Signal Transduction & Hormones

BCH 100 — Introductory Biochemistry · Dr. Radi

By the end of this unit, you can…

- Classify hormones and the types of cell signaling (endocrine, paracrine, autocrine) and the water- vs lipid-soluble receptor logic
- Explain second messengers (cAMP, Ca^{2+}, IP_3/DAG) and how signal cascades amplify
- Walk GPCR signaling through G proteins and adenylyl cyclase, and receptor tyrosine kinase (RTK) signaling
- Connect hormonal control of metabolism — insulin, glucagon, epinephrine — and the biochemistry of diabetes

Today's route

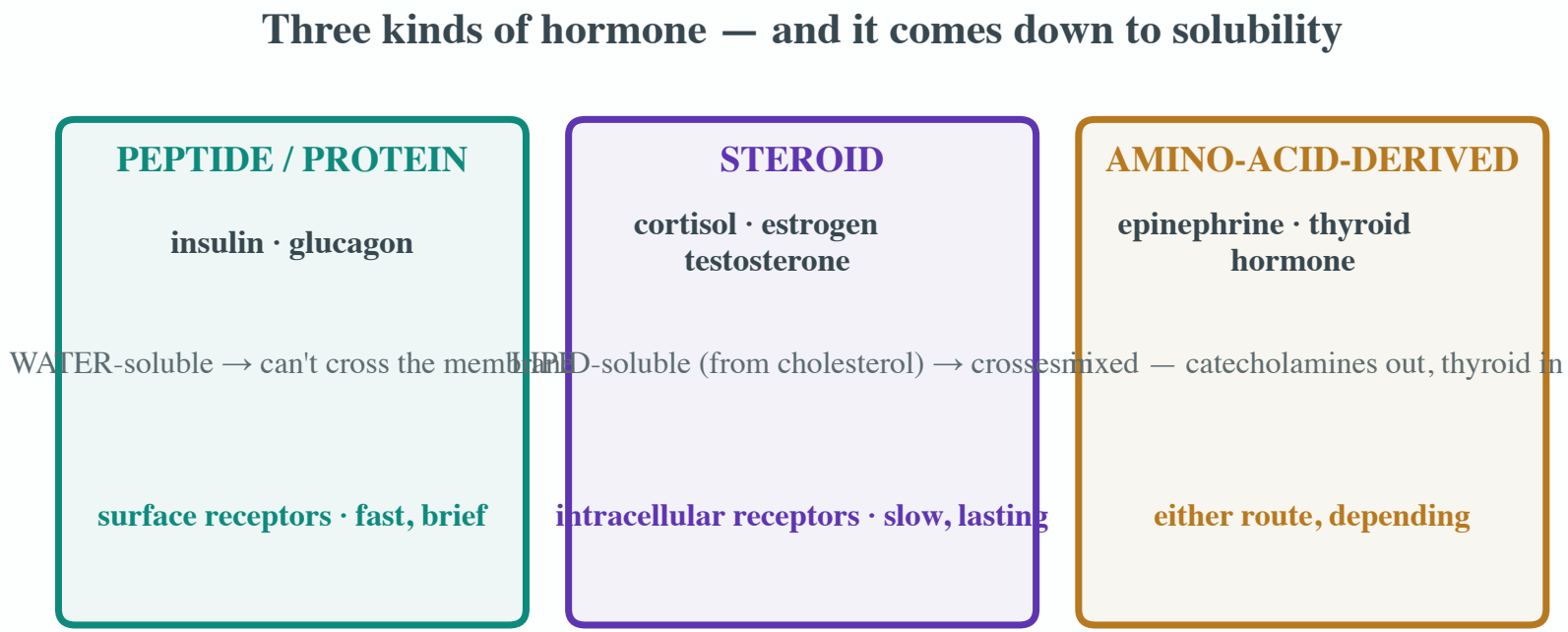
1. Hormones & How They Signal
2. Second Messengers & Amplification
3. GPCRs — The G-Protein Switch
4. Receptor Tyrosine Kinases
5. Metabolic Hormones & Diabetes

1 · Hormones & How They Signal

"A hormone is just a chemical message. What kind of message it is — and how a cell hears it — comes down to one thing: can it cross the membrane?"

