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LECTURE 3

Pharmacodynamics I

Drug targets, receptor families and signaling mechanisms

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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.
- In short: what the drug does to the body.
- Most drugs act by binding a specific target molecule, the receptor.
- 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.

5 Affinity

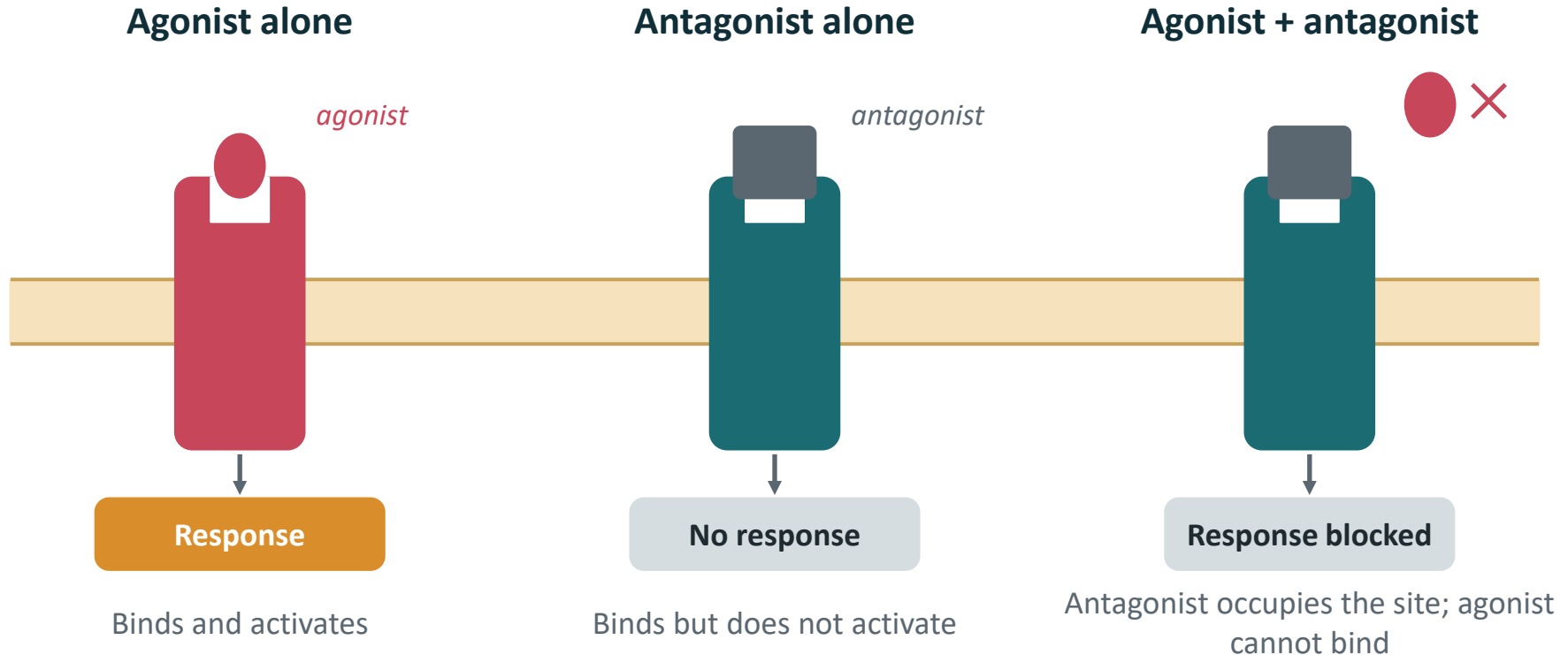
How tightly a drug binds its receptor.

6 Efficacy

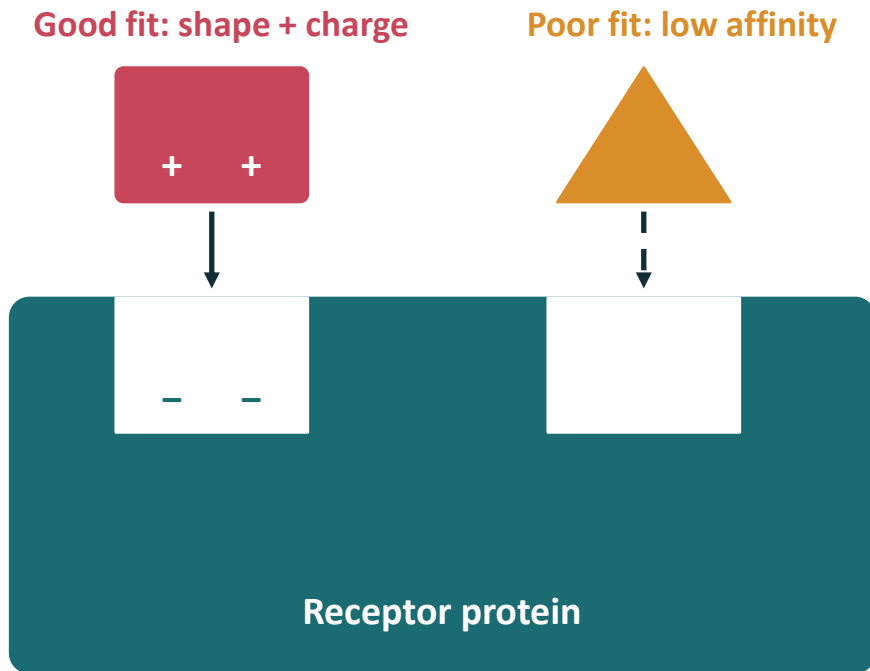
How well a bound drug activates the receptor and produces a response.

