Eicosanoids

BCH 120 — Metabolic & Endocrine Biochemistry · Dr. Radi

By the end of this unit, you can…

- Define eicosanoids as local (autocrine/paracrine) 20-carbon lipid signals, distinguish the families (prostaglandins, prostacyclin vs thromboxane, leukotrienes, lipoxins), and read prostaglandin nomenclature
- Trace eicosanoid synthesis from arachidonate (PLA_2 release; the COX vs LOX branches) and contrast constitutive COX-1 with inducible COX-2
- Explain COX inhibitors — NSAIDs/aspirin (irreversible, anti-platelet), selective COX-2 inhibitors and their cardiovascular risk, prostaglandin catabolism, and eicosanoid GPCR signaling

Today's route

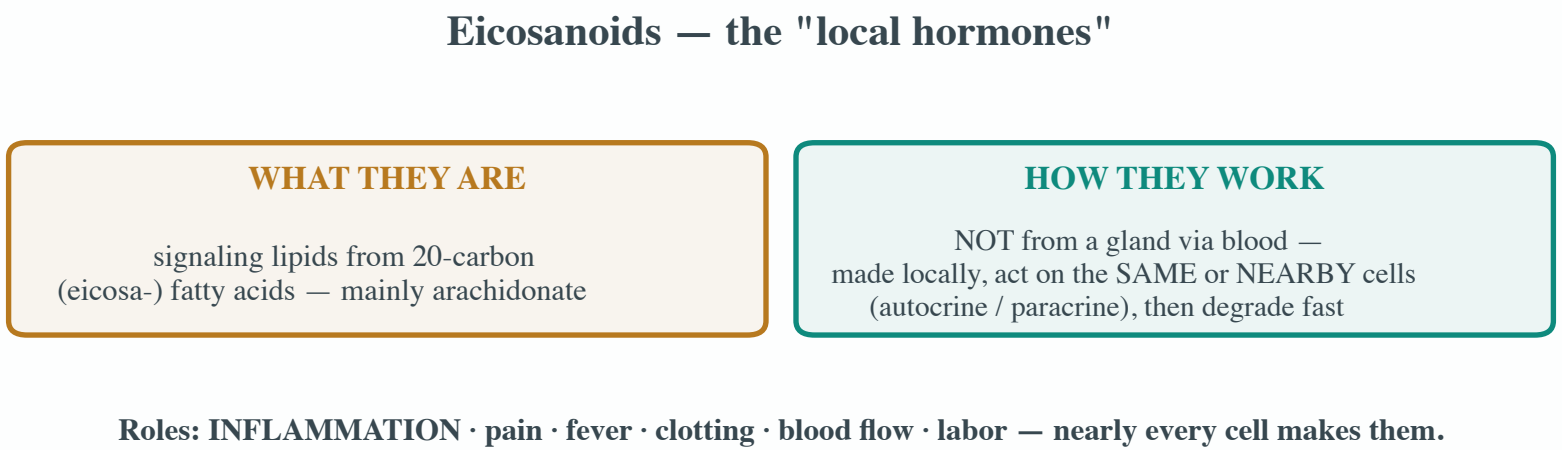
1. **Eicosanoids — Families & Structure**
2. **Eicosanoid Synthesis & the COX Enzymes**
3. **NSAIDs, Aspirin & the COX-2 Story**

1 · Eicosanoids — Families & Structure

"Eicosanoids are the body's 'local hormones' — short-lived lipid signals made from a 20-carbon fatty acid that act right where they're born. Learn the family tree, especially the one opposing pair that runs your blood clotting."

The "local hormones"

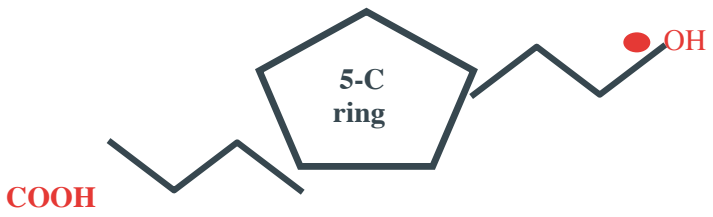
Eicosanoids break the usual hormone rules. They're signaling lipids built from **20-carbon (eicosa-) fatty acids** — mainly **arachidonic acid** — and unlike endocrine hormones, they're **not made in a gland and shipped through blood**. Instead, **nearly every cell makes them on the spot**, and they act on the **same cell (autocrine)** or its **neighbors (paracrine)**, then are **degraded within seconds**. That local, fast-fading design is perfect for their jobs: **inflammation, pain, fever, blood clotting, blood flow, and labor**.