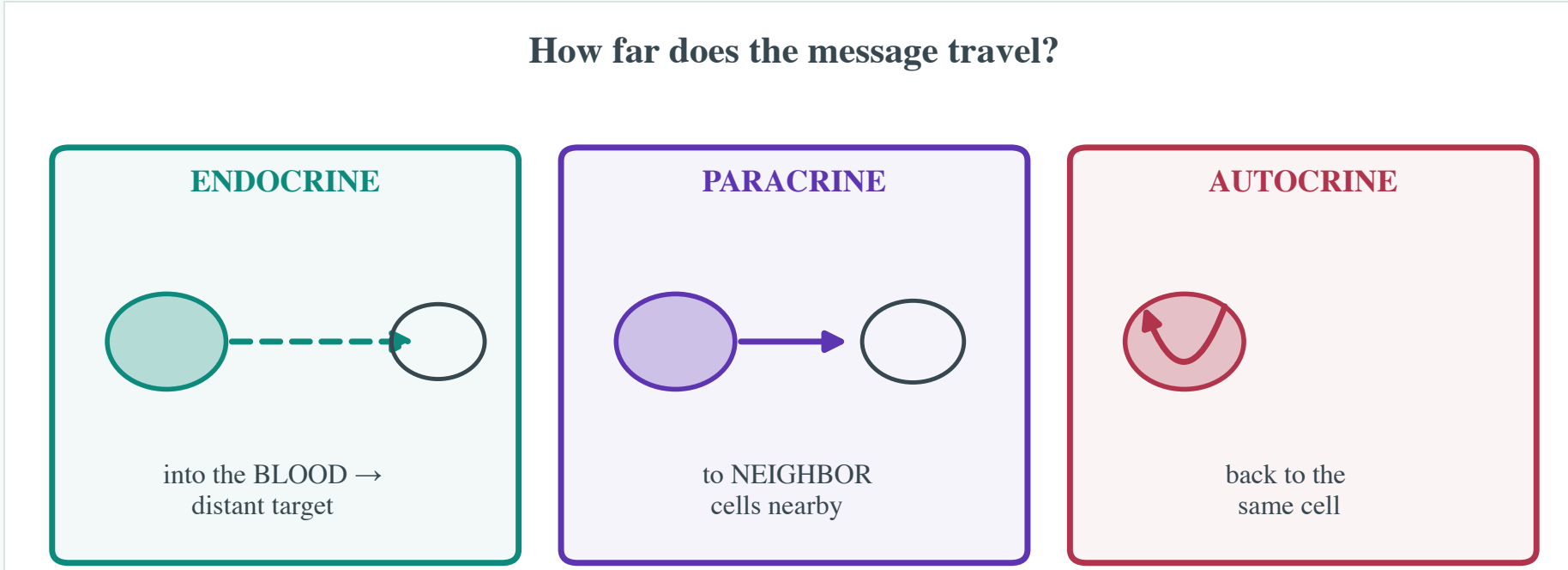
Three kinds of hormone

A **hormone** is a chemical messenger, and they come in **three chemical families**. **Peptide/protein** hormones (**insulin, glucagon**) are made of amino acids and are **water-soluble** – they can't cross the greasy membrane. **Steroid** hormones (**cortisol, estrogen, testosterone**) are built from **cholesterol** and are **lipid-soluble** – they slip right through. **Amino-acid-derived** hormones (**epinephrine, thyroid hormone**) are the mixed bag. That one property – **water- vs. lipid-soluble** – decides **everything** about how the message is delivered.



How far does the message travel?

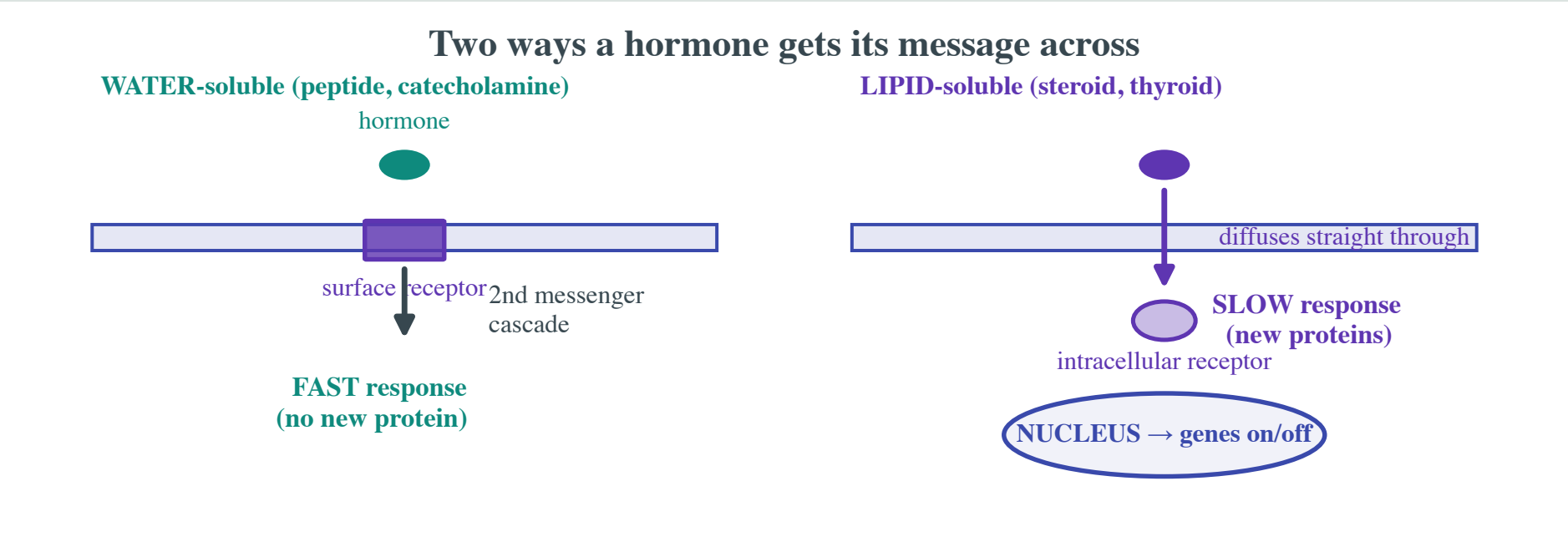
Signaling is sorted by **distance**. **Endocrine** signaling is long-range: a gland dumps the hormone into the **bloodstream** to reach **distant** targets (insulin from the pancreas acting on your whole body). **Paracrine** signaling is local — a cell talks to its **neighbors** (like the signals that coordinate inflammation). **Autocrine** signaling is a cell messaging **itself** (common in growth signals — and in cancer). Same molecule-and-receptor logic; three different ranges.



Same idea — a chemical message — over three different distances.

Two ways a cell hears a hormone

Now the payoff of that solubility rule. A **water-soluble** hormone is stuck **outside**, so it binds a **receptor on the cell surface**, which triggers a **second-messenger cascade** inside — a **fast** response that needs no new proteins (this is the rest of the unit). A **lipid-soluble** hormone **diffuses straight through** the membrane, binds an **intracellular receptor**, and the pair goes to the **nucleus to switch genes on or off** — a **slower** response that makes **new proteins**. Fast switch vs. slow rewiring.



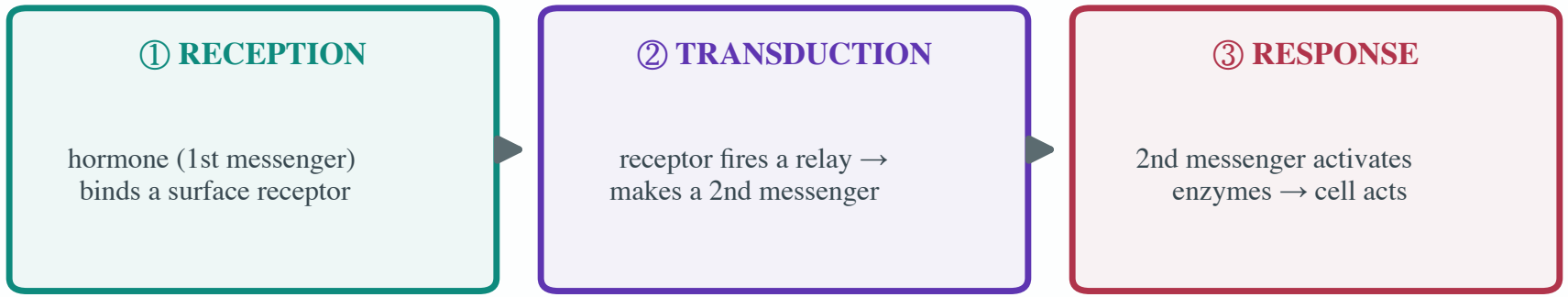
2 · Second Messengers & Amplification

"The hormone never comes inside. It knocks at the door — and the cell relays that knock through a chain of couriers that turns one signal into millions."