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

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

Chemical bonds in drug-receptor binding

Bond	Strength	Consequence
Covalent	Very strong	Usually irreversible. Effect lasts until new protein is made
Ionic (electrostatic)	Strong	Attraction between opposite charges
Hydrogen	Moderate	Directional; adds specificity
Van der Waals	Weak	Short range; needs a close fit
Hydrophobic	Weak	Holds lipid-soluble drugs in non-polar pockets

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

Properties of drug-receptor interactions

1 Saturable

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

2 Competitive

Drugs that bind the same site compete for it.

3 Selective, not absolute

Selectivity is lost as the dose rises.

4 Structure-activity

Small changes in structure change affinity or efficacy.

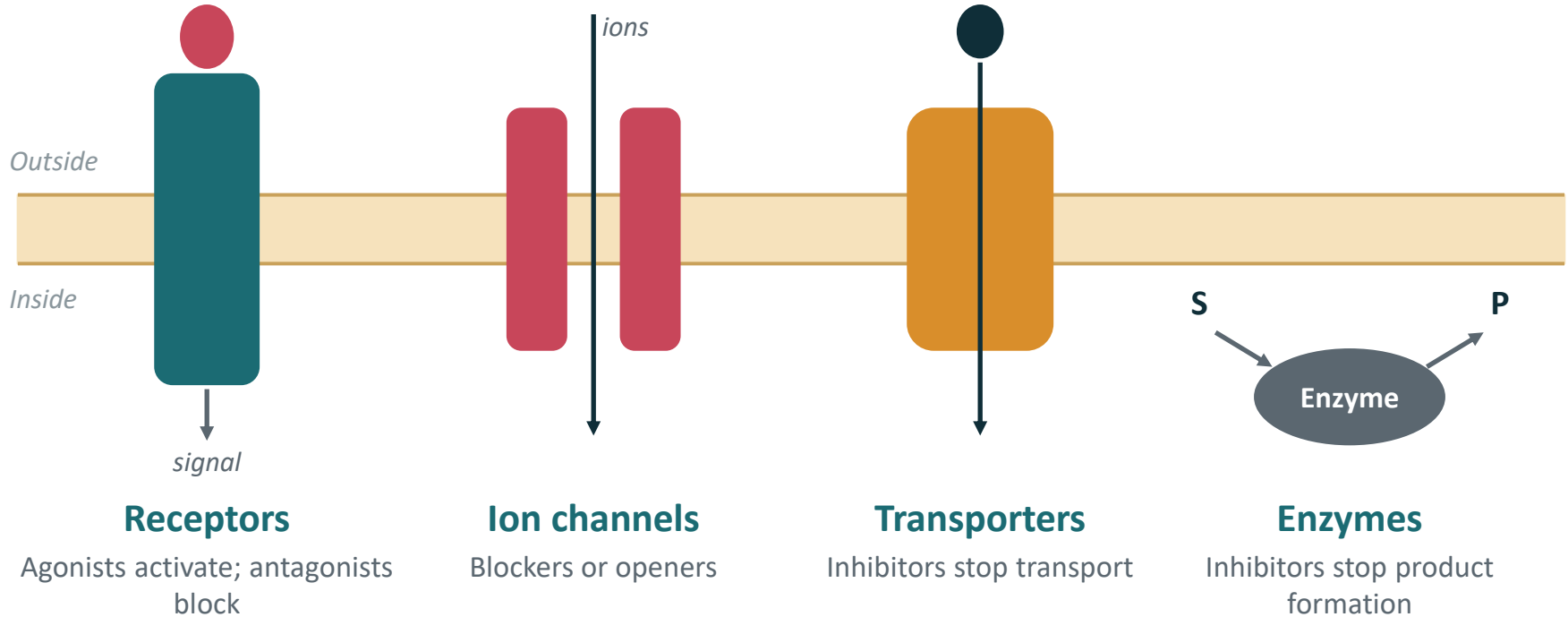
5 Transduced

Binding is converted into a cellular response.

