Hormone Signaling

BCH 120 — Metabolic & Endocrine Biochemistry · Dr. Radi

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By the end of this unit, you can…

- Explain how a hormone message crosses the membrane, and classify hormone actions (endocrine, paracrine, autocrine, cell-contact) and chemical classes (peptide, amine, steroid, thyroid)
- Apply the five features of signal-transducing systems, and read receptor-binding data (Kd, affinity, dose-response)
- Walk GPCR signaling — the β-adrenergic/epinephrine cascade, cAMP/PKA, amplification, GTPase self-inactivation, and βARK/β-arrestin desensitization
- Compare the second-messenger systems (cAMP, IP_3/DAG, Ca^{2+}/calmodulin, cGMP) and the receptor tyrosine kinases (insulin receptor, RTK family, JAK-STAT)
- Explain membrane polarization and gated ion channels (Na^+/K^+ ATPase, the acetylcholine receptor, voltage- vs ligand-gated), sensory GPCR signaling (sight, smell, taste), and nuclear-receptor gene regulation

Today's route

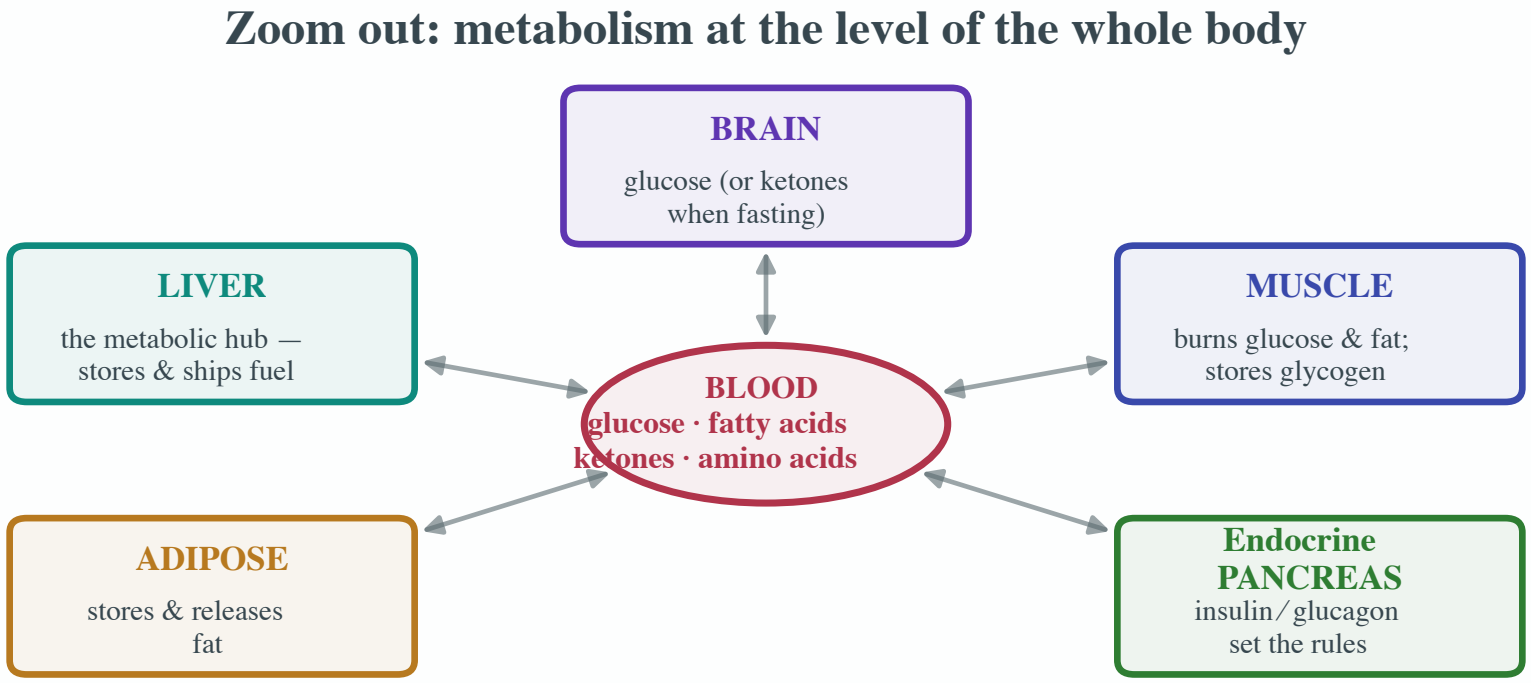
1. Signaling — The Big Picture
2. Hormone Chemistry & Two Mechanisms
3. Five Features & Reading Kd
4. GPCRs & the Epinephrine Cascade
5. Switching the Signal OFF
6. More Second Messengers — IP_3, DAG & Calcium
7. Receptor Tyrosine Kinases & Insulin
8. Guanylyl Cyclases & Ion Channels
9. Your Senses Run on GPCRs
10. Nuclear Receptors — Signaling to the Genes

1 · Signaling — The Big Picture

"In BCH 100 you lived inside one cell. Now we zoom all the way out — to a whole body of tissues that have to talk to each other. That conversation is endocrinology, and it all runs on one four-part relay."

Welcome — now zoom OUT

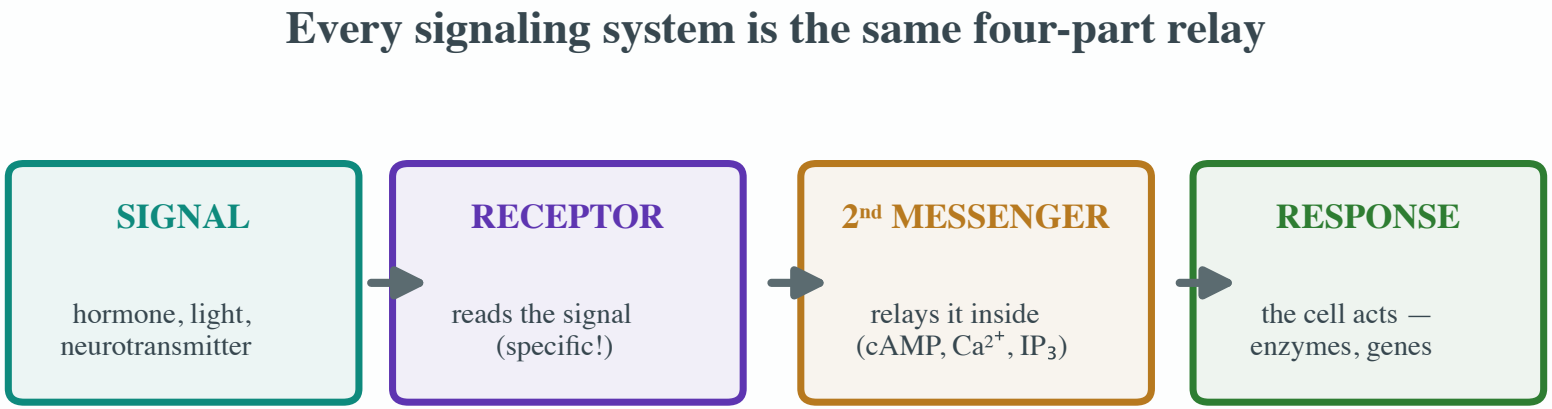
All of BCH 100 lived **inside one cell**: enzymes, pathways, feedback. This whole course lives at the **level of the body**. Your **brain** demands glucose, your **liver** ships fuel, **muscle** and **adipose** store and burn it, and the **endocrine pancreas** sets the rules. Nobody's in charge of the whole thing — so how do organs that never touch coordinate a meal, a fast, a sprint? **Hormones.** That's the story.



Each tissue has a job — and hormones coordinate the whole exchange. That coordination is this course.

Every signal is the same four-part relay

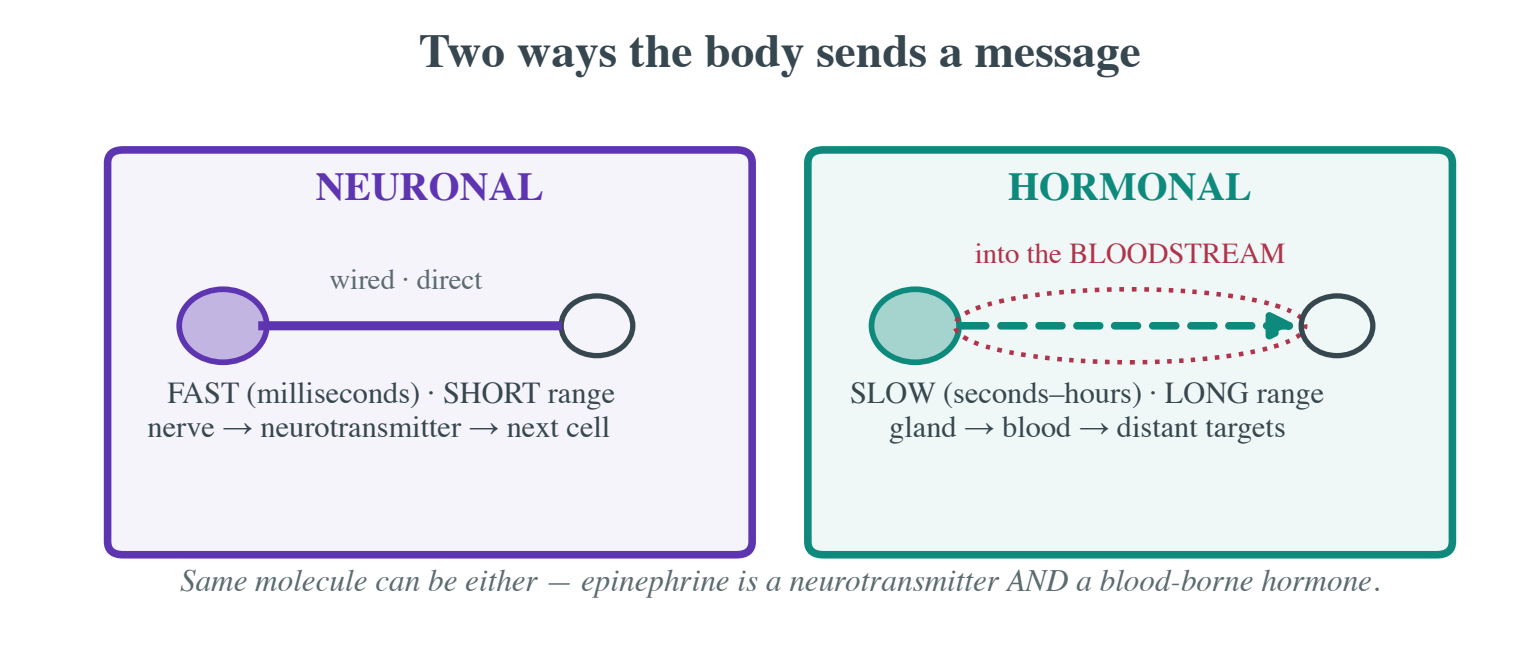
Here's the pattern you'll see **over and over** for ten weeks, so learn it now. A **signal** (hormone, light, a neurotransmitter) hits a **receptor** that's specific for it; the receptor triggers a **second messenger** inside the cell; the messenger drives a **response** — enzymes flip, genes turn on, the cell acts. Signal → receptor → messenger → response. It's a **doorbell**: finger, button, wires, chime.



Think of a doorbell: a finger (signal) → the button (receptor) → wires (messenger) → the chime (response).

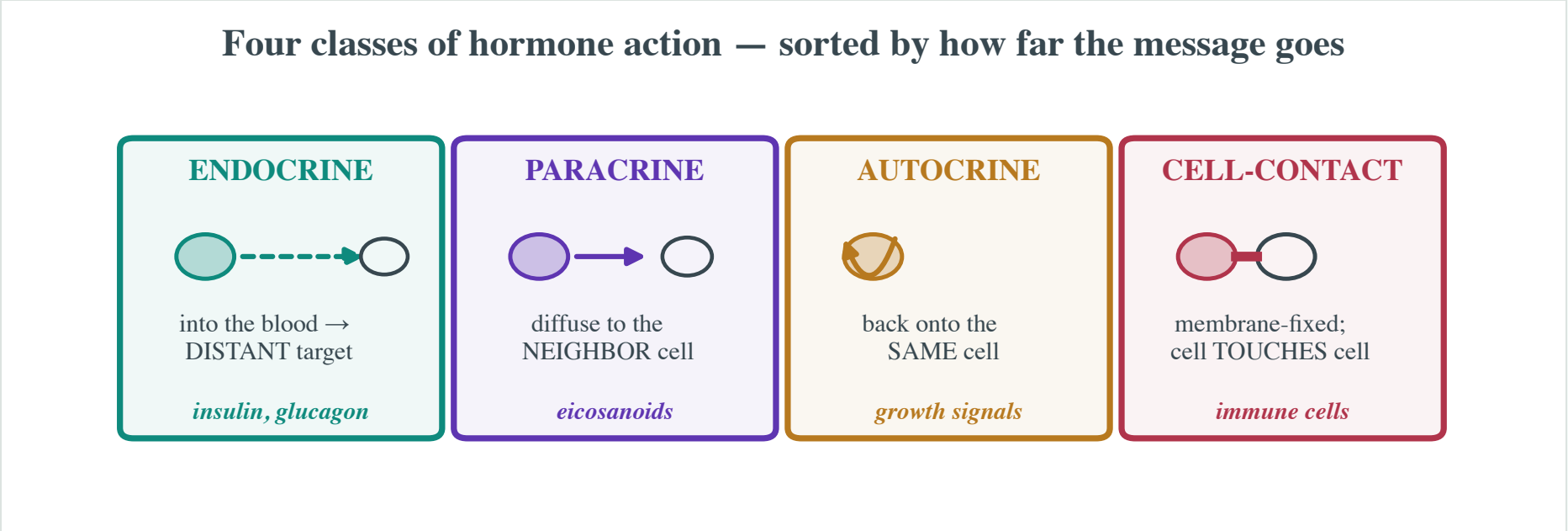
Two ways the body sends a message

The body has **two messaging systems**. **Neuronal** signaling is **wired** — **fast** (milliseconds), **short-range**. **Hormonal** signaling **broadcasts** into the **bloodstream** — **slower** but **body-wide**. The punchline: the **same molecule** can be either — epinephrine is a neurotransmitter **and** a blood-borne hormone.



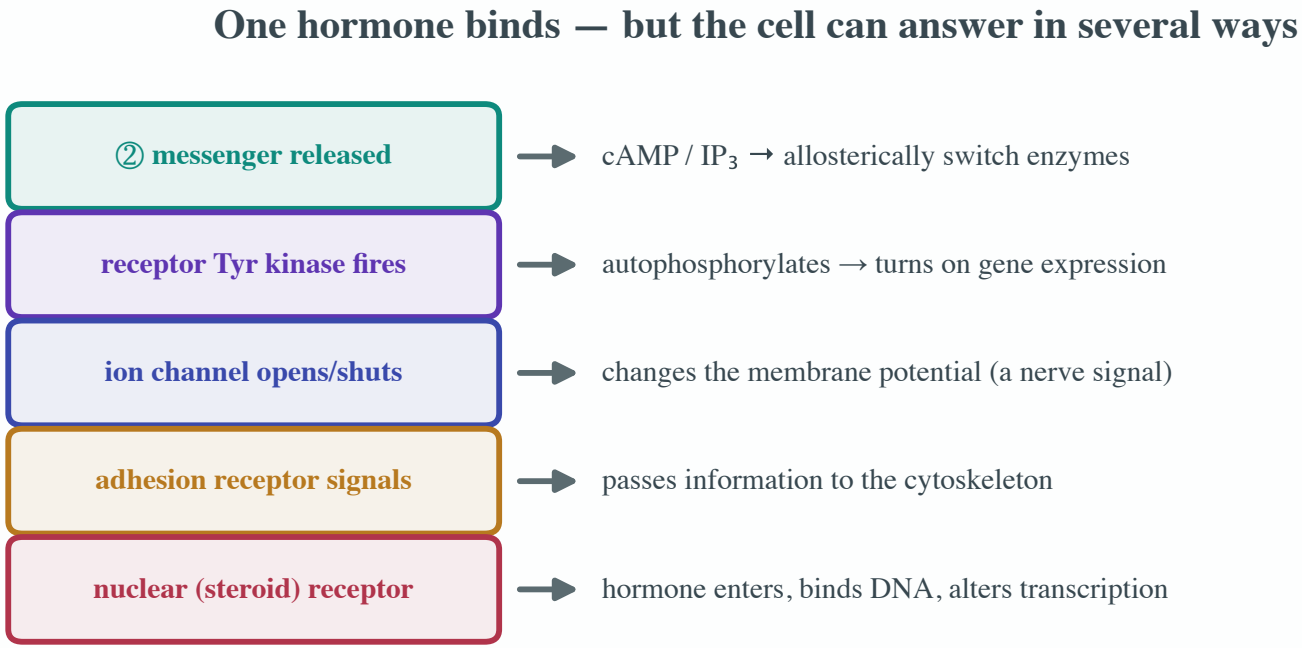
Four classes of hormone action

We classify hormones by **how far the message travels** from release to target. **Endocrine**: into the blood, to a **distant** organ (insulin, glucagon). **Paracrine**: diffuse to the **neighbor** cell (eicosanoids — we'll spend a whole lecture on those). **Autocrine**: right back onto the **same** cell (growth signals — and cancer loves this one). **Cell-contact**: the messenger stays **fixed to the membrane** and one cell literally touches another (your immune system).