What "signal transduction" means

A water-soluble hormone can't get in — so how does its message? Through **signal transduction**: **converting** an outside signal into an inside action. It goes in three moves. **Reception** — the hormone (the **first messenger**) binds a **surface receptor**. **Transduction** — the receptor fires an internal **relay** that produces a **second messenger**. **Response** — that second messenger switches on **enzymes** and the cell acts. The hormone just **knocks**; everything after happens **inside**.

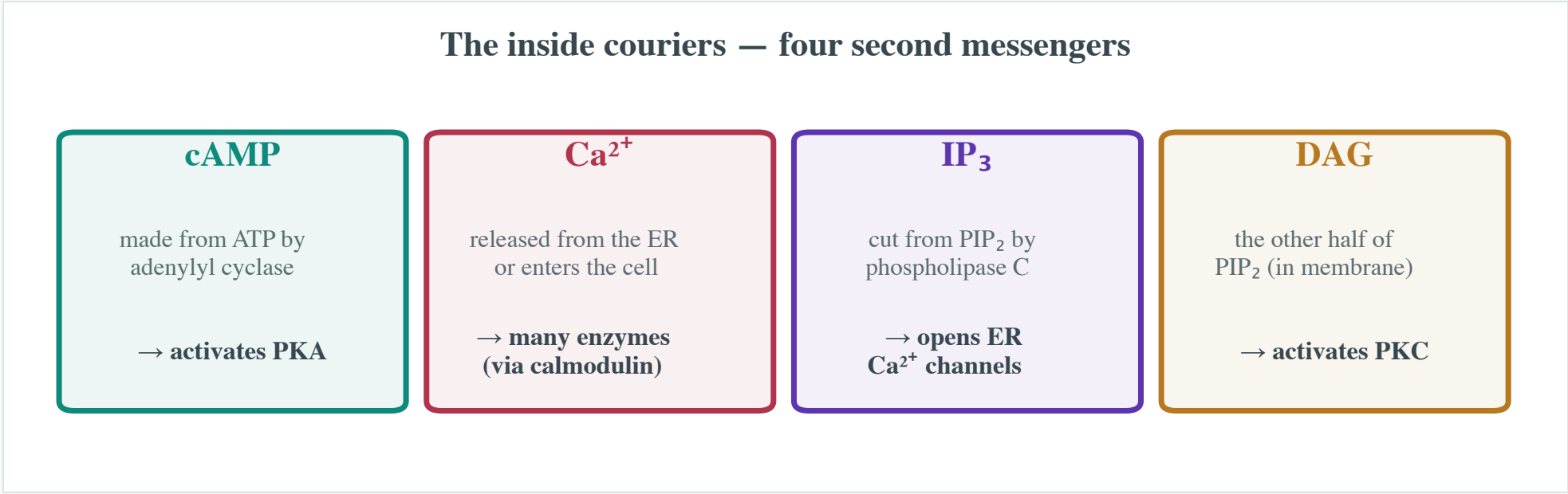
Signal transduction — outside message → inside action



The hormone never enters the cell — it just knocks; the message is relayed and amplified inside.

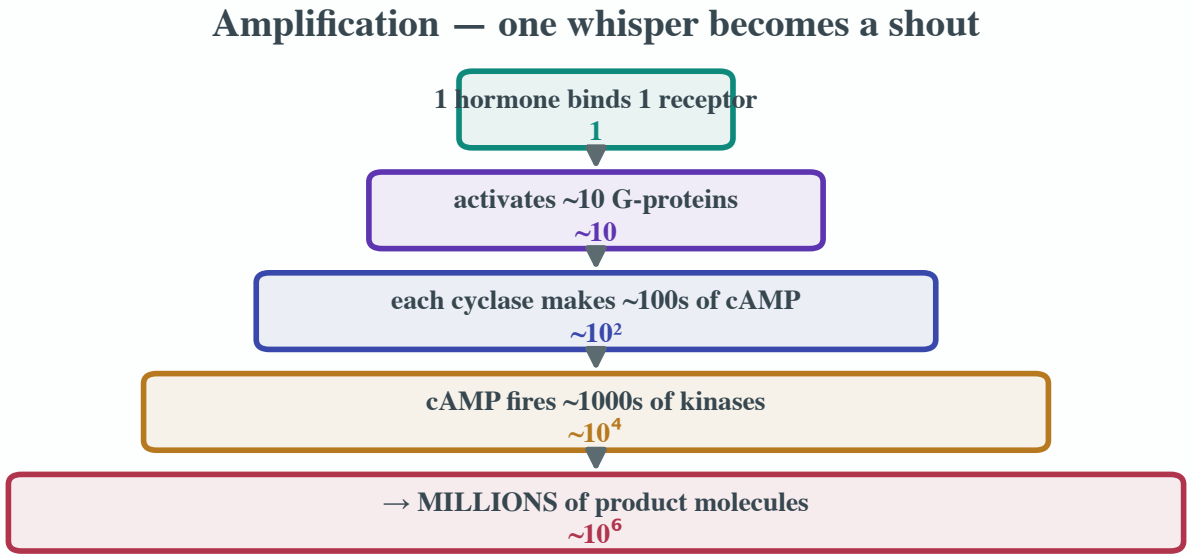
The inside couriers

The "second messengers" are a small set of small molecules that carry the signal onward — and you should know **four**. **cAMP**, made from ATP by **adenylyl cyclase**, switches on **protein kinase A (PKA)**. **Ca^{2+}**, released from the ER, activates a whole roster of enzymes (usually via **calmodulin**). And a **single** membrane lipid, **PIP_2**, is split by **phospholipase C** into **two** messengers at once: **IP_3**, which opens **ER calcium channels**, and **DAG**, which activates **protein kinase C (PKC)**.



