Cortisol & Glucocorticoids

BCH 120 — Metabolic & Endocrine Biochemistry · Dr. Radi

By the end of this unit, you can…

- Explain cortisol's stress response (gluconeogenesis, fuel mobilization, immune suppression), its synthesis in the zona fasciculata, and control by the HPA axis with negative feedback
- Describe cortisol's metabolic effects (catabolic, anti-insulin) and its anti-inflammatory mechanism (NF-κB blockade) with the glucocorticoid drugs
- Analyze the adrenal cortisol disorders — Cushing's syndrome, Addison's disease, and congenital adrenal hyperplasia

Today's route

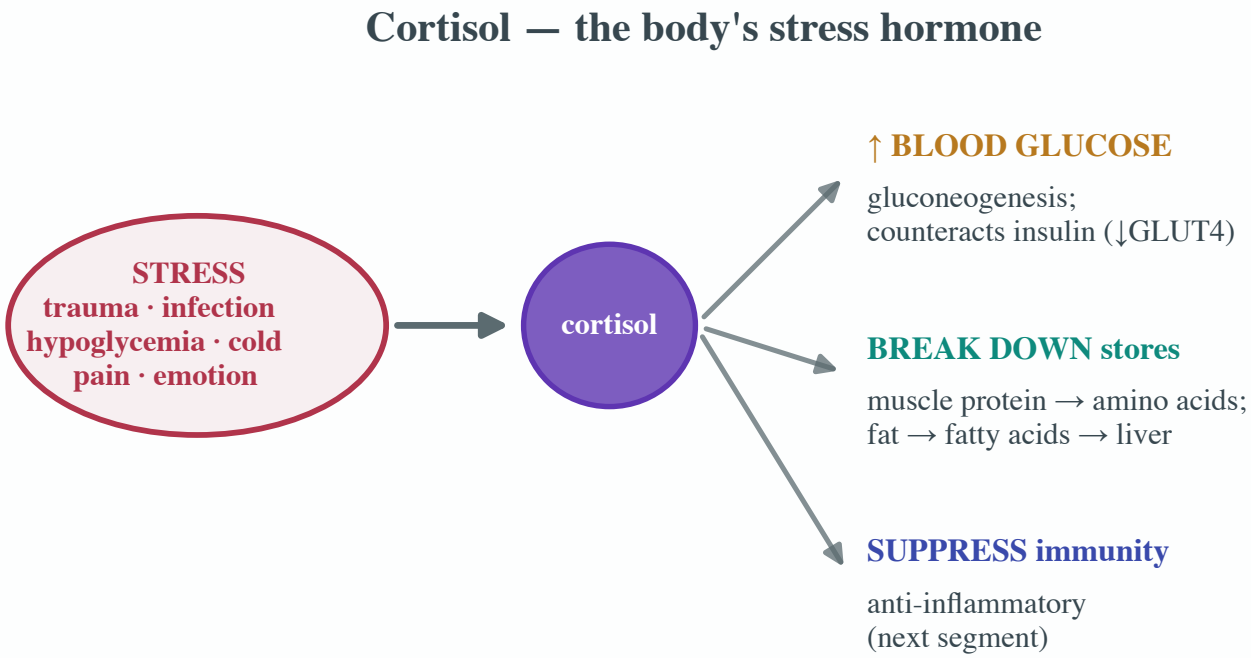
1. **Cortisol, Stress & the HPA Axis**
2. **Cortisol's Effects & Anti-Inflammatory Power**
3. **Cushing's, Addison's & CAH**

1 · Cortisol, Stress & the HPA Axis

"Cortisol is the hormone that gets you through a crisis — it raises blood sugar, mobilizes fuel, and quiets non-urgent systems. It's made in the adrenal fasciculata on command from the brain, through a feedback loop you should know cold."