One binding event — several possible answers

When a hormone lands on its receptor, the cell can respond in **more than one way**, and which one tells you a lot about the hormone. It can release a **second messenger** that switches enzymes; fire a **receptor tyrosine kinase** that reprograms gene expression; open an **ion channel** and change the membrane's voltage; signal the **cytoskeleton** through an adhesion receptor; or — for a steroid — walk **into the nucleus** and rewrite transcription directly. Keep this menu handy; the rest of the unit is these five, one at a time.

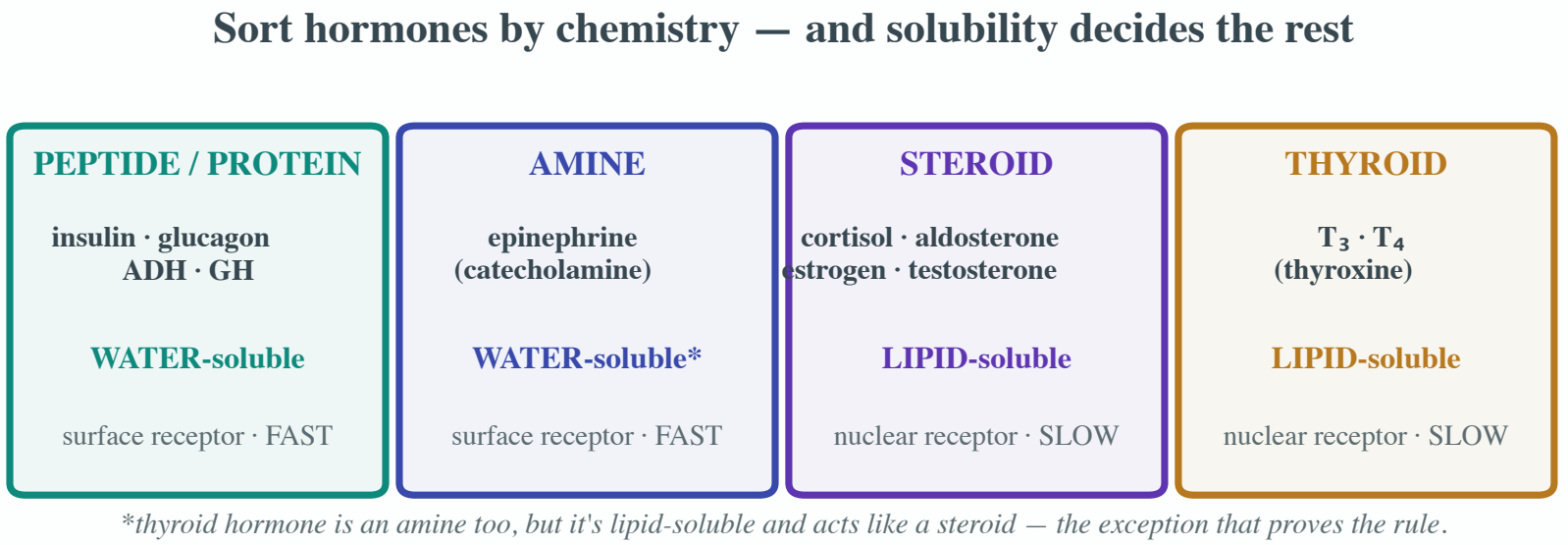


2 · Hormone Chemistry & Two Mechanisms

"There are dozens of hormones, but only a few chemical families — and one physical property, solubility, decides how each one works. Get that, and you can predict a hormone's whole mechanism from its structure."

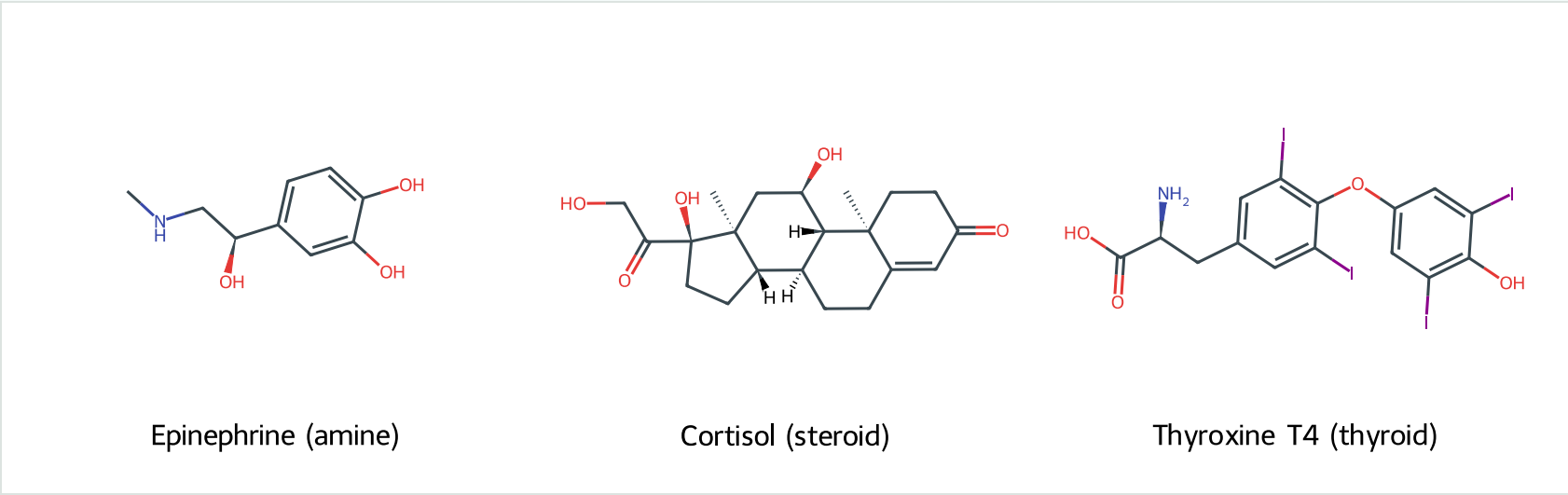
Sort hormones by their chemistry

Every hormone falls into one of a few **chemical families**, and the family tells you almost everything. **Peptide/protein** hormones (insulin, glucagon, ADH, growth hormone) and **amines** (epinephrine) are **water-soluble** — they're stuck outside the cell. **Steroids** (cortisol, aldosterone, the sex hormones) and **thyroid** hormone are **lipid-soluble** — they slip right through the membrane. One property, **can it cross the membrane?**, splits the whole endocrine system in two.



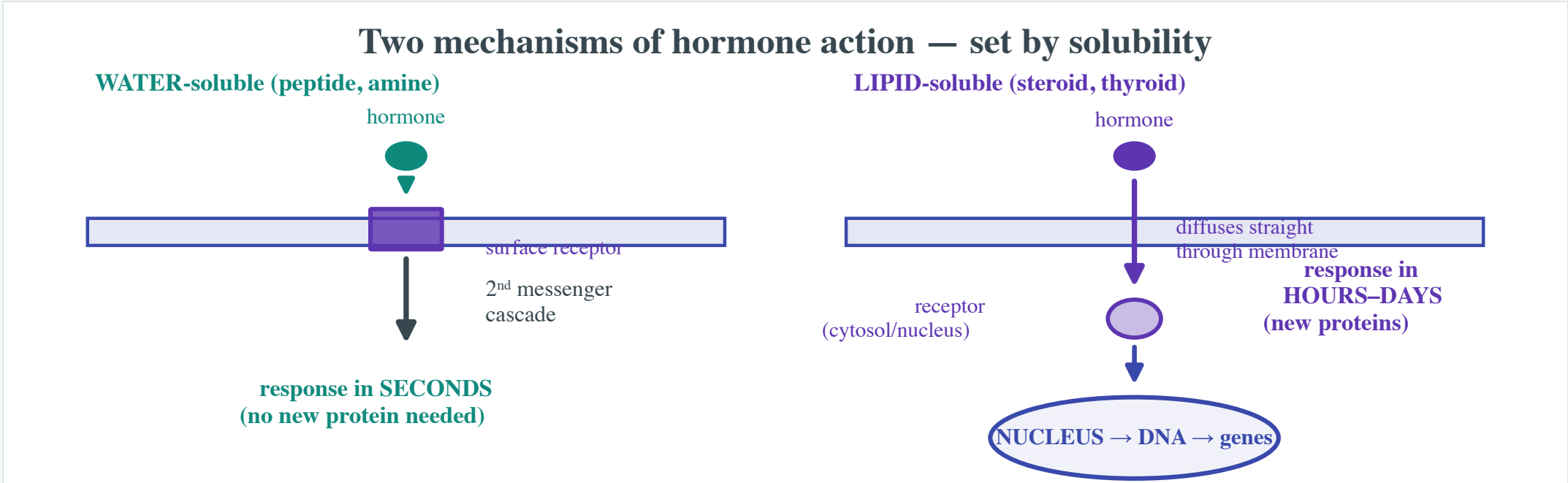
Meet three real hormones

Look at what you're actually dealing with. **Epinephrine** is a tiny amine — a catechol ring with a short amino tail (you'll build it from tyrosine soon). **Cortisol** is a **steroid** — that flat four-ring skeleton is pure cholesterol heritage, and it's greasy enough to cross any membrane. **Thyroxine (T_4)** is the oddball: an amino-acid derivative studded with **four iodines**, yet lipid-soluble enough to act like a steroid. Structure predicts behavior.



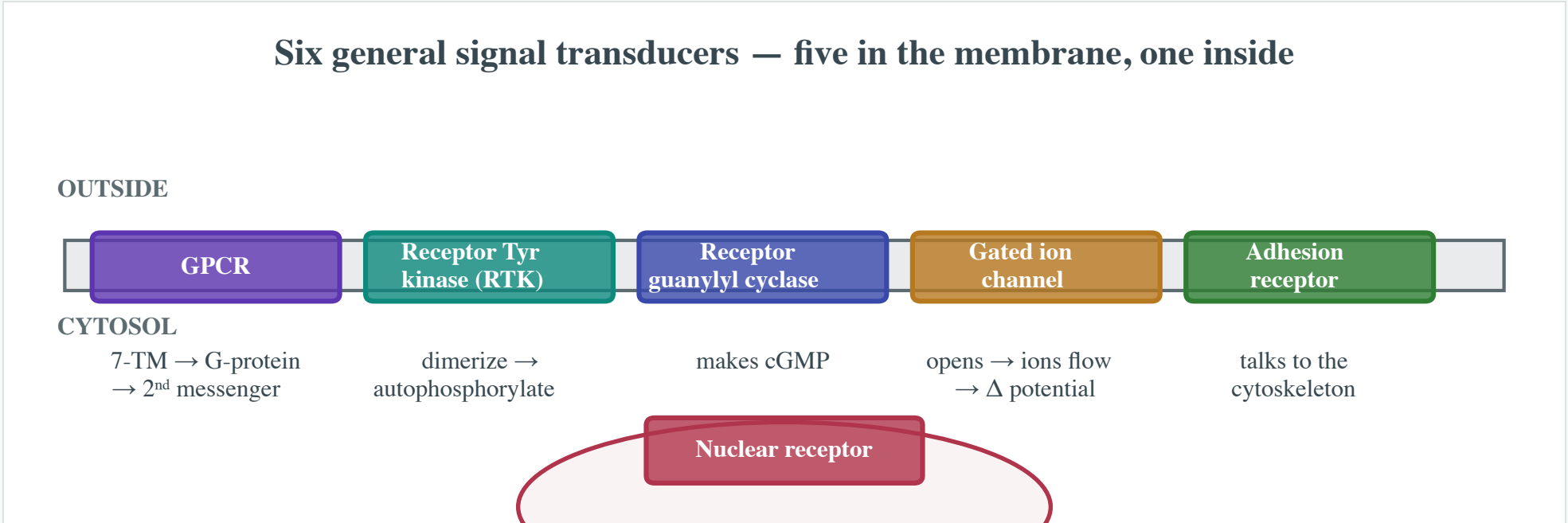
Two mechanisms, set by solubility

Now the payoff. A **water-soluble** hormone can't get in, so it knocks on a **surface receptor** and hands off to a **second-messenger cascade** — a response in **seconds**, no new protein required. A **lipid-soluble** hormone **diffuses straight through**, binds a receptor in the cytosol or nucleus, and the complex parks on **DNA** to change transcription — a response that takes **hours to days** but makes brand-new proteins. Fast switch versus slow rewiring.



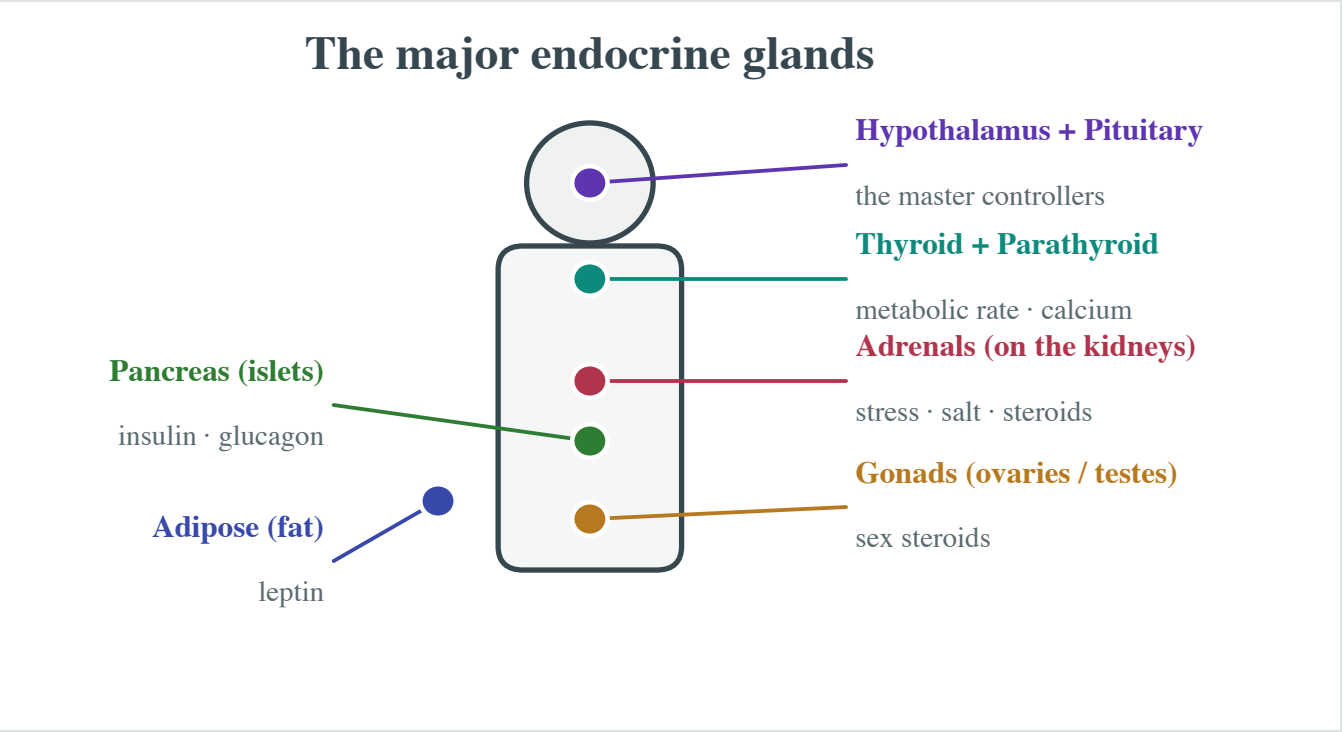
Six ways across the membrane

Across the whole unit there are exactly **six general types** of signal transducer — this slide is your **map**. **Five sit in the membrane**: **GPCRs** and **receptor tyrosine kinases (RTKs)** are the heavyweights, alongside **receptor guanylyl cyclases**, **gated ion channels**, and **adhesion receptors**. The **sixth**, the **nuclear receptor**, works **inside** — a lipophilic hormone crosses on its own and the receptor acts on DNA. We'll meet each one; when a new receptor shows up, come back here and place it.