Amplification: one whisper, a shout

Here's the payoff of the relay. **Every step multiplies.** One hormone activates one receptor — but that receptor switches on **~10 G-proteins**, each of which turns on an enzyme (**adenylyl cyclase**) that pumps out **hundreds of cAMP**, each of which fires a **kinase** that modifies **thousands** of target molecules. Down the chain, **one** hormone becomes **millions** of product molecules. That's why hormones work at **nanomolar** concentrations — a vanishingly small signal, enormously amplified.



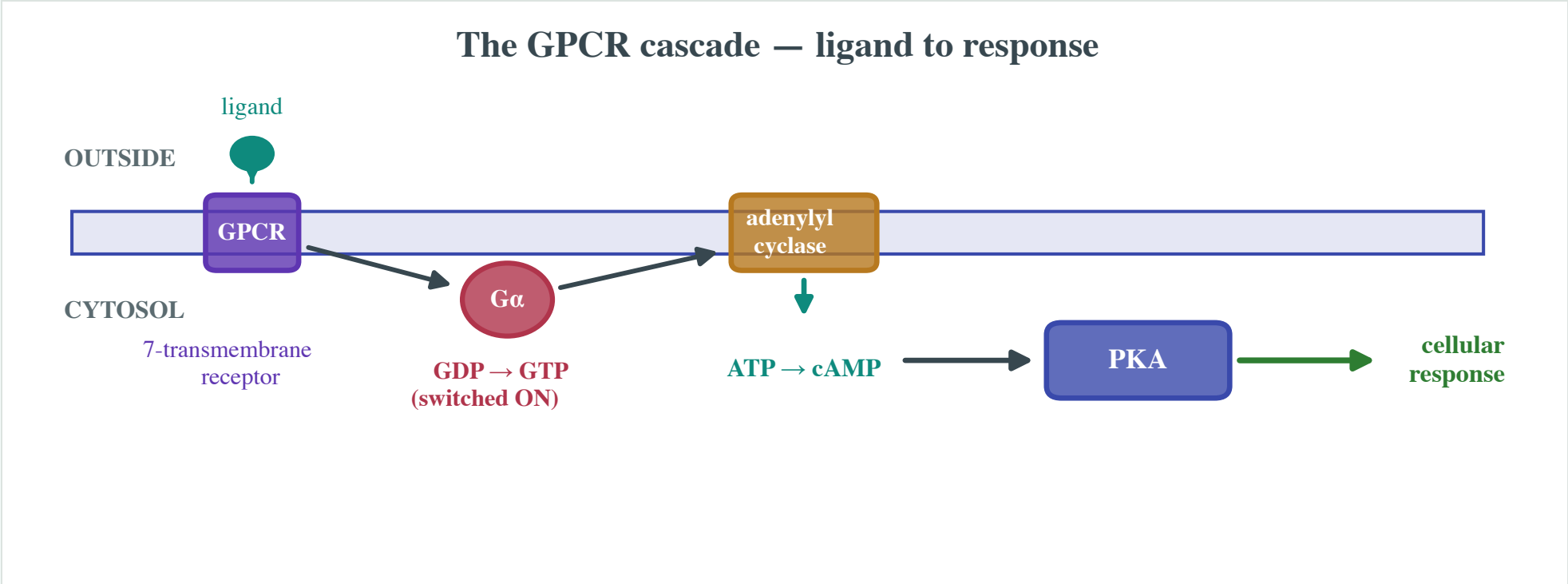
Each step multiplies the last — so a hormone at nanomolar concentration can flip a whole cell.

3 · GPCRs — The G-Protein Switch

"The most common receptor in your body, and the target of a third of all drugs, works like a molecular light switch — flicked on by a hormone and, crucially, timed to flick itself back off."

