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الَّذِي عَلَّمَ بِالْقَلَمِ ۝ عَلَّمَ الْإِنْسَانَ مَا لَمْ يَعْلَمْ



PHARMACOLOGY

MID | Lecture 3+4

Pharmacodynamics

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Color coding used in the modified:



Black: the original slides



Green: the doctor's explanation/words



Gray: additional information and explanation



Red: important information

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LECTURE 3

Pharmacodynamics I

Drug targets, receptor families and signaling mechanisms

Dr. Alia Shatanawi

Introduction to Pharmacology | Second-year Medicine

Content aligned with Katzung, Basic & Clinical Pharmacology

Learning objectives

By the end of this lecture you should be able to:

- 1 Define pharmacodynamics, receptor, ligand, agonist and antagonist.
- 2 Describe how drugs bind receptors and what makes binding specific.
- 3 Name the major drug targets: receptors, enzymes, ion channels, transporters.
- 4 Explain the five transmembrane signaling mechanisms and their speed.
- 5 Describe G proteins, second messengers and signal amplification.
- 6 Classify drugs as blockers, activators or unconventional agents.

What is pharmacodynamics?

- The study of the biochemical and physiological effects of drugs and their mechanisms of action.
- The relationship between drug concentration and drug effect. **To determine the suitable dose of certain drug**
- In short: what the drug does to the body.
- Most drugs act by binding a specific target molecule, the receptor. **There is another types of drug's target**
- A useful drug must bind enough target molecules at a tolerable dose.

R

Remember

Pharmacodynamics: what the drug does to the body.

Pharmacokinetics: what the body does to the drug.

Key terms before we start

1 Receptor

The molecule a drug binds to start its effect. Usually a protein.

2 Ligand

Any molecule that binds a receptor: a drug, hormone or neurotransmitter.

3 Agonist

Binds the receptor AND **activates** it. Produces a response.

4 Antagonist

Binds the receptor but does **NOT activate** it. Blocks the agonist.

From doing its job

Ex: Propranolol blocks β_1 -adrenergic receptors in the heart, preventing adrenaline from binding to them and decreasing heart rate, potentially causing bradycardia.

5 Affinity

How tightly a drug binds its receptor.

Higher affinity means stronger binding

6 Efficacy

Talks more about drug-receptor complex and its ability to give a response

How well a bound drug activates the receptor and produces a response.

After binding to it

An agonist has affinity AND efficacy . An antagonist has affinity but NO efficacy.

Binds with no response to produce

Receptors :

Molecule a drug binds to start an effect .

Then could be proteins (the majority) , lipid base or nucleotides(DNA or RNA)

They exist on the cell surface so that lipid insoluble ligands can bind to them .

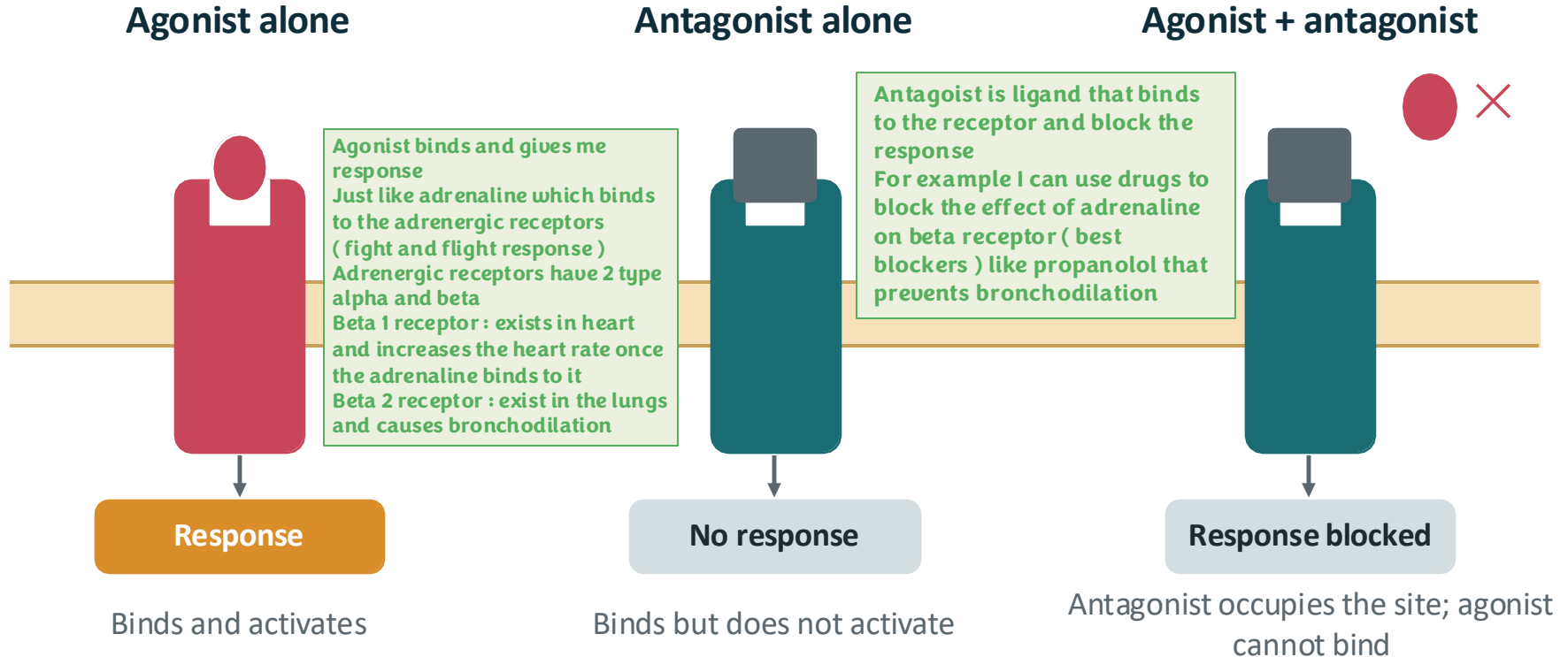
Binding of ligand do conformational changes to the receptor shape (change it's 3D structure .

On of the most important features of receptor is the specificity : each receptor has a specific 3D structure that makes it bind to specific molecules

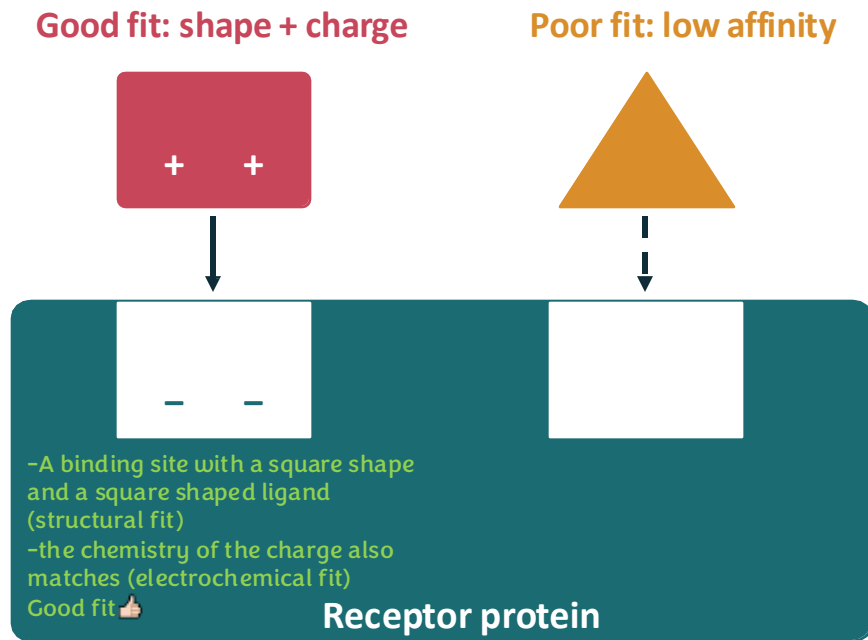
Ligand :

