drugs act by interfering with mediator receptors or their signaling pathways.

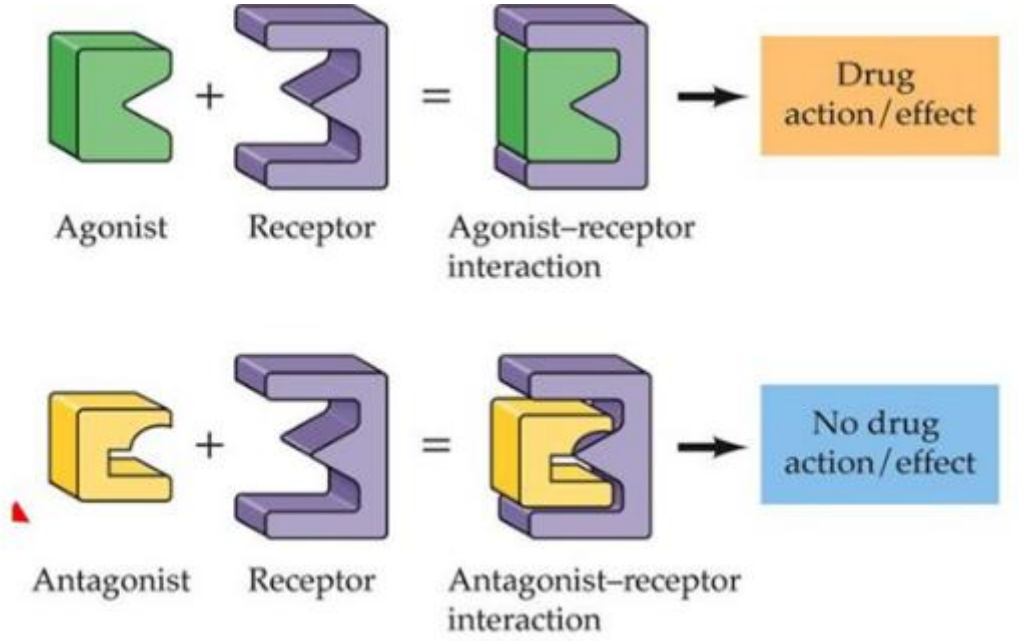


■ **Drug molecules: Agonists/Antagonists**

When a drug molecule binds to a target (a receptor), it can:

Activating it (inducing the effect) = AGONIST

Inhibiting it (blocking the effect) = ANTAGONIST



 Agonist : an analogue of an endogenous chemical mediator capable of causing intrinsic activity after interaction with its specific receptor.

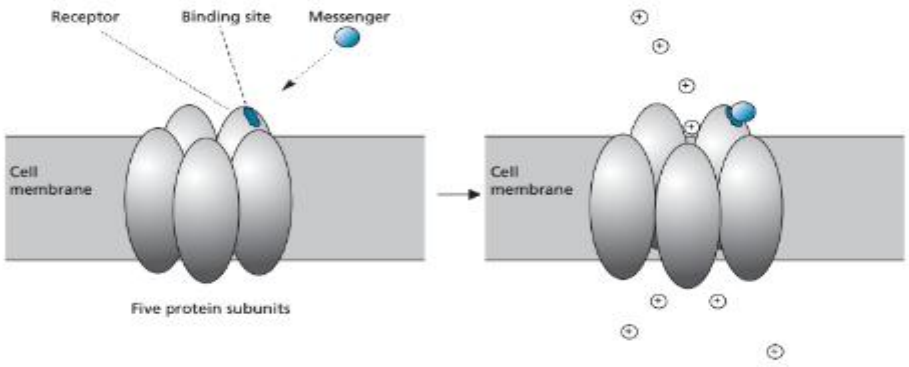
• **Antagonist** : an analog of an endogenous chemical mediator that is incapable of producing intrinsic activity after interacting with its specific receptor. It therefore has no independent action. Its pharmacological effect results from opposing the action of an endogenous chemical mediator or an agonist.

3.1.1. Membrane receptors

3.1.1.1. Ion channel receptors

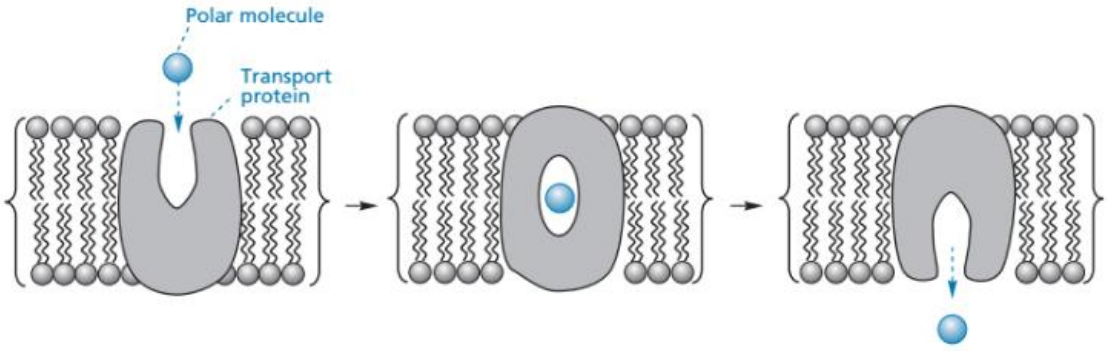
Family of proteins that are responsible for transmembrane ionic balances.

These are proteins that facilitate the transport of ions or various substances. They often require energy in the form of ATP. They are called ATP-dependent transporters.



Drugs or mediators (e.g., GABA) act on these channels; they can keep them open or closed.