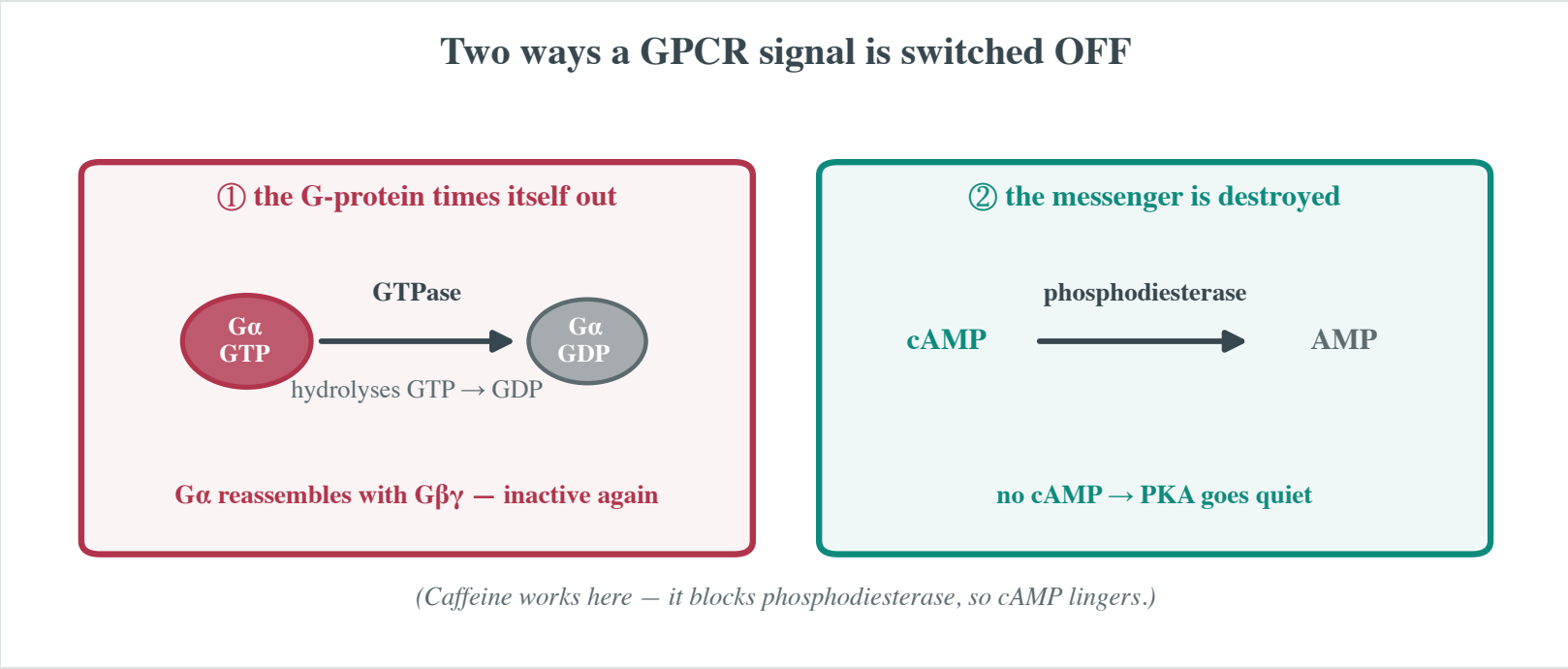
The GPCR cascade

A **G-protein-coupled receptor (GPCR)** is a protein that snakes through the membrane **seven times** — it's the **largest receptor family** in your body. When a **hormone binds** the outside, the receptor changes shape and pokes a nearby **G-protein**, which swaps its **GDP for GTP** and switches **ON**. The activated **Gα** then turns on **adenylyl cyclase**, which converts **ATP into cAMP** — and cAMP fires up **PKA**, driving the **cellular response**. One binding event, a whole relay.



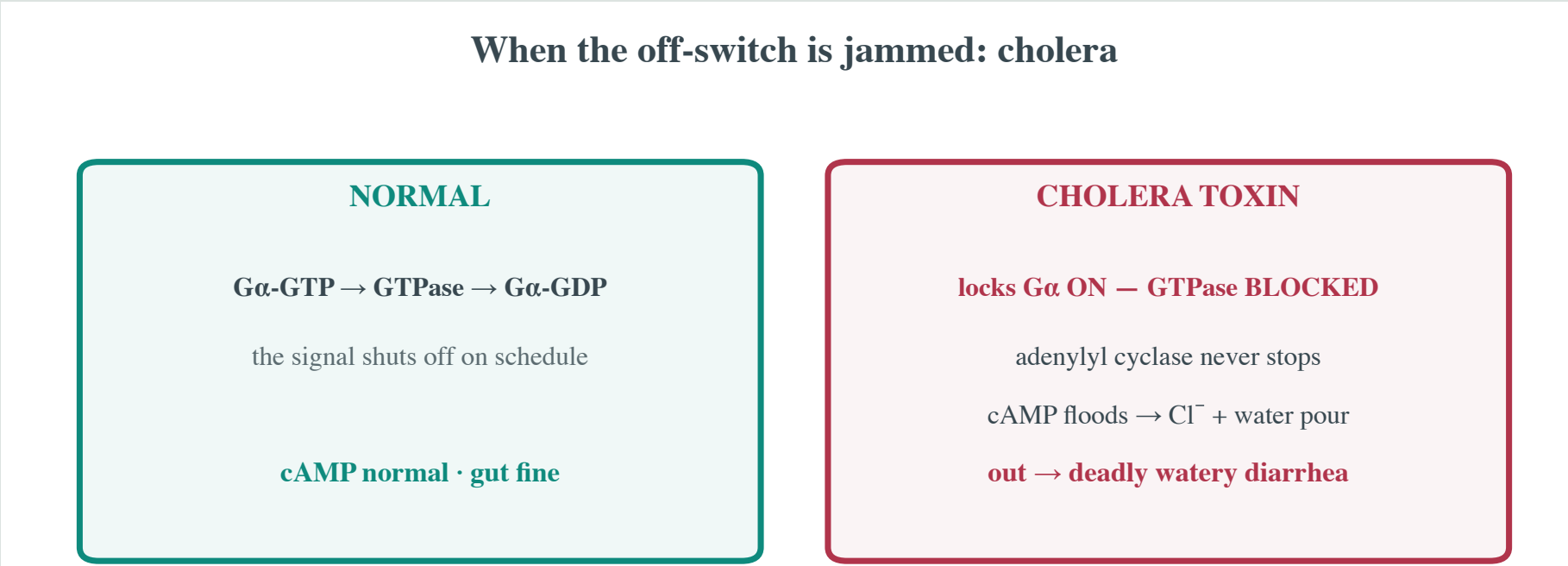
How the signal gets switched OFF

A switch that only turns **on** is useless — so the system has two built-in **off** mechanisms. First, **Gα is its own timer**: it has a slow **GTPase** activity that **hydrolyzes its GTP back to GDP**, flipping itself off and reassembling with Gβγ. Second, the second messenger is **destroyed** — **phosphodiesterase** chops **cAMP into plain AMP**, so PKA goes quiet. Turn off the G-protein **and** clear the messenger, and the cell returns to baseline, ready for the next signal.



When the off-switch is jammed: cholera

Here's what happens when that shut-off **fails**. **Cholera toxin** chemically modifies **Gα** so its **GTPase can't work** — it's stuck in the **GTP, "on" state forever**. Adenylyl cyclase never stops, **cAMP floods** the intestinal cells, and they pump out **chloride and water** without pause — producing the massive **watery diarrhea** that can kill by dehydration in a day. The entire deadly disease is nothing but a **signal that can't turn off** — which is exactly why the GTPase timer matters.

