GPCR signalling — a very simple, step-by-step guide

Quick picture in one line

A molecule outside the cell (the ligand) touches a protein on the cell surface (the GPCR). The GPCR changes shape, turns on helper proteins (G-proteins), and those helpers make small internal signals (second messengers) that change how the cell behaves. The cell then turns the signal off.

Step 1 — Ligand binds the receptor (the start)

A ligand is a small molecule that fits into the GPCR like a key into a lock. When the ligand sticks in the GPCR, the GPCR changes shape on the inside of the cell. That new shape lets the GPCR meet a G-protein just inside the membrane.

Analogy:

The GPCR is the door. The ligand is a key. Turn the key and the door opens a little for someone inside.

Simple drug example:

Albuterol (a drug for asthma) acts like a key on the β2 receptor. It tells airway cells to relax.

Quiz

Q1 — What is a ligand?

Answer: A molecule that binds (sticks to) the GPCR.

Q2 — What happens to the GPCR right after the ligand binds?

Answer: The GPCR changes shape inside the cell.

Step 2 — G-protein activation (switching on)

The G-protein sits on the inside of the membrane. It has three parts: α, β, γ. In the "off" state, the α part holds a small molecule called GDP. The activated GPCR helps the α part drop GDP and pick up GTP. When α has GTP, α separates from βγ. Both α-GTP and βγ can now go and work on other proteins.

Simple names and effects of α types:

Gs → turns on adenylyl cyclase → makes cAMP (a second messenger).

Gi → turns off adenylyl cyclase → lowers cAMP.

Gq → turns on phospholipase C → makes IP_3 and DAG → raises calcium inside the cell.

Drug example:

Morphine binds the μ-opioid GPCR. That receptor uses Gi, so the cell makes less cAMP and the nerve cell slows down pain signals.

Quiz

Q3 — Which G-protein type raises cAMP?

Answer: Gs.

Q4 — What changes on the α subunit when the G-protein turns on?

Answer: GDP is replaced by GTP.

Step 3 — Effectors and second messengers (making the internal message)

The activated α-GTP or βγ parts touch effectors (other proteins). An important effector is adenylyl cyclase → it makes cAMP. cAMP turns on PKA, which adds small tags (phosphates) to other proteins and changes what they do. Another path: PLC makes IP_3 and DAG. IP_3 tells the cell's internal calcium stores to release Ca^{2+}. DAG helps turn on PKC, another tagger. βγ can also open or close ion channels (for K^+ or Ca^{2+}), changing how excitable the cell is.

Drug example:

Isoproterenol activates β receptors → Gs → more cAMP → heart beats stronger and faster.

Quiz

Q5 — Name two second messengers made after GPCR activation.

Answer: cAMP and IP_3.

Q6 — What does IP_3 do?

Answer: It makes calcium leave internal stores, raising Ca^{2+} inside the cell.

Step 4 — Signal amplification (small start, big effect)
Plain explanation

One active GPCR can turn on many G-proteins. Each effector can make many second messenger molecules (many cAMP, many IP_3). Each activated kinase (like PKA) can change many proteins. This chain makes a small outside signal grow into a big inside effect.

Analogy:

One phone call that makes many memos and each memo tells many workers to act.

Quiz

Q7 — Why can a tiny amount of a drug cause a big response?

Answer: Because of amplification: one receptor triggers many downstream molecules.

Step 5 — Turning the signal off (stop and reset)
Plain explanation

The α part has a built-in timer: it slowly cuts GTP back to GDP. When that happens, α turns off and comes back with βγ. Helper proteins called RGS speed up that "turn-off" step. The active receptor can be tagged with phosphate by GRKs. Then arrestin binds to the tagged receptor. Arrestin blocks the receptor from turning on more G-proteins. The cell can pull the receptor inside (internalize it). The receptor can be cleaned and returned to the surface, or it can be destroyed.

Why this matters:
If receptors are removed or blocked for a long time, the drug works less well — this is tolerance.

Quiz

Q8 — Name two ways the cell stops GPCR signalling.

Answer: (1) α cuts GTP to GDP (turns off); (2) receptor is phosphorylated and bound by arrestin (blocked and taken inside).

Step 6 — How drugs can change GPCR signals

Agonist:
Binds the receptor and turns it on (like the natural ligand).

Antagonist:
Binds the receptor but does not turn it on. It blocks the real ligand.

Inverse agonist:
Binds and makes an already active receptor less active.

Allosteric modulator:
Binds a different spot on the receptor and increases or decreases the receptor's response.

Biased agonist:
Favors one internal path (for example, G-protein pathway) over another (for example, arrestin), which can change effects and side effects.

Examples:

1. Albuterol — agonist at β2 (helps breathing).

2. Propranolol — antagonist at β receptors (lowers heart rate).

3. New opioid drugs try to be biased so they give pain relief with fewer side effects.

Quiz

Q9 — What does an antagonist do?

Answer: Blocks the receptor so the real ligand cannot activate it.

Short review — the core facts in very simple words

1. Outside message (ligand) → fits GPCR (receptor) like a key.

2. GPCR changes shape and turns on G-protein (GDP → GTP).

3. G-protein parts activate effectors → make second messengers (cAMP, IP_3, DAG, Ca^{2+}).

4. One signal becomes many signals (amplification).

5. Cell stops the signal by GTP → GDP, by arrestin, and by pulling the receptor in.

6. Drugs can act as agonists, antagonists, inverse agonists, allosteric modulators, or biased agonists.

Final short quiz (test yourself)

1. Which subunit holds GDP/GTP in the G-protein?

2. Which second messenger rises when Gs is active?

3. What does arrestin do to the receptor?

4. Give one drug that is a β-blocker.

5. Why does tolerance to a drug sometimes happen?

Answers:

The α subunit.

cAMP.

It blocks the receptor from signalling and helps pull it into the cell (internalize it).

Propranolol (one example).

Because of receptor desensitization or internalization — the cell reduces the receptor response over time.