GI Hormones & Body-Mass Homeostasis

BCH 120 — Metabolic & Endocrine Biochemistry · Dr. Radi

By the end of this unit, you can…

- Describe how the classical GI hormones act both locally in the gut and on the brain, and the roles of gastrin (acid), secretin (bicarbonate), and CCK (bile + pancreatic enzymes) with their source cells, triggers, and regulation
- Explain leptin's control of appetite (adipose → hypothalamus; ob/ob vs db/db mice; NPY vs α-MSH; JAK-STAT) and its sympathetic thermogenesis via UCP1
- Integrate the appetite hormones — insulin, ghrelin, $PYY_{3–36}$ — with leptin, and explain leptin resistance in obesity

Today's route

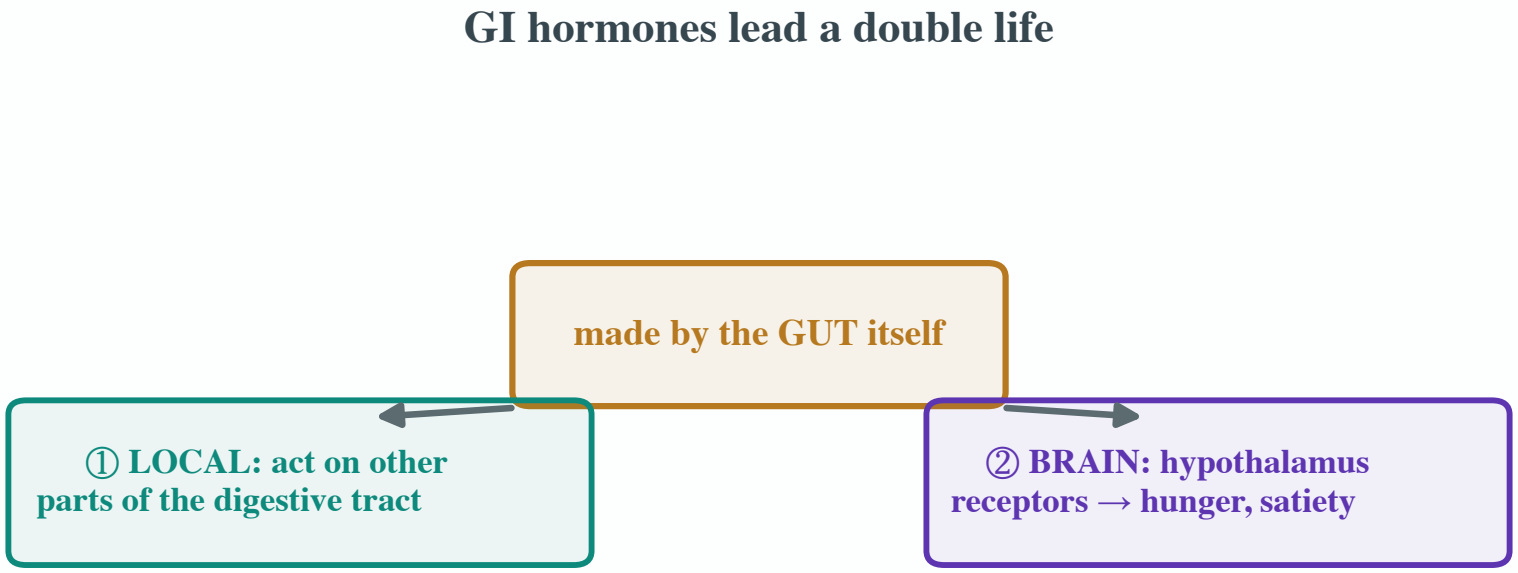
1. GI Hormones – The Classical Three
2. Gastrin, Secretin & CCK in Detail
3. Leptin & the Control of Appetite
4. Burning Fuel, Ghrelin, PYY & Leptin Resistance

1 · GI Hormones — The Classical Three

"Your gut is the body's largest endocrine organ. It runs digestion with its own hormones — and, surprisingly, the same hormones talk to your brain about hunger. Meet the three classics: gastrin, secretin, and CCK."