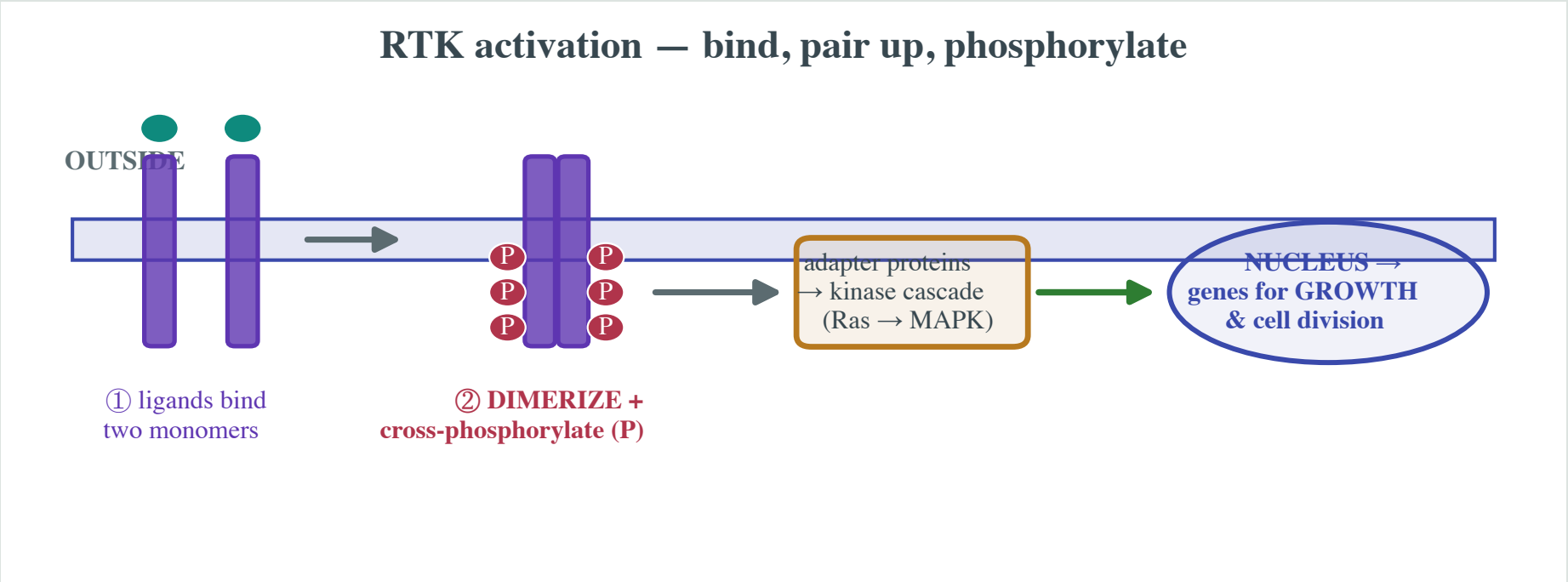


4 · Receptor Tyrosine Kinases

"The other great receptor family doesn't use a G-protein at all. It pairs up, phosphorylates itself, and — instead of a quick metabolic tweak — reprograms the cell to grow."

How an RTK switches on

A **receptor tyrosine kinase (RTK)** – the receptor for **insulin** and most **growth factors** – crosses the membrane **just once** and sits idle until a ligand binds. Then **two receptors pair up** (**dimerize**) and **phosphorylate each other** on **tyrosines** (**autophosphorylation**). Those phosphate tags recruit **adapter proteins** that launch a **kinase cascade** (Ras → MAPK), ending in the **nucleus** – switching on genes for **growth and division**.



GPCR vs. RTK: two strategies

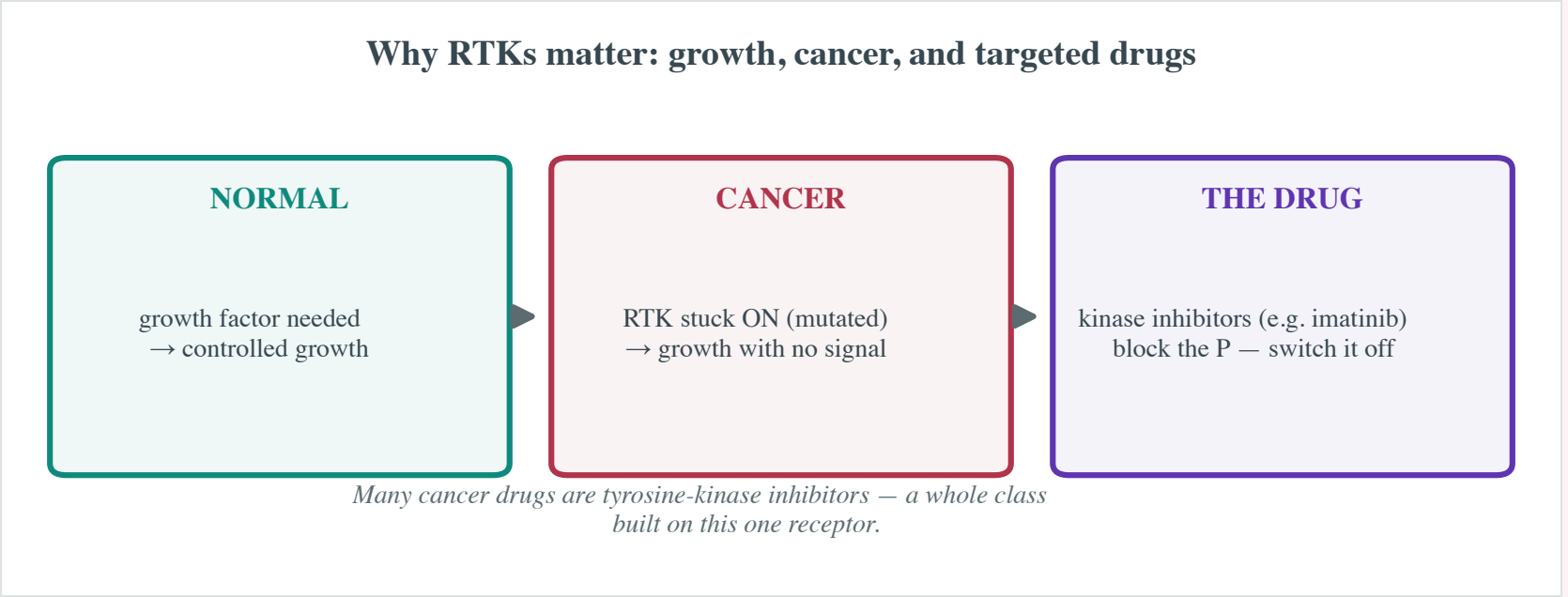
Step back and the two great receptor families make an instructive contrast. A **GPCR** threads the membrane **seven times** and works through a **G-protein** and **second messengers** — a **fast, metabolic** response measured in **seconds** (think **epinephrine**). An **RTK** crosses **once**, **dimerizes**, and signals by **tyrosine phosphorylation** through a **kinase cascade** — a **slower** response that usually reaches the **nucleus** to change **gene expression** (think **insulin** and growth factors). Quick tweak vs. deep rewiring.