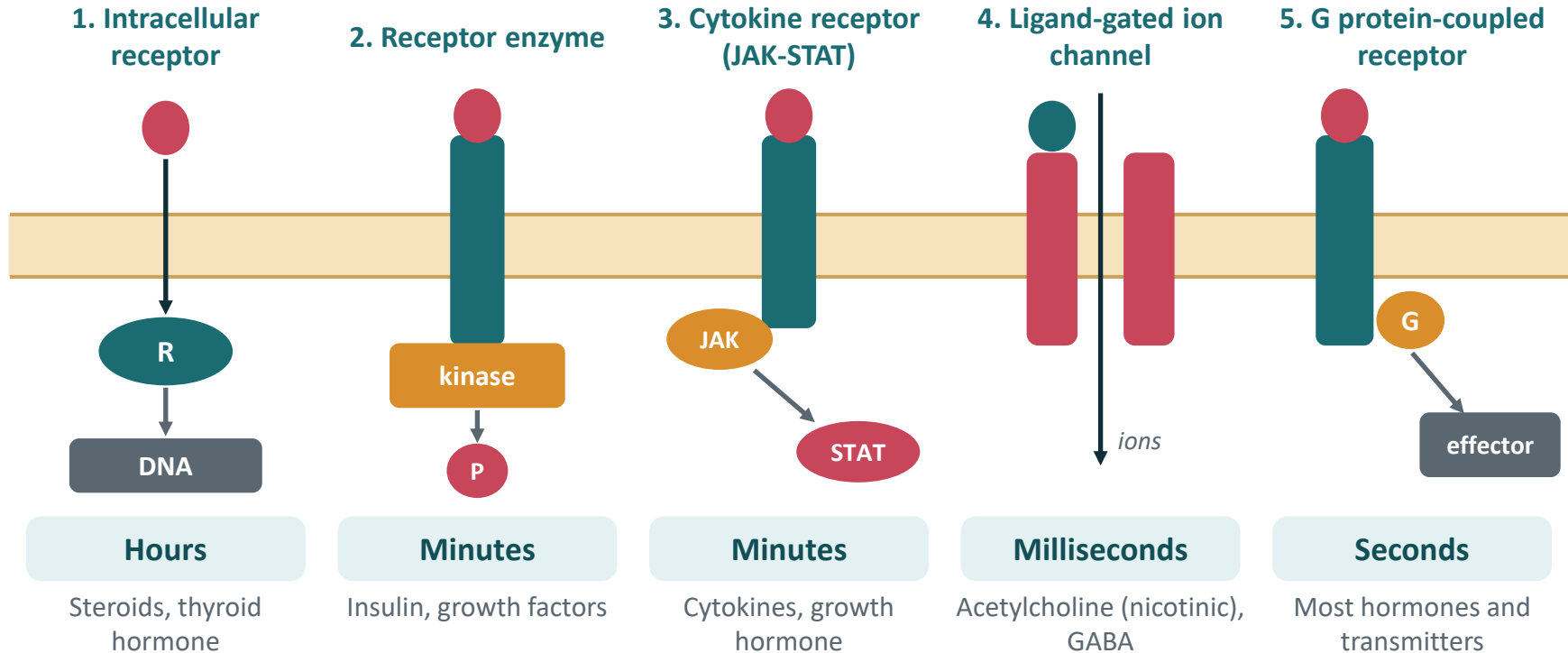
6 Regulated

Receptor number and function change with disease and drug use.

