Glucose Metabolism

BCH 100 — Introductory Biochemistry · Dr. Radi

By the end of this unit, you can…

- Walk all ten steps of glycolysis — the enzymes, the reactions, and the running ATP/NADH ledger (net 2 ATP + 2 NADH per glucose)
- Identify the regulated steps (hexokinase, PFK-1, pyruvate kinase) and the hormonal + fructose-2,6-bisphosphate control of glycolysis
- Trace the fates of pyruvate — aerobic oxidation, lactate fermentation, and ethanol fermentation — and the Cori cycle
- Explain how galactose and fructose feed into glycolysis, and the diseases when they can't (galactosemia, fructose→fat)
- Describe gluconeogenesis and its four bypass enzymes, and how glycogen is built and broken down under hormonal control

Today's route

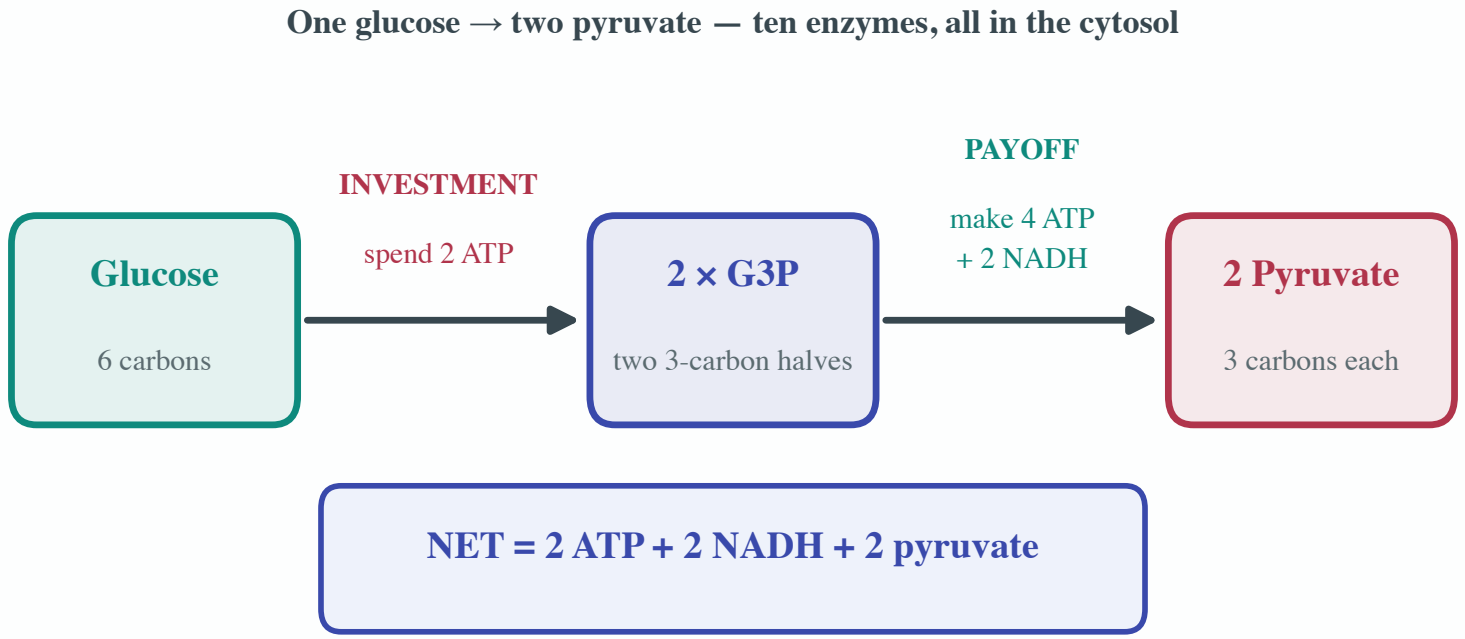
1. **Glycolysis – The Ten Steps**
2. **Glycolysis – Energy Yield & Regulation**
3. **Other Sugars – Galactose & Fructose**
4. **Fermentation & the Cori Cycle**
5. **Gluconeogenesis – Making Glucose**
6. **Glycogen – Storing & Mobilizing Glucose**

1 · Glycolysis — The Ten Steps

"SUGAAAARRRR!!! Walk glucose to pyruvate — all ten enzymes, two ATP invested, four made, two NADH banked."

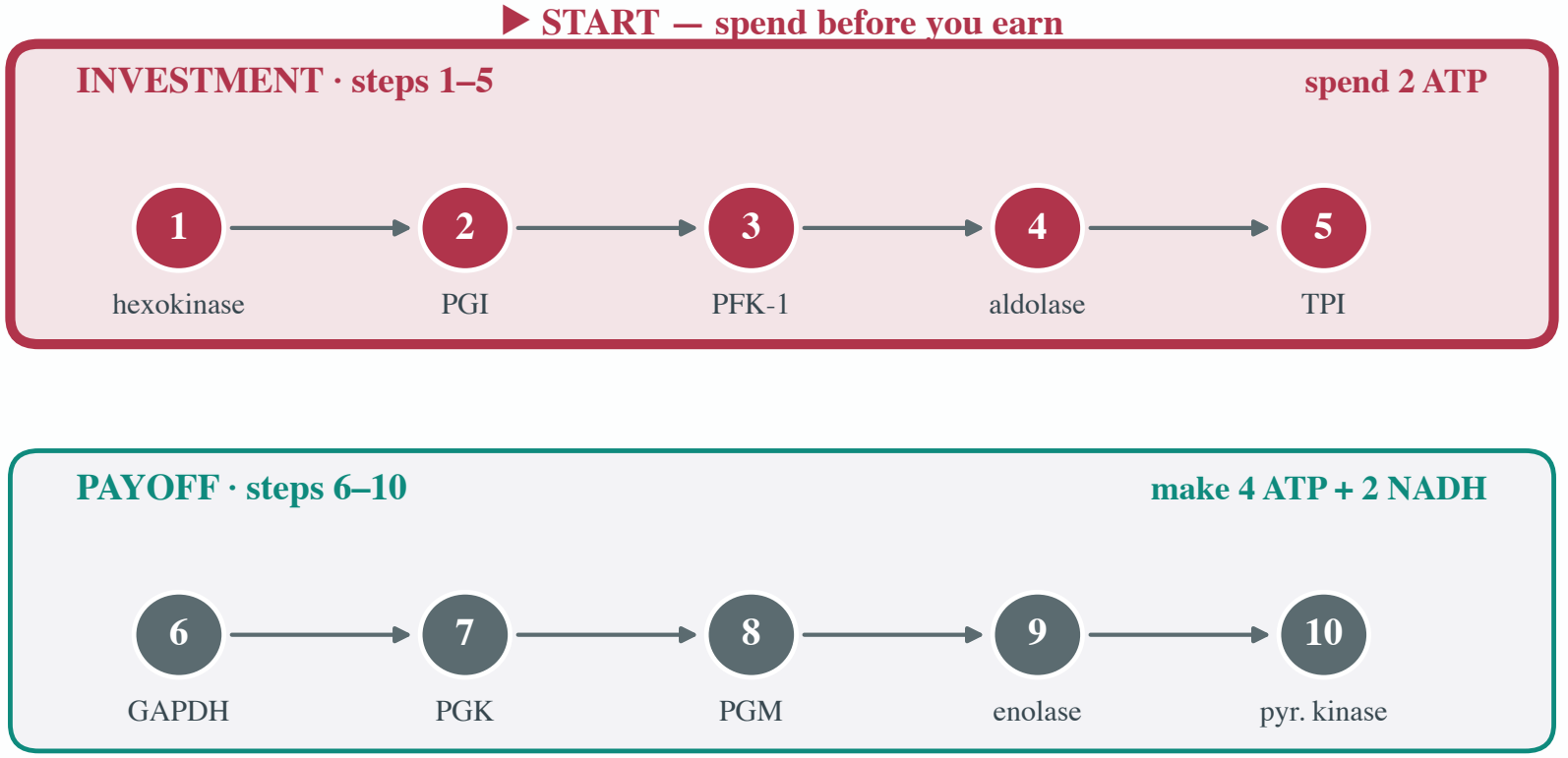
SUGAAAARRRR!!!