GI hormones lead a double life

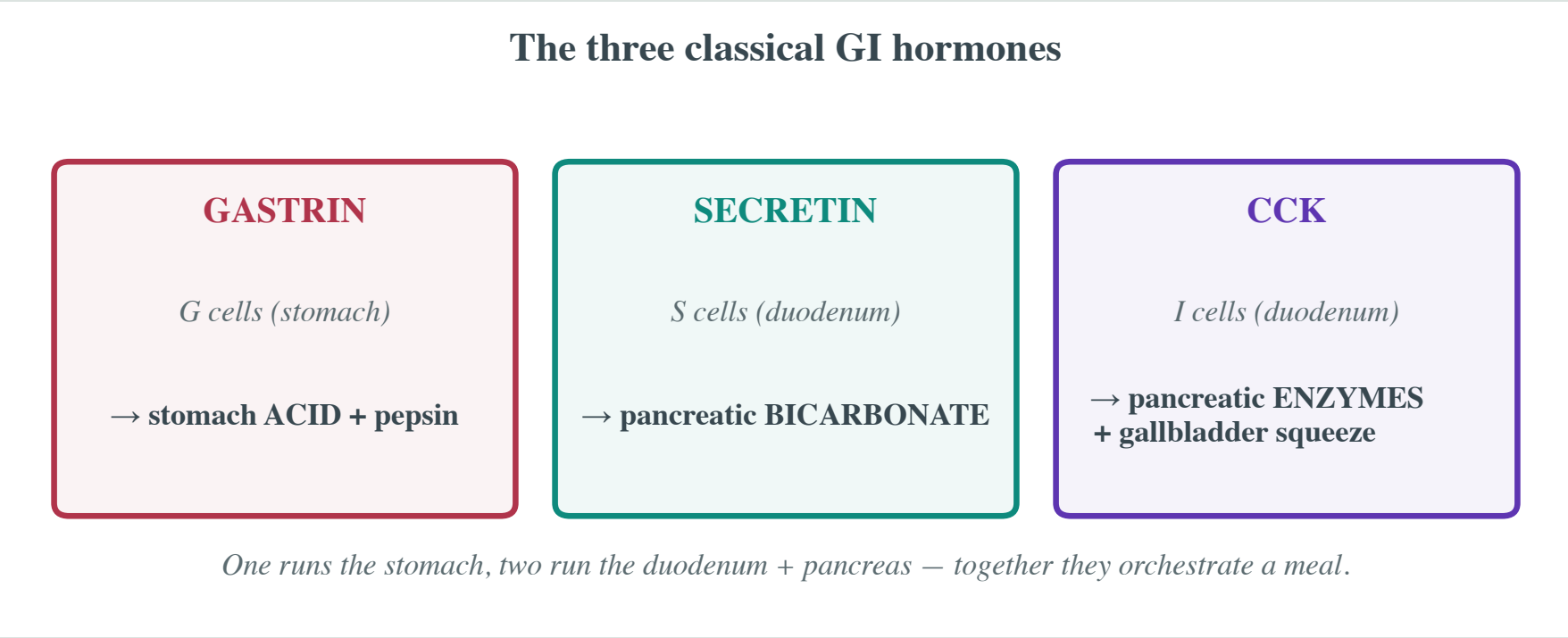
Your GI system has three core jobs — **digest** food, **absorb** nutrients, and **eliminate** waste — and it coordinates them with its own hormones. Here's what makes those hormones unusual: they're **made by the gut itself**, and though they ride the blood, their **main targets are right next door** — other parts of the gut (the **local** job). But they have a **second** audience: most also have **receptors in the hypothalamus**, where they shape **hunger and satiety**. So the gut isn't just digesting — it's **reporting to the brain** about the meal.



Carried by blood — but their targets are next door, and up in the brain shaping appetite.

The three classical hormones

Learn these three and their one-line jobs; the rest of the lecture just adds detail. **Gastrin**, from **G cells** in the stomach, drives **gastric acid** (and pepsin). **Secretin**, from **S cells** in the duodenum, triggers **pancreatic bicarbonate** to neutralize that acid. **CCK**, from **I cells** in the duodenum, releases **pancreatic enzymes** and squeezes the **gallbladder** for bile. One runs the stomach; two run the duodenum and pancreas — together, they **orchestrate a meal**.