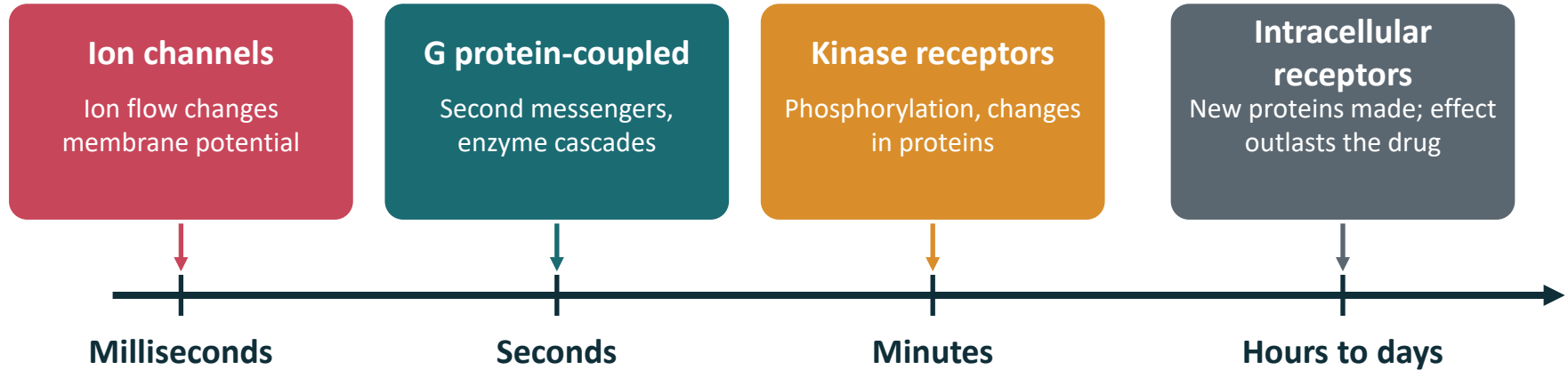
Four major drug targets



Five transmembrane signaling mechanisms



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.

Ligand-gated ion channels

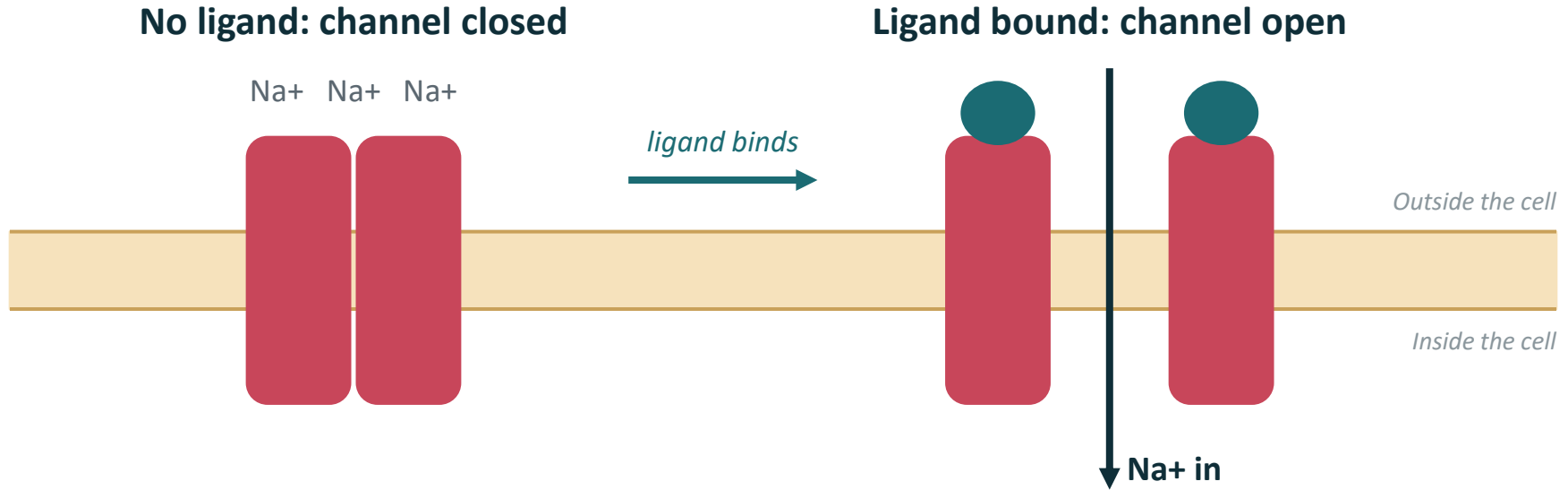
- Several subunits form a pore; the binding site is on the same protein.
- Ligand binding opens the pore within milliseconds: the fastest mechanism.
- Ions flow down their gradient and change the membrane potential.
- Cation channels (Na^+ , Ca^{2+}) depolarize and excite the cell.
- Chloride channels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