Glucose is a **freaking fantastic fuel** — the universal one, burned by almost every cell on Earth. **Glycolysis** ("sugar-splitting") is where it starts: ten enzymes in the **cytosol** chop one 6-carbon glucose into **two** 3-carbon **pyruvate**, banking a little **ATP** and **NADH** along the way.



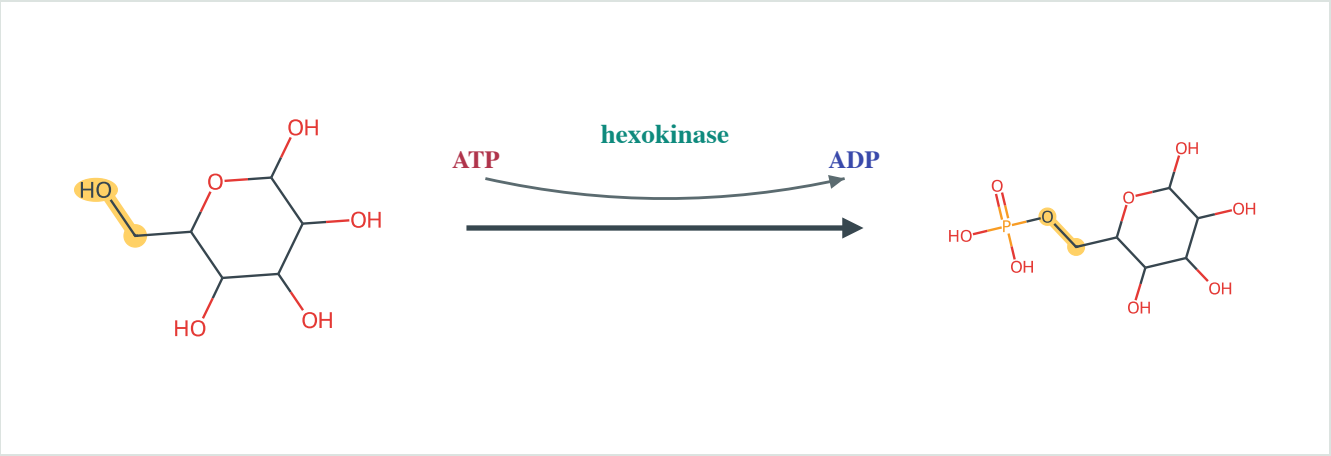
The plan: spend a little to make a lot

Glycolysis runs in **two halves**. The **investment phase** (steps 1–5) **spends 2 ATP** to prime and split the sugar. The **payoff phase** (steps 6–10) **earns** it back with interest — **4 ATP + 2 NADH**. You have to spend before you earn.



Step 1: Hexokinase

Glucose + ATP → glucose-6-phosphate + ADP. The very first thing we do is **phosphorylate C6** — and it costs us. That charged phosphate **traps glucose inside the cell** (it can't slip back across the membrane). **Irreversible** and **regulated**. Needs **Mg^{2+}**.



ATP −1 · **running total:** ATP −1

Why Step 1 only goes one way

Phosphorylating glucose by itself is **uphill**. Hexokinase **couples** it to **ATP hydrolysis** — and that downhill drop more than pays for it, so the whole step tips strongly **downhill**. A one-way valve like this is exactly where the cell puts a **control point**.

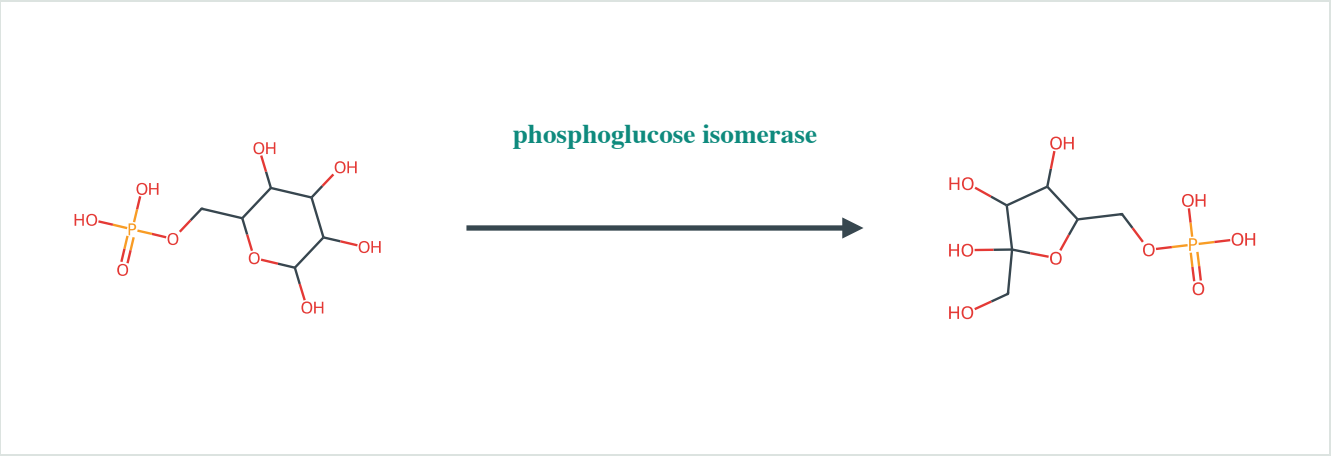
Step 1 · Hexokinase — why it's irreversible

glucose + Pi → glucose-6-P (uphill)	**ΔG°′ = +13.8 kJ/mol**
ATP → ADP + Pi (downhill)	**ΔG°′ = -30.5 kJ/mol**
NET (coupled)	**ΔG°′ = -16.7 kJ/mol**

Coupling to ATP makes it strongly downhill — a committed, regulated valve.

Step 2: Phosphoglucose isomerase

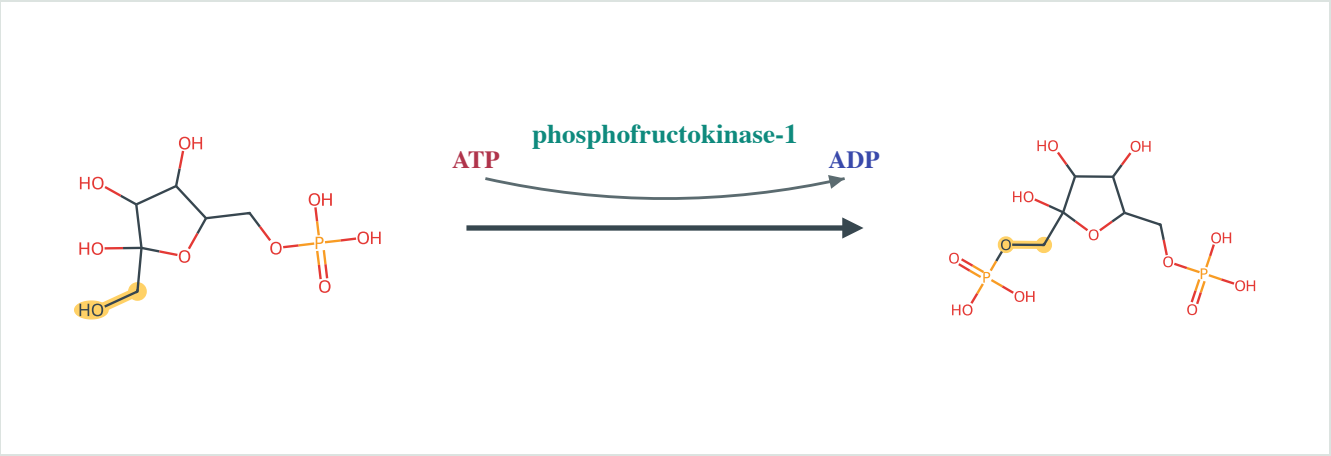
Glucose-6-P → fructose-6-P. A quick **isomerization**: an **aldose** (six-membered ring) becomes a **ketose** (five-membered ring). Why bother? It sets up a **symmetric** sugar we can cleanly split in half two steps from now. **Freely reversible.**



no ATP change · running total: ATP −1

Step 3: PFK-1 — the committed step

Fructose-6-P + ATP → fructose-1,6-bisphosphate + ADP. Phosphorylate the **other** end (C1) — spending our **second ATP**. **This is THE commitment:** past here, the sugar is going through glycolysis. PFK-1 is the **most regulated** enzyme in the pathway. **Irreversible.**



ATP −1 · running total: ATP −2

Why PFK-1 is the master switch

Same trick as hexokinase — coupled to **ATP hydrolysis**, so it's a strongly downhill, **irreversible** valve. But this one sits at the **branch point** where glucose is **committed**. Put your thermostat on the one-way door, and PFK-1 becomes the pathway's **main control point**.