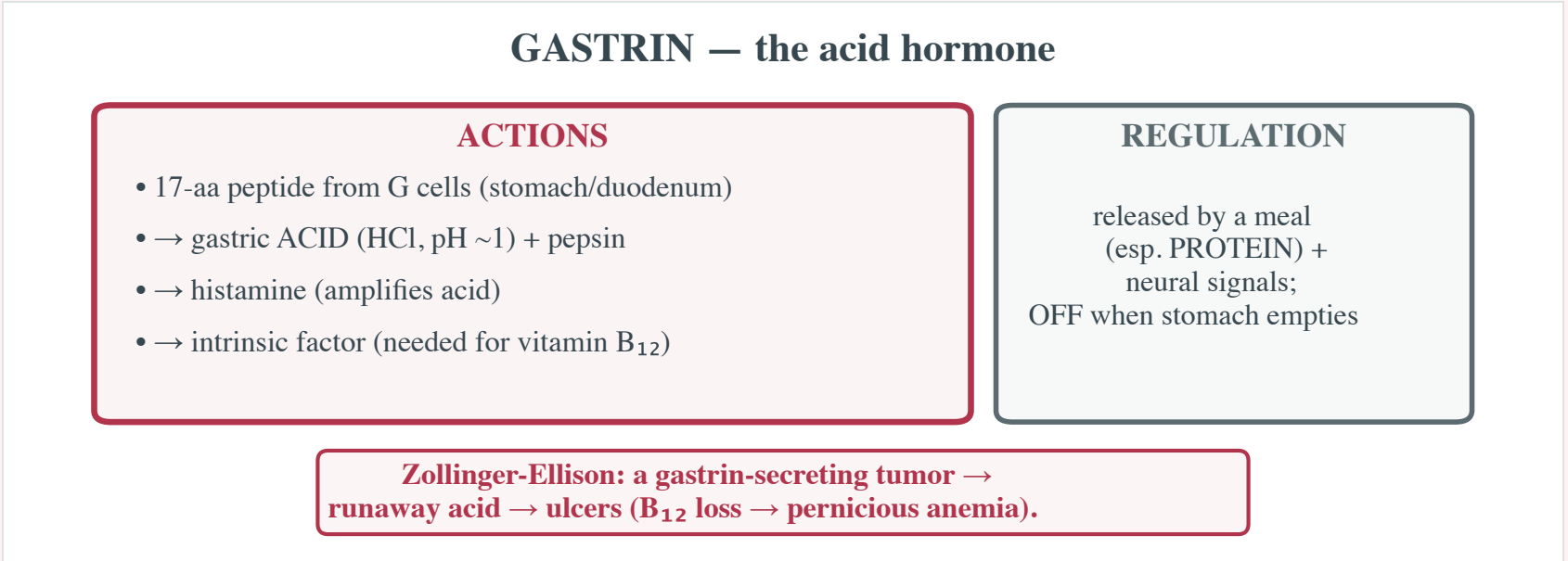


2 · Gastrin, Secretin & CCK in Detail

"Walk a meal through your gut and these three hormones fire in sequence — acid, then neutralize, then digest fat. Each one has a source cell, a trigger, and a clinical story worth knowing."

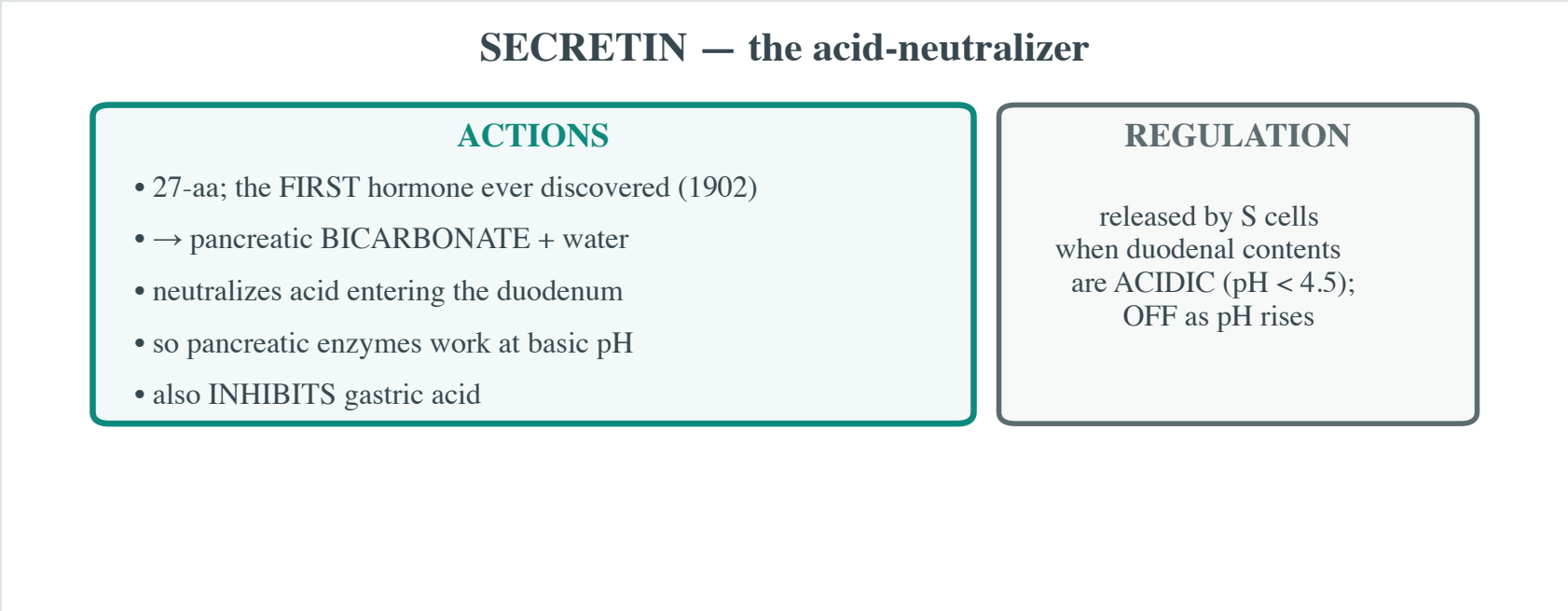
Gastrin — the acid hormone

Food hits the stomach and **gastrin** fires. Made by **G cells** (stomach and duodenum) in response to a **meal — especially protein** — plus neural signals, it drives **gastric acid** so hard the stomach can hit **pH 1**. That acid activates **pepsin**, kills pathogens, and gastrin also triggers **histamine** and **intrinsic factor** (needed to absorb **vitamin B_{12}**). Two clinical hooks: a gastrin-secreting tumor causes **Zollinger-Ellison** (runaway acid, ulcers); losing intrinsic factor causes **pernicious anemia**. Gastrin shuts off when the stomach empties.