The glands that make it all

And where does all this hardware live? In the **endocrine glands** — the org chart for the whole course. The **hypothalamus and pituitary** are the master controllers up top; the **thyroid and parathyroids** set metabolic rate and calcium; the **adrenals** handle stress, salt, and steroids; the **pancreatic islets** run glucose; the **gonads** make sex steroids; even **fat** is an endocrine organ (it makes leptin). We'll tour these one gland at a time.

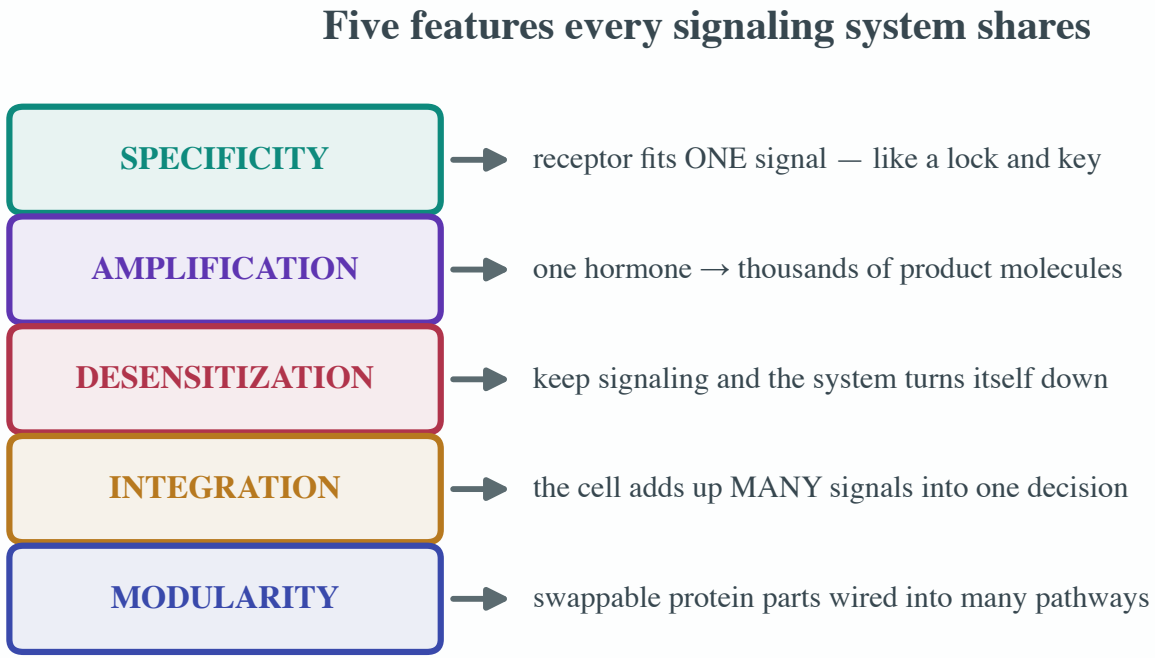


3 · Five Features & Reading Kd

"Every signaling system — from insulin to your sense of smell — shares five features. And the very first, specificity, is a number you can measure: the dissociation constant, Kd. Low Kd, tight grip."

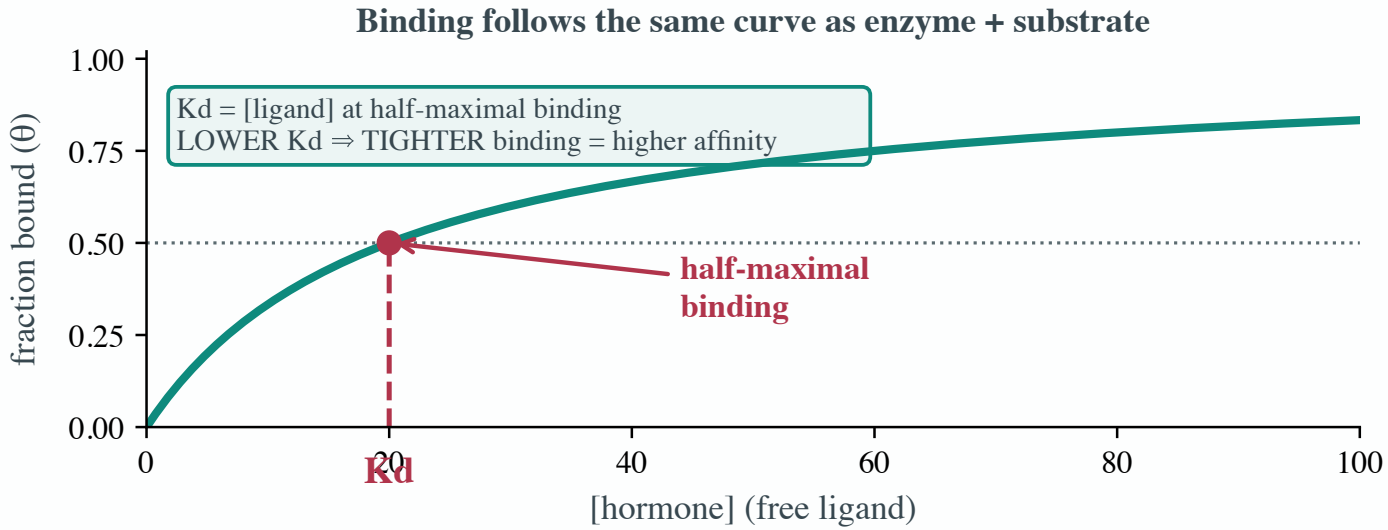
Five features every signaling system shares

No matter which receptor, the same **five features** show up — so if you learn them once you understand them all. **Specificity**: a receptor fits one signal, lock-and-key. **Amplification**: one hormone triggers thousands of downstream molecules. **Desensitization**: keep the signal on and the system dials **itself** down. **Integration**: a cell adds up many signals into one decision. **Modularity**: the same protein parts get rewired into many pathways. Watch for these all unit.



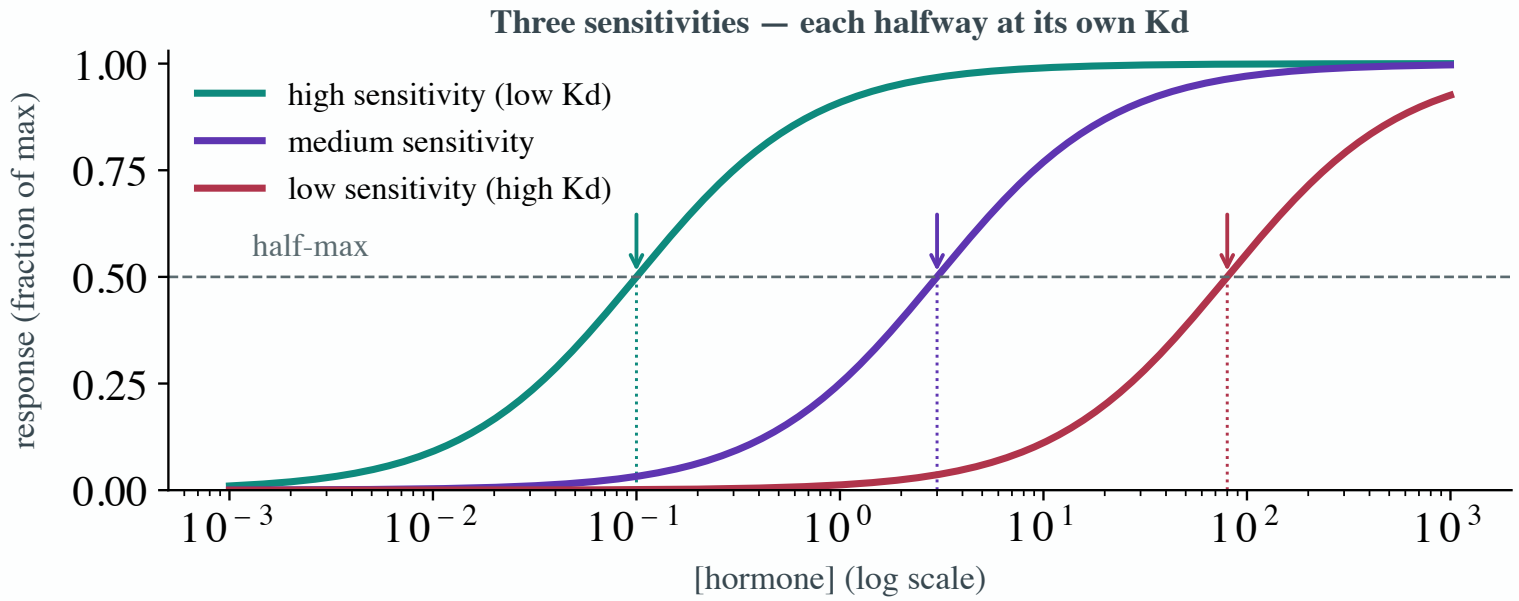
Specificity is a number: Kd

Specificity isn't hand-waving — it's **measurable**, and it's the same math you learned for enzymes and substrates. Plot the **fraction of receptors bound** against **[hormone]** and you get a saturation curve. The concentration that gets you **half-maximal binding** is the **dissociation constant, Kd**. Here's the whole trick: a **lower Kd means tighter binding** — the receptor grabs its hormone at a lower concentration. High affinity = low Kd. Say it back to yourself; students flip it every year.



Sensitivity, on a log scale

Real dose-response curves are plotted on a **log** concentration axis, which turns that saturation curve into a tidy S. Three receptors with three different **Kd** values give three curves — each one crosses **half-maximal response** at its own Kd (the arrows). A **high-sensitivity** receptor (low Kd, left) responds to a whisper of hormone; a **low-sensitivity** one (high Kd, right) needs a shout. Same hormone, very different cells — that's how one signal does many jobs.



Try this one: which grips tighter?

Two versions of a β-adrenergic receptor bind epinephrine. **Variant A:** Kd = **2 nM**. **Variant B:** Kd = **50 nM**. Which one binds epinephrine more tightly — and by how many fold?

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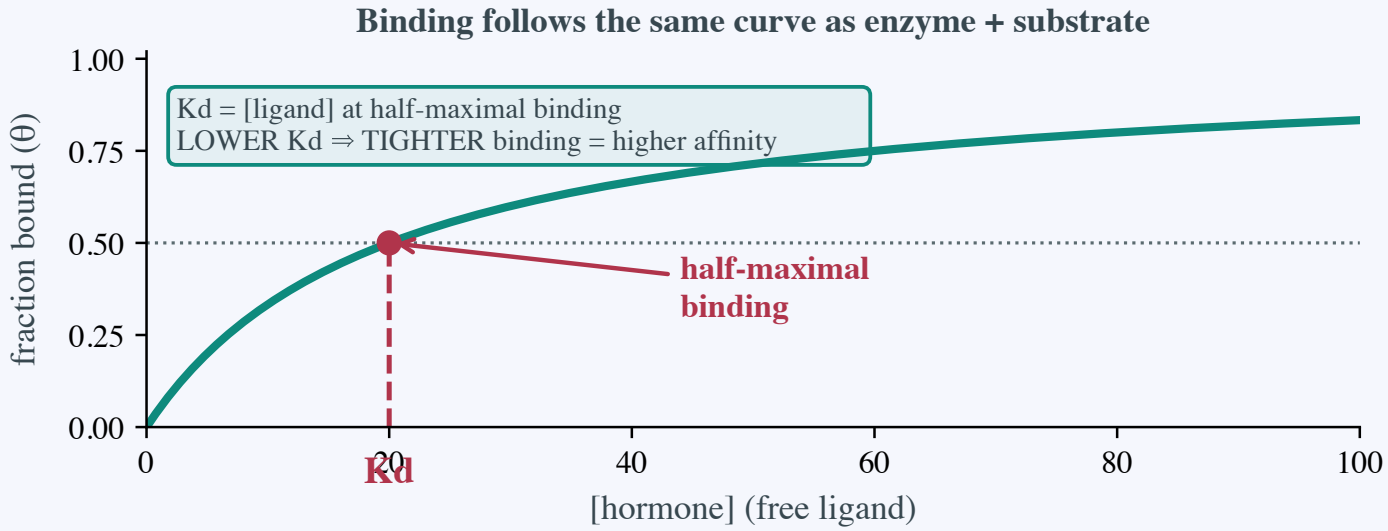
Answer: Variant A. Lower Kd = higher affinity, so A grabs epinephrine at 25× lower concentration. Fold difference = 50 ÷ 2 = **25×**. (Remember: the **smaller** Kd wins — it's the concentration you need to half-fill the receptor, so needing less means gripping harder.)

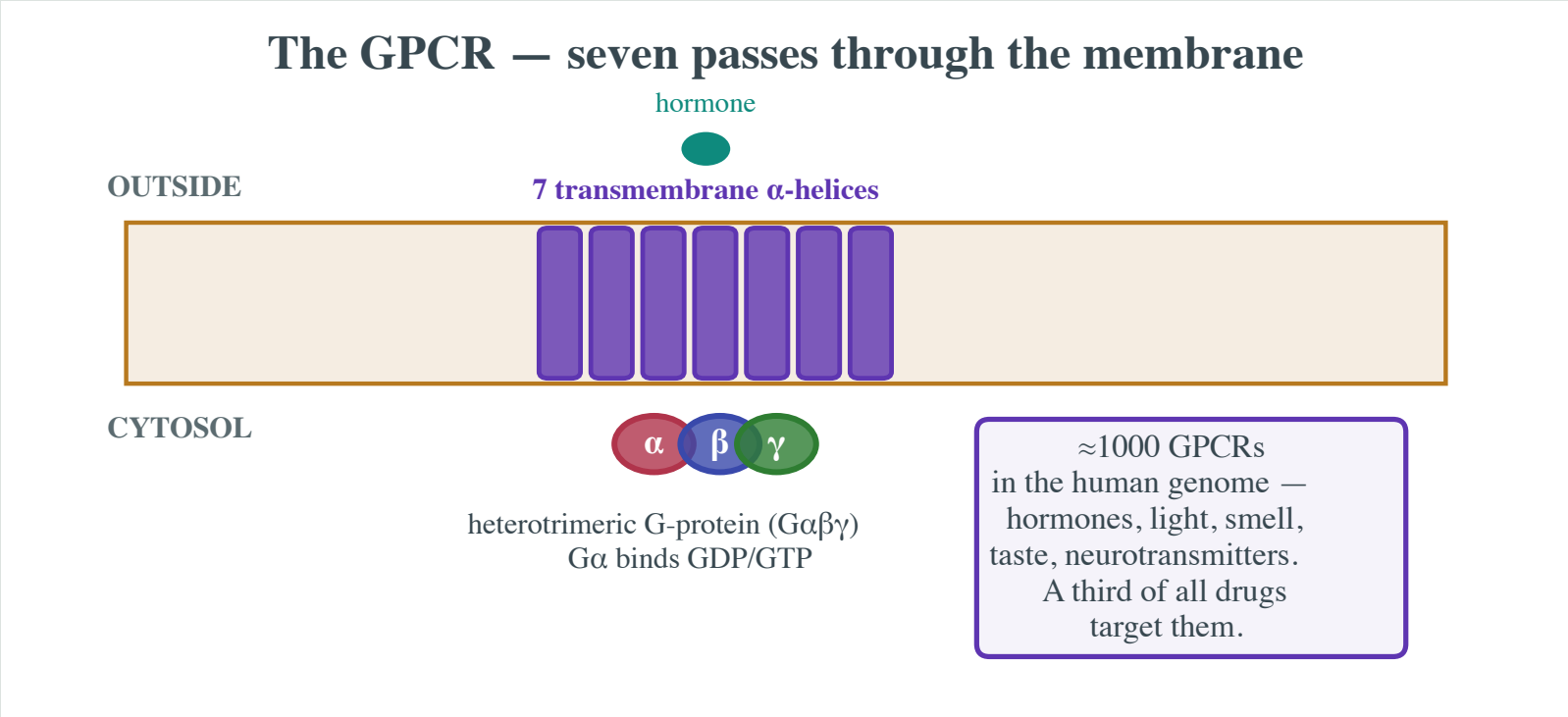


4 · GPCRs & the Epinephrine Cascade

"The GPCR is the most common receptor in your body and the target of a third of all drugs. Watch one — the β-adrenergic receptor — turn a whiff of epinephrine into a flood of blood glucose, amplifying the signal ten-thousand-fold along the way."