Do not confuse

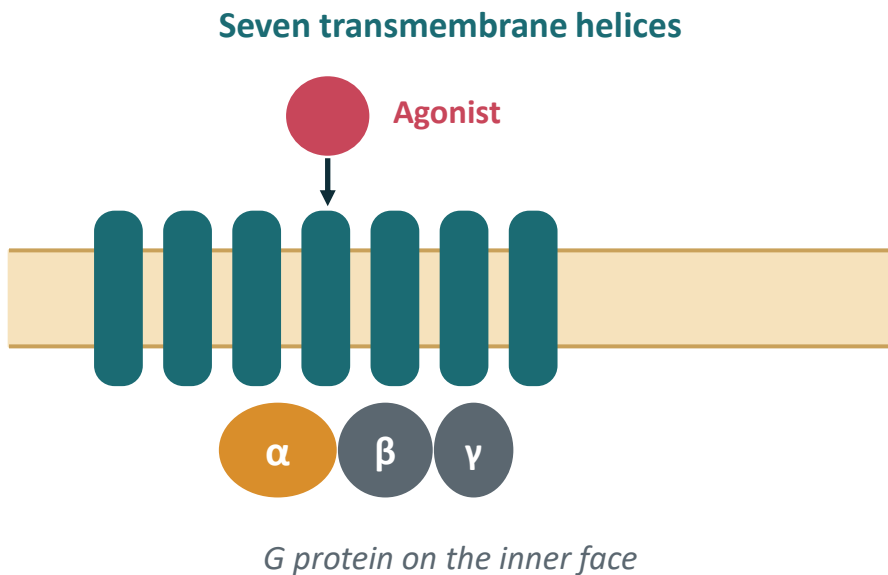
Voltage-gated channels are also drug targets, but they are opened by membrane voltage, not by a ligand.

Ligand-gated ion channel: closed and open



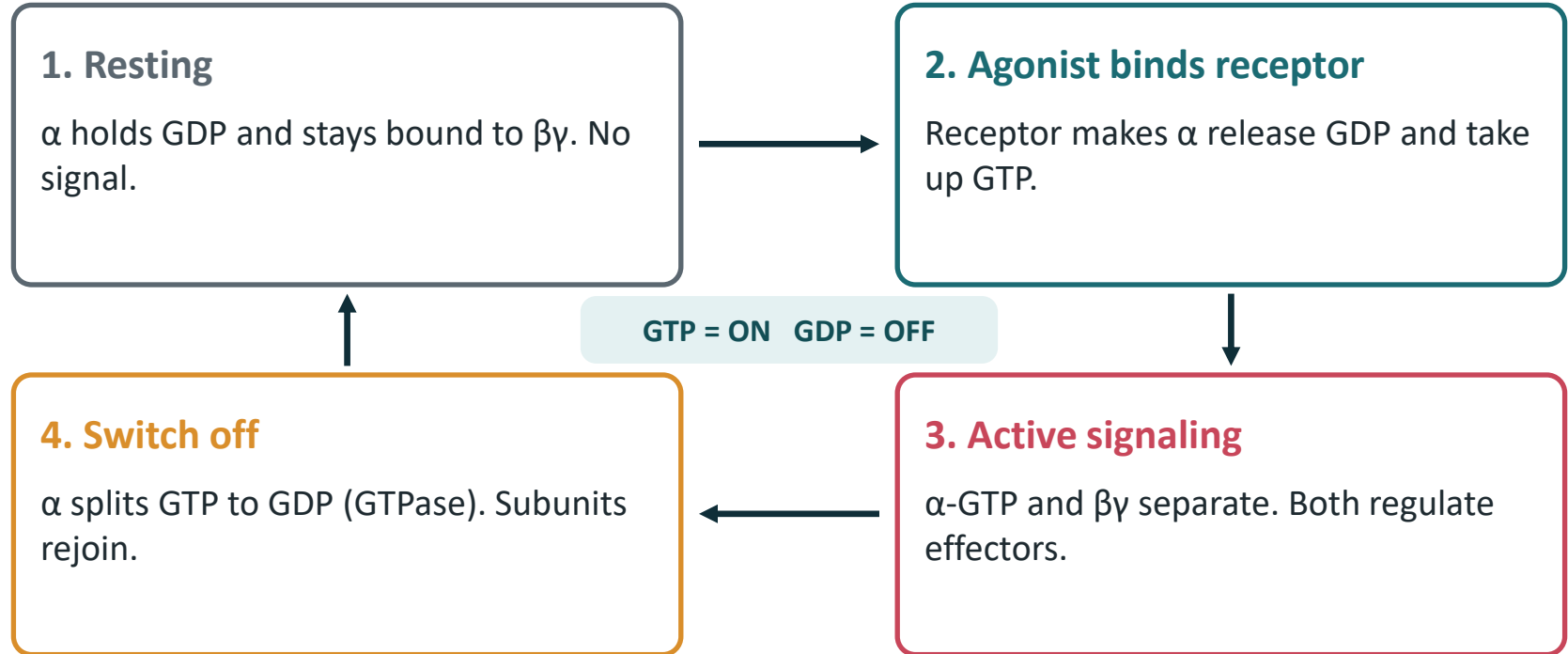
Example: acetylcholine opens the nicotinic receptor at the neuromuscular junction. Na^+ enters, the end-plate depolarizes, and the muscle contracts.