The precursor and the blueprint

It all starts with **arachidonic acid**, a 20-carbon fatty acid with **four double bonds (20:4)**, released from membrane lipids. The **prostaglandins** made from it share a common blueprint: **20 carbons folded around a five-carbon (cyclopentane) ring**, with two tails. Two features name each one: the **letter** (PGA, PGE, PGF…) tells you **what's on the ring**, and the **subscript** (**PGE_1, PGE_2**) tells you the **number of double bonds in the side chains** – which traces back to the essential fatty acid it came from. Small structural tweaks → big changes in biology.

The prostaglandin blueprint — one ring, two chains



FAMILY (A, E, F…) = what's on the RING

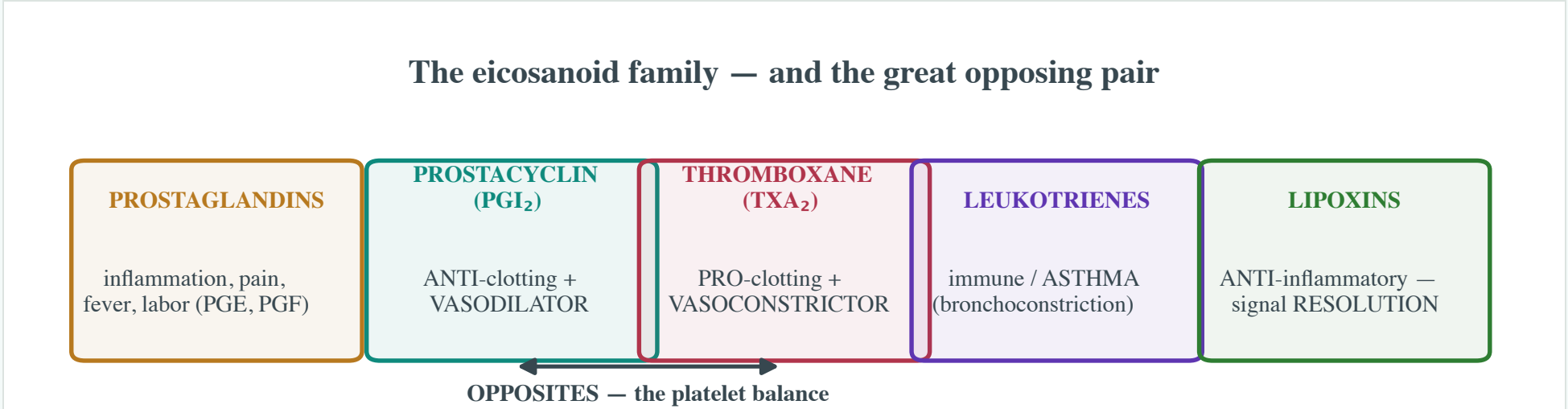
E: keto + OH on ring F: two OH on ring

SUBSCRIPT (PGE_1, PGE_2) = # double bonds in the side chains

20 carbons, a cyclopentane ring, two tails. Small ring/chain changes → very different biology.

The family — and the great opposing pair

Arachidonate branches into a whole **family**. The **prostaglandins** (PGE, PGF) drive **inflammation, pain, fever, labor**; the **leukotrienes** run **immune responses** (LTD_4 constricts bronchioles — key in **asthma**); and the **lipoxins** do the opposite, **signaling the resolution of inflammation**. But the pair to burn in: **prostacyclin (PGI_2)**, from vessel walls, is **anti-clotting and a vasodilator**, while **thromboxane (TXA_2)**, from platelets, is **pro-clotting and a vasoconstrictor**. These **opposites balance your clotting** — and that's exactly what a famous drug class would tip the wrong way.