1.1.1.1. Transport receptors



1.1.1.2. Receptors with enzymatic activity

A number of drugs act directly on the active site of enzymes. This most often involves inhibiting (sometimes activating) their catalytic activity or diverting their activity to reduce the role of the normally synthesized protein. There is also a class of enzyme-receptor receptors that combine, within the same structure, a ligand-binding and recognition site and enzymatic activity (tyrosine kinase receptors: insulin, growth factors, etc.).

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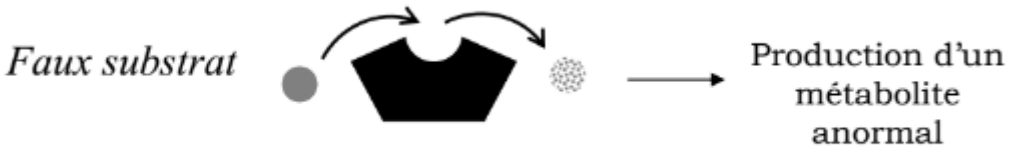
There is also a category of enzyme-receptor receptors that combine, within the same structure, a ligand-binding and recognition site and enzymatic activity (e.g., receptors with tyrosine kinase activity: insulin, growth factors, etc.).

Some substances are substrates analogous to the natural substrate and act as inhibitors of the enzyme at its site of activity.

This inhibition can be reversible or irreversible.

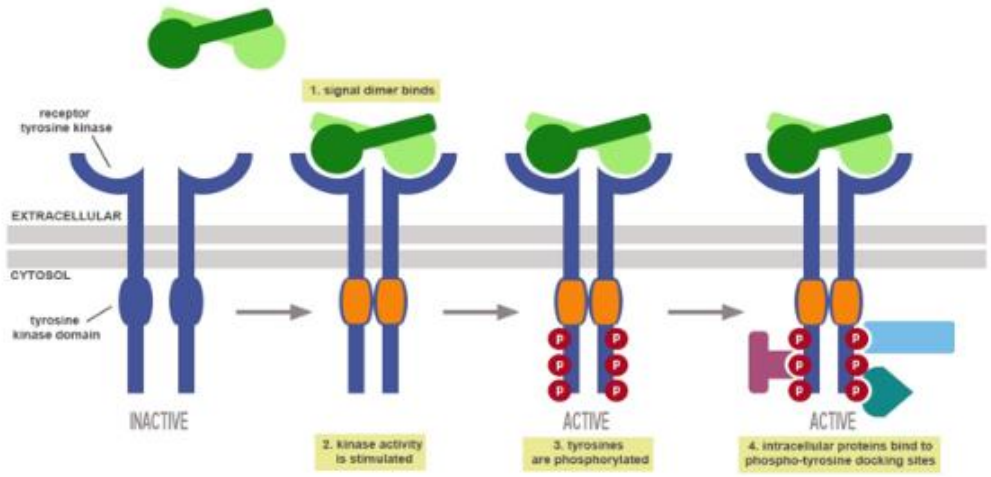
Some substances are false substrates for enzymes. These substances are modified by the enzyme into a reaction product which itself interferes with a function of the cell.



1.1.1.3. Receptors with activity or coupled to tyrosine kinases

Intrinsic tyrosine kinase receptors (RTKs) are transmembrane glycoproteins composed of a highly variable extracellular domain capable of binding the ligand, a transmembrane domain allowing anchoring in the cell membrane, and an intracellular (cytoplasmic) domain that contains the tyrosine kinase activity and enables signal transduction within the cell. The enzymatic activity of RTKs is localized in the cytoplasm and allows the transfer of the γ-phosphate from ATP to the hydroxyl group of tyrosines on target proteins and/or the receptor itself; this is called autophosphorylation.

RTKs are important regulators of intercellular communication; they play a significant role in the control of many biological processes, such as the cell cycle, cell migration, metabolism, growth, proliferation, and cell differentiation.



Activation de récepteur à activité ou couplé aux tyrosines kinase

1.1.1.4. G protein-coupled receptors

G protein-coupled receptors (GPCRs) are membrane proteins with a seven-transmembrane domain structure responsible for recognizing external (light, odors, etc.) or internal (hormones, neurotransmitters) signals. They are composed of a chain of amino acids that crosses the membrane several times in the form of an α-helix. The molecule can be glycosylated at several locations within its extracellular domain .

The seven transmembrane segments are arranged in a circle containing a central cavity and a binding site for the ligand or drug. The association of the ligand, or a pharmacological analog with agonist activity, induces a conformational change in the receptor, allowing it to bind to a G protein.

1.1.2. Nuclear receptors

A family of proteins that bind to the promoter region of genes to either increase or repress their transcription into messenger RNA. Nuclear receptors are transcription factors: activated by lipophilic ligands (circulating hormones, or mediators synthesized by the cell, or cytosolic metabolites of an extracellular mediator) through phosphorylation.

3.2. The target is a nucleic acid

There are also many medications that target nucleic acids. In fact, the vast majority of medications used in medicine target proteins or nucleic acids. These are receptors located in the

nucleus. To enter the cell, the molecules must be fat-soluble because the extracellular membranes are made of triglycerides (fats). Corticosteroids are medications that act on the nucleus and therefore increase or decrease gene expression.

3.3. The target is a lipid

There are very few drugs of this type. Their main action is to disrupt the lipid structure of cell membranes.

3.4. The target is a carbohydrate

It was once thought that the main function of carbohydrates was structural (cellulose, starch) or energetic (glycogen). But today, we know that they constitute the majority of cellular targets. These targets allow cells to identify themselves in relation to others (immunological detection), to respond to certain hormones (insulin receptor, etc.), and can also serve as entry points for viruses. Researchers are therefore trying to develop drugs of this type to prevent viruses from entering cells.