G protein-coupled receptors (GPCRs)

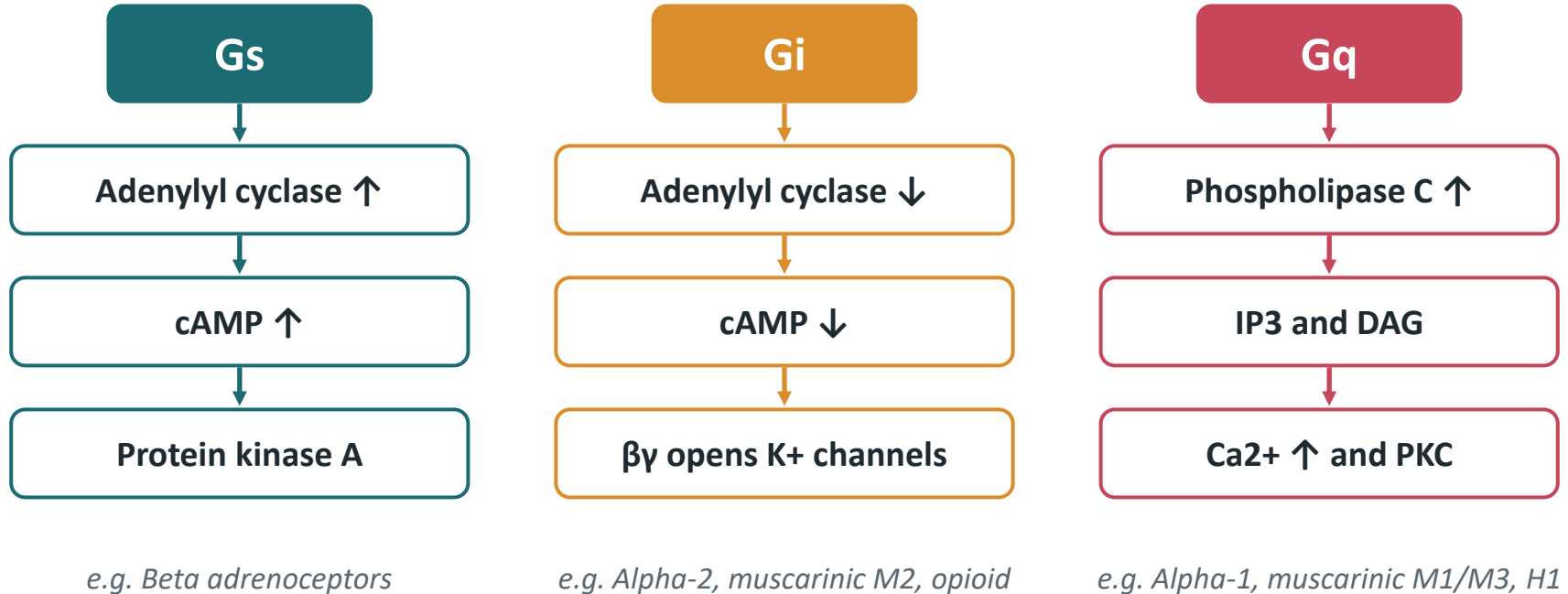


- The largest receptor family and a major drug target.
- One protein that crosses the membrane seven times.
- Coupled to a G protein made of three subunits: α , β and γ .
- α binds GDP or GTP and has its own GTPase activity.
- The $\beta\gamma$ pair also signals, for example by opening K^+ channels.

The G protein cycle: on and off



The three main G protein pathways



Second messengers carry the signal inside the cell

1 cAMP

Made by adenylyl cyclase. Activates protein kinase A. Broken down by phosphodiesterases.