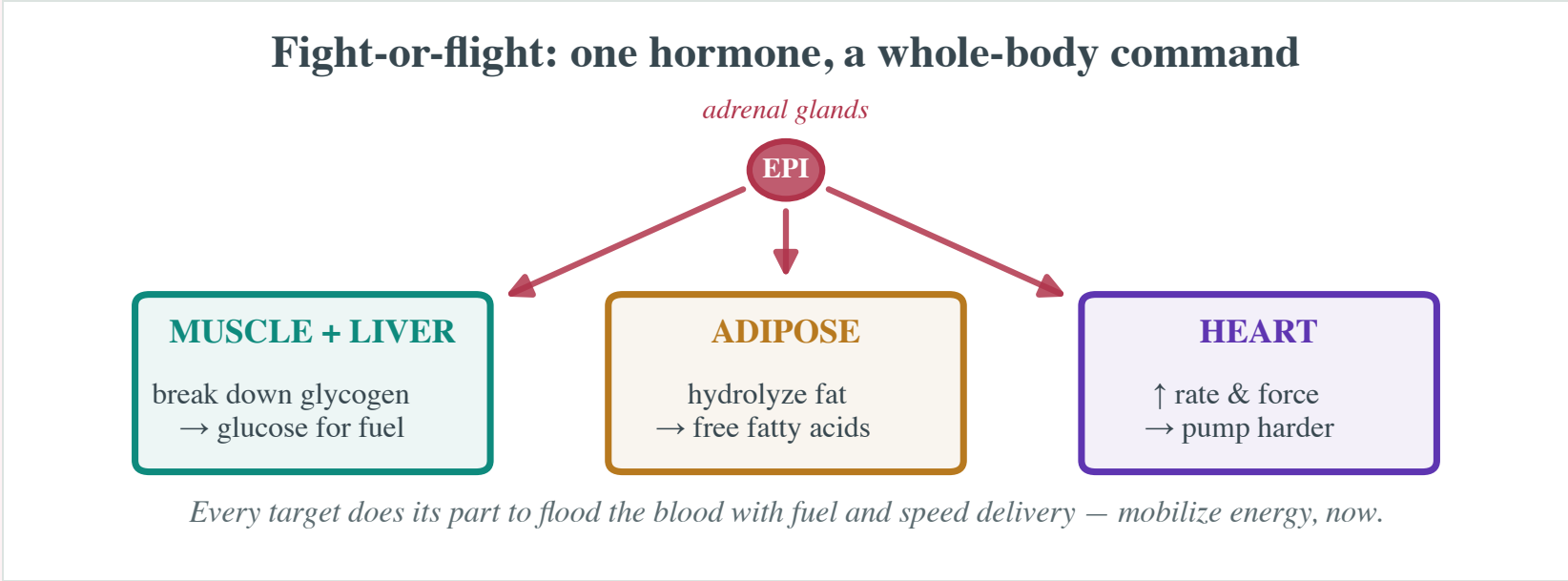
Meet the GPCR

The **G-protein-coupled receptor** is the workhorse of signaling — about **1000** of them in your genome, sensing hormones, light, smells, tastes, and neurotransmitters. The receptor snakes through the membrane **seven times** (it's α-helical, integral). Docked underneath is a **heterotrimeric G-protein** — three subunits, **α, β, γ** — and the **Gα** subunit is the business end: it holds **GDP when off, GTP when on**.



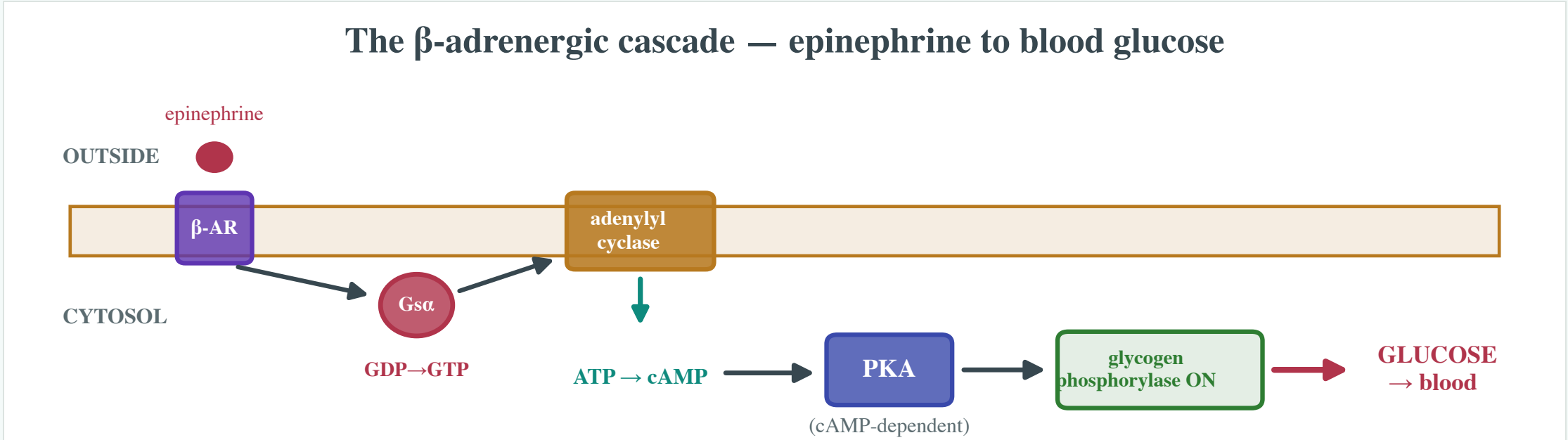
Epinephrine: the fight-or-flight hormone

Our star signal is **epinephrine** (adrenaline), fired from the **adrenal glands** on top of your kidneys. Its whole job is **mobilize energy, now**: in **muscle and liver** it triggers **glycogen breakdown** to glucose; in **fat** it drives **lipolysis** to free fatty acids; in the **heart** it cranks up **rate and force**. One hormone, a coordinated whole-body command — all through GPCRs.



The β-adrenergic cascade

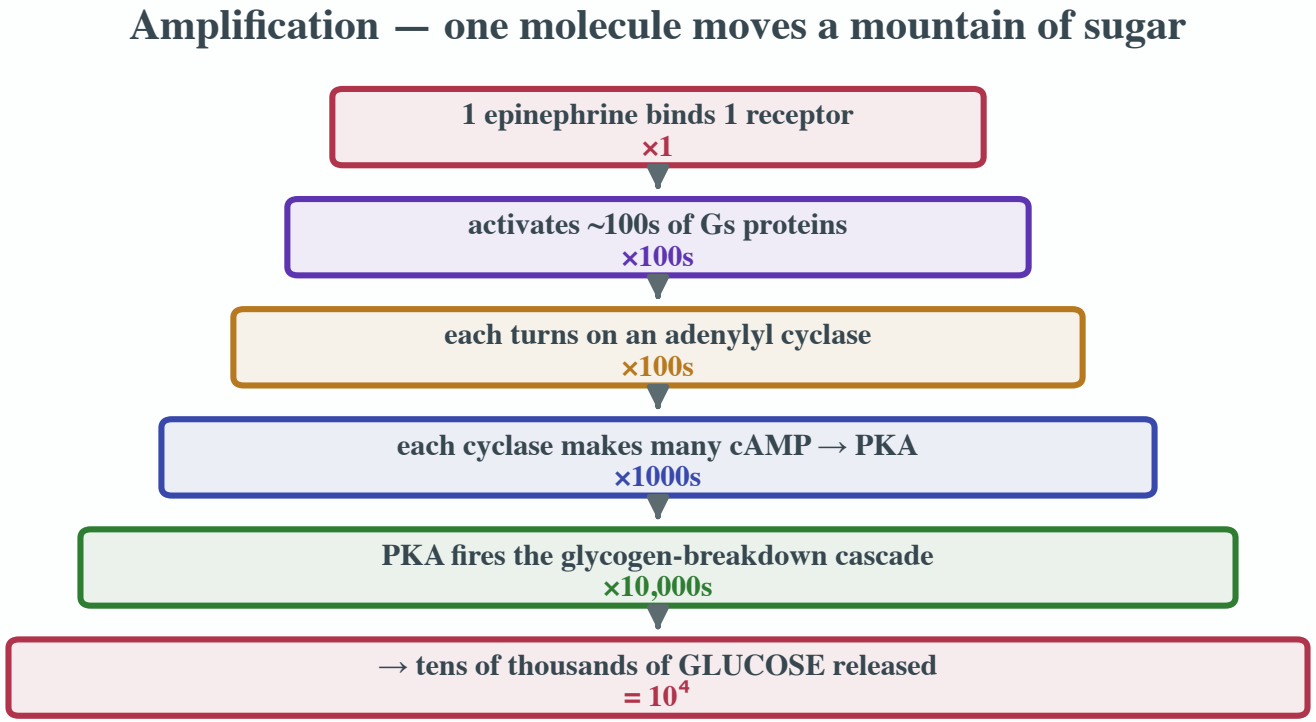
Here's the relay, receptor to fuel. Epinephrine binds the **β-adrenergic receptor**; the receptor flips **Gsα** from GDP to **GTP**; active Gsα switches on **adenylyl cyclase**, which converts **ATP → cAMP**; cAMP is the **second messenger** that activates **protein kinase A (PKA)**; and PKA sets off the cascade that turns on **glycogen phosphorylase** – ripping glycogen apart into **glucose** for the blood. Outside knock, inside surge.



One hormone on the outside → a cAMP surge on the inside → glycogen ripped apart for fuel. Fight-or-flight, in one line.

Amplification: one whisper, a shout

Why route the signal through all those middle-men? **Amplification.** Each step is a **catalyst making catalysts**. One epinephrine activates **hundreds** of G-proteins; each turns on an adenylyl cyclase; each cyclase pumps out **many** cAMP; PKA fires **thousands** of downstream enzymes — and at the bottom, **tens of thousands of glucose** molecules pour out. A hormone at **nanomolar** concentration moves a mountain of sugar. That's the point of the cascade.

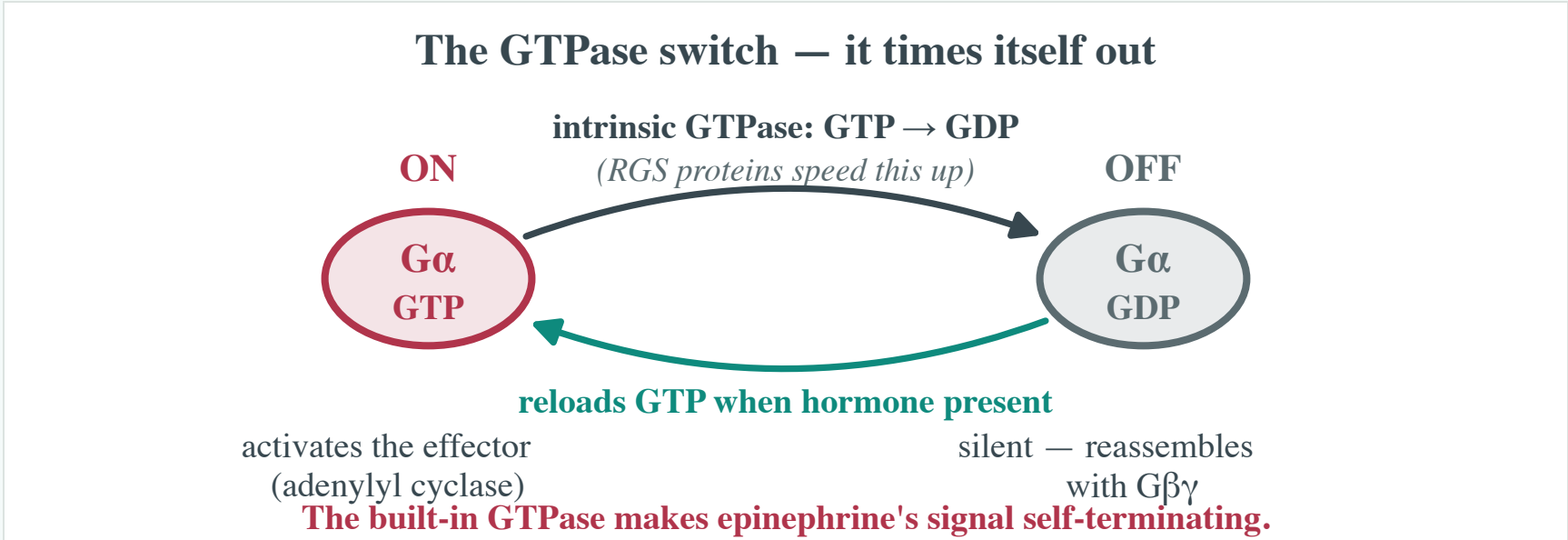


5 · Switching the Signal OFF

"A switch that only turns ON is useless — and dangerous. Epinephrine is meant to be brief, so a GPCR signal has two ways to stop: the G-protein times itself out, and the receptor itself gets muffled when the signal won't quit."

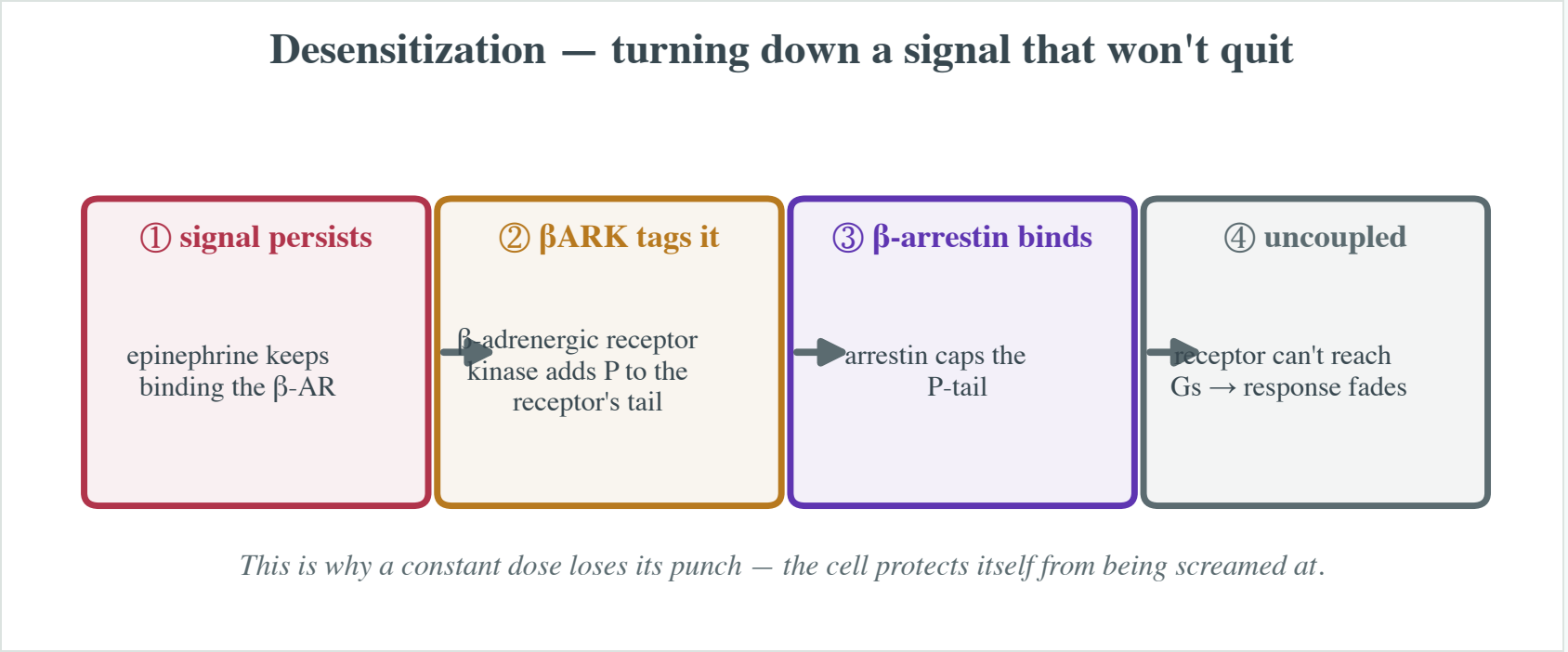
Self-inactivation: the GTPase switch

The G-protein is its own **off-timer**. Active **Gα** carries **GTP** – but Gα has a slow, built-in **GTPase** that **hydrolyzes GTP back to GDP**, flipping itself off and reassembling with Gβγ. How fast? That sets how long the signal lasts, and **RGS proteins** can speed it up. Epinephrine is supposed to be a **short** shout – the GTPase makes sure the alarm stops when the danger passes.