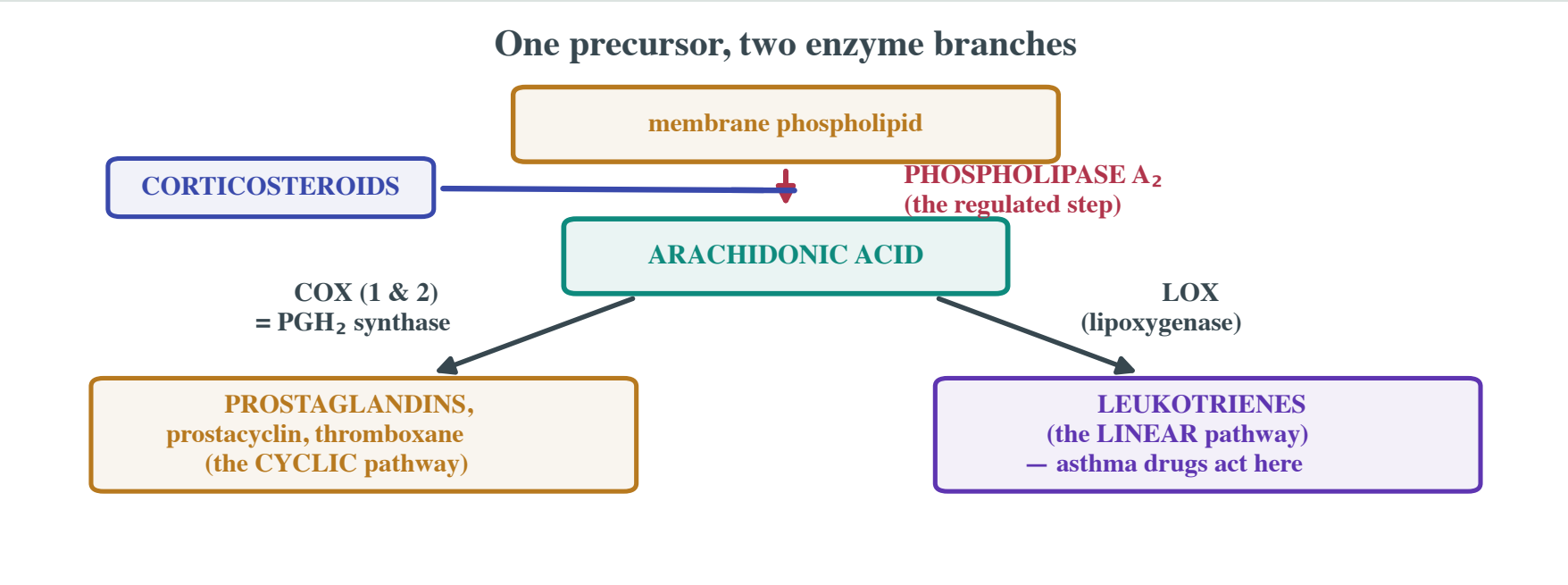


2 · Eicosanoid Synthesis & the COX Enzymes

"Every eicosanoid starts the same way — an enzyme frees arachidonate, then the path forks. The COX fork makes prostaglandins, and COX-1 vs COX-2 is the whole story of the anti-inflammatory drugs."