2 IP3 and DAG

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

3 Calcium

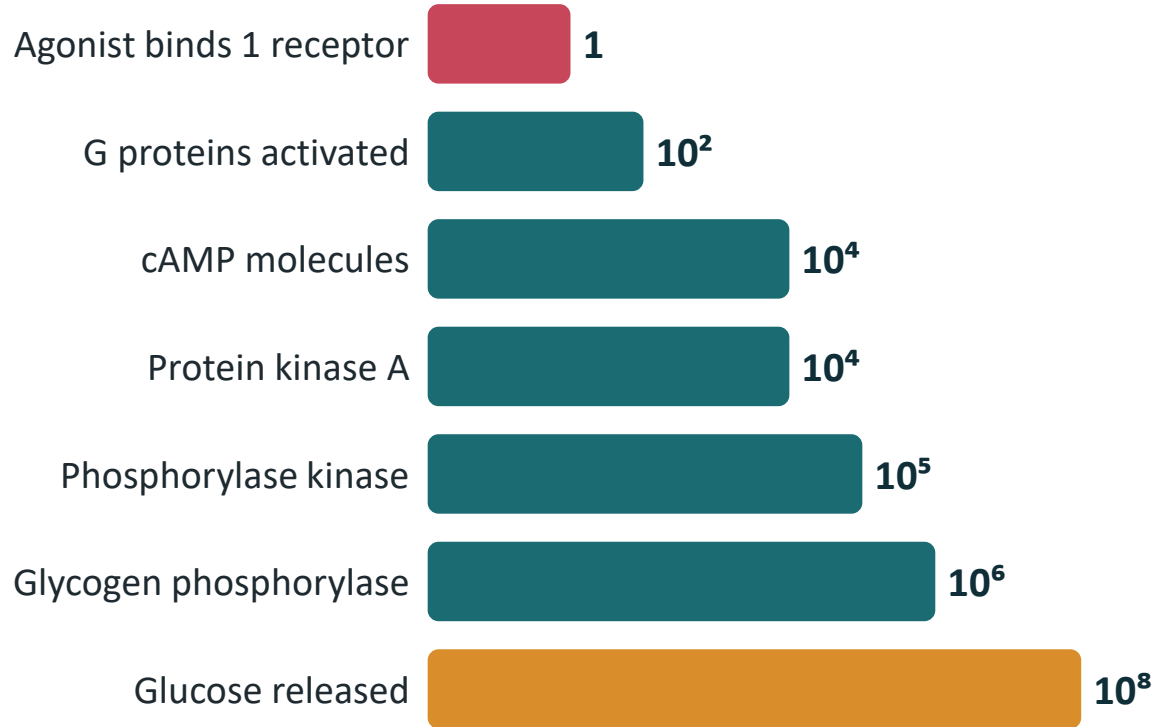
Binds calmodulin and other proteins. Triggers contraction and secretion.