Cortisol: the stress hormone

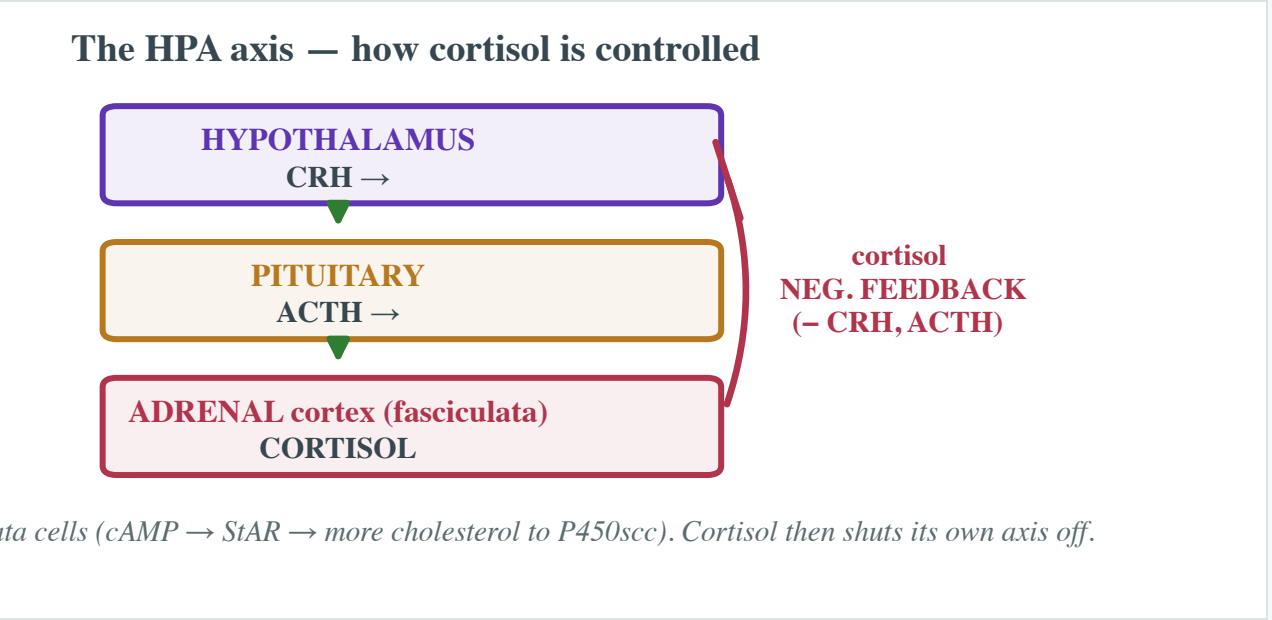
Cortisol is your body's response to **stress** — trauma, infection, cold, pain, low blood sugar, even emotion. Its whole job is to **get you through the crisis**: it **raises blood glucose** (gluconeogenesis, and it **counteracts insulin** by pulling GLUT4 off the membrane), it **breaks down stores** (muscle protein → amino acids, fat → fatty acids, all shipped to the liver), and it **suppresses the immune system**. Brilliant for a short emergency — but **chronically high cortisol** wastes muscle, weakens bone, and impairs memory.



Readies you to survive a crisis — raise fuel, hold pressure, pause non-urgent systems. Great short-term; harmful if chronic.

The HPA axis and its feedback

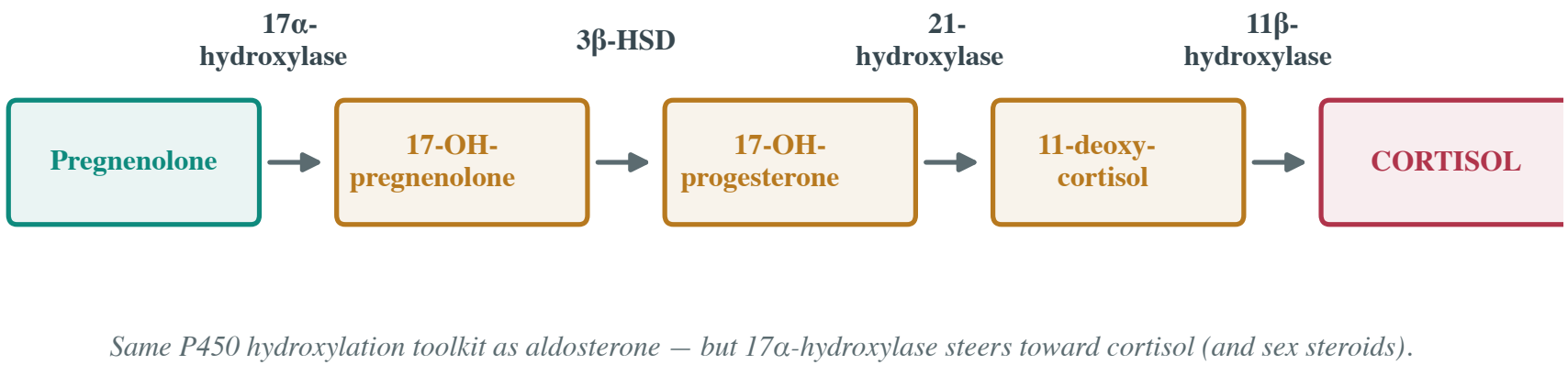
Cortisol is controlled by the **hypothalamic-pituitary-adrenal (HPA) axis** — the same three-tier logic as the thyroid. The **hypothalamus** sends **CRH**, which tells the **pituitary** to release **ACTH**, which drives the **adrenal cortex** (zona fasciculata) to make **cortisol**. Then the control knob: **cortisol feeds back negatively** on both the pituitary and hypothalamus to **shut its own axis off**. ACTH works the fasciculata cell through **cAMP → StAR → more cholesterol to P450scc** — exactly the steroidogenesis you learned last unit.