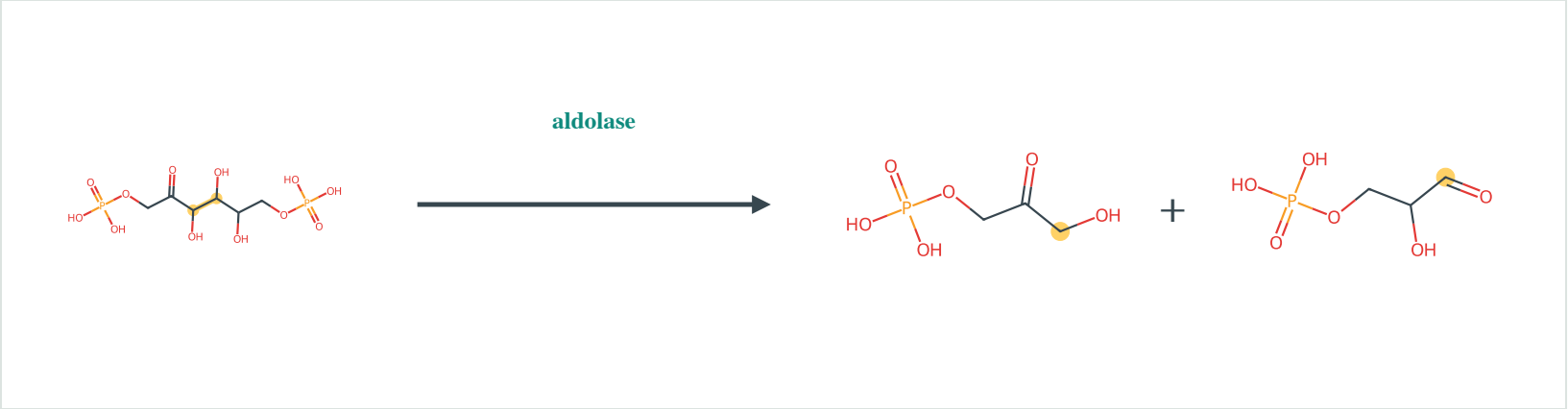
Step 3 · PFK-1 — the committed step

fructose-6-P + Pi → fructose-1,6-BP (uphill)	**ΔG°′ = +16.3 kJ/mol**
ATP → ADP + Pi (downhill)	**ΔG°′ = -30.5 kJ/mol**
NET (coupled)	**ΔG°′ = -14.2 kJ/mol**

The pathway's main control point — past here, glucose is committed to glycolysis.

Step 4: Aldolase — the split!

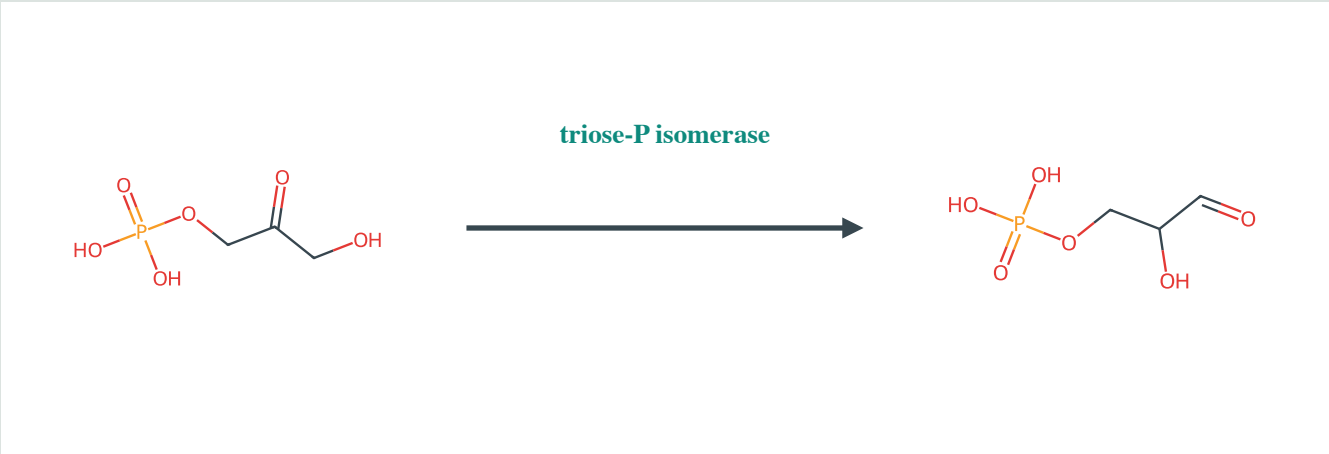
Fructose-1,6-bisphosphate → DHAP + glyceraldehyde-3-phosphate. Aldolase **cleaves the C3–C4 bond**, breaking one 6-carbon sugar into **two 3-carbon** pieces. This is the **lysis** in glyco-**lysis**. From here on, **everything happens twice.**