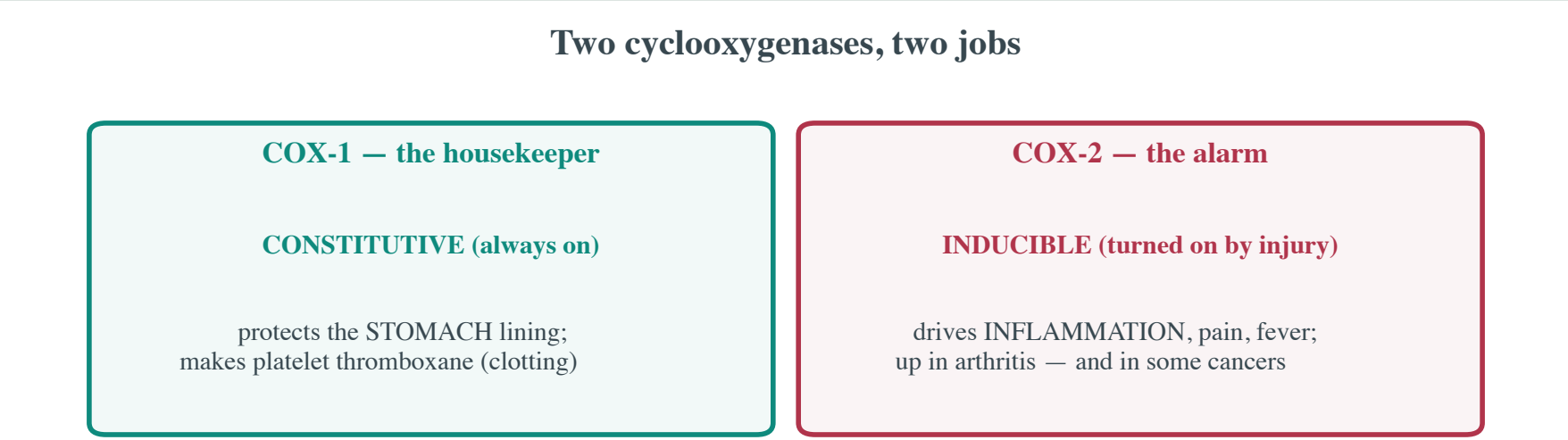
One precursor, two branches

Eicosanoid synthesis is a **fork with a gate**. First the regulated step: **phospholipase A_2 (PLA_2)** clips **arachidonic acid** from a membrane lipid. Then it forks. The **COX** road (**cyclic pathway**) makes **prostaglandins, prostacyclin, and thromboxane**; the **LOX** road (**linear pathway**) makes **leukotrienes** (where some asthma drugs act); and a third, **minor cytochrome-P450** branch makes a few more. Beautiful tie-back: **corticosteroids block PLA_2**, cutting off arachidonate — killing inflammation at its **source**.



COX-1 vs COX-2

The COX enzyme comes in two flavors, and telling them apart is the key to the drugs. **COX-1** is the **housekeeper** — **always on (constitutive)**, quietly protecting the **stomach lining** and making the **thromboxane** platelets need to clot. **COX-2** is the **alarm** — normally low, but **induced by injury** to pump out the prostaglandins of **inflammation, pain, and fever** (it's up in arthritis, and even in some cancers). That split sets up an obvious drug idea: **block COX-2 to kill inflammation while sparing COX-1 to protect the stomach**. It seemed perfect — until it wasn't.



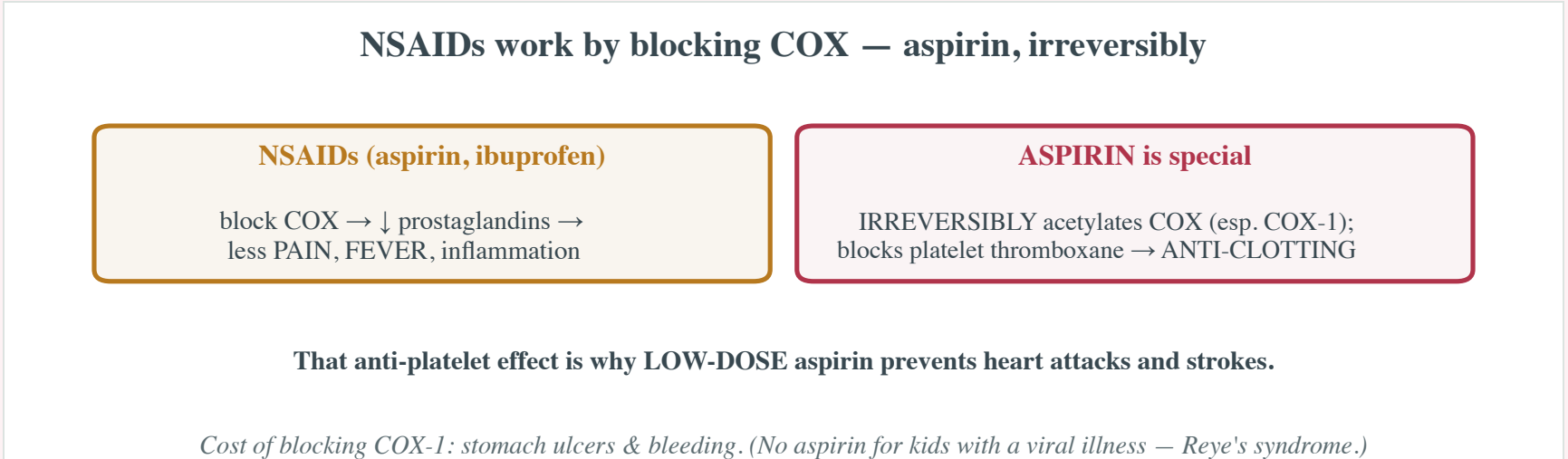
The dream drug: block COX-2 (kill inflammation) while sparing COX-1 (protect the stomach). It didn't go as planned…