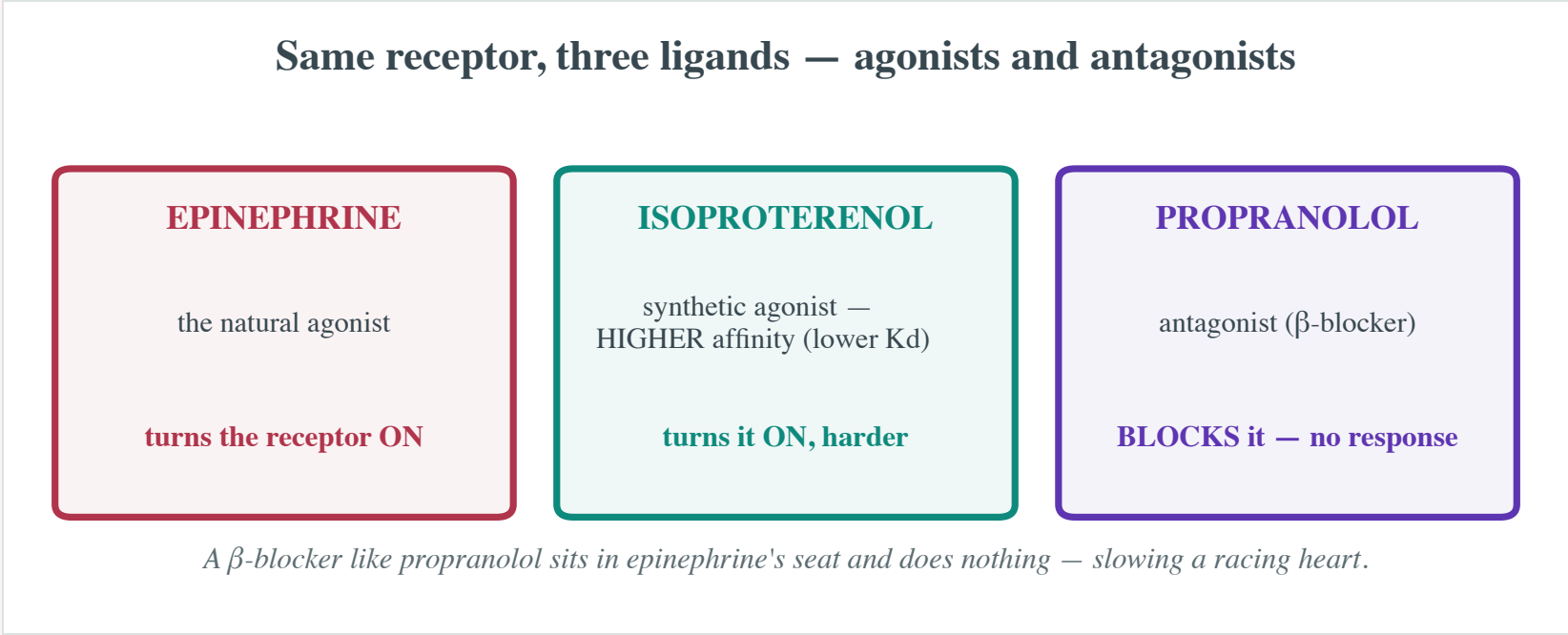
Desensitization: turning down a signal that won't quit

What if the hormone just **keeps binding**? The cell muffles the receptor itself. First, **β-adrenergic receptor kinase (βARK)** phosphorylates the receptor's cytoplasmic tail. Then **β-arrestin** binds that phosphorylated tail and **caps it** — physically blocking the receptor from reaching its G-protein. The receptor is still there, still binding epinephrine, but **uncoupled**. This is why a constant dose slowly **loses its punch**.



Agonists, antagonists, and β-blockers

The receptor doesn't care where the molecule comes from — only whether it fits and flips the switch. **Epinephrine** is the **natural agonist**. **Isoproterenol** is a synthetic agonist with **higher affinity** (lower Kd) — it turns the receptor on even harder. **Propranolol** is an **antagonist**: it sits in epinephrine's seat and does **nothing** — a **β-blocker** that slows a racing heart. Same pocket, opposite outcomes.

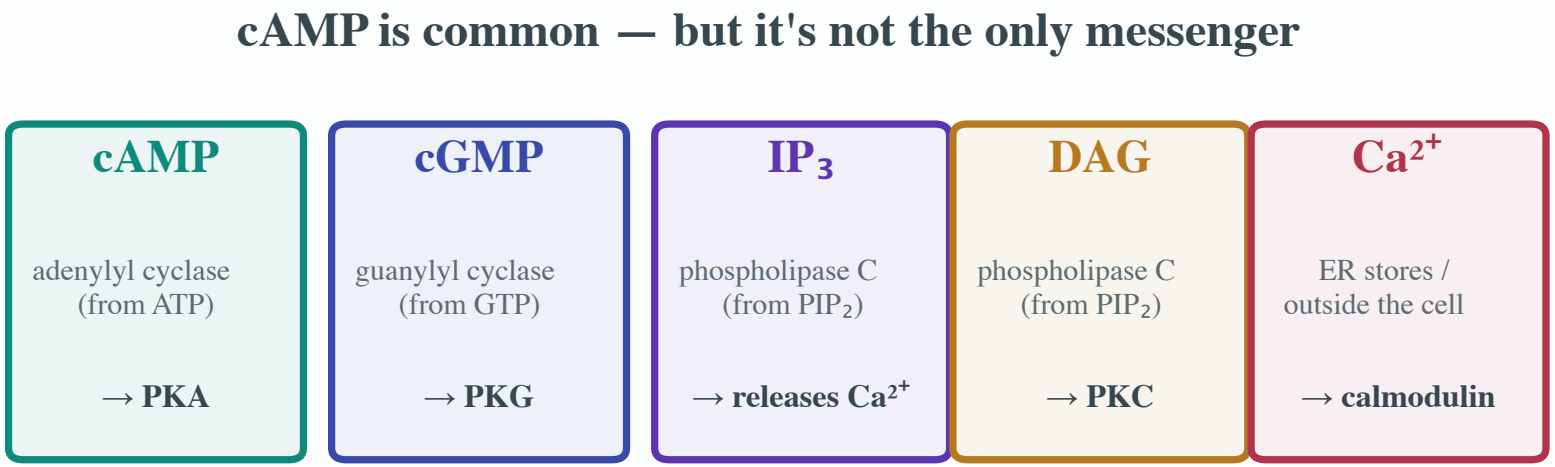


6 · More Second Messengers — IP_3, DAG & Calcium

"cAMP is famous, but it's not the only messenger a GPCR can make. Meet the phosphoinositide pathway — one enzyme, two messengers — and calcium, the ion the cell keeps almost empty so that even a whisper of it screams."

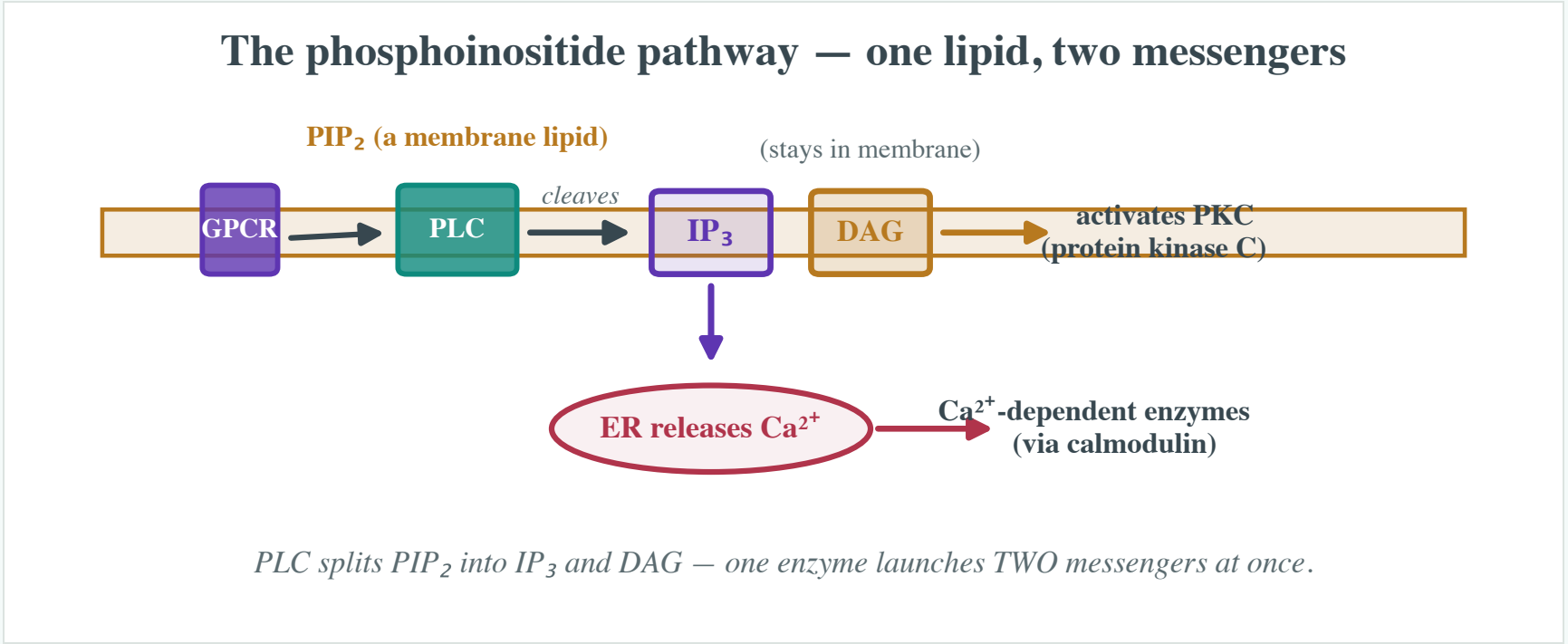
cAMP isn't the only messenger

You just watched a GPCR make **cAMP** — but that's one option, not the whole story. GPCRs are **versatile**: different ones activate different **second messengers**. **cAMP** (from adenylyl cyclase) fires **PKA**; **cGMP** fires **PKG**; **IP_3** and **DAG** (both cut from a membrane lipid) split the signal two ways; and **Ca^{2+}** works through calmodulin. Same receptor architecture, a whole panel of inside couriers.



One enzyme, two messengers: PLC

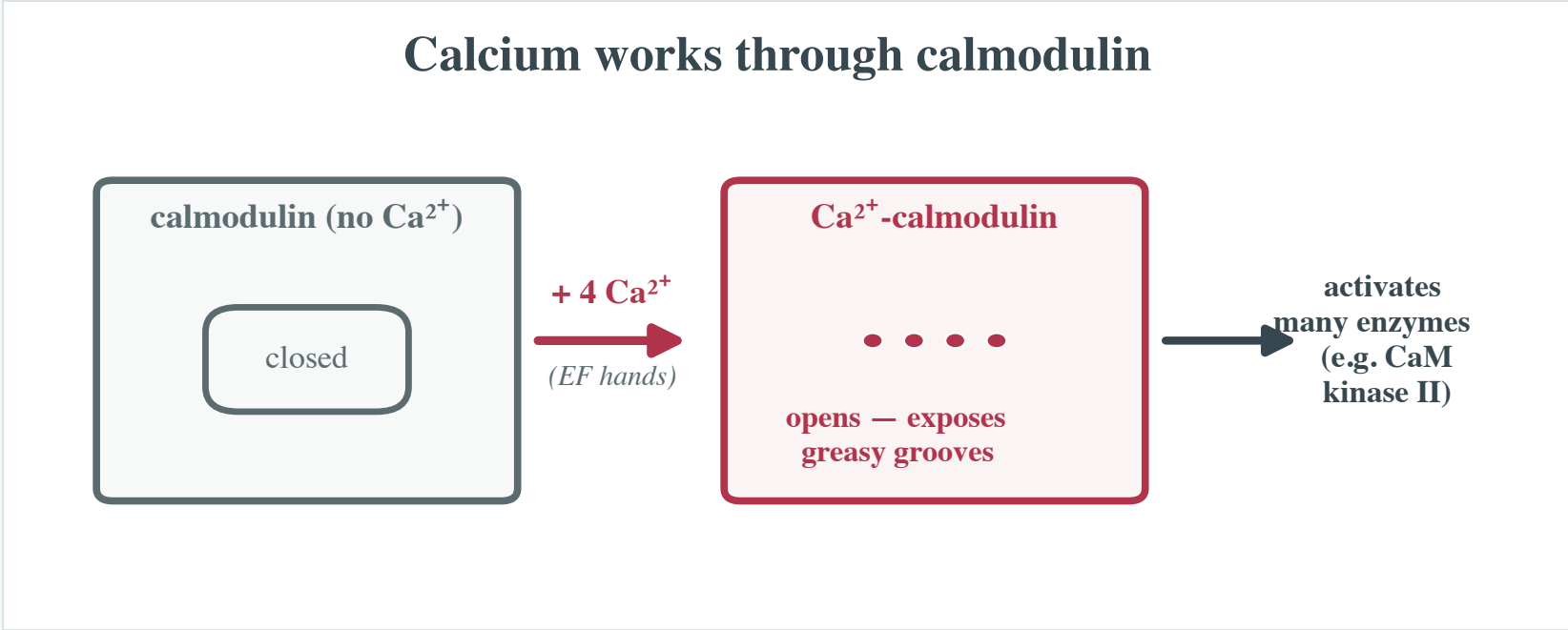
Here's the elegant one. A GPCR turns on **phospholipase C (PLC)**, which grabs a membrane lipid called **PIP_2** and **cuts it in two**. One half, **IP_3**, drifts to the **ER and opens Ca^{2+} channels** – flooding the cytosol with calcium. The other half, **DAG**, stays in the membrane and switches on **protein kinase C (PKC)**. One cleavage, **two** simultaneous messengers – and calcium is now in play as a third.



PLC splits PIP_2 into IP_3 and DAG — one enzyme launches TWO messengers at once.

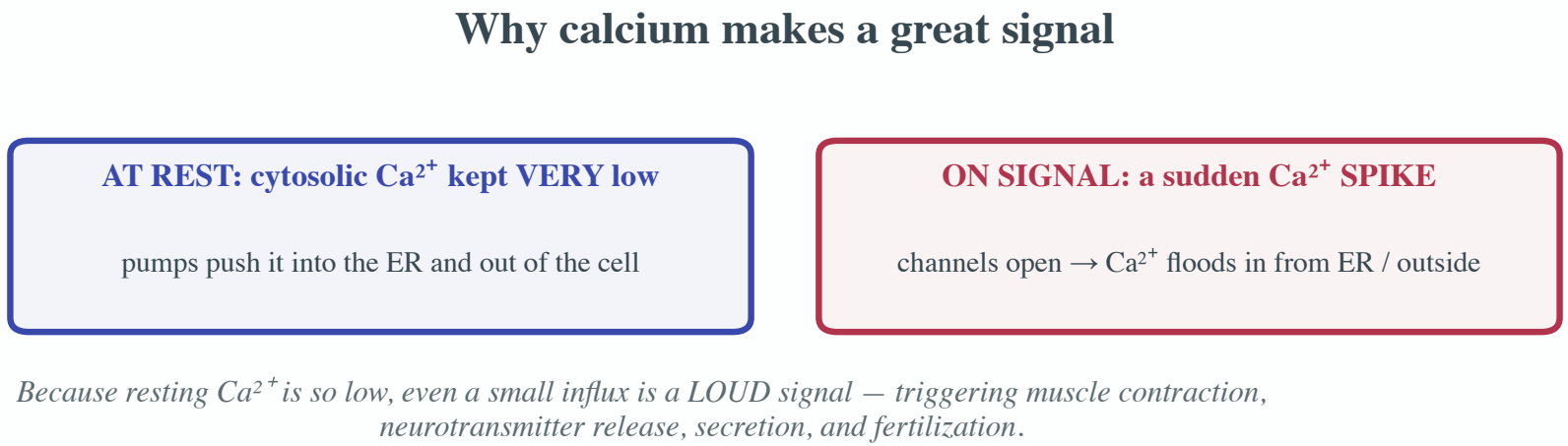
Calcium works through calmodulin

Calcium doesn't act alone — it works through **calmodulin**, a small protein with **four Ca^{2+}-binding sites** (the "EF-hand" motif). When calcium rises, it clamps onto calmodulin, which **changes shape** and exposes greasy grooves that grab and **switch on target enzymes** — like **CaM kinase II**. So a calcium spike becomes a wave of enzyme activity. Calmodulin is the universal calcium **reader**.