×2 begins · one glucose is now two 3-carbon molecules · running total: ATP −2

Step 5: Triose phosphate isomerase

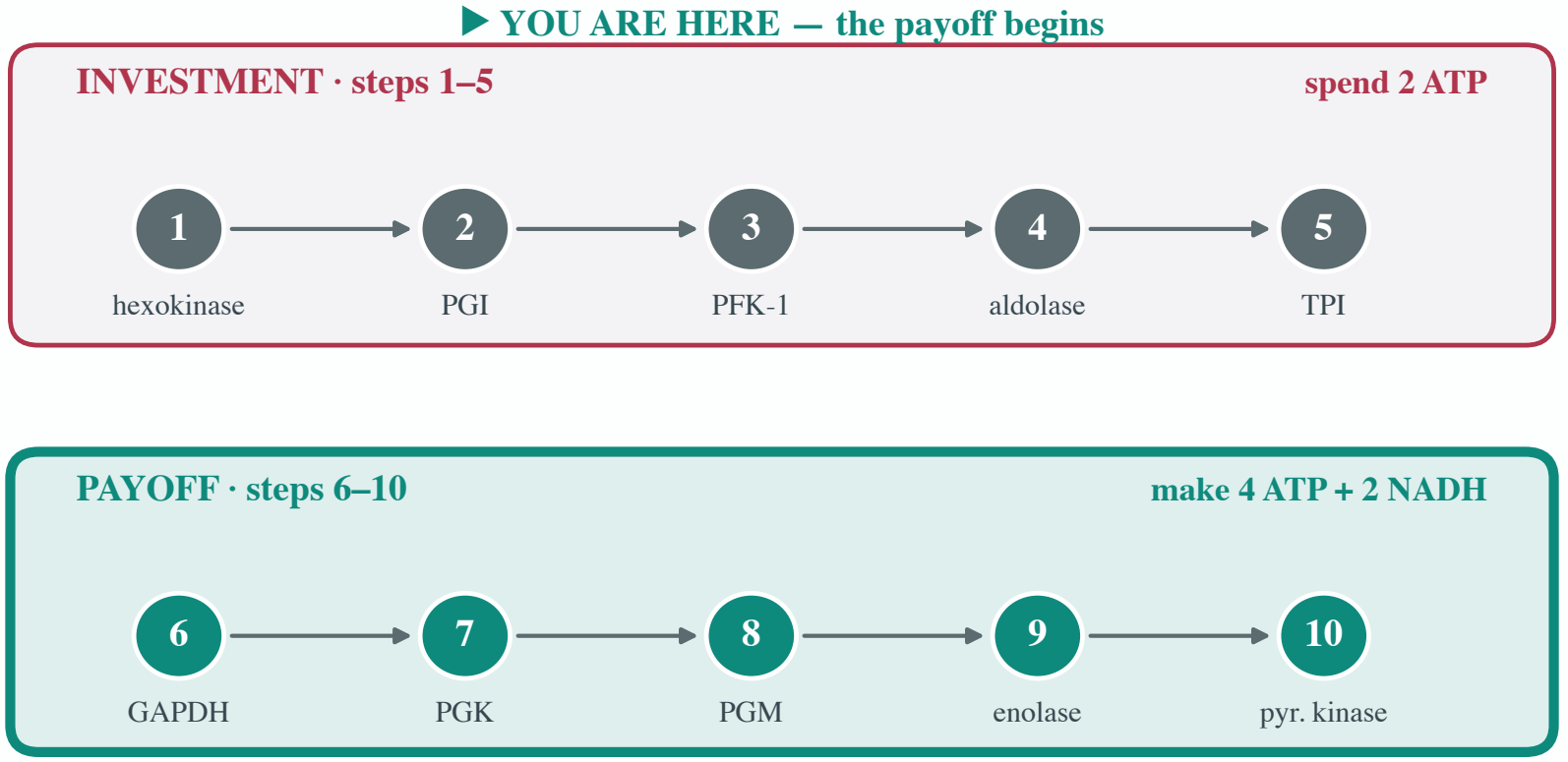
DHAP → glyceraldehyde-3-phosphate. Only **G3P** can continue — so TPI converts the "dead-end" **DHAP** into a second G3P. Now we have **two identical G3P**, and one of the **fastest enzymes known** makes sure neither carbon is wasted.



no ATP change · now ×2 · running total: ATP −2

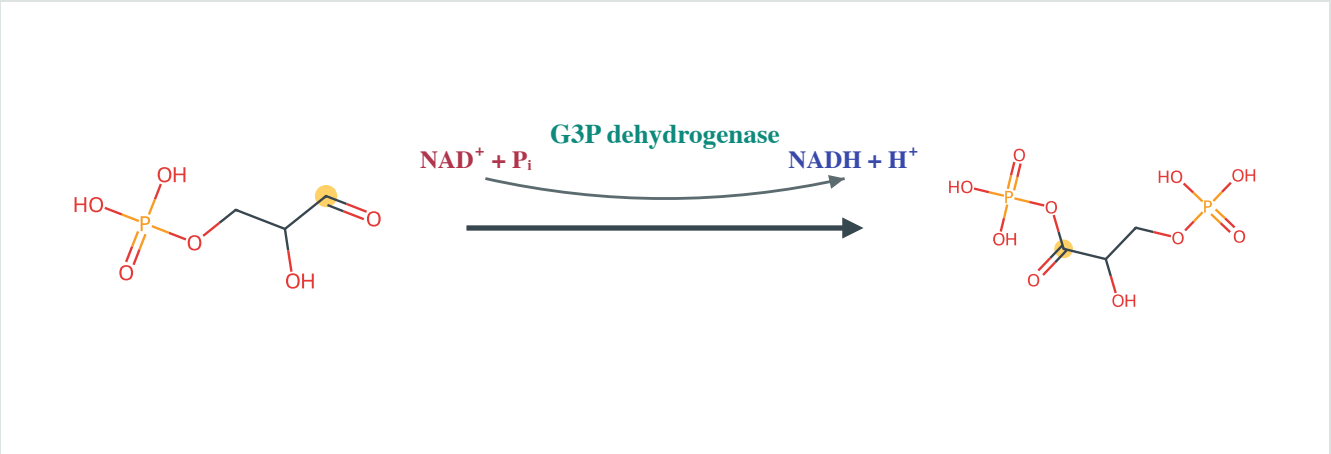
You are here — the payoff begins

We've spent our **2 ATP** and split the sugar into **two G3P**. The books are in the red. Everything from here **counts twice**, and it's all **downhill earnings** — 4 ATP and 2 NADH on the way to pyruvate.



Step 6: G3P dehydrogenase (GAPDH)

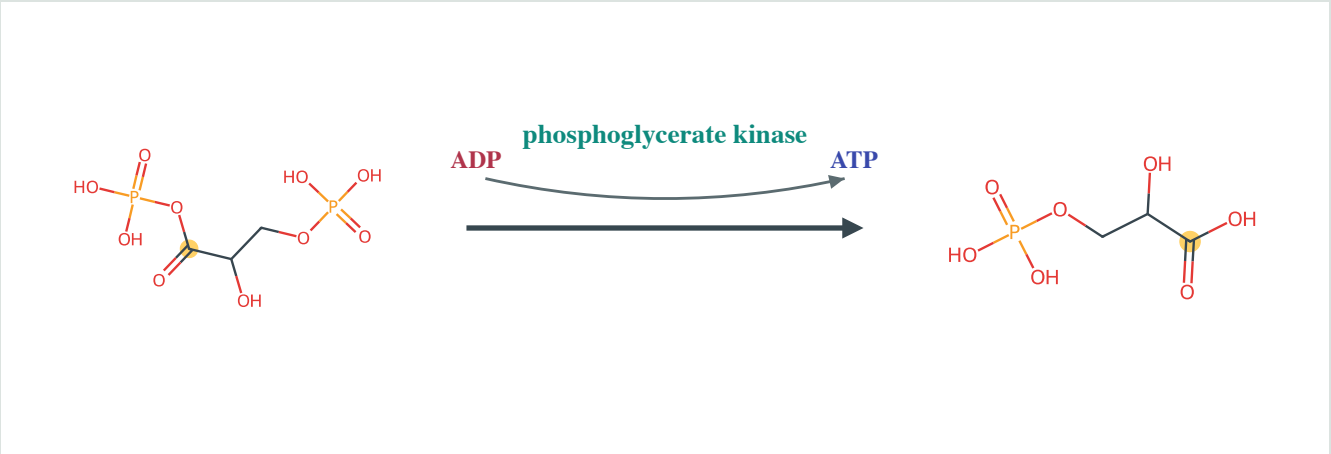
G3P + NAD^+ + P_i → 1,3-bisphosphoglycerate + NADH. The first energy capture! We **oxidize** the aldehyde (reducing **NAD^+ → NADH**) and use that energy to attach a phosphate, making a **high-energy acyl-phosphate**. **Reversible.**