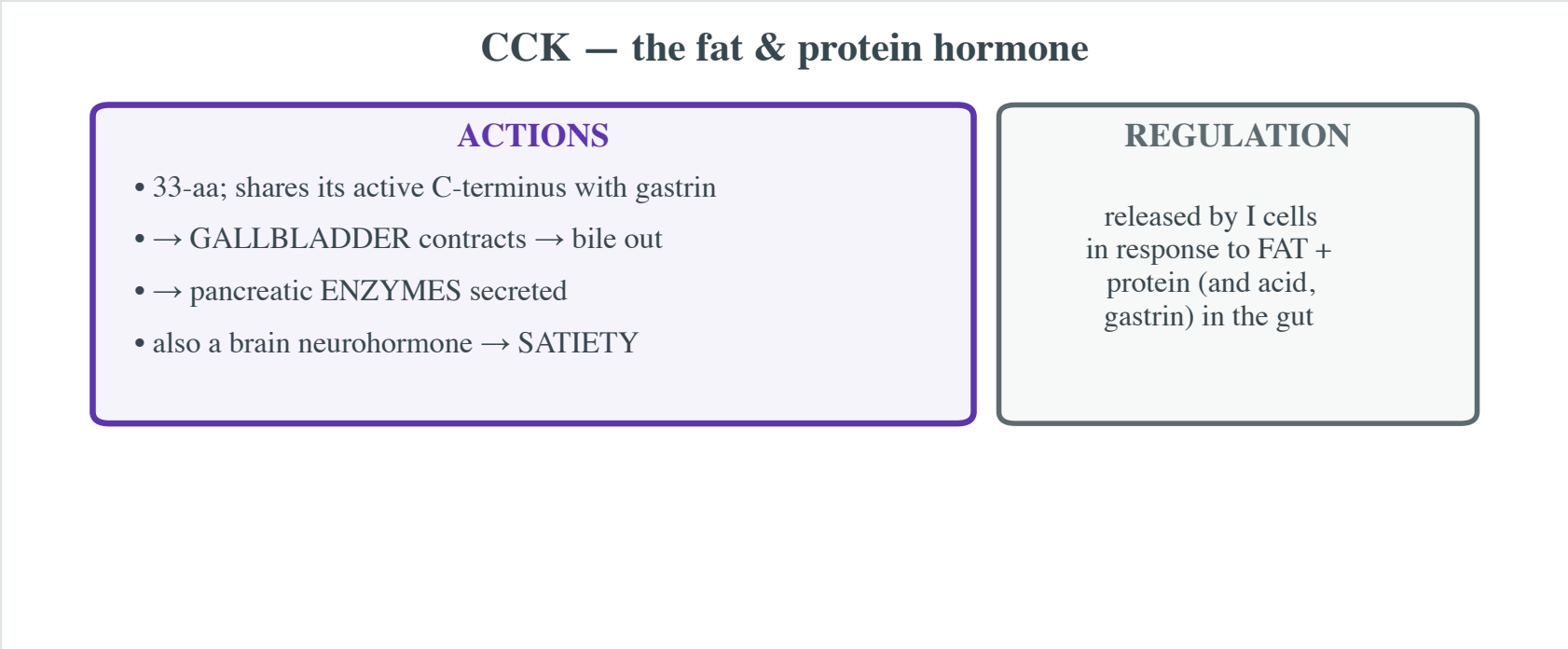
Secretin – the acid-neutralizer

As that acidic stomach content pours into the **duodenum**, the pH drops – and **secretin** answers. Released by **S cells** whenever duodenal contents turn **acidic (pH < 4.5)**, secretin tells the **pancreas to pump out bicarbonate and water**, neutralizing the acid so the **pancreatic enzymes can work at their basic optimum**. It also **inhibits gastric acid**, easing off the stomach. Historical note: secretin was the **very first hormone ever discovered** (Bayliss & Starling, 1902) – the experiment that coined the word "hormone."



CCK – the fat & protein hormone

Now the **fat** arrives, and **cholecystokinin (CCK)** takes over. Released by **I cells** in response to **fat and protein** in the gut, CCK does two things its name and old name spell out: it makes the **gallbladder contract** (**chole-cysto-kinin** → bile out to emulsify fat) and it triggers **pancreatic enzyme** secretion (its "pancreozymin" activity). CCK is also made by **neurons in the brain**, where it's a **satiety** signal – one more gut hormone telling you you're full.