Why calcium makes a perfect signal

Here's the trick that makes Ca^{2+} such a great messenger: the cell keeps its **resting cytosolic calcium absurdly low**, pumping it relentlessly into the ER and out of the cell. So when a channel finally opens and calcium **rushes in**, even a tiny amount is a **huge relative change** – a loud, unambiguous signal. That's how one ion triggers **muscle contraction, neurotransmitter release, secretion, and even fertilization**.

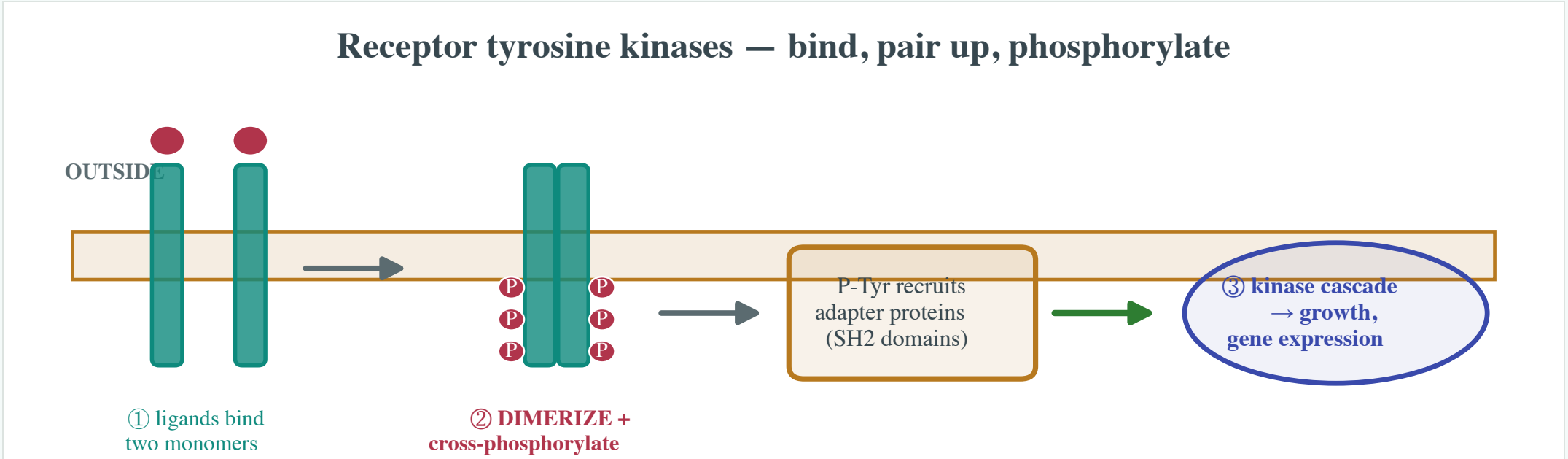


7 · Receptor Tyrosine Kinases & Insulin

"GPCRs hand off to a G-protein. The other great receptor family, the receptor tyrosine kinases, ARE the enzyme — they phosphorylate themselves and launch a cascade straight to your genes. The insulin receptor is the one you have to know."

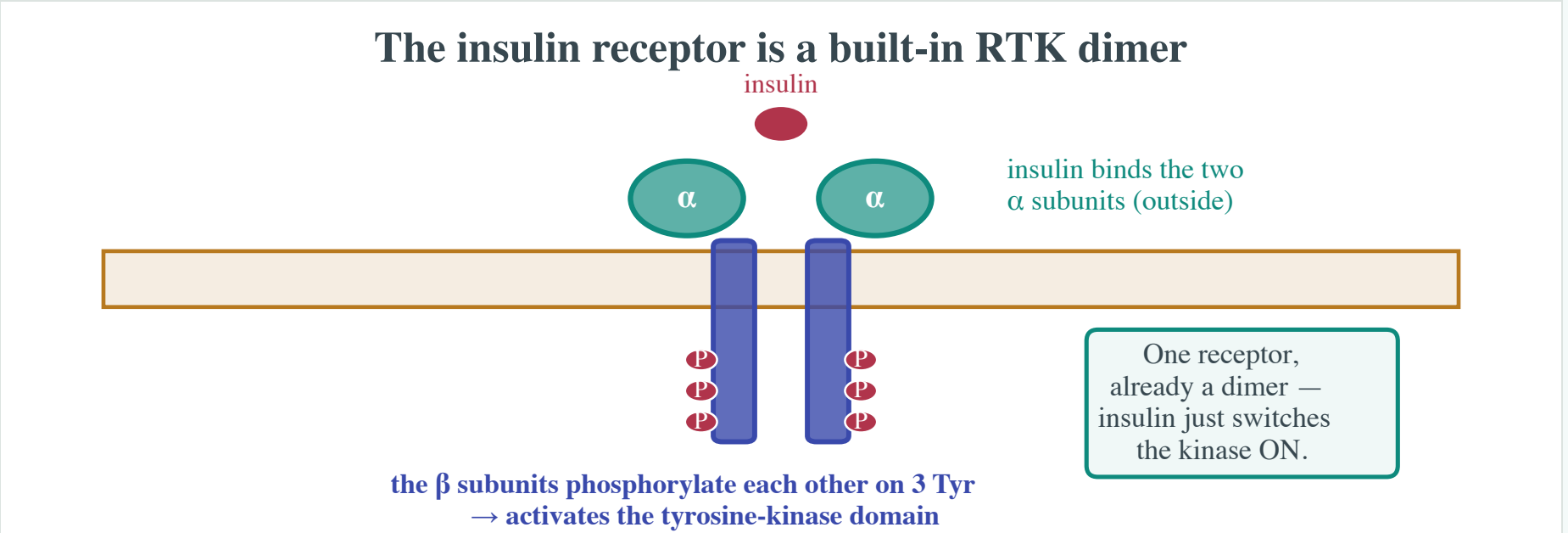
Receptor tyrosine kinases: the receptor IS the enzyme

A **receptor tyrosine kinase (RTK)** doesn't need a middleman G-protein — its own cytoplasmic tail is a **kinase**. The logic: a growth factor binds, **two receptors pair up (dimerize)**, and the paired kinases **phosphorylate each other** on tyrosine residues (**autophosphorylation**). Those new **phosphotyrosines** become docking sites that recruit **adapter proteins**, launching a kinase cascade toward **growth and gene expression**.



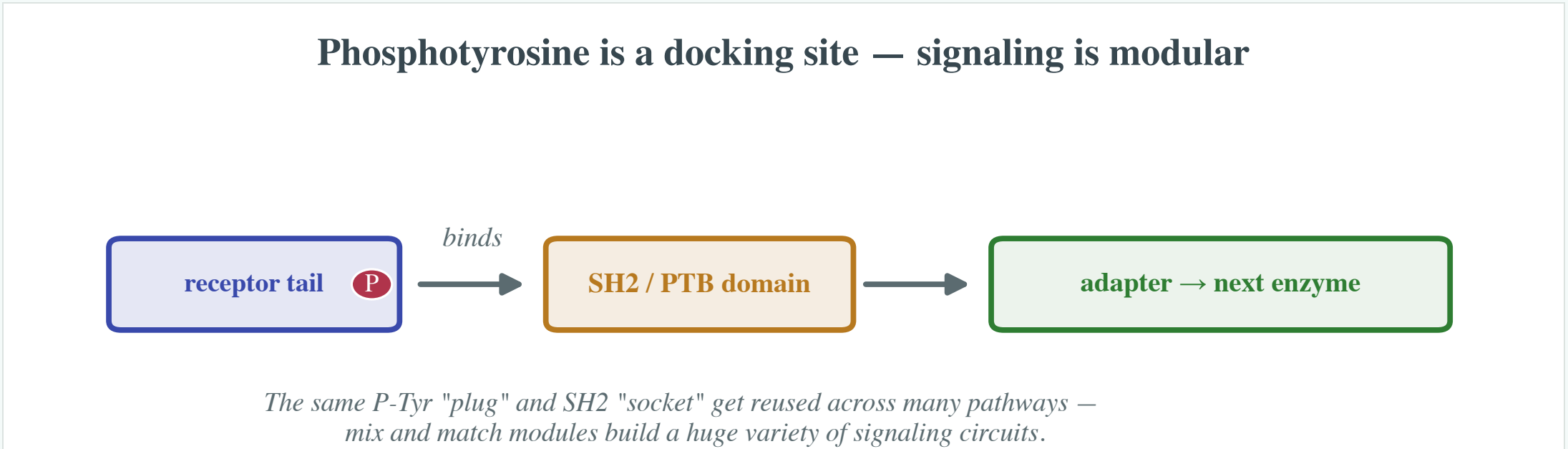
The insulin receptor

Insulin's receptor is the RTK you must know — and it's **already a dimer**: two **α** subunits outside, two **β** subunits spanning the membrane. Insulin binds the **α** subunits; that squeezes the **β** subunits so they **phosphorylate each other on three tyrosines**, snapping the **tyrosine-kinase domain ON**. No dimerization step needed — insulin just flips the switch on a receptor that's pre-assembled and waiting.



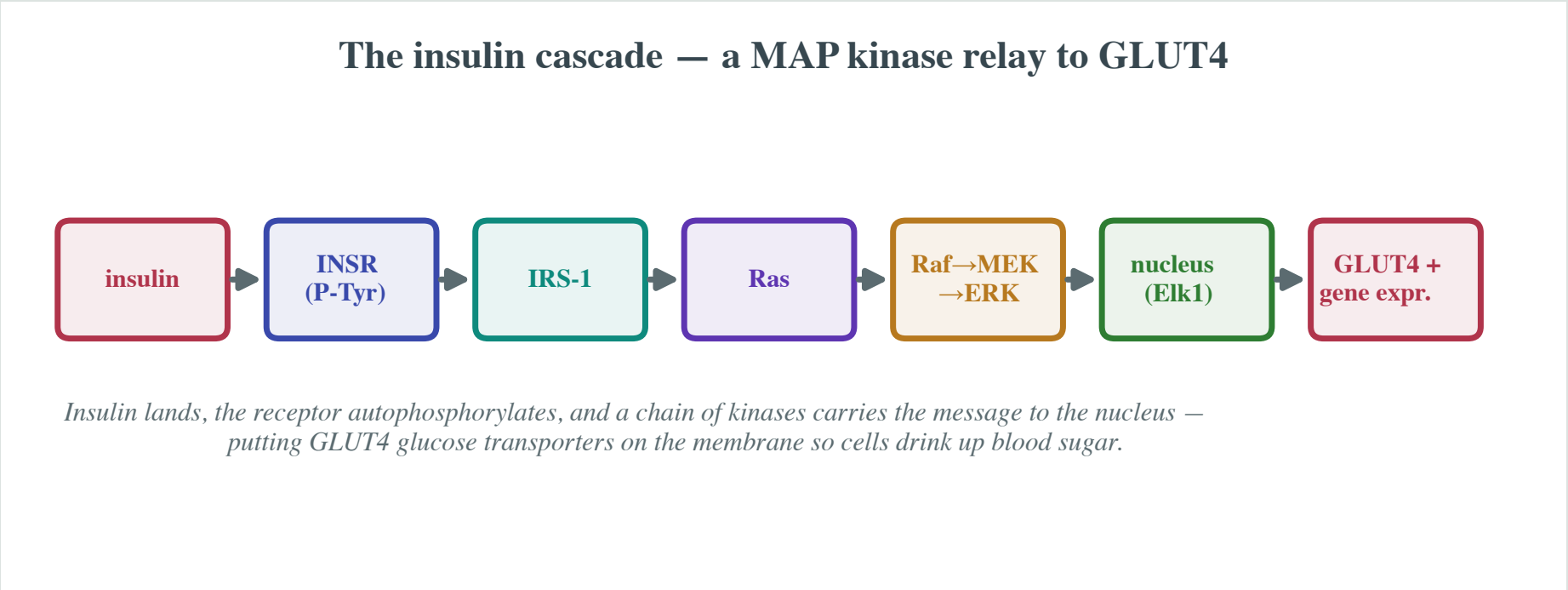
Phosphotyrosine is a docking plug

Why does autophosphorylation matter so much? Each **phosphotyrosine** is a **docking plug**, and specific protein modules – **SH2** and **PTB domains** – are the matching **socket**. An adapter with an SH2 domain snaps onto the P-Tyr and brings the **next enzyme** into position. The beauty is **modularity**: the same plug-and-socket parts get **mixed and matched** across dozens of pathways, building a huge variety of circuits from a few interchangeable pieces.



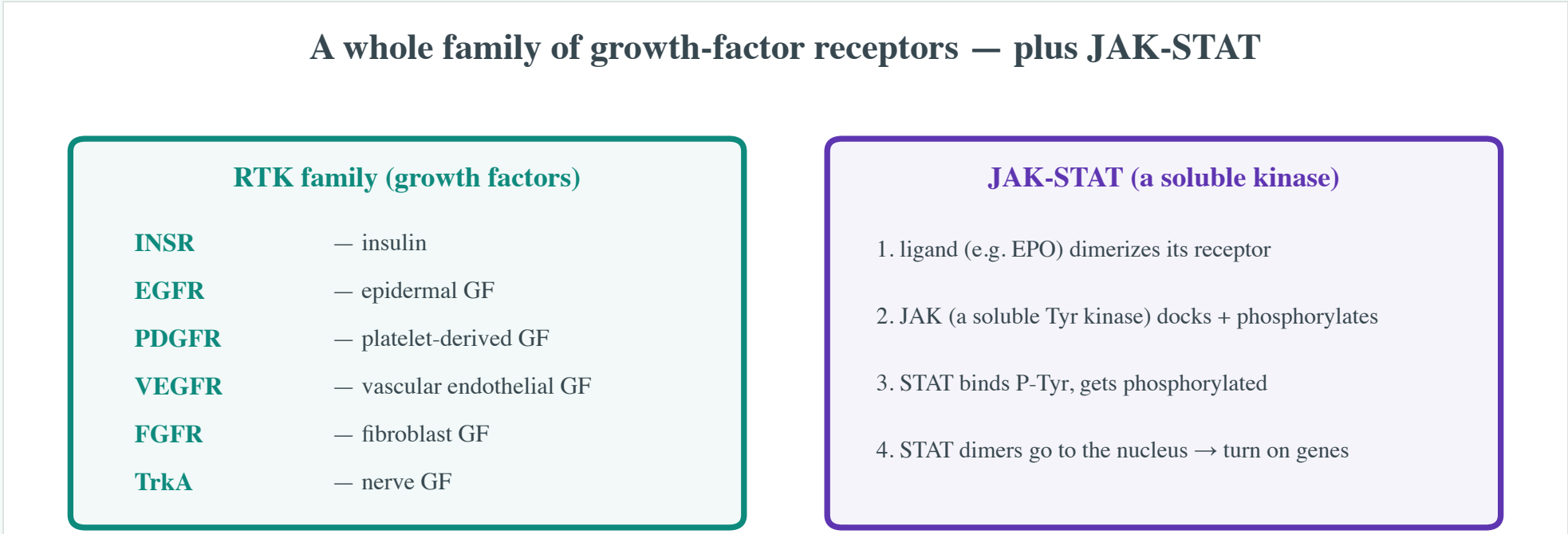
The insulin cascade → GLUT4

Now trace the whole relay. Insulin activates its receptor; the receptor phosphorylates **IRS-1**; IRS-1 switches on **Ras**, which fires the classic **MAP kinase cascade** — **Raf → MEK → ERK**. ERK walks into the nucleus, phosphorylates the transcription factor **Elk1**, and turns on genes — including the **GLUT4** glucose transporter that moves to the membrane so cells **drink up blood sugar**. This is how "I just ate" becomes "store the glucose."