ACTH drives fasciculata cells (cAMP → StAR → more cholesterol to P450scc). Cortisol then shuts its own axis off.

Making cortisol in the fasciculata

The cortisol pathway uses the **same P450 hydroxylation toolkit** as aldosterone, with one key branch. Starting from **pregnenolone**, the enzyme **17α-hydroxylase** adds a 17-OH (this is the step that steers toward cortisol and the sex steroids, **away** from aldosterone). Then **3β-HSD**, **21-hydroxylase**, and **11β-hydroxylase** finish the job: pregnenolone → 17-OH-pregnenolone → 17-OH-progesterone → 11-deoxycortisol → **cortisol**. Remember those enzyme names — a **block at 21- or 11-hydroxylase** starves cortisol and causes CAH.



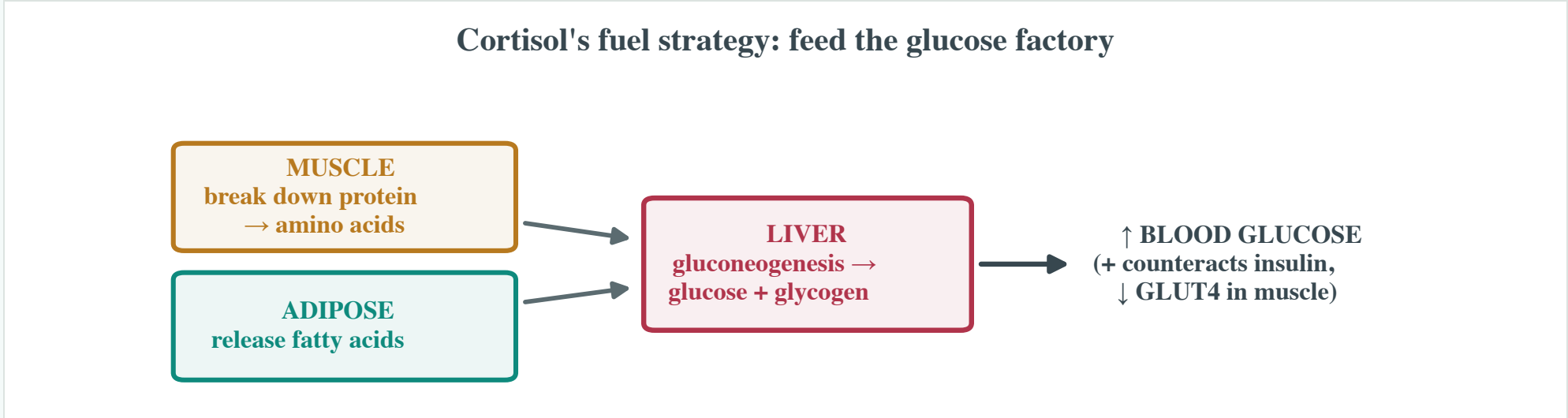
Same P450 hydroxylation toolkit as aldosterone — but 17α-hydroxylase steers toward cortisol (and sex steroids).

2 · Cortisol's Effects & Anti-Inflammatory Power

"Cortisol has two claims to fame: it's a catabolic fuel-mobilizer that raises blood sugar by robbing the periphery, and it's the most powerful anti-inflammatory the body makes — which is why glucocorticoid drugs are everywhere in medicine."