NADH +2 (×2) · running total: ATP −2, NADH +2

Step 7: Phosphoglycerate kinase

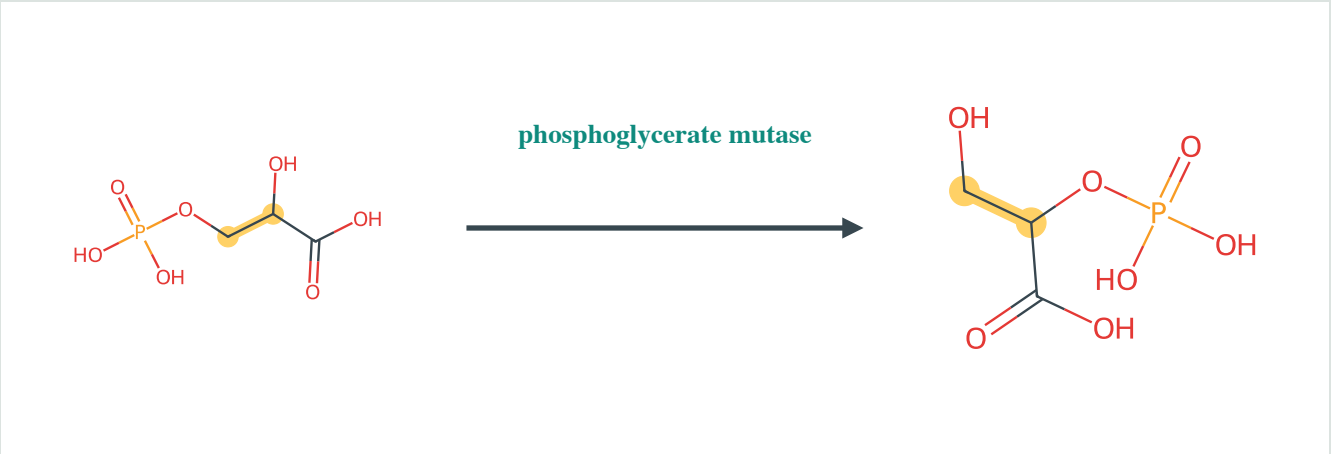
1,3-bisphosphoglycerate + ADP → 3-phosphoglycerate + ATP. That high-energy phosphate we just installed gets handed straight to **ADP → ATP**. This is **substrate-level phosphorylation** — and it's our **first ATP made** (×2, so we've now broken even).



ATP +2 (×2) · first ATP made! · **running total:** ATP 0, NADH +2

Step 8: Phosphoglycerate mutase

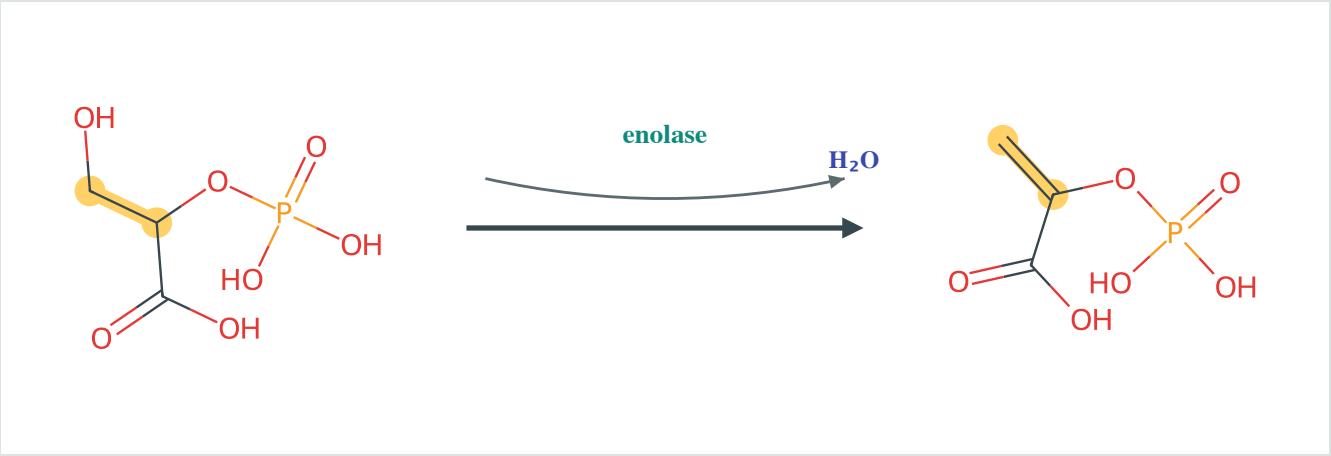
3-phosphoglycerate → 2-phosphoglycerate. A little housekeeping: **move the phosphate from C3 to C2.** No energy in, no energy out — but this sets up the next enzyme to build a **really** high-energy phosphate. **Reversible.**



no ATP change · running total: ATP 0, NADH +2

Step 9: Enolase

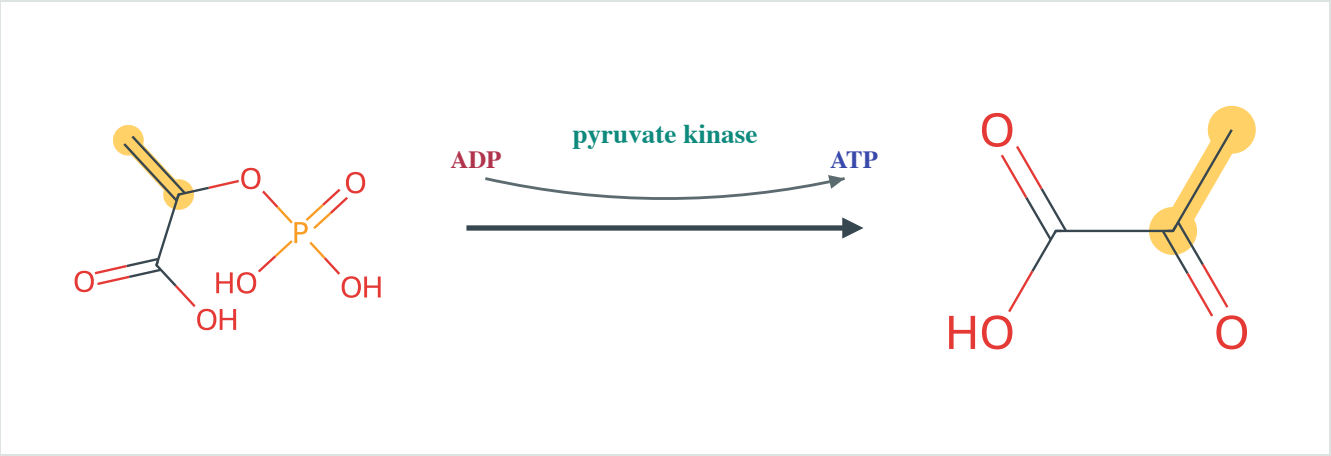
2-phosphoglycerate → phosphoenolpyruvate (PEP) + H_2O. Enolase pulls out a **water**, forming a **double bond** — and that turns the phosphate into a **super high-energy enol phosphate (PEP)**, one of the most energetic little molecules in the cell. **Reversible.**



no ATP change · running total: ATP 0, NADH +2

Step 10: Pyruvate kinase

PEP + ADP → pyruvate + ATP. PEP is so high-energy it powers a **second substrate-level phosphorylation** — our **last ATP**. The enol snaps to the stable keto form of **pyruvate**, locking the step **irreversible** and **regulated**. We made it!



ATP +2 (×2) · running total: ATP +2, NADH +2 → NET

Why Step 10 is a one-way payoff

PEP is **so** high-energy that even after paying to build an ATP, the step still drops **strongly downhill** — that's why it's **irreversible** and a **control point**. This enormous drop is what makes glycolysis able to make ATP with no oxygen at all.