A whole family — and the JAK-STAT shortcut

The insulin receptor has lots of cousins: **EGFR, PDGFR, VEGFR, FGFR, TrkA** — a whole family of **growth-factor RTKs**, each with a unique outside domain but the same inside kinase. And there's a variation worth knowing: **JAK-STAT**. Here the receptor has **no built-in kinase** — a **soluble** kinase, **JAK**, docks on, phosphorylates the receptor, and loads **STAT** proteins that dimerize and march to the nucleus. Same idea, different hardware.

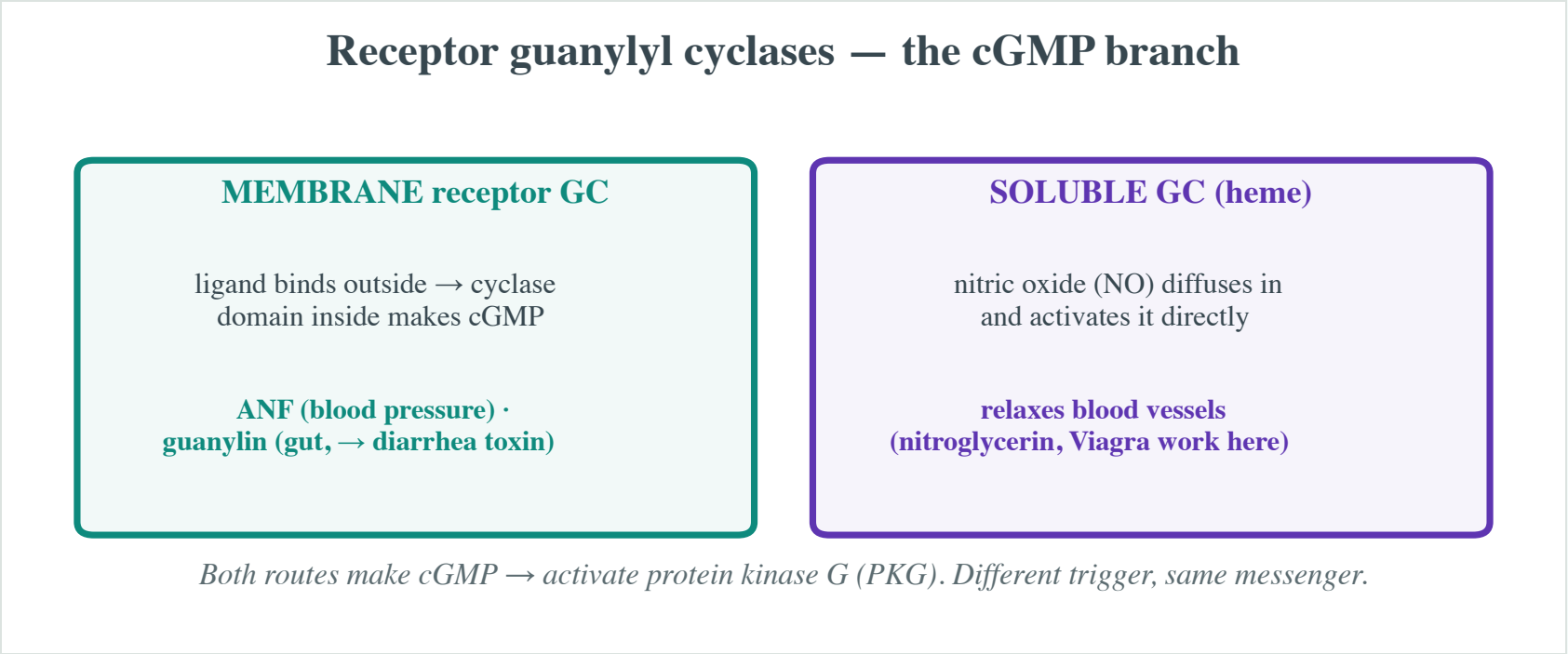


8 · Guanylyl Cyclases & Ion Channels

"Two more transducer types round out the membrane. Guanylyl cyclases make cGMP — the messenger behind nitroglycerin and Viagra. And gated ion channels turn a signal into raw electricity: the polarized membrane, the nerve impulse, and the acetylcholine receptor."

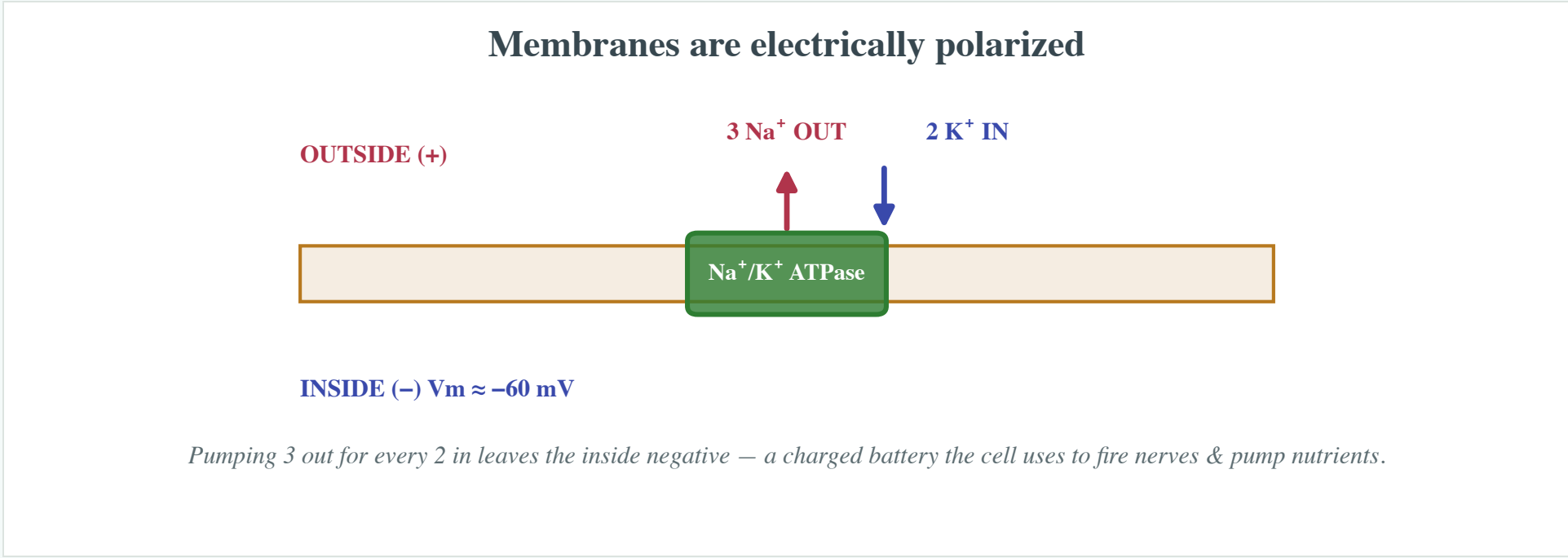
Receptor guanylyl cyclases → cGMP

A third receptor type makes its own messenger: **guanylyl cyclase** converts **GTP → cGMP**, which activates **protein kinase G (PKG)**. It comes in two flavors. A **membrane receptor** version detects ligands like **ANF** (which lowers blood pressure) and **guanylin** in the gut. A **soluble** version carries a **heme** and is switched on by **nitric oxide (NO)** – the pathway that **relaxes blood vessels**, and exactly where **nitroglycerin and Viagra** do their work.



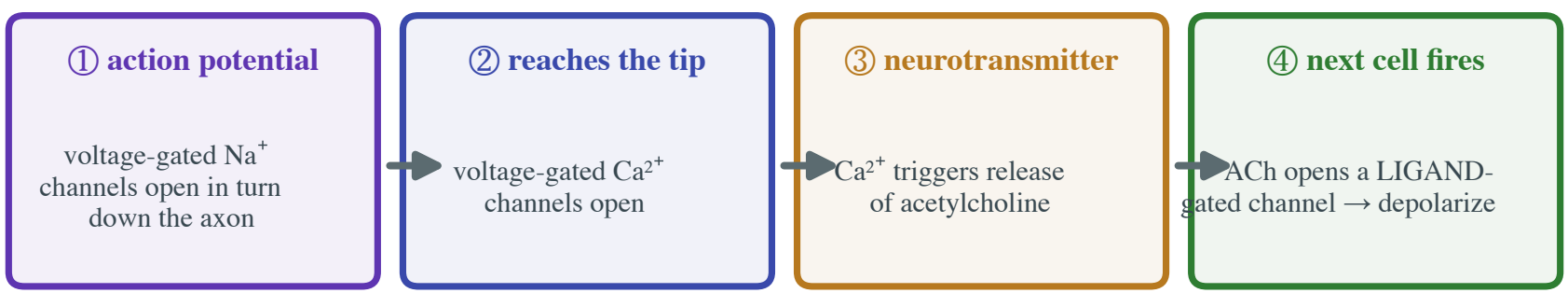
Membranes are electrically polarized

Some signals don't use a chemical messenger at all — they use **voltage**. The **Na^+/K^+ ATPase** pumps **3 Na^+ out** for every **2 K^+ in**, and because it moves more charge out than in, it leaves the inside **negative** — a resting potential of about **−60 mV**. That charge separation is a **loaded battery**: the cell spends it to fire nerves, to pump nutrients, and — next slide — to send an impulse.



Nerve signaling: two kinds of gate

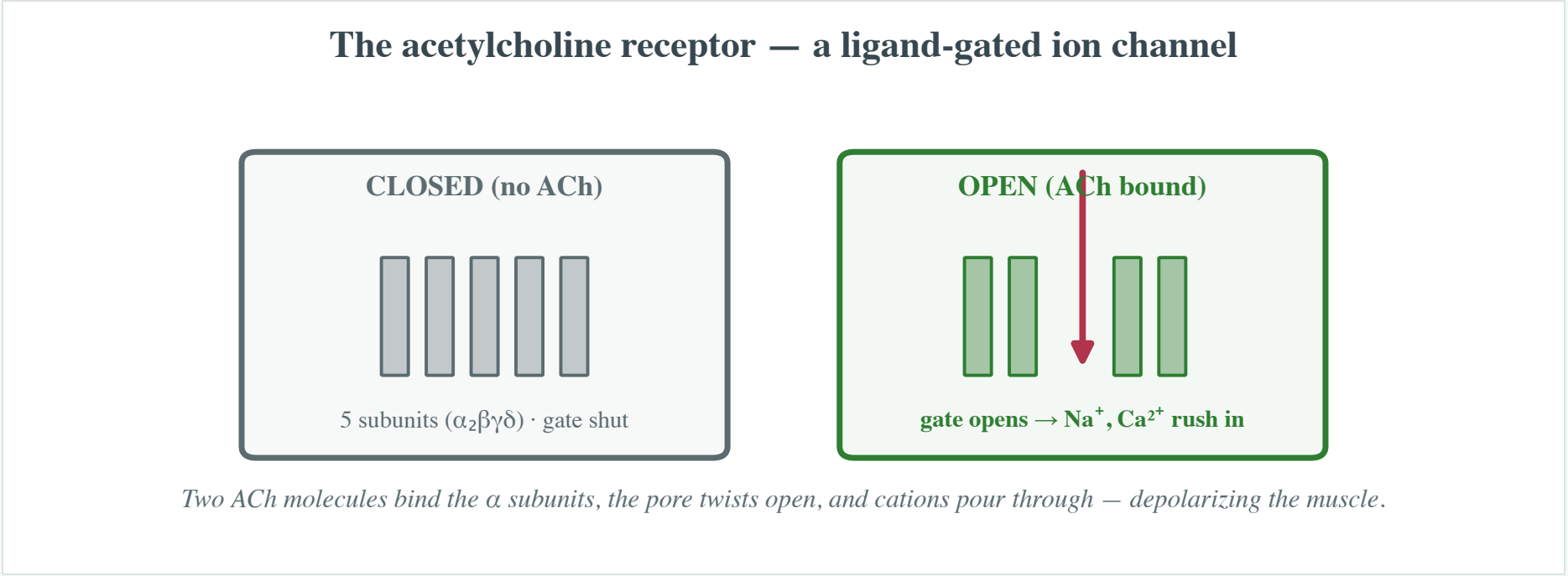
A nerve impulse is a **channel relay**. A stimulus opens **voltage-gated Na^+ channels**, and the local depolarization pops the next one open — an **action potential** racing down the axon. At the tip, **voltage-gated Ca^{2+} channels** open; the calcium triggers release of the neurotransmitter **acetylcholine**; and across the gap, ACh opens a **ligand-gated channel** on the next cell. **Voltage-gated** carries it **along**; **ligand-gated** hands it **across**.



Voltage-gated channels carry the signal ALONG the nerve; ligand-gated channels hand it ACROSS the gap.

The acetylcholine receptor

That receiving channel is the **nicotinic acetylcholine receptor** — a beautiful machine of **five subunits** ($\alpha_2\beta\gamma\delta$) arranged around a central pore. At rest the gate is **shut**. When **two ACh molecules** bind the α subunits, the pore **twists open**, and **Na^+ and Ca^{2+} pour through**, depolarizing the muscle or neuron. It's a **ligand-gated ion channel**: chemical signal in, electrical signal out, in a millisecond.

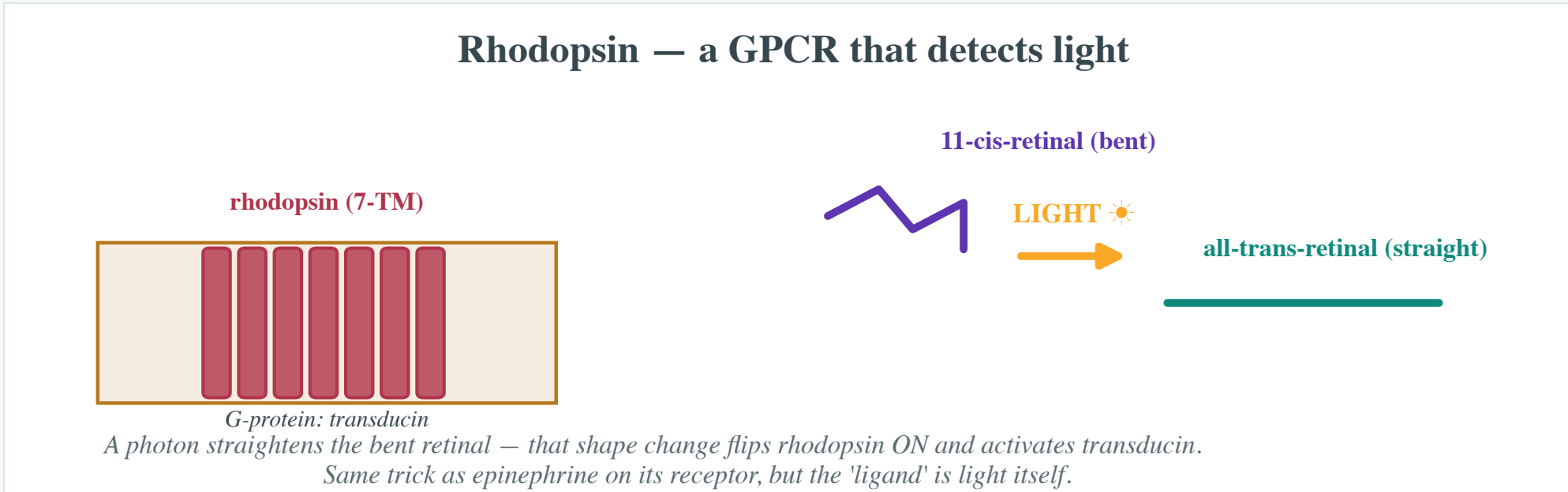


9 · Your Senses Run on GPCRs

"Here's the payoff that makes signaling feel real: the same GPCR machinery that reads epinephrine also lets you see, smell, and taste. Rhodopsin is a GPCR whose 'hormone' is a single photon of light."