Molecules that bind to receptor and it can be endogenous (exist in the body like hormones , neurotransmitters and cytokines) or exogenous (coming from outside the body like drugs)

Agonist vs antagonist: what happens at the receptor



Receptors: the molecular basis of drug action



- Most receptors are proteins with a precise 3D shape.
- Specificity depends on two kinds of fit:
 - **Shape:** lock and key (or induced fit).
 - **Chemistry:** matching charges, hydrogen bonds, hydrophobic surfaces.
- Most drugs bind reversibly, by weak non-covalent bonds.

Most of drugs act on receptors (that are proteins)
Making receptors great drug targets

- Not all drugs act on receptors: antacids act chemically.

Antacids are calcium carbonate(bases) that act and affect stomach acidity by purely chemical reactions (unconventional mechanism of action)
Don't go through bloodstream nor cells' receptors

Don't mix chemical bonds of the drugs that act on receptors with chemical acts of non-receptor effectors

Most of drugs act on receptors making receptors great drug targets

Why?

Receptors are proteins that have precise 3-D forms, post translation modifications(certain carbohydrate chains with specific charges) which give the receptor specificity and affinity to certain molecules to bind with

And what determine the types of molecules to bind with receptors are

- 1) Shape of the molecule** in this case the drug
- 2) The electrochemical structure of it**

Note :the electrochemical fits of the ligand (charges match) determines what type of bond will occur between them and how strong it is

Chemical bonds in drug-receptor binding

Bond	Strength	Consequence
Covalent Aren't favorable because with the environment in the body (37° and internal pressure) covalent bonds cannot be broken	Very strong	Usually irreversible. Effect lasts until new protein is made Take days for clearance (long effect)
Ionic (electrostatic)	Strong	Attraction between opposite charges Take hours for clearance
Hydrogen	Moderate	Directional; adds specificity
Van der Waals	Weak	Short range; <u>needs a close fit</u>
Hydrophobic	Weak	Holds lipid-soluble drugs in non-polar pockets

The most favorable bonds are ionic and hydrogen bonds because they allow the drug to bind and break which gives a balanced "bound and unbound effect" of the drug and can be controlled in case of overdose, unlike irreversible binding

In case of binding irreversibly to a drug, the effect will still be produced until the cell autophages the receptor with the drug binding to it, degrades it and produces new receptors, which takes days

Weak, reversible bonds give selective, short-acting drugs. Covalent bonds give long, irreversible effects.

Properties of drug-receptor interactions

Some drugs are agonists, and some drugs are antagonists:
Morphine is an opioid drug (agonist) which acts on opioid receptors (pain receptors in the brain). Propranolol is an antagonist, the blocks adrenaline from binding with adrenergic receptors

1 **Saturable** Pretty much like the enzyme-substrate concentration mechanism

Receptors are limited. Once all are occupied, more drug gives no more effect.

Receptors are finite in number, so receptor binding is saturable. Once the maximum response is reached, increasing the drug concentration does not increase that particular response

2 **Competitive**

Drugs that bind the same site compete for it.

An agonist and a competitive antagonist compete for the same receptor-binding site. Their relative occupancy depends on their concentrations and affinities. With reversible competitive antagonism, increasing the agonist concentration can overcome the blockade

3 **Selective, not absolute**

Selectivity is lost as the dose rises. Knowing the selectivity of adrenergic receptors helps us making agonist and antagonist that bind to these receptors with affinity and act on them

4 **Structure-activity**

Small changes in structure change affinity or efficacy.

4) Structure-activity:

For example, morphine is a strong analgesic used in hospitals after surgery. However, after patients go home, they may take a medication such as Revacod, which contains paracetamol (a moderate analgesic) and codeine (a weaker analgesic than morphine, but still an opioid that belongs to the same family).

Both codeine and morphine have affinity for opioid receptors, and both act as agonists at these receptors. However, one produces a stronger analgesic effect than the other. This is because morphine has greater intrinsic efficacy than codeine.

So, the structure of the drug can affect not only its ability to bind to the receptor (affinity), but also its intrinsic activity (intrinsic efficacy), which determines how effectively the drug activates the receptor to produce an effect.

5 **Transduced**

Binding is converted into a cellular response.

6 **Regulated**

Receptor number and function change with disease and drug use.

Disease and repeated drug exposure can change receptor number or responsiveness, altering the response to a drug.

Adrenergic receptors and their effects

Adrenaline (epinephrine) activates α - and β -adrenergic receptors. Two important examples are:

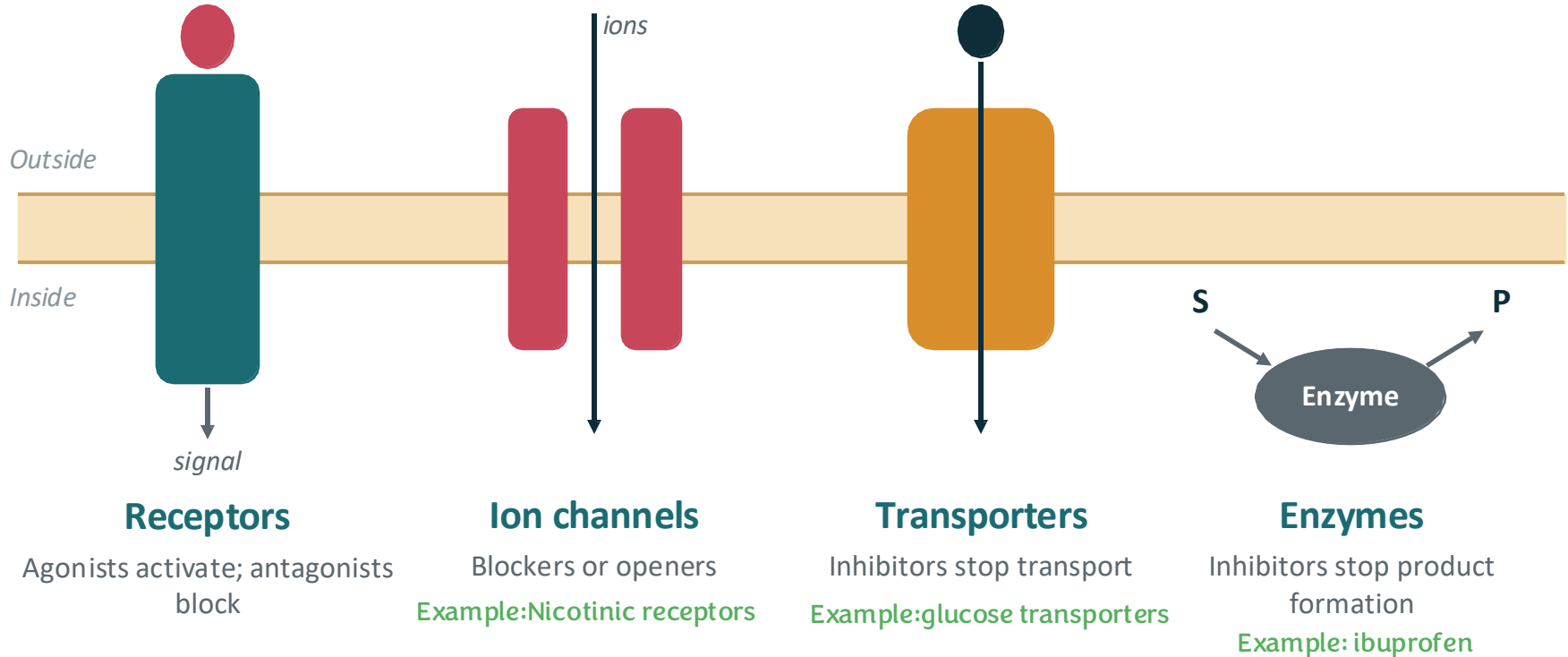
- Beta 1 in myocardial cells
- Beta 2 in bronchial smooth muscle cells