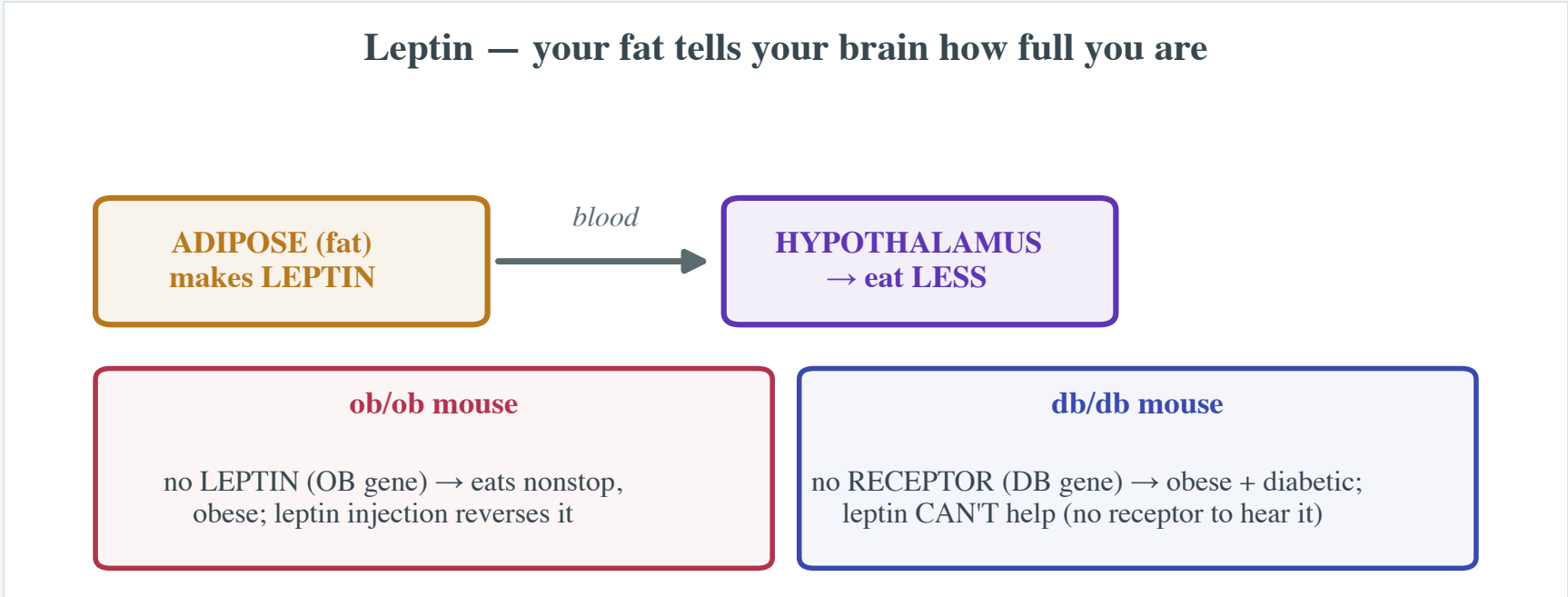


3 · Leptin & the Control of Appetite

"How does your body know how much fat it's carrying? A hormone called leptin, sent from fat to brain. Two famous obese mice — one missing leptin, one missing its receptor — cracked the whole system open."