The fuel strategy: rob the body to feed the brain

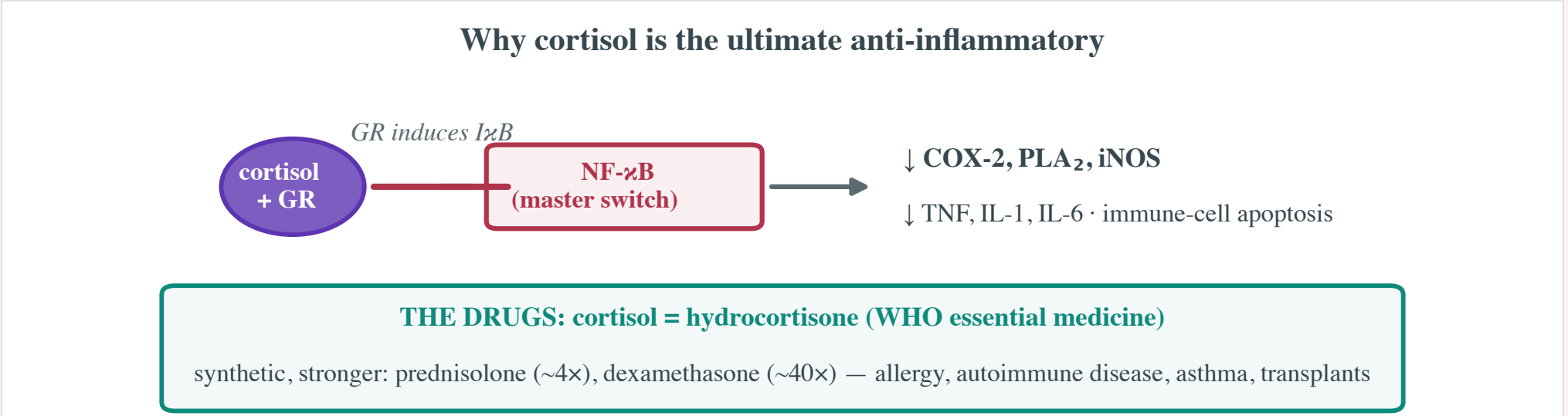
Cortisol is **catabolic and anti-insulin** — it strips the periphery to keep glucose flowing. In **muscle**, it **breaks down protein** to free amino acids; in **adipose**, it **releases fatty acids**; both are shipped to the **liver**, which runs **gluconeogenesis** and packs away **glycogen**, raising **blood glucose**. At the same time it **blocks glucose uptake** in muscle (fewer GLUT4 transporters), so more sugar stays in the blood. Perfect for surviving a fast or a fight — but sustained, it causes the muscle-wasting, thin skin, and **"steroid diabetes"** of cortisol excess. (Spent cortisol is later **inactivated by 11β-HSD to cortisone** and cleared by the liver.)



Cortisol is catabolic and anti-insulin: it robs muscle and fat to keep the brain fueled — chronic excess wastes the body.

The ultimate anti-inflammatory

This is cortisol's blockbuster role. It shuts down inflammation mostly by **blocking NF-κB** – the master switch of the inflammatory response. Cortisol's receptor (**GR**) **induces IκB** (which traps NF-κB outside the nucleus) and **directly interferes** with NF-κB, so the cell stops making **COX-2, PLA_2, iNOS** and the cytokines **TNF, IL-1, IL-6** – and immune cells even undergo **apoptosis**. That's why **glucocorticoid drugs** – **hydrocortisone** (a WHO essential medicine) and the stronger synthetics **prednisolone (~4×)** and **dexamethasone (~40×)** – treat allergy, autoimmune disease, asthma, and transplants.