Binding of adrenaline/ other agonists that activate these receptors lead to:

- Beta 1 $\rightarrow$ tachycardia (increased heart rate)
- Beta 2 $\rightarrow$ relaxation of smooth muscle $\rightarrow$ bronchodilation (for asthma patients/ any bronchoconstriction symptoms)
- Albuterol is the agonist for beta 2 adrenergic receptors

Four major drug targets

We said that drug targets are molecules in our body that a drug (ligand) must bind to in order to produce a specific effect.



Ion Channels:

Some ion channels also function as receptors. For example, acetylcholine receptors are divided into two main types: muscarinic (M) receptors and nicotinic (N) receptors.

Nicotinic receptors are further divided into two subtypes: neuronal (N_n) and muscle (N_m) receptors. N_m receptors are located on skeletal muscle cells.

When acetylcholine binds to an N_m receptor, the channel opens, allowing sodium ions (Na^+) to enter the cell. This makes the membrane potential less negative, causing depolarization. If the threshold is reached, an action potential is triggered.

The action potential then leads to an increase in intracellular calcium (Ca^{2+}), which causes the skeletal muscle to contract.

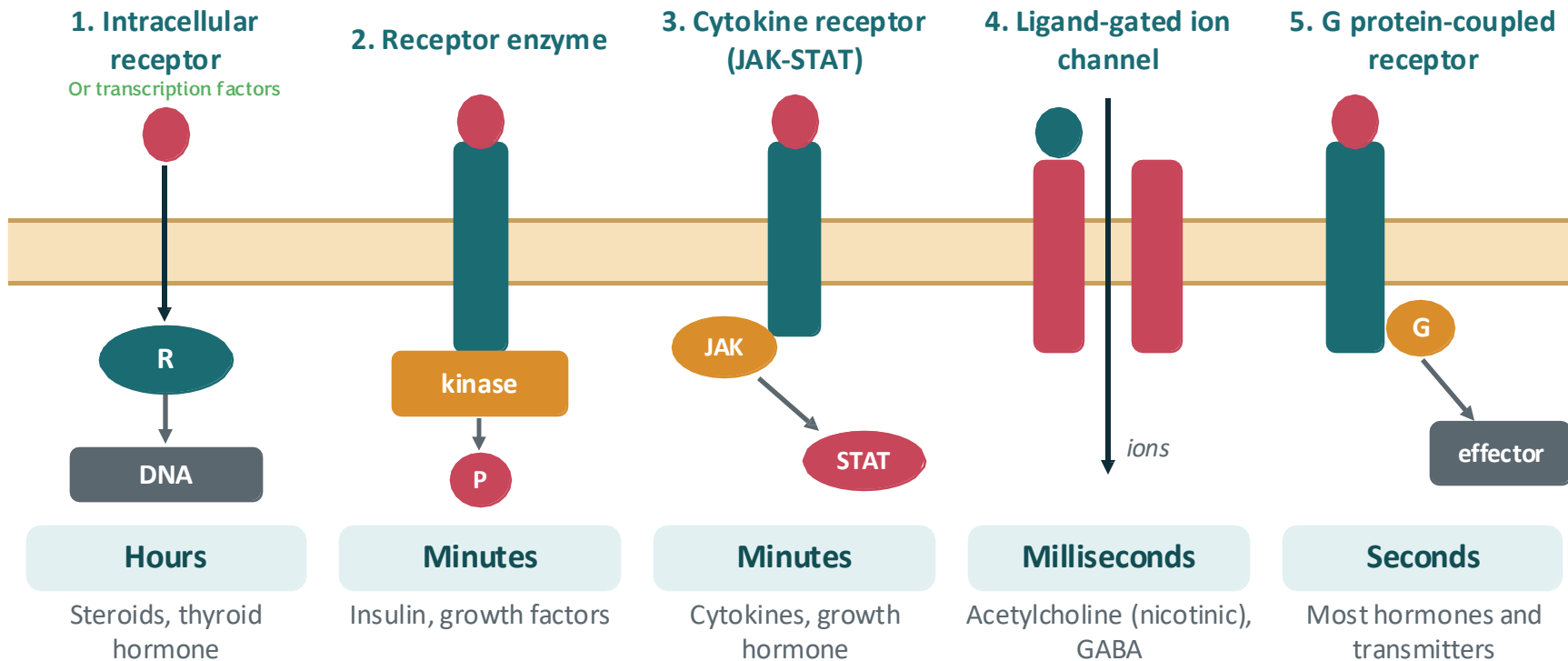
Transporters:

Insulin stimulates the movement of glucose transporters from intracellular vesicles to the cell membrane. These transporters are then inserted into the membrane, allowing glucose to enter muscle and fat cells.

Enzymes:

Ibuprofen binds to and inhibits cyclooxygenase (COX), an enzyme involved in prostaglandin synthesis. It acts as a reversible competitive inhibitor of COX, reducing prostaglandin production. As a result, it reduces pain, inflammation, and fever.

Five transmembrane signaling mechanisms



For a drug to act on an intracellular receptor, it generally needs to have a small molecular weight (Mr) and be lipid-soluble so that it can cross the plasma membrane and enter the cell.

1 is intracellular receptor
2,3,4,5 are cell membrane receptors

Why do we need all of these receptors?

Most drugs are water-soluble and cannot easily cross the cell membrane because the membrane is made of a lipid bilayer.

However, some drugs are lipid-soluble, so they can cross the plasma membrane by simple diffusion and enter the cell.

Even after entering the cell, these drugs still need to bind to a specific receptor to produce their effects. These receptors are called **intracellular receptors** because they are located inside the cell.