Two receptor strategies — GPCR vs. RTK

	GPCR	RTK
membrane	7 passes (7-TM)	1 pass · pairs up
triggered by	shape change → G-protein	ligand → DIMERIZATION
the switch	Gα: GDP ↔ GTP	tyrosine phosphorylation
relay	2nd messengers (cAMP, Ca^{2+})	adapters + kinase cascade
response	fast · metabolic (seconds)	slower · growth, gene expression
example	epinephrine	insulin, growth factors

Why RTKs matter: growth and cancer

Because RTKs command **growth and division**, they're exactly the wires that go wrong in **cancer**. Normally an RTK only fires when its **growth factor** is present — but a **mutation** can lock one **permanently ON**, so the cell keeps dividing **with no signal at all**. That makes RTKs one of the biggest families of **oncogenes** — and also one of the best **drug targets**: a whole class of cancer therapies, the **tyrosine-kinase inhibitors** (like **imatinib/Gleevec**), work by **blocking that phosphorylation** and switching the runaway receptor back off.

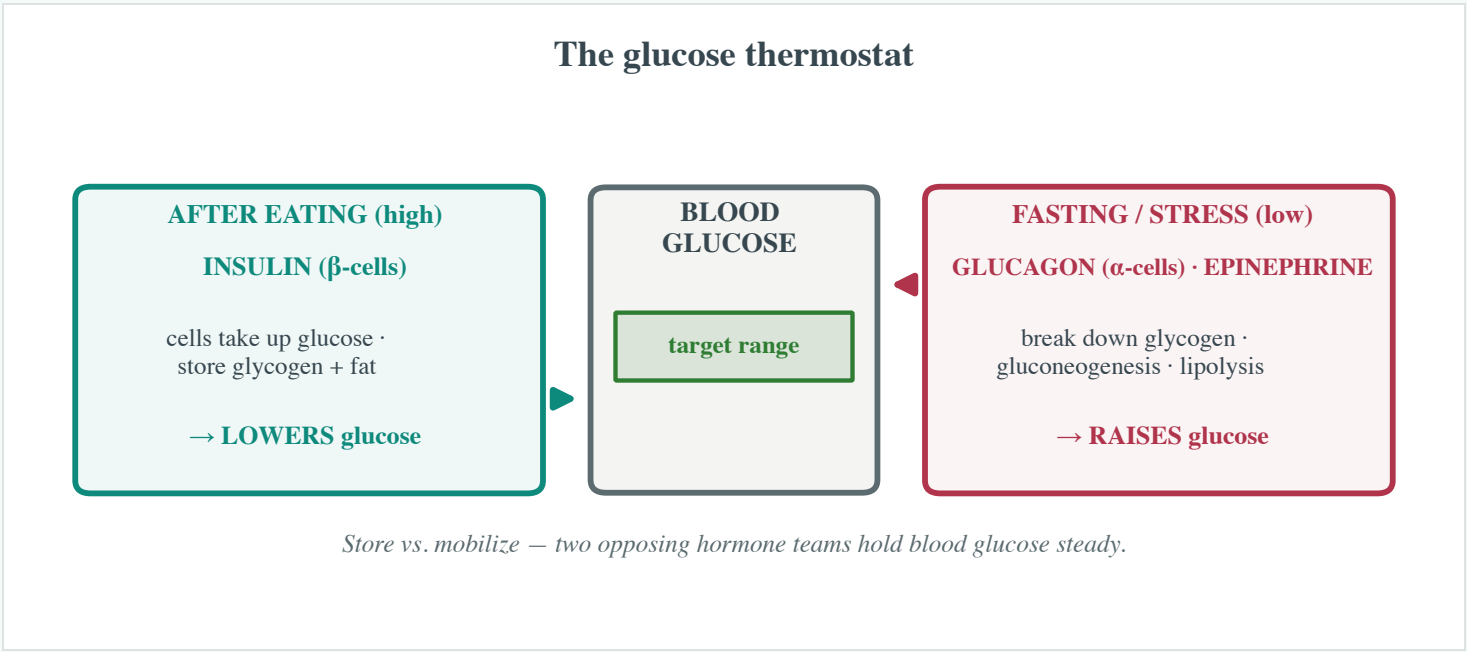


5 · Metabolic Hormones & Diabetes

"Everything in this unit comes together here: the hormones that hold your blood sugar steady are the GPCR and RTK systems you just learned — and diabetes is what happens when the signal breaks."

The glucose thermostat

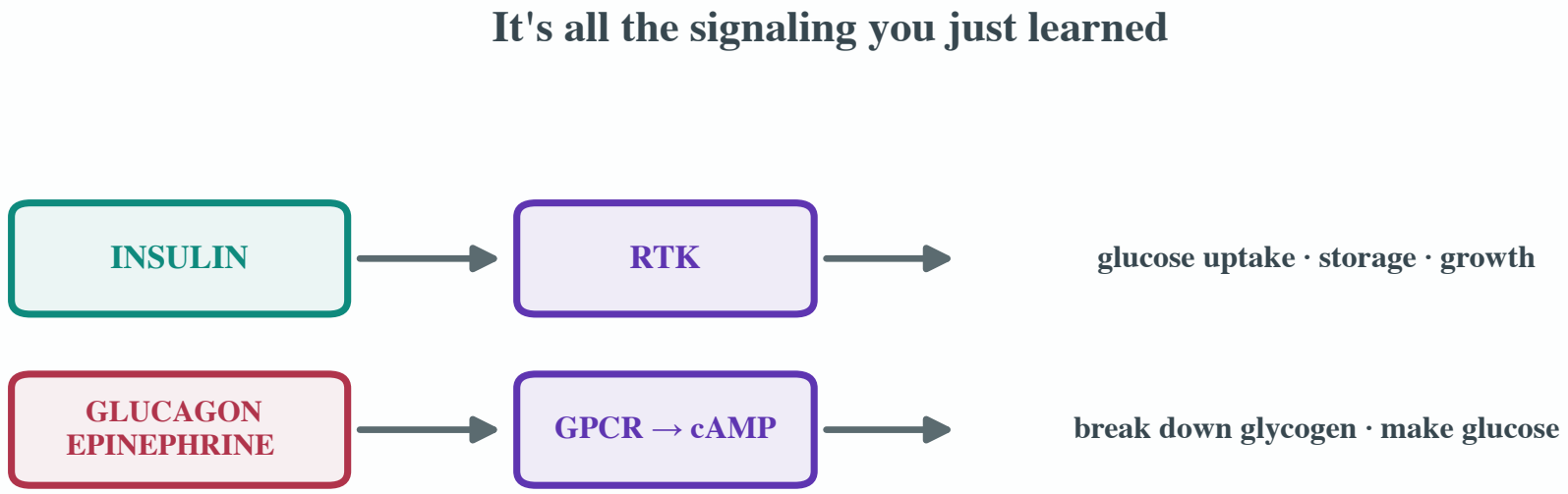
Your blood glucose has to stay in a narrow band, and **three hormones** keep it there — two teams pulling opposite ways. **After a meal**, when glucose is **high**, the pancreas releases **insulin**, which tells cells to **take glucose up** and stash it as **glycogen and fat** — insulin **lowers** blood glucose. **Between meals or under stress**, when glucose is **low**, **glucagon** and **epinephrine** do the reverse: **break down glycogen**, run **gluconeogenesis**, and **release fat** — they **raise** blood glucose. Store vs. mobilize, holding the line.