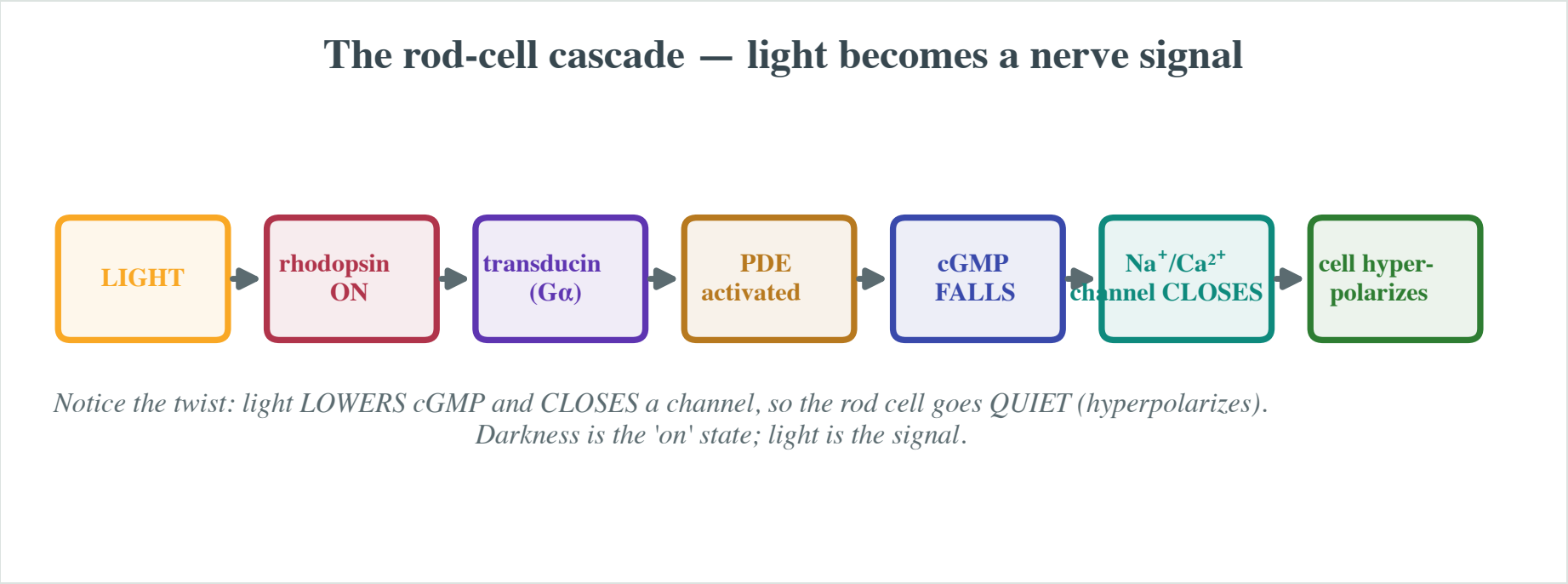
Rhodopsin: a receptor for light

The **rod cells** in your eye carry a specialized GPCR called **rhodopsin**, and its "ligand" is a **photon**. Tucked inside is a chromophore, **11-cis-retinal**. When light hits it, the retinal **isomerizes** – the bent **11-cis** form snaps straight to **all-trans** – flipping rhodopsin **ON** and activating its G-protein, **transducin**. Afterward the all-trans falls out (the receptor is **bleached**), and enzymes rebuild **11-cis** to **reset** it for the next photon – the **visual cycle**.



The rod-cell cascade — with a twist

Follow the relay and watch for the surprise. Active **transducin** switches on a **phosphodiesterase (PDE)**; the PDE **destroys cGMP**, so cGMP levels **fall**; and falling cGMP **closes** a Na^+/Ca^{2+} channel that was held open in the dark. Closing the channel makes the rod **hyperpolarize** — it goes **quiet** — and that silence is the nerve signal for "light!" In the eye, **darkness is the 'on' state**; light **shuts the cell up**. Beautifully backwards.



Smell and taste, too

Once you see the pattern, your whole sensory world is GPCRs. **Smell**: odorant molecules bind **olfactory receptors** (hundreds of different GPCRs), which activate **G-olf → adenylyl cyclase → cAMP**, opening a channel. **Taste**: sweet and bitter tastants bind taste-receptor GPCRs coupled to **gustducin**, a close cousin of transducin. One receptor design — a GPCR, its G-protein, an effector — **reused to build three senses**. That's the power of modularity.

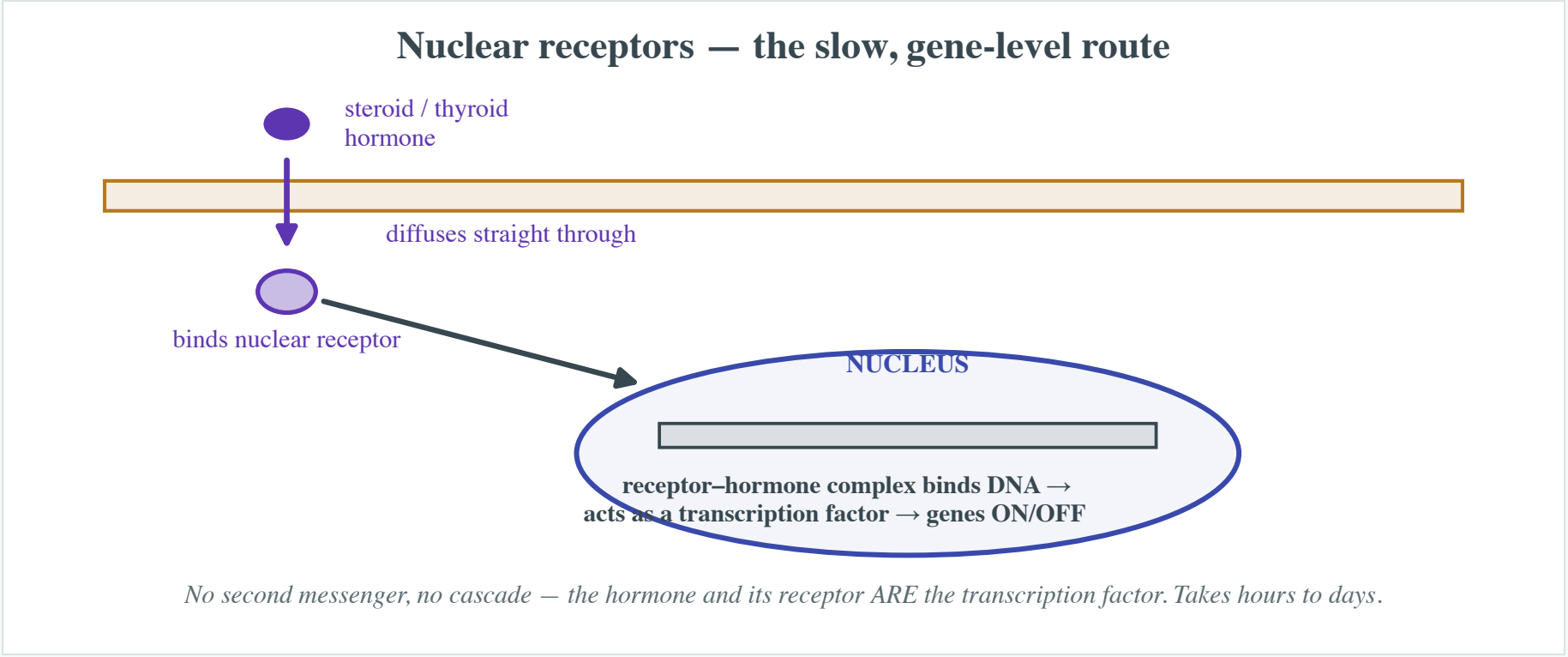
A GPCR + its G-protein + an effector — evolution reused one design to build three senses.

10 · Nuclear Receptors — Signaling to the Genes

"We opened the unit with two mechanisms. We've spent four lectures on the fast one — surface receptors and cascades. Now the slow one: lipid-soluble hormones that skip the middleman entirely and act as transcription factors themselves."

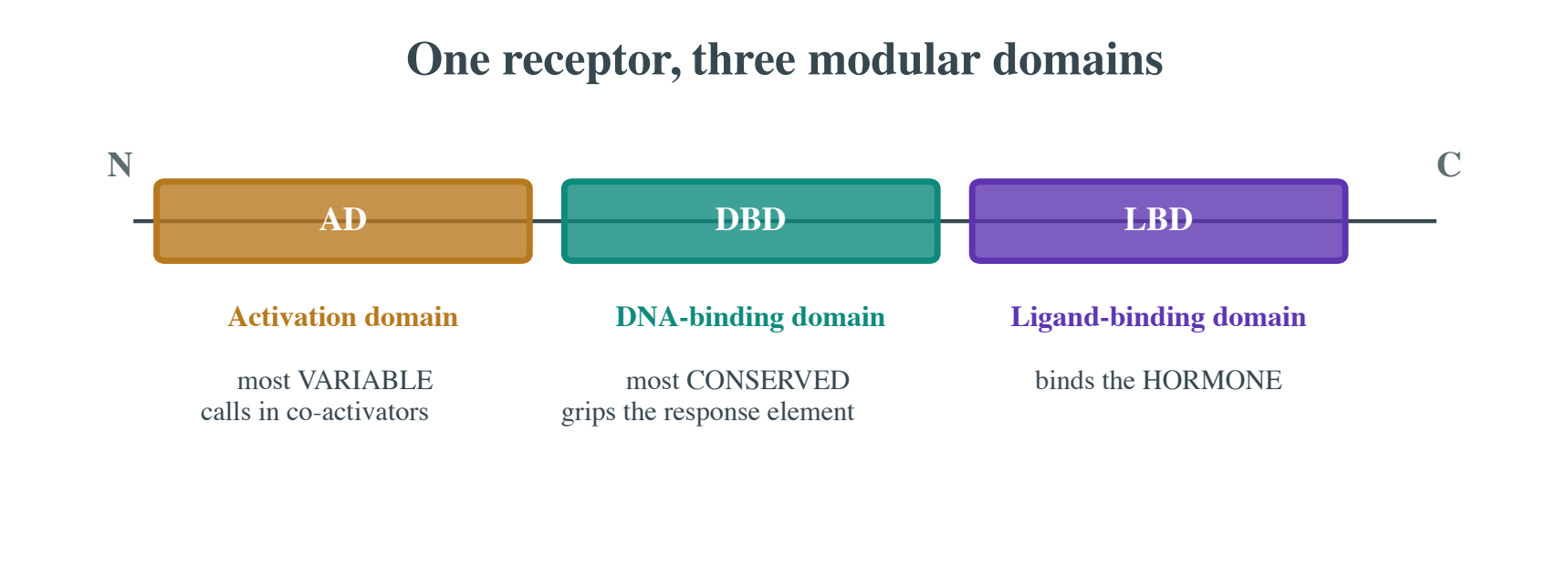
Nuclear receptors: no cascade needed

Steroids, thyroid hormone, retinoids, and vitamin D are **lipid-soluble** — so they skip everything you just learned. The hormone **diffuses through** the membrane, binds an **intracellular receptor**, and the **complex goes to DNA as a transcription factor**, switching genes **on or off**. No messenger, no cascade — slow (hours to days), but it builds brand-new proteins.



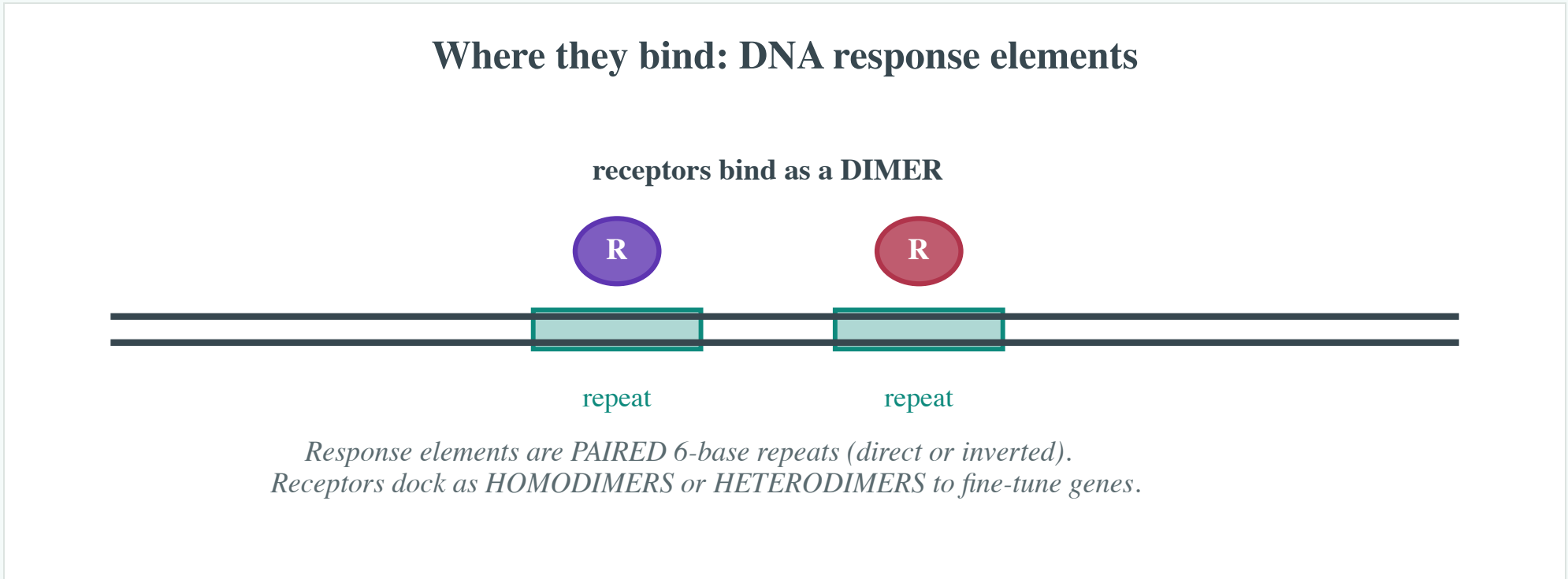
A modular receptor

Nuclear receptors are a **family**, and they're built from **shared modules**. The **DNA-binding domain** is the **most conserved** part — it's how they all grip DNA. The **ligand-binding domain** is what makes each one specific to **its** hormone. And the **activation domain** is the **most variable** — it's where the receptor recruits its helpers. Same three-part blueprint, swappable parts: that's how one gene family reads dozens of different hormones.



Where they bind: response elements

The DNA-binding domain is picky — it recognizes specific short sequences called **response elements**, parked in the control region **upstream of target genes**. These are usually **paired six-base repeats** (arranged as **direct** or **inverted** repeats). And receptors dock on them **as dimers**: sometimes **homodimers** (two of the same receptor), sometimes **heterodimers** (two different ones). Which pair sits down helps decide **which genes** respond.



Turning the gene up or down

Once bound, the receptor acts as a transcriptional **activator or a repressor**. Its **activation domain** reaches out and grabs **co-activators** (or **co-repressors**) — bridge proteins that connect the receptor to the **RNA polymerase II** machinery. Recruit coactivators and transcription goes **up**; recruit corepressors and it goes **down**. That single handshake is how one steroid can **rewire a cell's entire protein output** — and it's where we head next: the steroid hormones themselves.

The payoff: turning transcription up or down

The activation domain is the receptor's handshake with the transcription machinery — a coactivator turns the gene UP, a corepressor turns it DOWN. That's how one steroid rewires a cell's whole protein output.

Can you…?

- □ explain how a hormone message crosses the membrane, and classify hormone actions (endocrine, paracrine, autocrine, cell-contact) and chemical classes (peptide, amine, steroid, thyroid)?
- □ apply the five features of signal-transducing systems, and read receptor-binding data (Kd, affinity, dose-response)?
- □ walk GPCR signaling — the β-adrenergic/epinephrine cascade, cAMP/PKA, amplification, GTPase self-inactivation, and βARK/β-arrestin desensitization?
- □ compare the second-messenger systems (cAMP, IP_3/DAG, Ca^{2+}/calmodulin, cGMP) and the receptor tyrosine kinases (insulin receptor, RTK family, JAK-STAT)?
- □ explain membrane polarization and gated ion channels (Na^+/K^+ ATPase, the acetylcholine receptor, voltage- vs ligand-gated), sensory GPCR signaling (sight, smell, taste), and nuclear-receptor gene regulation?

If any box stays empty, the practice site has a drill for it.

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