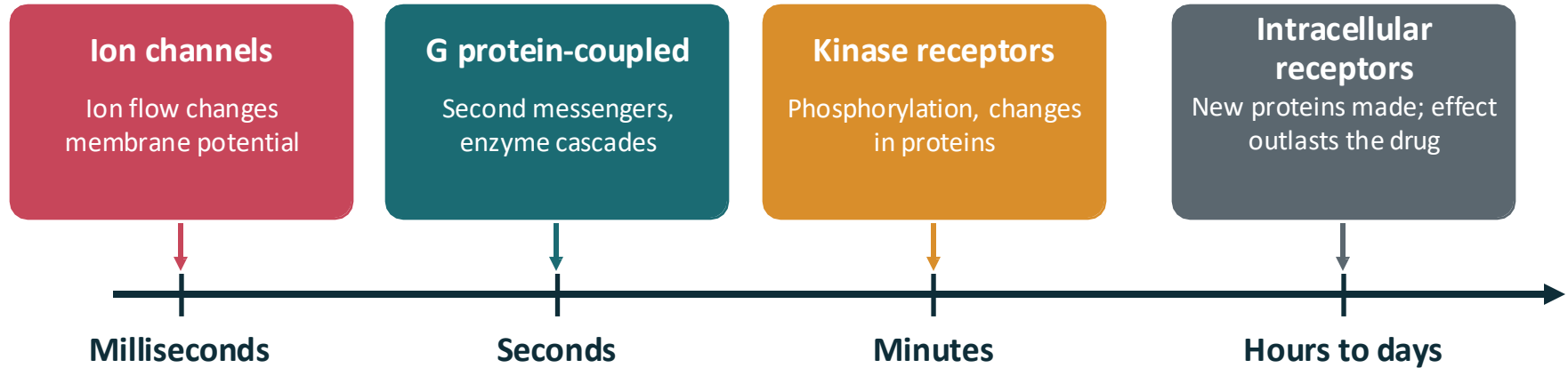
Intracellular Receptors:

Intracellular receptors are also called *transcription factors* because, when activated, they can regulate gene transcription, leading to the production of mRNA and, subsequently, proteins.

When a drug such as cortisone diffuses through the plasma membrane into the cell, it binds to a specific intracellular receptor. The drug-receptor complex then translocates into the nucleus, where it binds to specific DNA sequences and regulates the transcription of certain genes.

Another example is vitamin D

Speed of response depends on the mechanism



Clinical meaning: drugs acting on intracellular receptors start slowly and their effect persists after the drug is gone.

That's because the drug-receptor complex influences gene expression. Meaning that cell will produce new proteins that will remain active even after the drug has been eliminated

Receptors are broadly classified into two main categories based on their location and mechanism:

.1 Cell Surface Receptors

Located on the plasma membrane, these bind to hydrophilic (water-soluble) ligands that cannot cross the cell membrane. They include :

Ligand-Gated Ion Channels (Ionotropic Receptors) :

Example: Nicotinic receptors .

Mechanism: When a ligand (such as acetylcholine) binds to the channel, it induces a conformational change that immediately opens the channel, allowing ion influx.

Characteristics: Known for their ultra-fast action, responding within milliseconds .

G-Protein Coupled Receptors (GPCRs) :

Mechanism: Ligand binding triggers a conformational change that acts as a molecular switch, converting the bound GDP to GTP on the G-protein to initiate downstream signaling.

Enzyme-Linked / Cytokine Receptors (e.g., JAK-STAT pathways) :

Mechanism: Ligand binding activates intrinsic or associated enzymatic activity to trigger intracellular signaling cascades .

2. Intracellular (Nuclear) Receptors

Characteristics: Located inside the cytoplasm or nucleus. They bind to lipophilic (lipid-soluble) ligands, such as steroid hormones and cortisol.

Mechanism: Most of these receptors function as transcription factors. Once activated by their ligand, they translocate into the nucleus and modulate the transcription of specific genes.

Order of Receptors by Speed of Action:

(From the fastest to the slowest response)

Ion Channels (Fastest): Operates in milliseconds (e.g., Nicotinic receptors opening to allow ion flow).

G-Protein Coupled Receptors (GPCRs): Operates in seconds.

Enzyme-Linked / Cytokine Receptors: Operates in minutes to hours.

Intracellular Receptors (Slowest): Takes hours to days.

Why? Because their mechanism requires multiple complex biological steps, including DNA transcription, translation, protein folding, and post-translational modifications.

Ligand-gated ion channels

- Several subunits form a pore; the binding site is on the same protein.
- Ligand binding opens the pore within milliseconds: the fastest mechanism.
- Ions flow down their gradient and change the membrane potential.
- Cation channels (Na^+ , Ca^{2+}) depolarize and excite the cell.
- Chloride channels hyperpolarize and inhibit the cell.

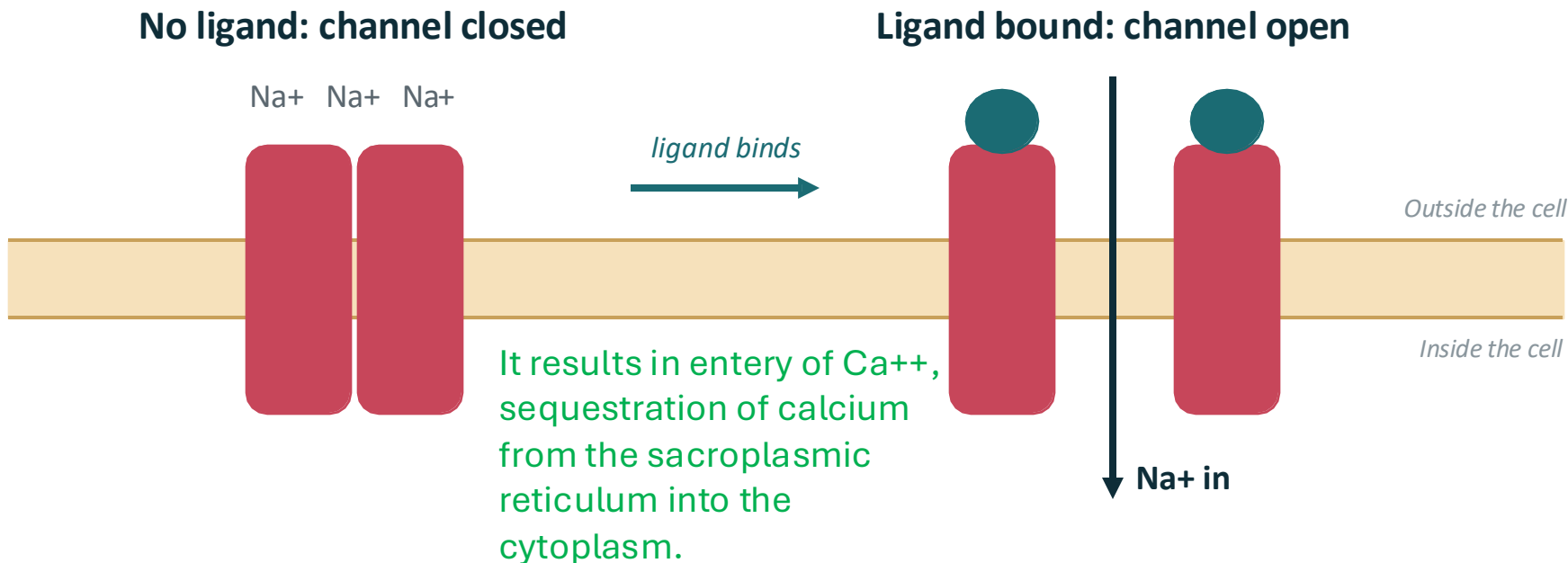


Do not confuse

Voltage-gated channels are also drug targets, but they are opened by membrane voltage, not by a ligand.