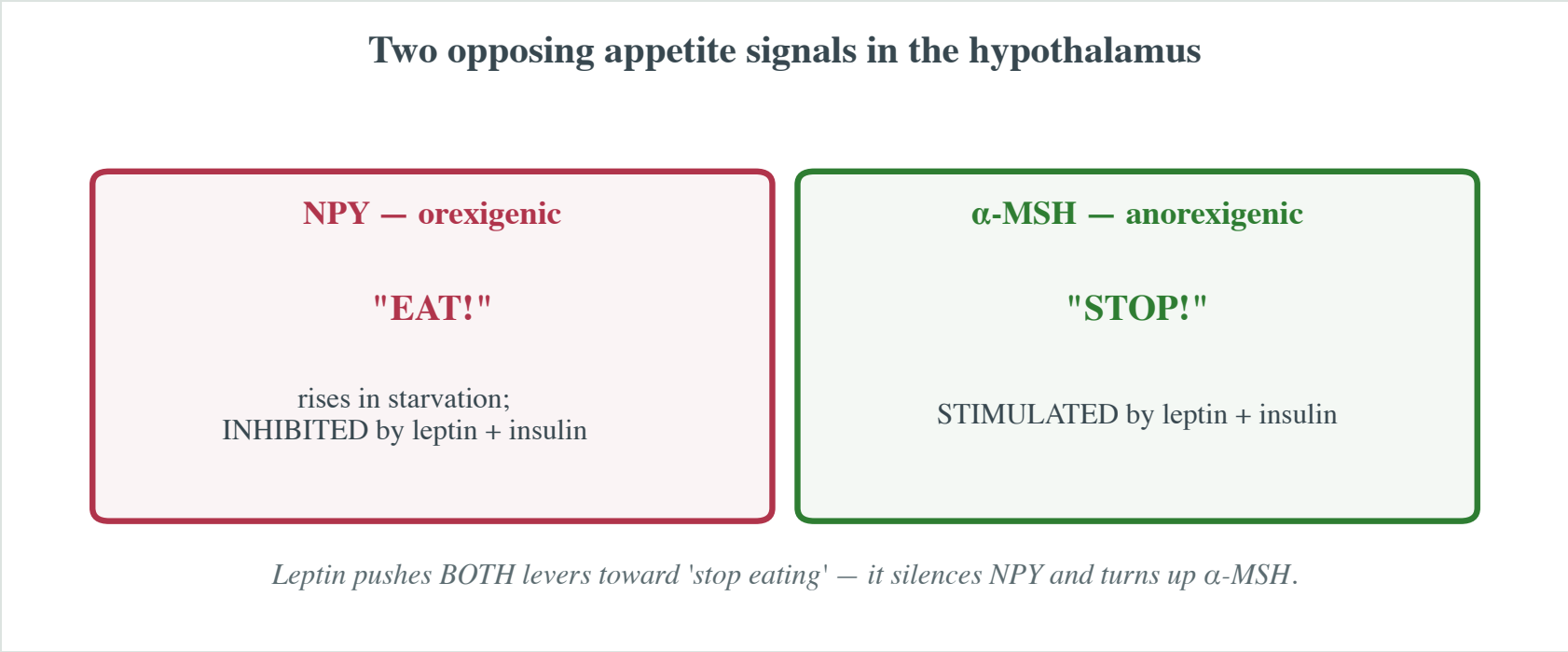
Leptin: fat talks to the brain

Leptin is the body's **fuel gauge**. It's made by **adipose tissue** in proportion to how much fat you carry, travels to the **hypothalamus**, and says: **eat less**. We know this from two obese mice. **ob/ob** mice can't make leptin (**OB gene**) — they eat nonstop and balloon, but **leptin injections reverse it**. **db/db** mice can't **hear** leptin — the **DB gene** encodes its **hypothalamic receptor**, so they're obese and diabetic and leptin **can't help them**. Hormone missing vs receptor missing — same result.



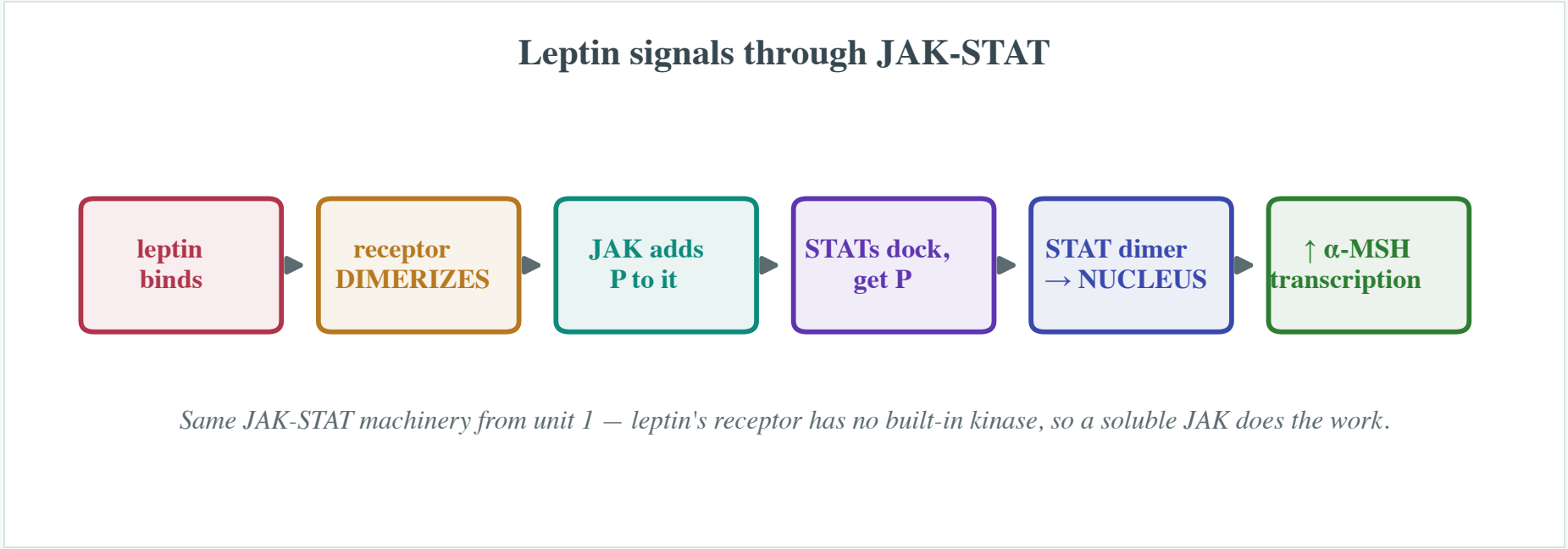
Two opposing appetite signals

In the hypothalamus, appetite is a **tug-of-war** between two neurohormones. **NPY (neuropeptide Y)** is **orexigenic** — it screams **"eat!"**, and it **rises in starvation**. **α-MSH** is **anorexigenic** — it says **"stop!"** Leptin wins the war for **stop**: it **silences NPY** and **turns up α-MSH**, pushing both levers toward eating less. Insulin does the same. So a well-fed body quiets the "eat" neuron and boosts the "stop" neuron.



Leptin signals through JAK-STAT

How does leptin turn up α-MSH? Through a pathway you already know — **JAK-STAT** (from unit 1). Leptin binds and its receptor **dimerizes**; a soluble **JAK** kinase phosphorylates the receptor; **STAT** proteins dock, get phosphorylated, **dimerize, and go to the nucleus** to **raise transcription of the α-MSH precursor**. The leptin receptor has **no built-in kinase**, so it borrows JAK — exactly the erythropoietin trick. Same machinery, new job: telling you you've eaten enough.