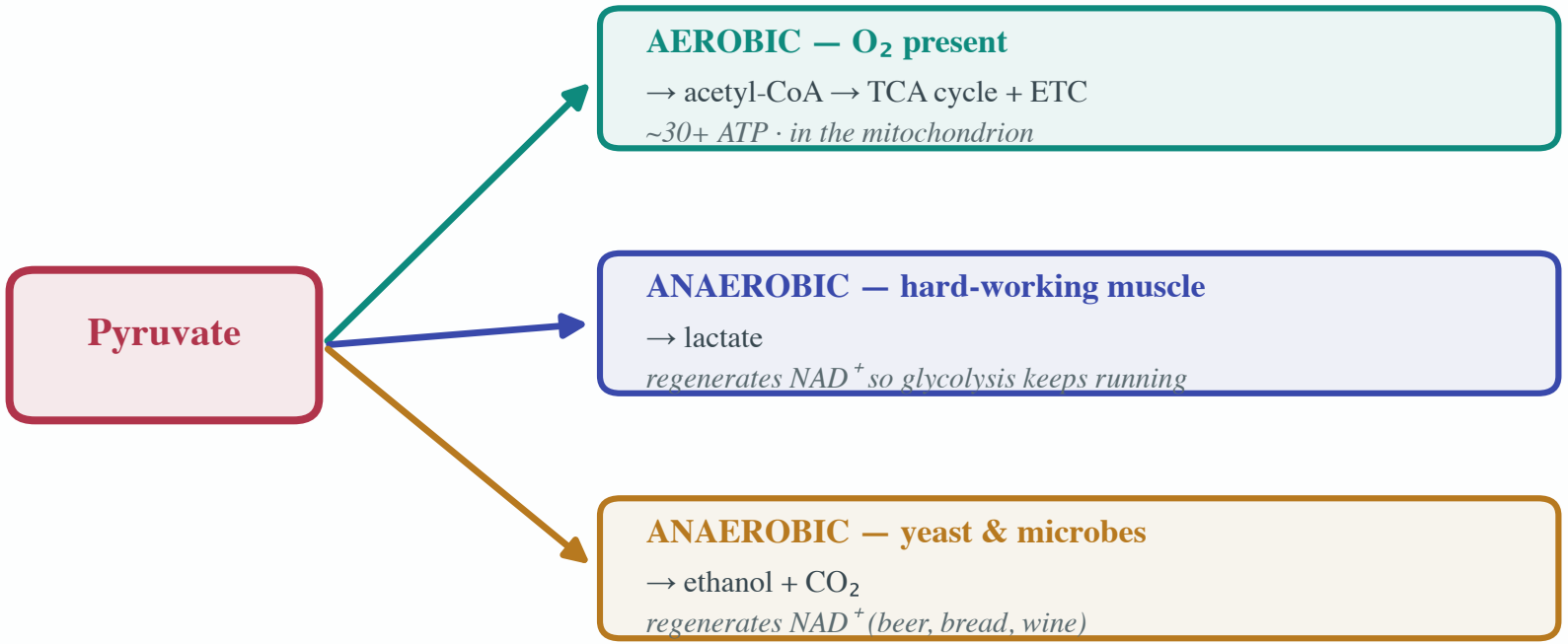
Step 10 · Pyruvate kinase — the big payoff

PEP → pyruvate (huge drop)	**ΔG°′ = -61.9 kJ/mol**
ADP + Pi → ATP (uphill)	**ΔG°′ = +30.5 kJ/mol**
NET (coupled)	**ΔG°′ = -31.4 kJ/mol**

PEP is so high-energy the step still drives ATP synthesis — irreversible, regulated.

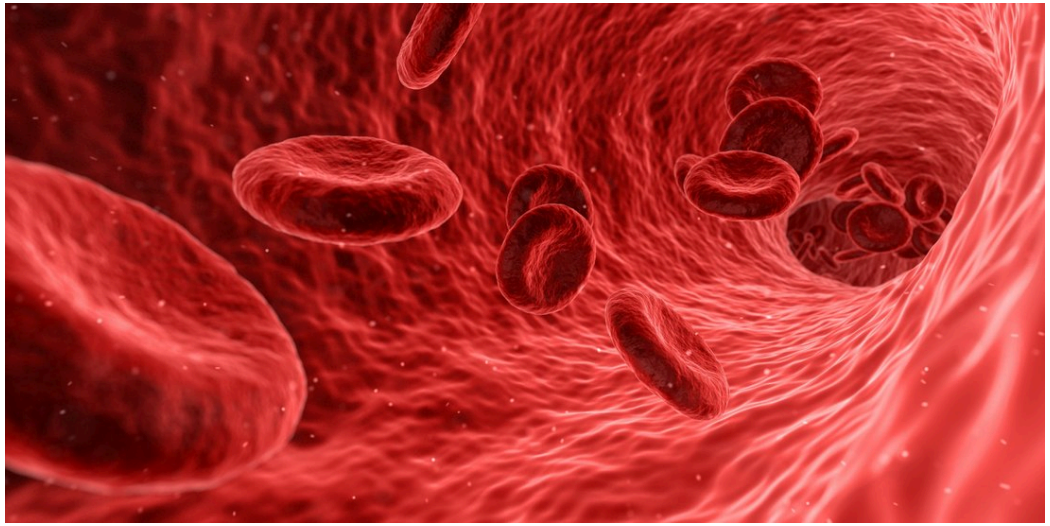
So what happens to pyruvate?

We netted **2 ATP + 2 NADH** – but the **2 pyruvate** still hold **most** of glucose's energy. What happens next comes down to **oxygen**: with O_2, pyruvate is fully burned in the mitochondria; without it, we **ferment** to keep glycolysis running.



Cells that live on glycolysis alone

Some cells run **almost entirely** on glycolysis. Your **red blood cells** have **no mitochondria** at all – glycolysis is their **only** ATP source. **Fast-twitch muscle** leans on it during a sprint, and many **tumors** crank it up (the **Warburg effect**). Two ATP per glucose, no oxygen required – humble, but life-saving.



Red blood cells: Arek Socha, CC0 (Wikimedia Commons)

2 · Glycolysis — Energy Yield & Regulation

"Add up the ATP, then meet the control panel — the three valves, fructose-2,6-bisphosphate, and the hormones that flip the switch."

Was it worth it? Do the accounting

Let's settle the books. We **invested 2 ATP** (hexokinase, PFK-1) and **earned 4 ATP + 2 NADH** – remember, everything past the split counts **×2**. **Net: 2 ATP + 2 NADH per glucose.** And those 2 NADH cash in for **~5 more ATP** later in the electron transport chain!

INVEST (spend)

Step 1 · hexokinase	**–1 ATP**
Step 3 · PFK-1	**–1 ATP**
subtotal	**–2 ATP**

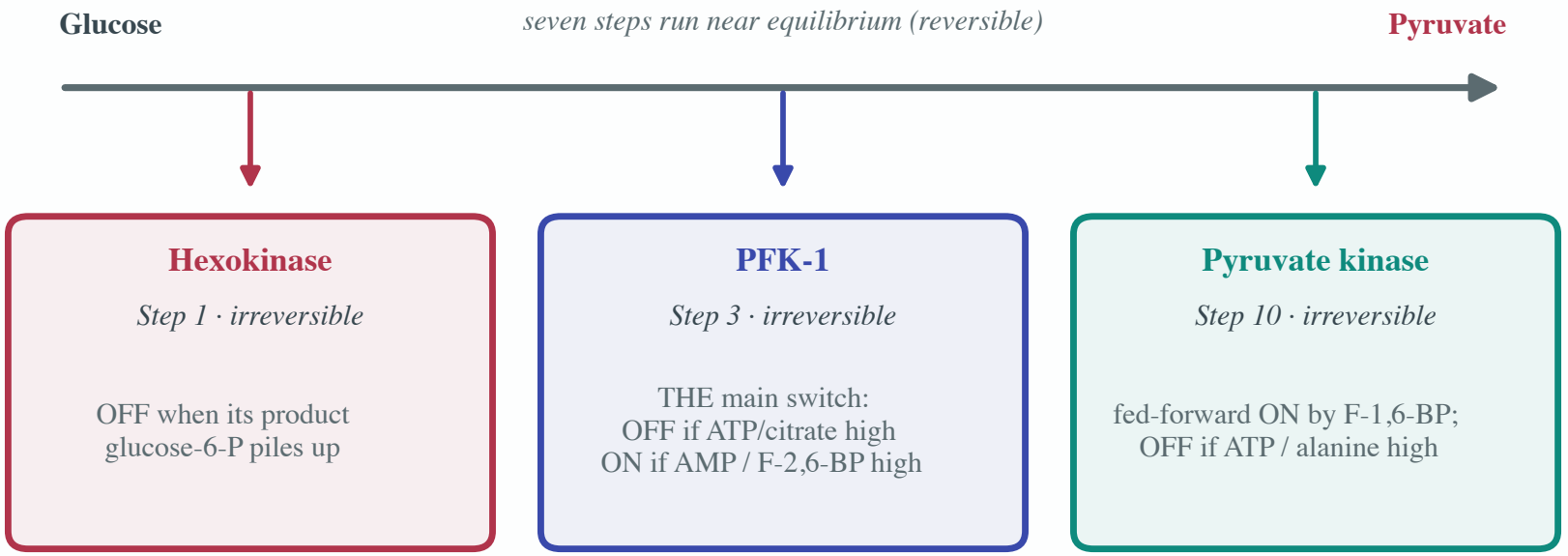
EARN (×2 — two trioses)

Step 6 · GAPDH	**+2 NADH**
Step 7 · PGK	**+2 ATP**
Step 10 · pyruvate kinase	**+2 ATP**
subtotal	**+4 ATP · +2 NADH**

NET = 4 – 2 = +2 ATP +2 NADH +2 pyruvate

Where do you put the controls?