Ligand-gated ion channel: closed and open

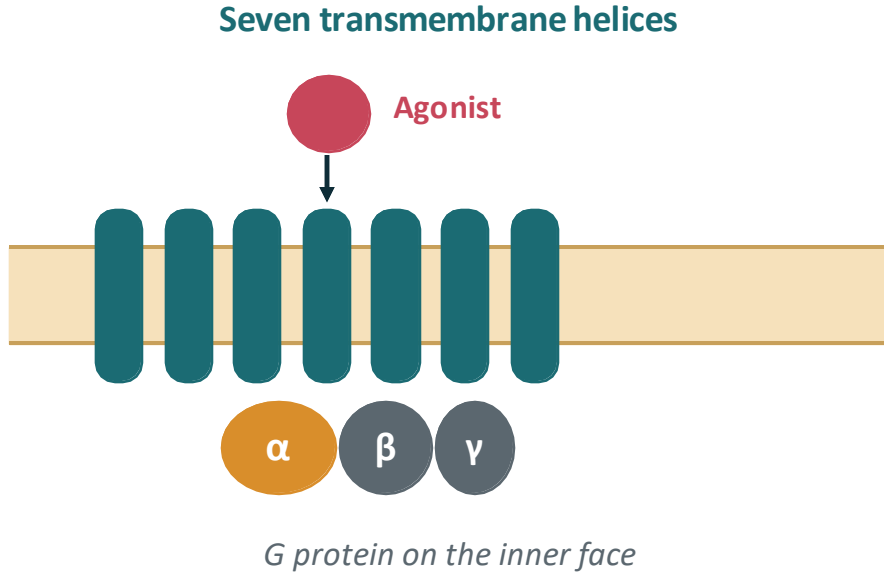


Example: acetylcholine opens the nicotinic receptor at the neuromuscular junction. Na⁺ enters, the end-plate depolarizes, and the muscle contracts.

ACh → nAChR opens → Na⁺ influx → End-plate depolarization → Muscle action potential → Ca²⁺ release from SR → Muscle contraction

G protein-coupled receptors (GPCRs)

For example: muscarinic receptor.



- The largest receptor family and a major drug target.
- One protein that crosses the membrane seven times.
- Coupled to a G protein made of three subunits: α , β and γ .
- α binds GDP or GTP and has its own GTPase activity.
- The $\beta\gamma$ pair also signals, for example by opening K^+ channels.

The autonomic nervous system is divided into two main divisions: Sympathetic and Parasympathetic. Each utilizes specific types of receptors at ganglia and effector organs.

1. Parasympathetic Nervous System (PNS)

utilizes Acetylcholine (ACh) as its neurotransmitter and acts through two main types of receptors:

- Nicotinic Receptors (Ligand-gated ion channels):

Locations: Autonomic ganglia (both sympathetic and parasympathetic ganglia) and the neuromuscular junction (skeletal muscles).

- Muscarinic Receptors (GPCRs): Locations: Effector organs innervated by the parasympathetic system (e.g., heart, smooth muscles, and glands).

(Note: A classic physiological exception is that sweat glands receive sympathetic innervation, yet they exceptionally use muscarinic receptors responding to acetylcholine).

2. Sympathetic Nervous System (SNS)

predominantly uses Norepinephrine and Epinephrine and acts almost exclusively through a specialized family of cell-surface receptors:

- Adrenergic Receptors (GPCRs):

- *Alpha (alpha) Receptors: (e.g., alpha 1, alpha 2) - involved mainly in smooth muscle contraction/vasoconstriction.

- *Beta (beta) Receptors: (e.g., beta 1 in the heart, beta 2 in the lungs) - involved in heart stimulation and bronchodilation.

Mechanism of G-Protein Coupled Receptors:

Resting State: In the inactive state, the G-protein is bound to guanosine diphosphate.

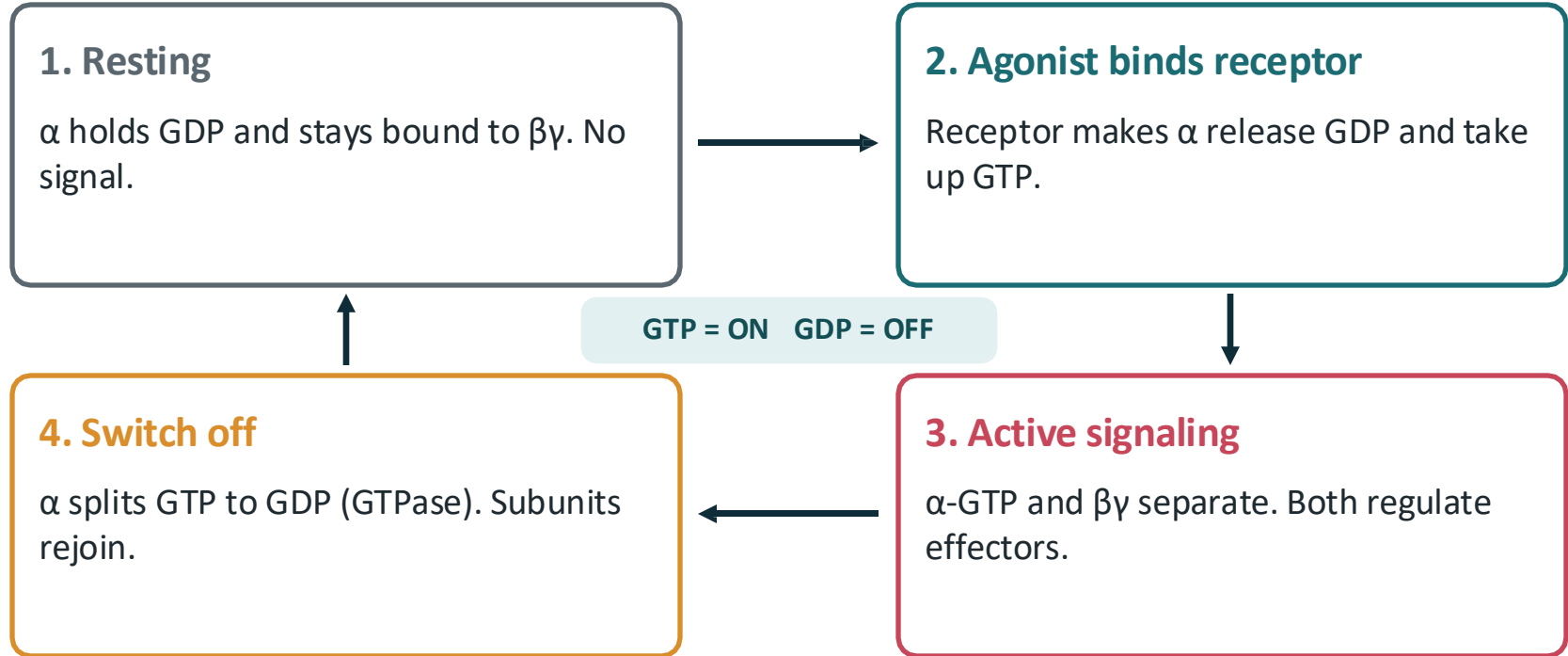
Activation: When a ligand binds to the receptor, it triggers an exchange where guanosine diphosphate is replaced by guanosine triphosphate, activating the protein.