Store vs. mobilize — two opposing hormone teams hold blood glucose steady.

It's all the signaling you just learned

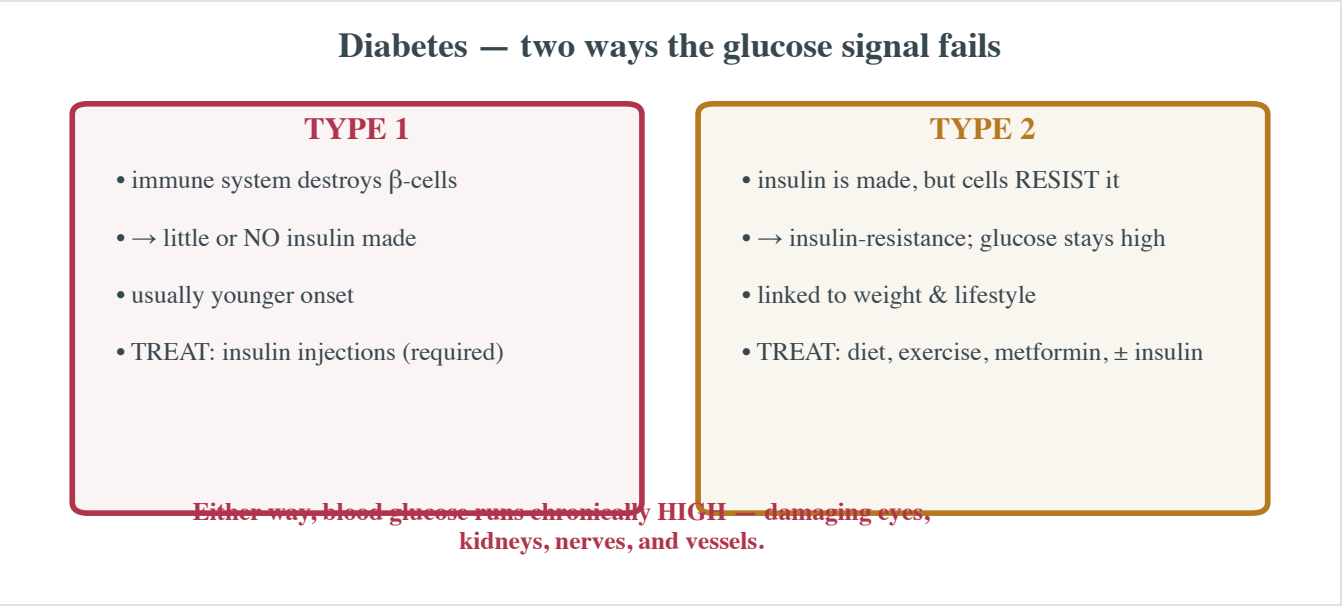
Here's the satisfying part: these metabolic hormones aren't new machinery — they're the **exact receptor systems** from this unit. **Insulin** works through a **receptor tyrosine kinase (RTK)** — which is why its effects include **growth** as well as glucose uptake. **Glucagon** and **epinephrine** work through **GPCRs**, raising **cAMP** to switch on the enzymes that **break down glycogen** and make glucose. Same two signaling strategies you met on the last two slides — now doing the most important homeostatic job in your body.



Insulin signals through an RTK; glucagon and epinephrine through GPCRs — same machinery, opposite jobs.

Diabetes: when the signal fails

Diabetes is what happens when this glucose signal breaks — and it breaks in **two ways**. In **Type 1**, the immune system **destroys the insulin-making β-cells**, so there's **little or no insulin** at all — these patients **must inject insulin**. In **Type 2** (far more common), the β-cells still make insulin, but the **cells stop responding** to it — **insulin resistance** — so glucose piles up despite plenty of hormone. Either way, blood glucose runs **chronically high**, slowly damaging **eyes, kidneys, nerves, and blood vessels**.



Living with a broken thermostat

Because the body's automatic glucose control is gone, people with diabetes have to **run the thermostat by hand** — checking blood glucose (a drop of blood on a **meter**, or a continuous sensor) and dosing accordingly. **Type 1** needs **insulin**, always. **Type 2** is often managed first with **diet and exercise** and drugs like **metformin** (which curbs the liver's glucose output), adding insulin later if needed. It's biochemistry you can hold in your hand — a whole disease, and its treatment, written in one hormone's signal.

Blood-glucose testing: Tomwsulcer, CC0 (Wikimedia Commons)

Can you…?

- □ classify hormones and the types of cell signaling (endocrine, paracrine, autocrine) and the water- vs lipid-soluble receptor logic?
- □ explain second messengers (cAMP, Ca^{2+}, IP_3/DAG) and how signal cascades amplify?
- □ walk GPCR signaling through G proteins and adenylyl cyclase, and receptor tyrosine kinase (RTK) signaling?
- □ connect hormonal control of metabolism — insulin, glucagon, epinephrine — and the biochemistry of diabetes?

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