You regulate a pathway at its **irreversible** steps — the one-way valves, where there's no going back. Glycolysis has exactly **three**: **hexokinase**, **PFK-1**, and **pyruvate kinase**. The other seven run near equilibrium and just follow along. Control the valves, control the flow.

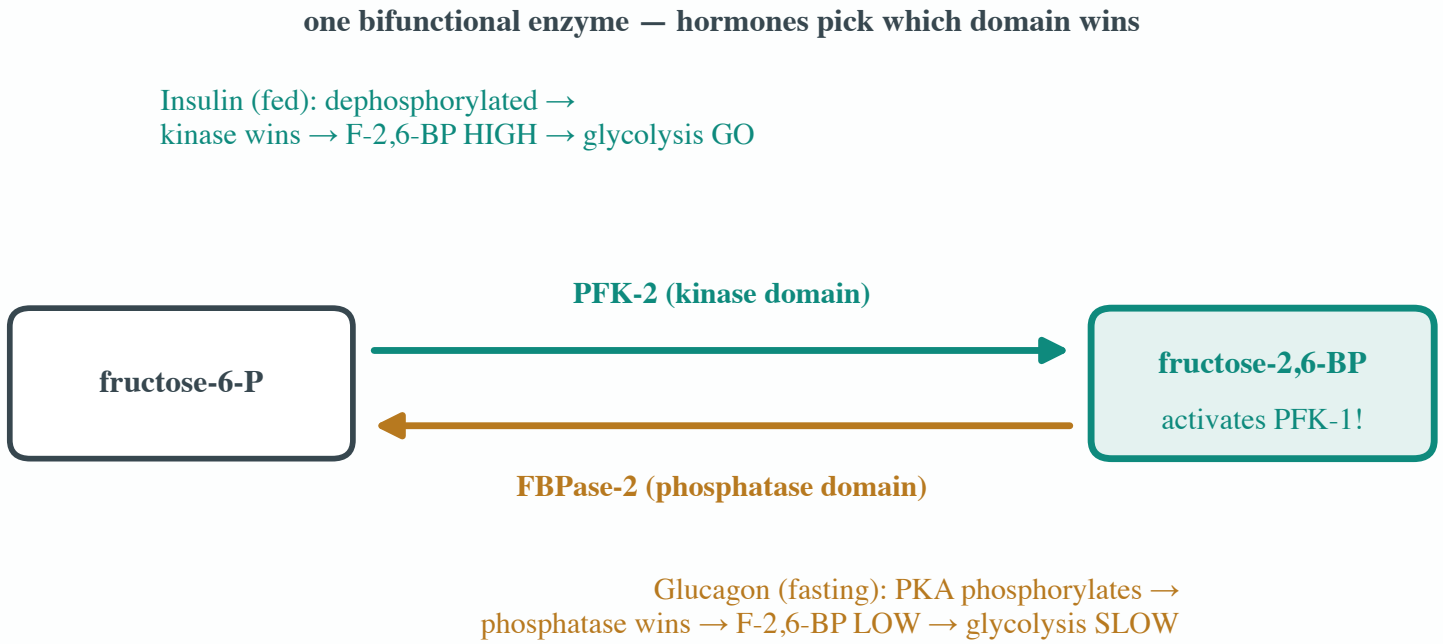


PFK-1: the master switch

PFK-1 is where the cell **reads its own energy level** and decides. Plenty of **ATP** or **citrate**? Turn glycolysis **down** – we don't need more fuel. Lots of **AMP** (energy's running low)? Turn it **up**. It's a beautiful piece of feedback – the pathway listens to the cell.

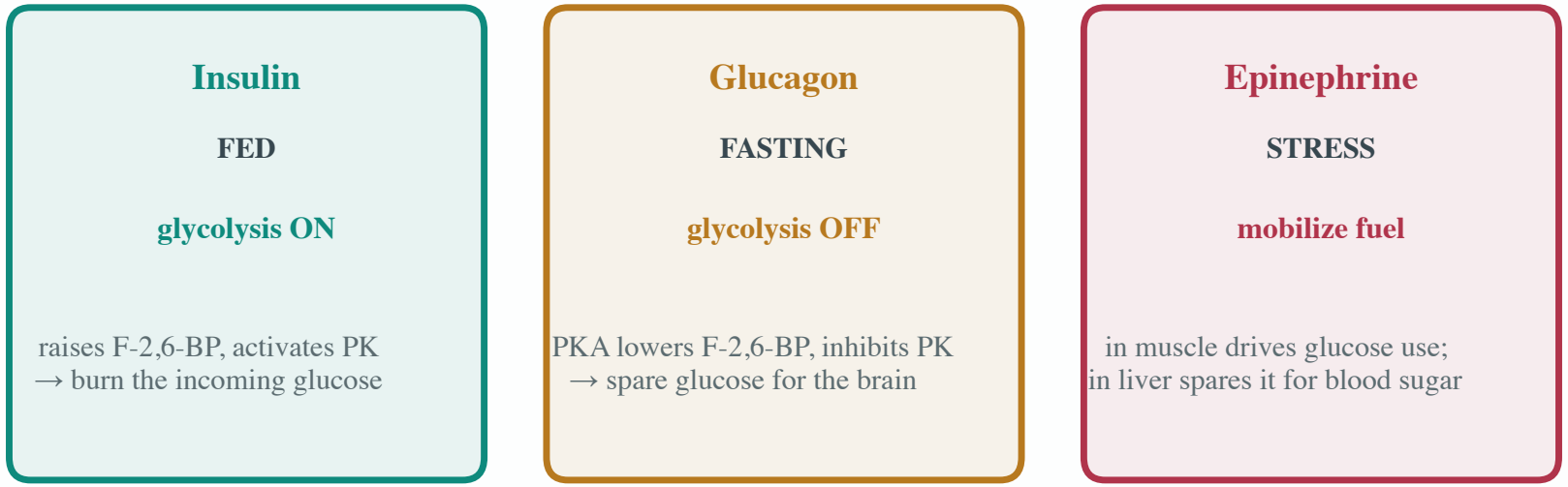
The secret weapon: fructose-2,6-bisphosphate

The **most powerful activator of PFK-1** isn't ATP or AMP – it's **fructose-2,6-bisphosphate**. It's made by a wild **bifunctional enzyme (PFK-2)** that's **both** a kinase and a phosphatase. Which half wins? **Hormones decide** – by phosphorylating it.