3 · NSAIDs, Aspirin & the COX-2 Story

"Now the payoff — the drugs. NSAIDs and aspirin block COX; aspirin does it irreversibly and doubles as a blood thinner. And the cautionary tale of the selective COX-2 inhibitors is a perfect lesson in why you can't safely tip a balanced system."

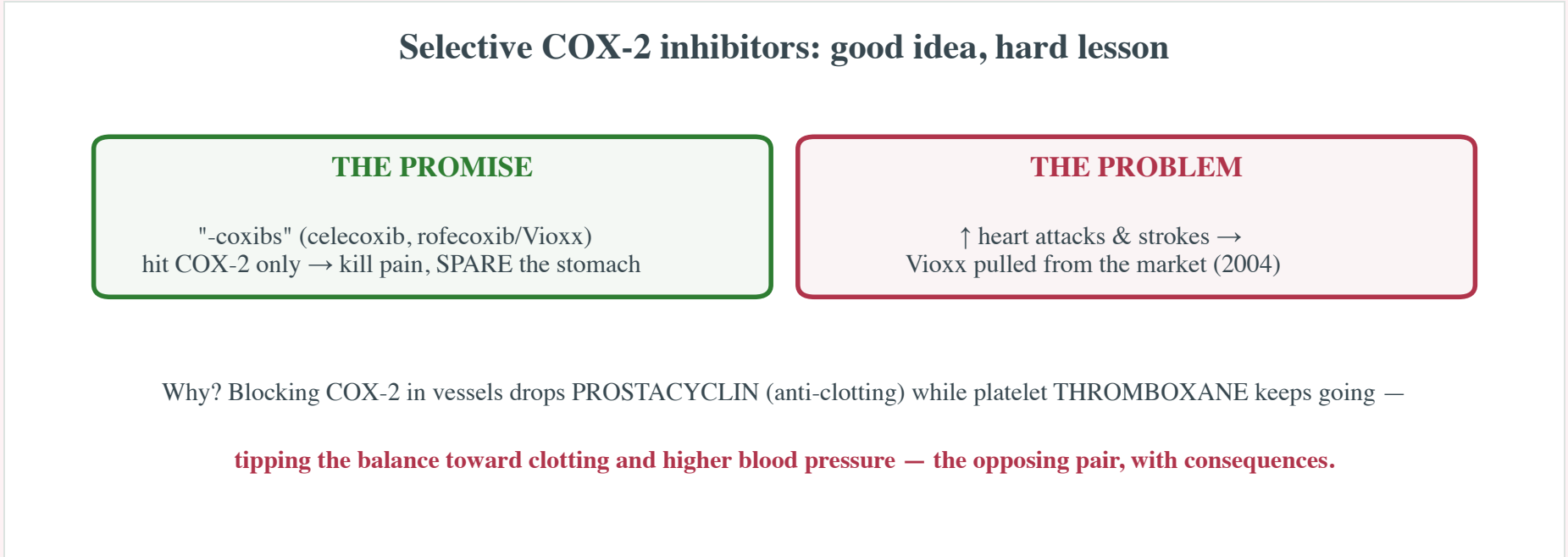
NSAIDs and aspirin

The **NSAIDs** — non-steroidal anti-inflammatory drugs like **ibuprofen** and **aspirin** — all work by **blocking COX**, cutting prostaglandin production to relieve **pain, fever, and inflammation**. **Aspirin** is the special one: it **irreversibly acetylates COX** (hitting **COX-1** more), so it also **shuts down platelet thromboxane** — making it an **anti-clotting** drug. That's why **low-dose aspirin prevents heart attacks and strokes**. The catch is the flip side of COX-1: because that enzyme protects the gut, blocking it causes **stomach ulcers and bleeding** — and because prostaglandins also maintain **renal blood flow**, NSAIDs can **impair kidney function**. (And never give aspirin to a child with a viral illness — **Reye's syndrome**.)