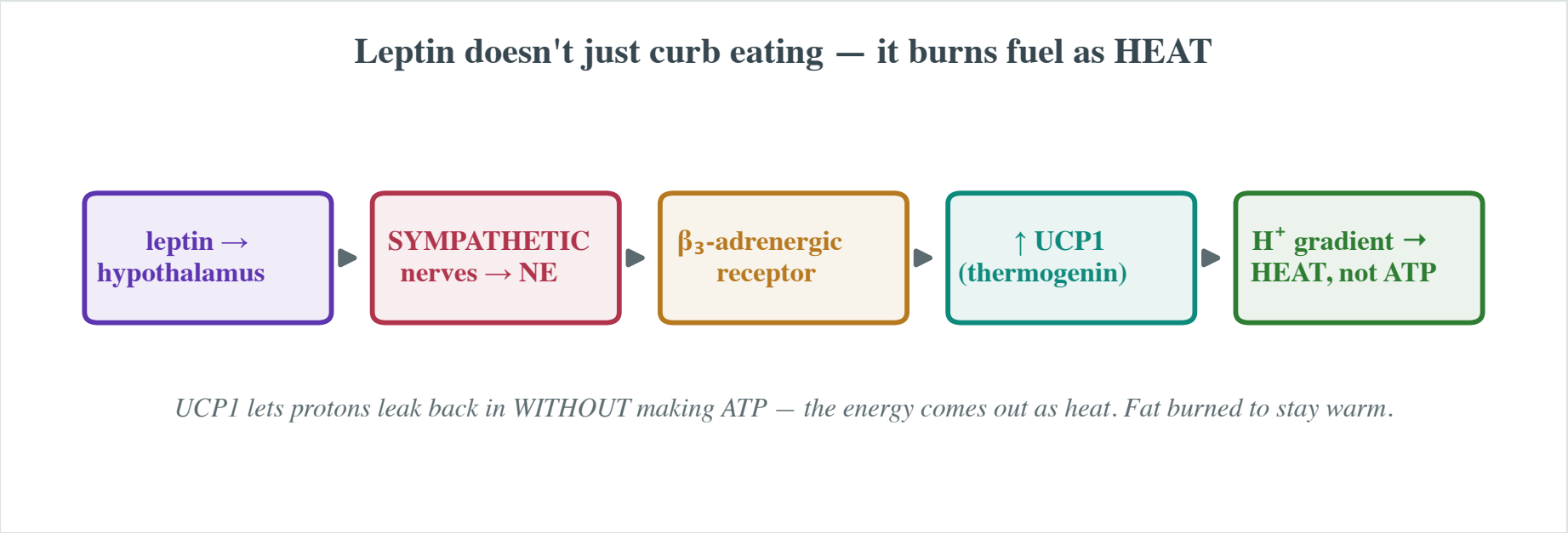


4 · Burning Fuel, Ghrelin, PYY & Leptin Resistance

"Appetite isn't one hormone — it's a whole committee. Leptin also burns fat as heat, insulin and PYY say 'stop,' ghrelin says 'eat now,' and the sad twist: in obesity, the leptin signal stops working."