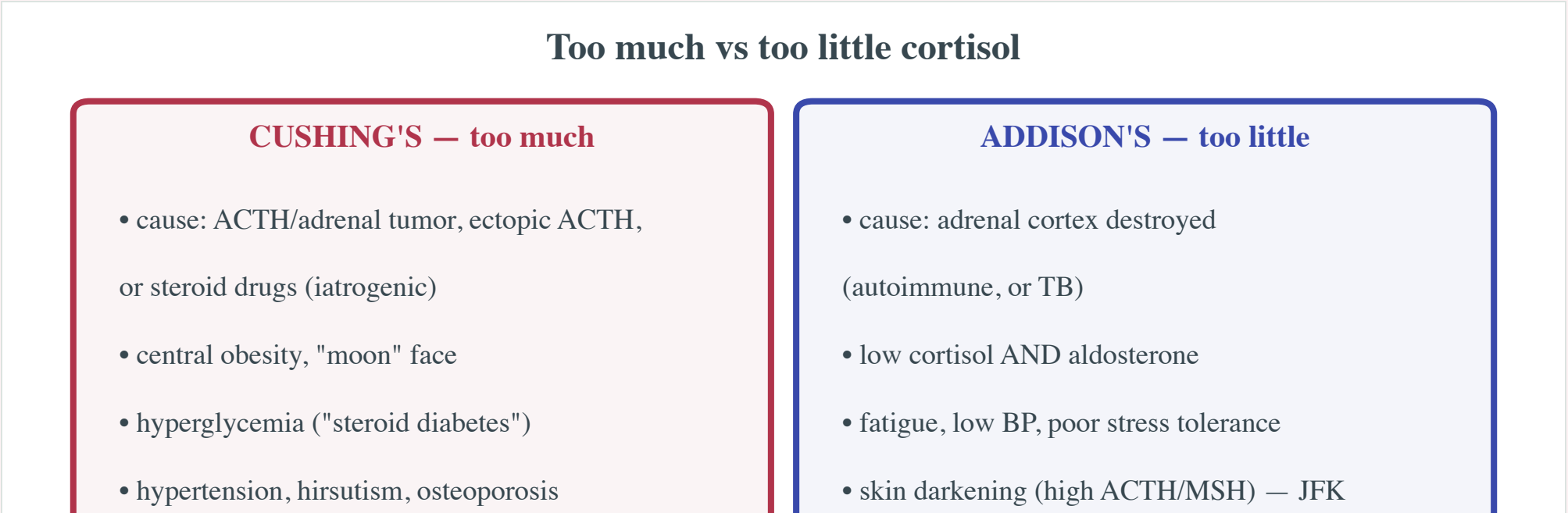


3 · Cushing's, Addison's & CAH

"Cortisol disease comes in two directions and one clever detour. Too much is Cushing's; too little is Addison's; and a synthesis block gives congenital adrenal hyperplasia — where a missing enzyme reroutes the whole gland into making androgens."

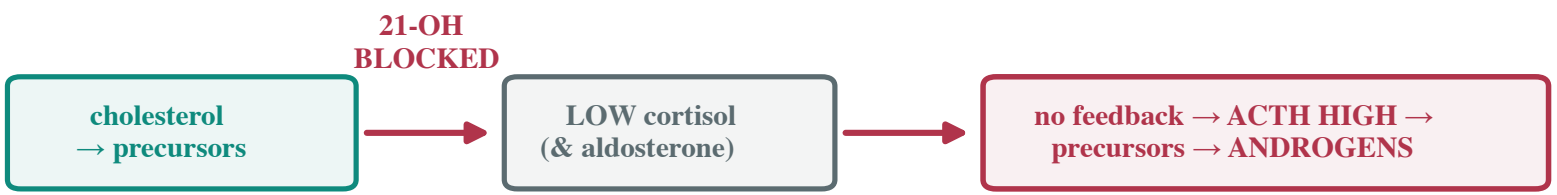
Too much vs too little cortisol

Two mirror-image diseases. **Cushing's** = **too much cortisol** (an ACTH/adrenal tumor, ectopic ACTH, or — most often — **steroid drugs**): **central obesity, moon face, hyperglycemia, hypertension, osteoporosis**. **Addison's** = **too little** (the **adrenal cortex destroyed**, autoimmune or TB), so **both cortisol and aldosterone** fall: fatigue, low BP, **skin darkening** (high ACTH/MSH); JFK had it. Diagnose with the **dexamethasone-suppression** and **ACTH-stimulation** tests; treat by **removing the tumor** or **replacing the hormones**.



CAH: a block that makes androgens

Here's an elegant piece of pathophysiology. In **CAH**, an enzyme in the cortisol pathway is missing — usually **21-hydroxylase** (~90% of cases). Low cortisol means **no feedback**, so **ACTH stays sky-high** — but since it can't finish cortisol, precursors are **shunted into androgens**, causing **virilization of newborn girls** and early puberty in boys. (An **11-hydroxylase** block adds **hypertension**, as deoxycorticosterone builds up.) The fix is logical: **give glucocorticoids** to restore feedback and switch off the androgens.



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