Subunit Separation: Once activated, the alpha subunit separates from the beta and gamma dimer while carrying the guanosine triphosphate molecule. Each separated part then triggers its own intracellular signaling cascade.

Inactivation: An enzyme breaks down the guanosine triphosphate back into guanosine diphosphate.

Return to Rest: The alpha subunit reunites with the beta and gamma dimer, restoring the complex to its original resting state.

The G protein cycle: on and off



The three main G protein pathways

stimulatory

Gs

Adenylyl cyclase ↑

cAMP ↑

Protein kinase A

inhibition

Gi

Adenylyl cyclase ↓

cAMP ↓

$\beta\gamma$ opens K⁺ channels

Increases the calcium inside the cells (neurons and muscle cells)

Gq

In the membrane

Phospholipase C ↑

IP3 and DAG

Ca²⁺ ↑ and PKC

e.g. Beta adrenoceptors

Beta 1 receptor present in the heart. Activation of this receptor leads to the increase of blood flow to the heart and contraction of cardiac muscle (sympathetic mechanism)

e.g. Alpha-2, muscarinic M2, opioid

Opioid receptors in the brain (for exp: morphine which is a pain killer). -so we mean here in pain inhibition and the inhibition of cAMP.

e.g. Alpha-1, muscarinic M1/M3, H1

Alpha adrenergic receptor exists in smooth muscles of blood vessels, which leads to vasoconstriction and increase in blood pressure.

Second messengers carry the signal inside the cell

1 cAMP

Made by adenylyl cyclase. Activates protein kinase A. Broken down by **phosphodiesterases (could be a drug target)**.

2 IP3 and DAG

Made from a membrane lipid by phospholipase C. IP3 releases Ca^{2+} ; DAG activates PKC. PKC = protein kinase C

3 Calcium

Binds calmodulin and other proteins. Triggers contraction and secretion. Triggers the excretion of the vesicle containing the neurotransmitter.

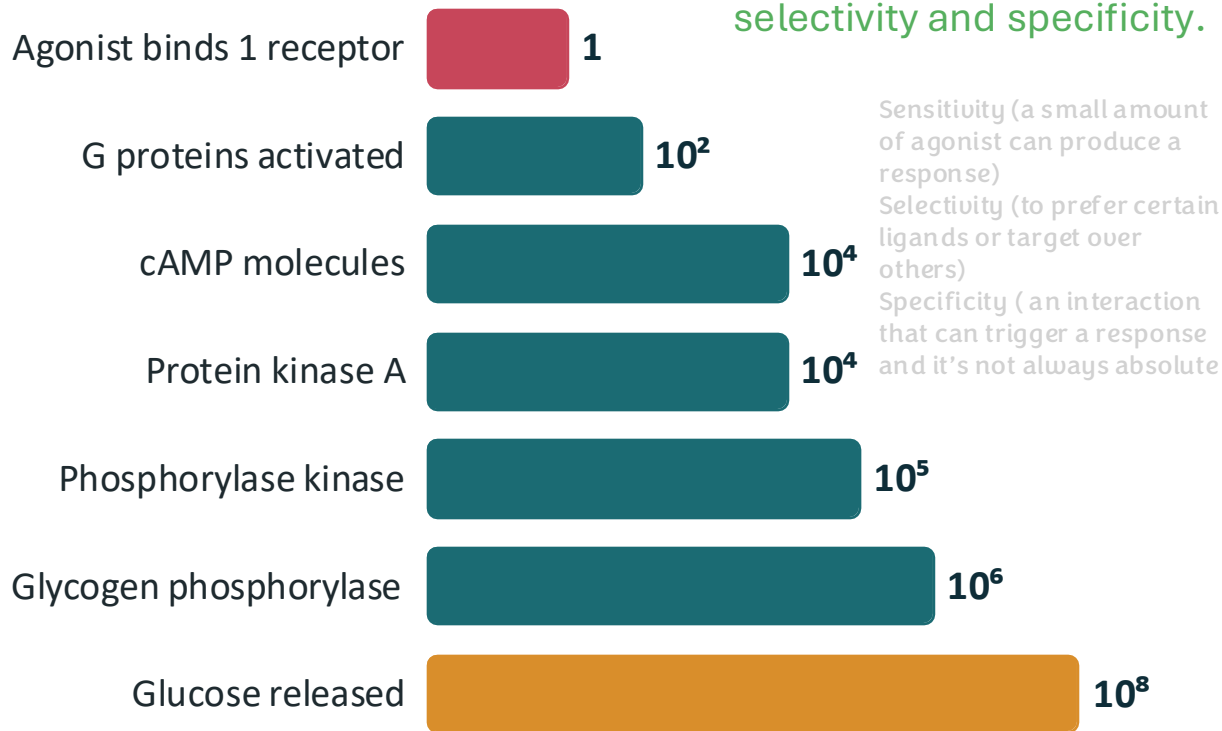
4 cGMP

Made by guanylyl cyclase. Relaxes smooth muscle. Broken down by **phosphodiesterases**.

Blocking the enzyme that breaks down a second messenger raises its level and prolongs the signal.

Signal amplification

Recall that receptors are great drug targets because they possess sensitivity, selectivity and specificity.



Sensitivity (a small amount of agonist can produce a response)
Selectivity (to prefer certain ligands or target over others)
Specificity (an interaction that can trigger a response and it's not always absolute)

x Why it matters

Each step activates many molecules. A tiny amount of agonist gives a large response.

Epinephrine acting on liver cells. Numbers are illustrative orders of magnitude.

The doc explained the correlation between selectivity and receptors such as beta 1 and 2.
(Both beta 1 and beta 2 are Gs .)

Think of a drug as a key designed for a specific lock. A selective drug acts like a private key that opens only its intended lock, whereas a non-selective drug acts like a master key that opens multiple different doors, which often leads to numerous unwanted side effects.

-The principle of selectivity is critical in developing targeted therapies:

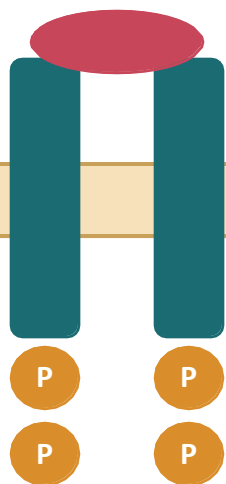
1. Asthma Treatments (beta2 Agonists): An asthma patient requires bronchodilation, which means activating beta2 receptors in the lungs. If given a non-selective beta agonist, the drug would stimulate beta2 in the lungs (desired) but also stimulate beta1 in the heart (undesired), causing tachycardia and heart palpitations. Therefore, scientists developed selective beta2 agonist which target airway receptors directly while largely avoiding the heart.

2. Cardiovascular Treatments (beta1 Blockers): A patient with hypertension or heart failure needs to slow and protect the heart by blocking beta1 receptors. A non-selective blocker might inadvertently block beta2 receptors in the lungs as well, leading to dangerous bronchospasm in asthmatic patients. Consequently, cardiologists use cardioselective beta1 blockers which block heart receptors exclusively without interfering with lung receptors.