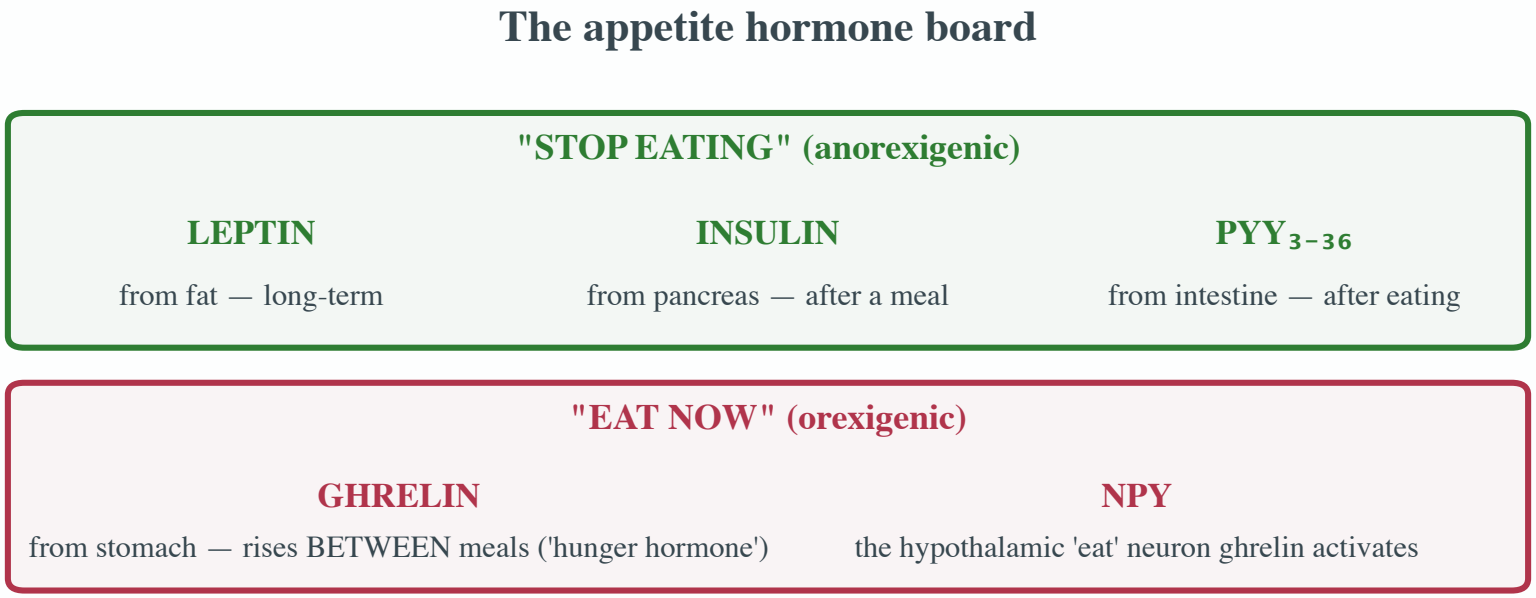
Leptin also burns fuel as heat

Leptin doesn't just curb eating — it **spends** energy too. From the hypothalamus it fires the **sympathetic nervous system**, releasing **norepinephrine** onto fat cells' **β_3-adrenergic receptors**, which crank up transcription of **UCP1 (thermogenin)**. Remember UCP1 from bioenergetics? It lets protons **leak back** into the mitochondrion **without making ATP** — so the energy comes out as **heat**, and fat is burned to stay warm. Leptin thus works both ends: eat less **and** burn more.



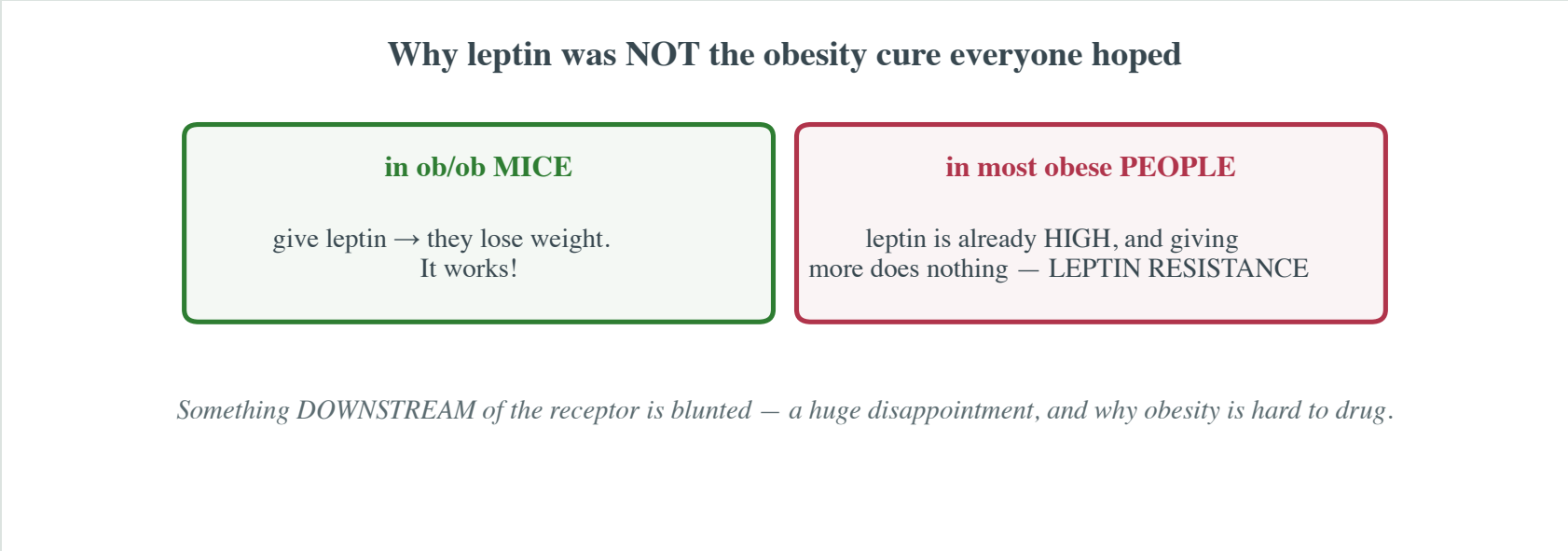
The appetite hormone board

Zoom out and appetite is a **committee vote**. On the **"stop eating"** side: **leptin** (from fat, long-term), **insulin** (from the pancreas after a meal), and **PYY_{3-36}** (from the intestine and colon after you eat). On the **"eat now"** side: **ghrelin** – the **hunger hormone** from the **stomach** that **rises between meals** – which switches on the hypothalamic **NPY** neurons. Your appetite at any moment is the sum of these signals.



Why leptin wasn't the obesity cure

Here's the twist that broke a lot of hearts (and a few stock prices). In **ob/ob mice**, giving leptin **melts the weight off** — it works. So the drug companies raced to give leptin to **obese people** — and it **did almost nothing**. Why? Most obese people already have **high leptin**; the problem is **downstream** — the signal arrives but isn't heard. It's called **leptin resistance**, and it's a big reason obesity is so hard to treat with a single hormone.



Can you…?

- □ describe how the classical GI hormones act both locally in the gut and on the brain, and the roles of gastrin (acid), secretin (bicarbonate), and CCK (bile + pancreatic enzymes) with their source cells, triggers, and regulation?
- □ explain leptin's control of appetite (adipose → hypothalamus; ob/ob vs db/db mice; NPY vs α-MSH; JAK-STAT) and its sympathetic thermogenesis via UCP1?
- □ integrate the appetite hormones — insulin, ghrelin, $PYY_{3–36}$ — with leptin, and explain leptin resistance in obesity?

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