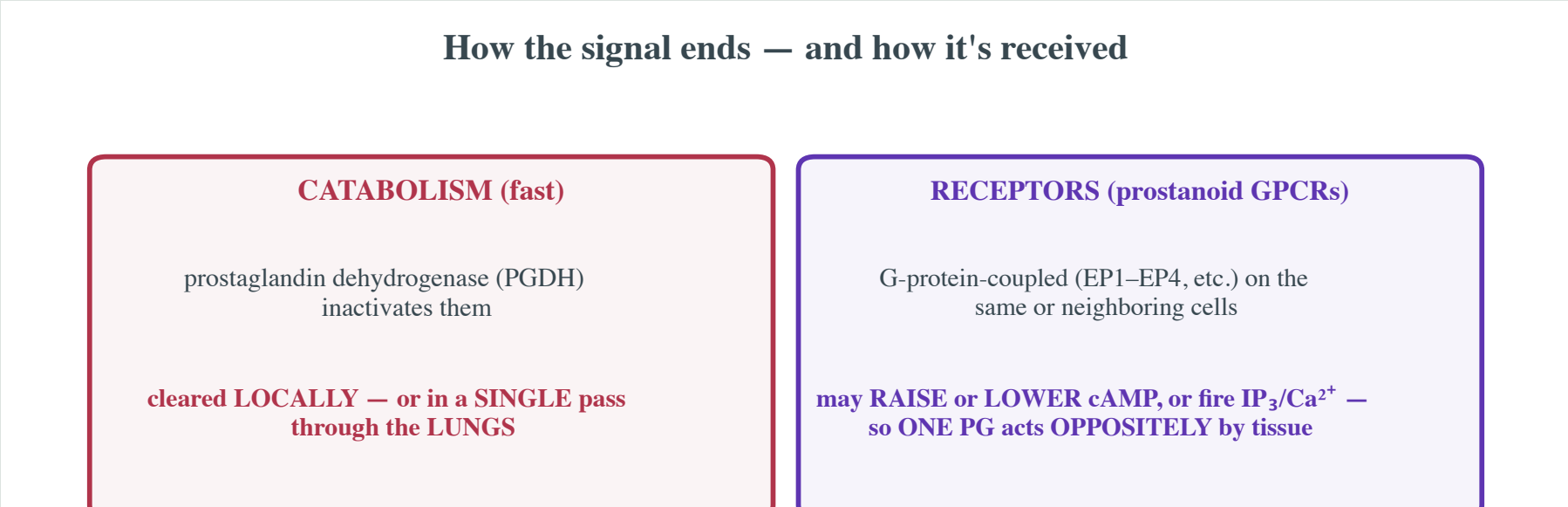
The COX-2 inhibitor lesson

One of pharmacology's great cautionary tales. The idea was elegant: hit **only COX-2** — killing inflammation while **sparing COX-1 and the stomach**. The **"-coxibs"** (**celecoxib, rofecoxib/Vioxx**) did just that. But post-approval data showed a **jump in heart attacks and strokes**, and **Vioxx was pulled in 2004**. Why? Blocking vessel COX-2 **drops prostacyclin** (anti-clotting) while platelet **thromboxane keeps going** — tipping that opposing pair toward **clotting**. You can't safely knock out one side of a balanced system.



Ending the signal, and reading it

Two last pieces close the loop. **Catabolism**: eicosanoids are meant to be **short-lived**, so **prostaglandin dehydrogenase (PGDH)** inactivates them fast — locally, or in a **single pass through the lungs** — which is what keeps their action **local**. **Reception**: they act through **prostanoid GPCRs** (the **EP1–EP4** family and others) on the same or neighboring cells. And here's the elegant part — depending on which receptor a tissue expresses, the **same** prostaglandin can **raise or lower cAMP, or fire IP_3/Ca^{2+}** — so one molecule produces **opposite effects in different tissues**. Fast to clear, flexible to interpret.



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