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



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

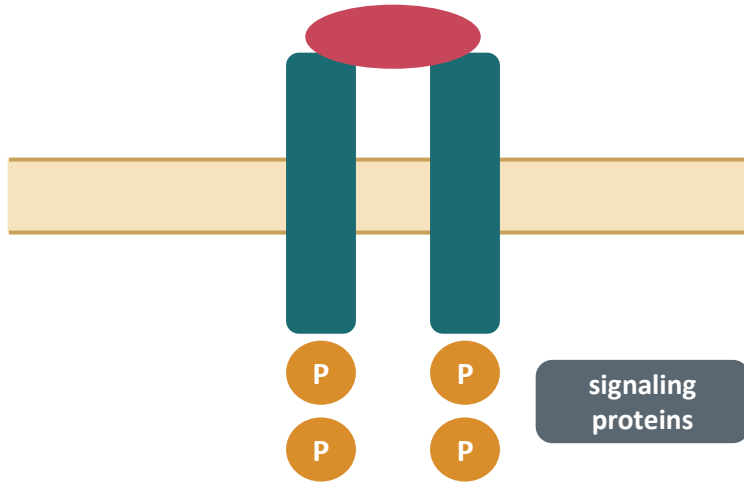


Why it matters

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

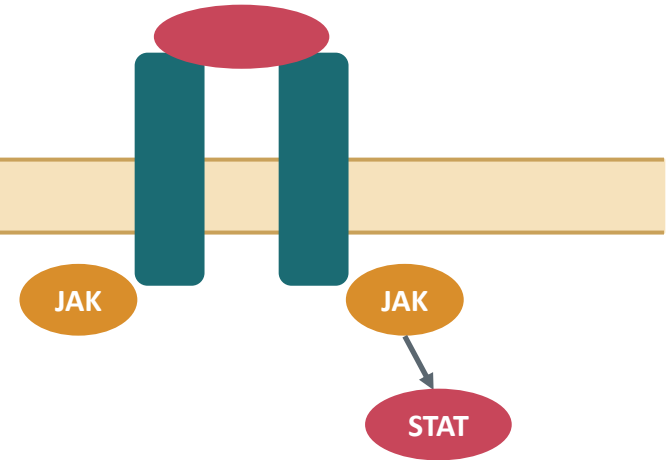
Enzyme-linked and cytokine receptors

Receptor tyrosine kinase



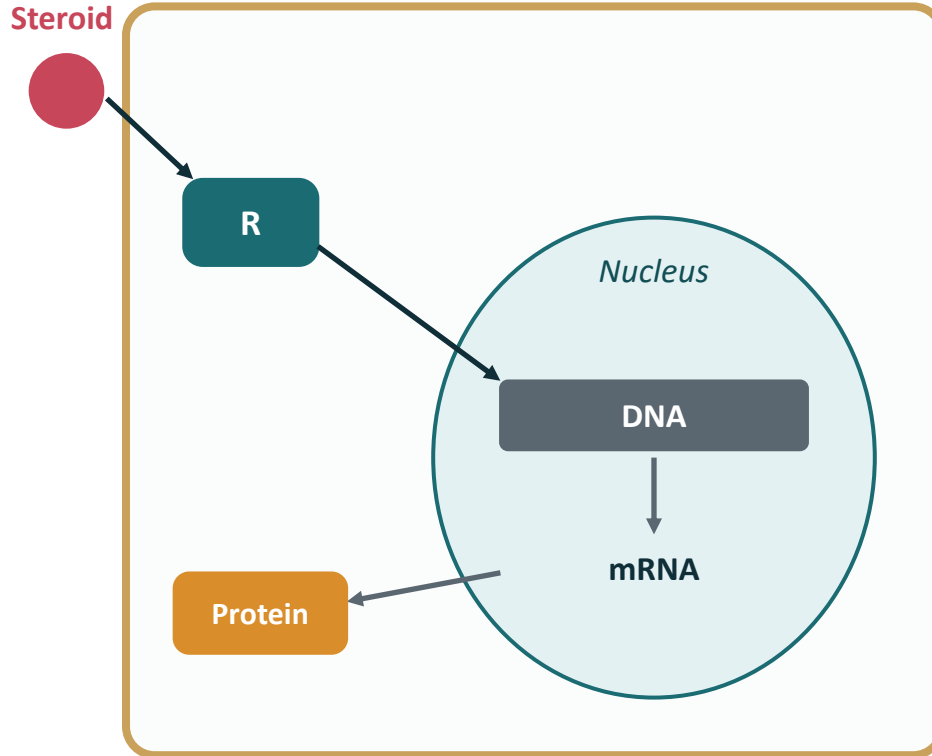
Ligand brings two receptors together. They phosphorylate each other on tyrosine. Signaling proteins dock.

Cytokine receptor (JAK-STAT)



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

Intracellular (nuclear) receptors



- The ligand must be lipid-soluble to cross the membrane.
- Ligand-receptor complex binds DNA and changes gene transcription.
- **Lag:** 30 minutes to hours before the effect appears.
- **Persistence:** effect lasts after the drug is gone, while the new proteins remain.

How do drugs work?

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

Three ways drugs act

1 Block or inhibit

- Receptor antagonists (cell surface and nuclear)
- 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

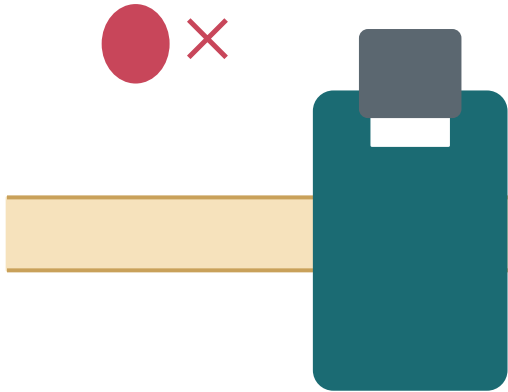
3 Unconventional

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

How antagonists block receptors

Competitive antagonist

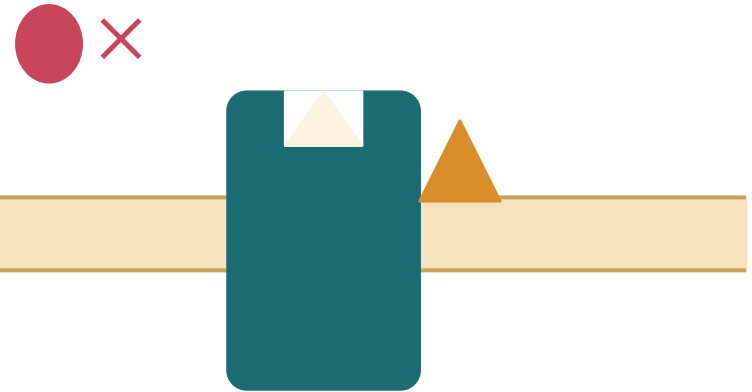
Binds the SAME site as the agonist



Reversible: enough agonist displaces it. The block can be overcome.

Allosteric antagonist

Binds a DIFFERENT site and changes the receptor shape



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

Examples: blocking receptors and enzymes

Mechanism	Target	Example drug and use
Receptor antagonist	Angiotensin AT1 receptor	Losartan: hypertension, heart failure
	Beta-adrenoceptors	Propranolol: angina, hypertension
Nuclear receptor antagonist	Mineralocorticoid receptor	Spironolactone: heart failure
	Estrogen receptor	Tamoxifen: breast cancer
Enzyme inhibitor	Cyclooxygenase	Aspirin, ibuprofen: pain, inflammation
	HMG-CoA reductase	Atorvastatin: high cholesterol
	Angiotensin-converting enzyme	Captopril: hypertension

Examples: blocking channels, transporters and signaling

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

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