Enzyme-linked and cytokine receptors

Receptor tyrosine kinase

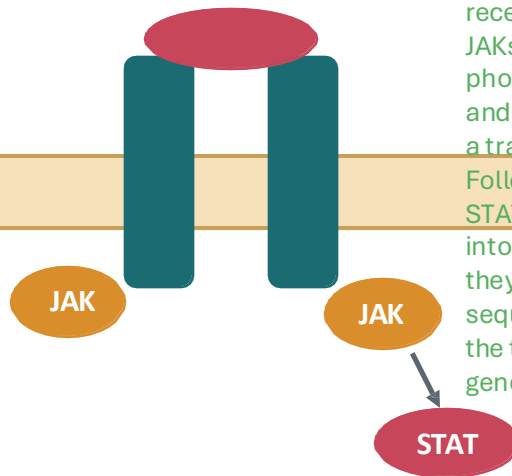
Through these pathways, insulin produces several cellular effects. One important effect of insulin signaling is the increased expression and translocation of glucose transporters to the cell membrane. This facilitates glucose uptake from the extracellular fluid into the cell. Therefore, insulin signaling regulates glucose transport and can also influence the activity of enzymes and the transcription of certain genes.



The insulin receptor is an example of a receptor tyrosine kinase. In this type of receptor, the tyrosine kinase activity is a part of the receptor itself. When insulin binds to its receptor, the receptor becomes activated, resulting in autophosphorylation of its intracellular residues. This phosphorylation other cellular signaling cascades.

Ligand brings two receptors together. They phosphorylate each other on tyrosine. Signaling proteins dock.

Cytokine receptor (JAK-STAT)



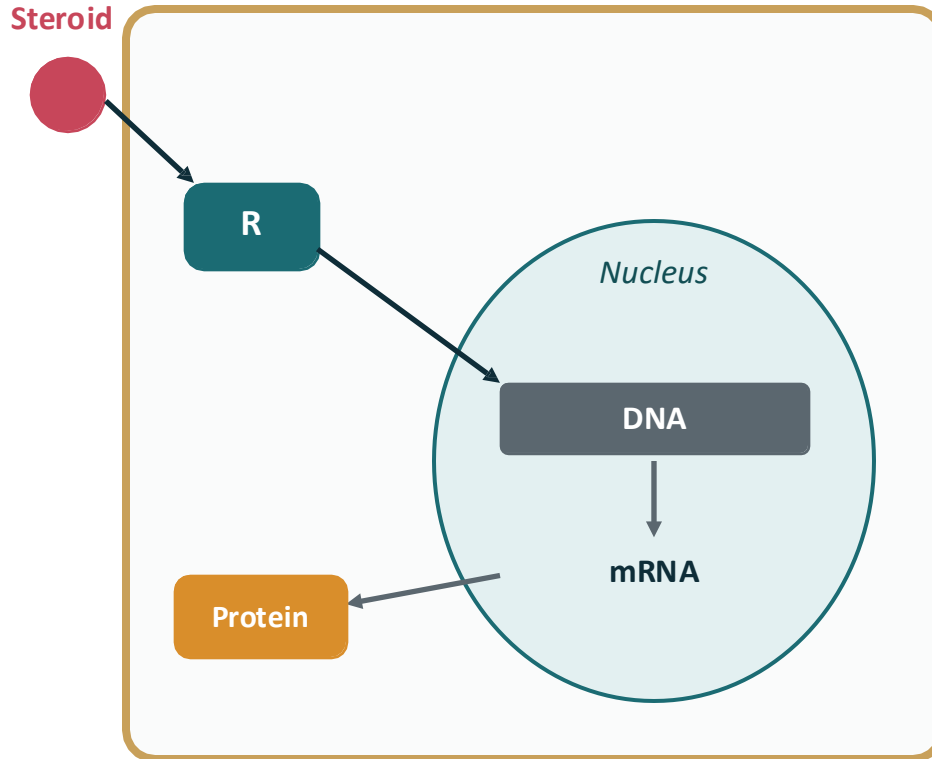
When a ligand binds to its receptor, the associated JAKs become activated and phosphorylate the receptor and STAT proteins. STAT is a transcription factor. Following phosphorylation, STAT proteins translocate into the nucleus, where they bind to specific DNA sequences and modulate the transcription of target genes.

Receptor has no enzyme of its own. It recruits JAK kinases, which activate STAT proteins. STAT goes to the nucleus.

Ex: 1) Growth Hormone Receptor ,following growth hormone binding, the receptor-associated JAK proteins become activated, leading to STAT phosphorylation. The STAT then enter the nucleus and stimulate gene transcription.

2) Erythropoietin is produced mainly by the kidneys that stimulates the bone marrow to produce red blood cells.

Intracellular (nuclear) receptors



- The ligand must be **lipid-soluble** to cross the membrane. (And small enough to cross the membrane)
- Ligand-receptor complex binds DNA and changes (up or down) gene transcription.
- **Lag:** 30 minutes to hours before the effect appears.
- **Persistence:** effect lasts after the drug is gone, while the new proteins remain. (the effects may persist even after the drug has been eliminated from the body)

Intracellular (nuclear) receptors

Some drugs, such as steroid hormones, act through intracellular receptors. Because these drugs are lipid-soluble, they can cross the plasma membrane and bind to their receptors inside the cell. After the ligand binds to its receptor, a ligand-receptor complex is formed. The activated steroid-receptor complex then translocates into the nucleus, where it binds to specific DNA sequences and modulates gene expression. This modulation may either increase or decrease the transcription of particular genes, depending on the target gene and the regulatory mechanisms involved.

How do drugs work?

Most drugs block or activate an endogenous protein. A few act by unconventional mechanisms.

~70% receptors ← → ~30% Enzymes

Three ways drugs act

A base interacts chemically with HCl in the stomach, and simply generates salt, water and sometimes CO₂, without requiring the drug to bind to a receptor or inhibit an enzyme.

1 Block or inhibit

- Receptor antagonists (cell surface and nuclear **-intracellular-**)
- Enzyme inhibitors
- Ion channel blockers
- Transport inhibitors
- Signal transduction inhibitors

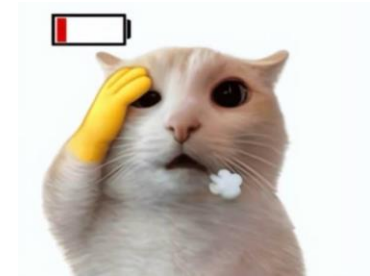
2 Activate

- Receptor agonists (cell surface and nuclear)
- Enzyme activators
- Ion channel openers and positive modulators

3 Unconventional

- Chemical reactions (antacids)
- Binding free molecules (chelators, antibodies)
- Physical effects (osmotic agents)
- Being enzymes, nutrients or antigens

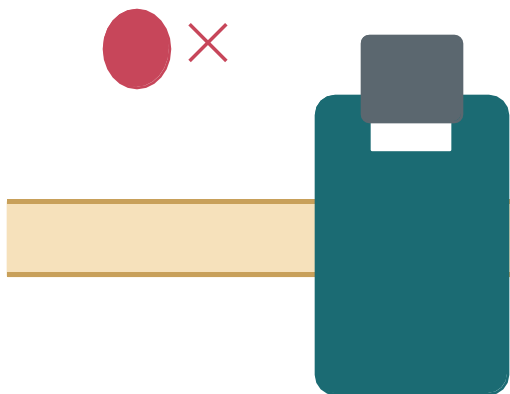
- The term antagonist is generally used for drugs that block receptors, whereas the terms blocker and inhibitor are commonly used for drugs that inhibit the activity of enzymes. Example of receptor antagonists: Beta-blockers such as propranolol act as antagonists at beta-adrenergic receptors.
- Nuclear receptors are intracellular receptors that regulate gene expression in response to specific ligands. Some are located in the cytoplasm before ligand binding and subsequently translocate into the nucleus, whereas others are already located in the nucleus. After ligand binding, these receptors regulate the transcription of target genes, either increasing or decreasing their expression. Ex: Mineralocorticoid receptors, for excretion of excess water and salts from the body (Diuretics).
- Enzyme Inhibitors: Some drugs act by inhibiting enzymes involved in the production of biologically active substances. For example, cyclooxygenase (COX) inhibitors reduce prostaglandin synthesis by inhibiting the cyclooxygenase enzymes, such as Aspirin and Ibuprofen, they are used for analgesic, antipyretic, and anti-inflammatory effects.



How antagonists block receptors

Competitive antagonist

Binds the SAME site as the agonist

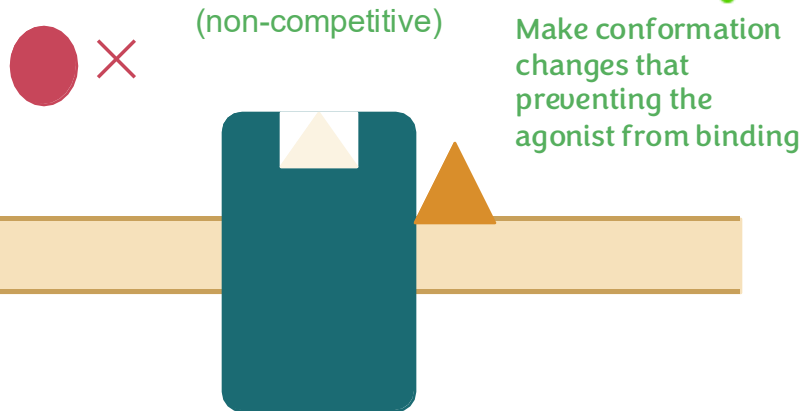


Reversible: enough agonist displaces it. The block can be overcome. By increasing the agonist concentration.

- Increasing the agonist concentration can displace the competitive antagonist from the receptor and the same thing in increasing the antagonist concentration, it can overcome and has more ability to bind to the receptor.
- The binding is reversible.

Allosteric antagonist

Binds a DIFFERENT site and changes the receptor shape



Agonist cannot bind or activate normally. More agonist does not overcome the block.

The underlying information is what the doctor mentioned in the lecture, but she said that we should know the target and the common drugs with their uses not all names of example drugs

Examples: blocking receptors and enzymes

Mechanism	Target	Example drug and use
Receptor antagonist	Angiotensin AT1 receptor	Losartan: hypertension, heart failure
	<u>Beta-adrenoceptors</u>	<u>Propranolol</u> : <u>angina</u> , <u>hypertension</u>
Nuclear receptor antagonist	<u>Mineralocorticoid receptor</u> once they bind to their receptors, cause retaining of fluid in our body.	<u>Spironolactone</u> : <u>heart failure</u>
	Estrogen receptor	Tamoxifen: breast cancer
Enzyme inhibitor	<u>Cyclooxygenase</u>	<u>Aspirin, ibuprofen</u> : <u>pain</u> , <u>inflammation</u>
	<u>HMG-CoA reductase</u> cholesterol-lowering drug	<u>Atorvastatin</u> : <u>high cholesterol</u>
	<u>Angiotensin-converting enzyme</u>	<u>Captopril</u> : <u>hypertension</u>

HMG-CoA reductase is an enzyme involved in cholesterol synthesis. These drugs inhibit the enzyme, thereby reducing cholesterol synthesis.

Examples: blocking channels, transporters and signaling

When calcium ions enter the cell, they cause contraction, this leads to vasoconstriction so the drugs that block Ca^{2+} channels can treat hypertension

Mechanism	Target	Example drug and use
Ion channel blocker	<u>L-type Ca^{2+} channel</u>	<u>Amlodipine: angina, hypertension</u>
	Voltage-gated Na^{+} channel	Lidocaine: local anesthesia, arrhythmia
Transport inhibitor	<u>Serotonin transporter</u>	<u>Fluoxetine: depression</u>
	$\text{Na}^{+}/\text{K}^{+}/2\text{Cl}^{-}$ symporter	Furosemide: edema
	Proton pump ($\text{H}^{+}/\text{K}^{+}$ -ATPase)	Omeprazole: peptic ulcer
Signaling inhibitor	BCR-ABL tyrosine kinase	Imatinib: chronic myeloid leukemia
	Phosphodiesterase 5	Sildenafil: erectile dysfunction

Serotonin is released and then it undergoes reuptake so that it can be reused; a transporter facilitates this reuptake, bringing it back into the nerve terminals. Therefore, if we want to increase its levels to treat depression, we block this reuptake process.

Doctor will complete the examples in the next lecture

Examples: drugs that activate

Mechanism	How it works	Example
Receptor agonist	Mimics the endogenous ligand	Salbutamol (beta-2), morphine (opioid)
Nuclear receptor agonist	Switches on gene transcription	Hydrocortisone, levothyroxine
Enzyme activator	Increases enzyme activity	Nitroglycerin releases NO, which activates guanylyl cyclase
Channel opener	Opens the channel	Minoxidil opens K ⁺ channels
Positive allosteric modulator	Increases the effect of the natural ligand; cannot act alone	Benzodiazepines at the GABA-A receptor

Unconventional mechanisms

Mechanism	Example
Disrupting structural proteins	Colchicine, vinca alkaloids bind tubulin
Acting as an enzyme	Alteplase dissolves clots
Covalent binding to DNA	Cyclophosphamide (cancer)
Chemical reaction	Antacids neutralize stomach acid
Binding a free molecule or ion	Chelators bind metals; infliximab binds TNF
Physical (osmotic) action	Mannitol, osmotic laxatives
Replacing a nutrient	Vitamins, iron
Acting as an antigen	Vaccines

Quiz

<https://forms.gle/DFHD4ZwXEUjHD6549>

done 

Additional resources:

Reference Used:

Dr. Alia Shatanawi's live lecture

فإنَّ الإنسان لا يُفتح عليه في العبوديَّة
بمجرّد الجُهود الشخصيَّة والتخطيط
للإنجاز، وإنما فتوحات العبوديَّة من
بركات اللجوء إلى الله.

Extra References for The Reader to Use:

• إبراهيم السكران — فك الله أسره.

رسالة من الفريق العلمي:

For any feedback, scan the code or click on it.



Versions	Slide # and Place of Error	Before Correction	After Correction
$V_0 \rightarrow V_1$			
$V_1 \rightarrow V_2$			