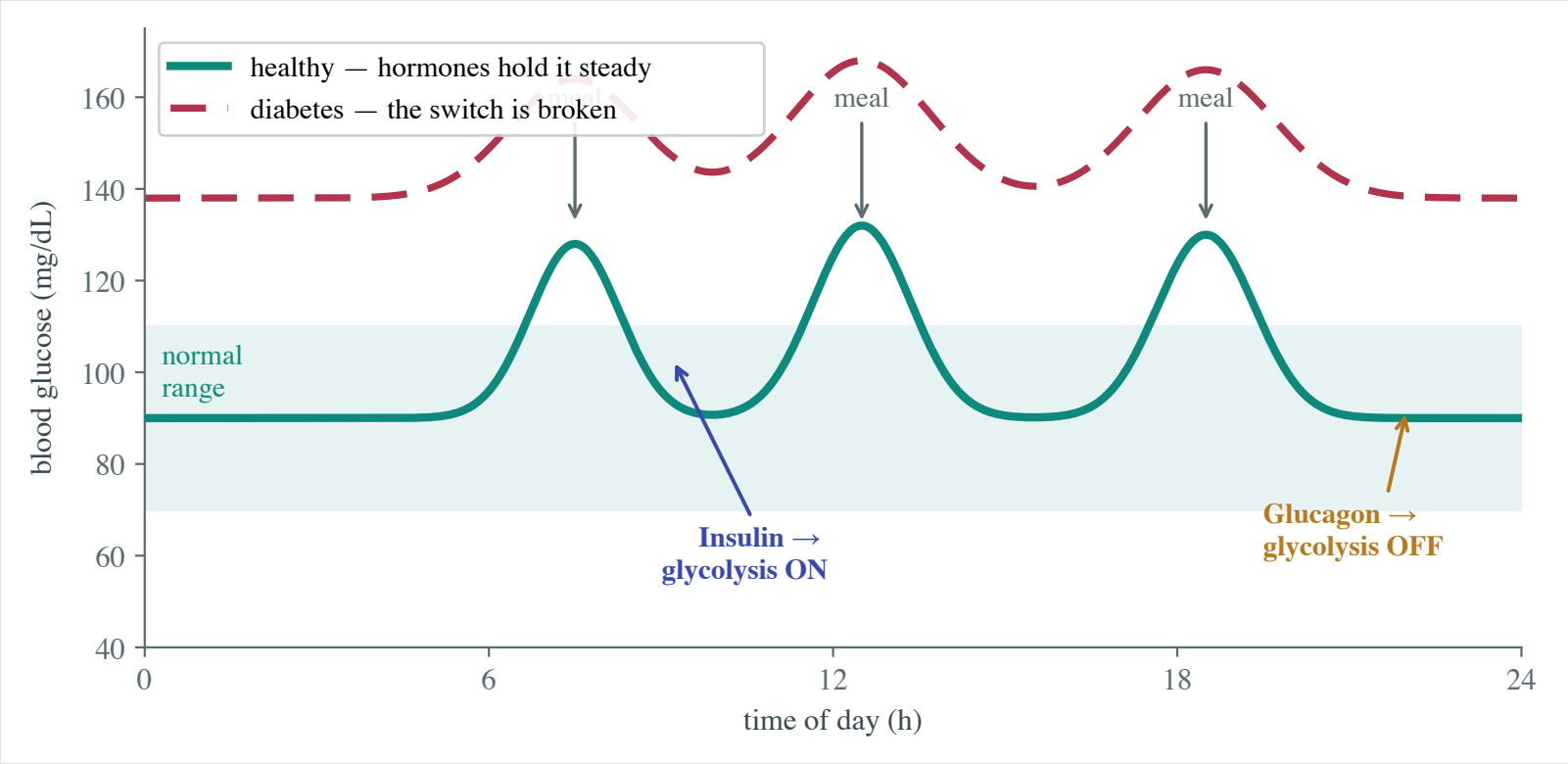
Hormones flip the whole switch

Zoom out: the hormones set the tone for the whole body. **Insulin** (fed) says **burn the glucose** – glycolysis **ON**. **Glucagon** (fasting) says **save it for the brain** – glycolysis **OFF**. **Epinephrine** (stress) mobilizes fuel fast. They act largely **through fructose-2,6-bisphosphate**.



The switch, in real life — and in diabetes

This is why your blood sugar stays **remarkably steady**: after a meal, **insulin** flips glycolysis on and stashes the glucose; while you fast, **glucagon** flips it off. In **diabetes**, that hormonal switch is **broken** — glucose can't get the "burn me" signal, so it stays **dangerously high**.

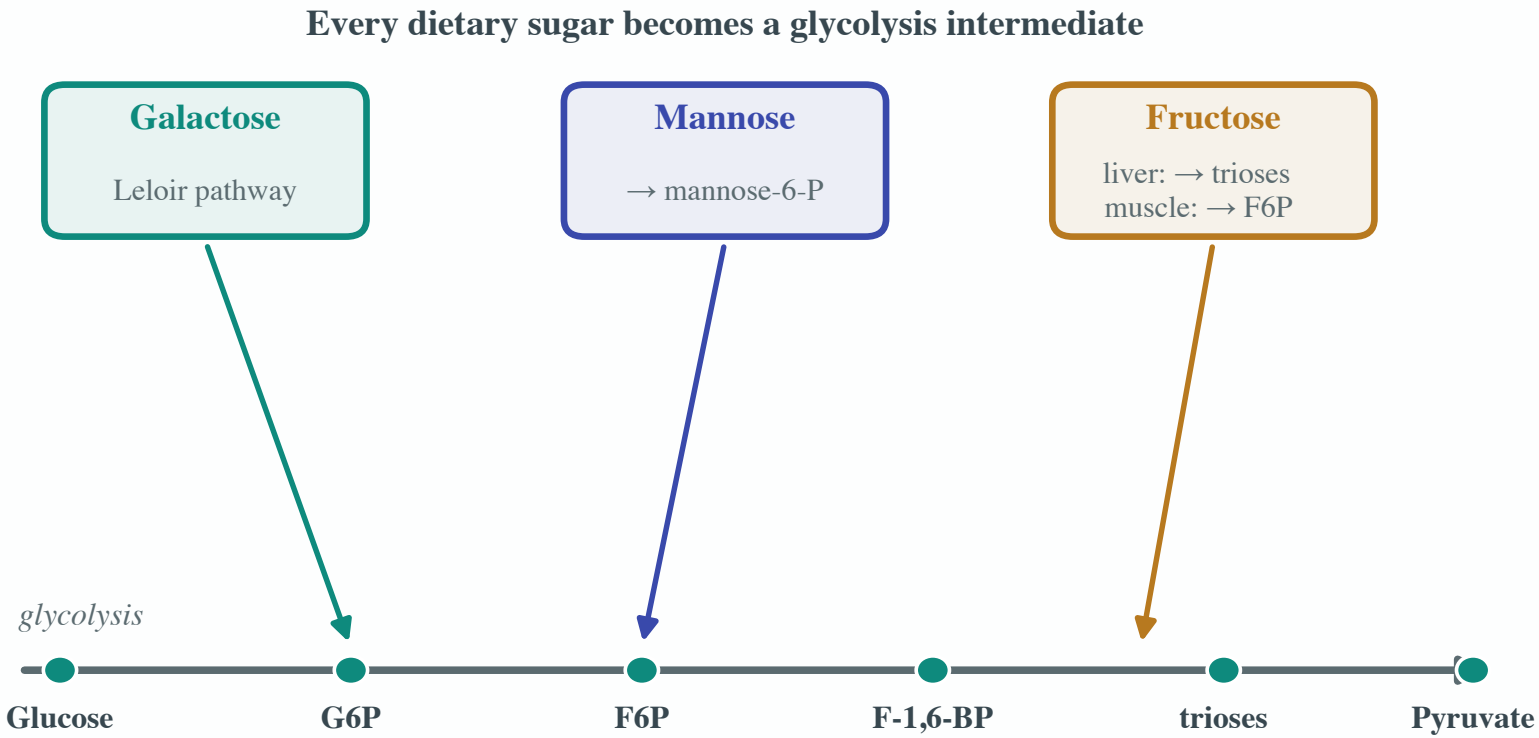


3 · Other Sugars — Galactose & Fructose

"Glucose isn't the only sugar you eat — see how galactose and fructose sneak into glycolysis, and what goes wrong when they can't."

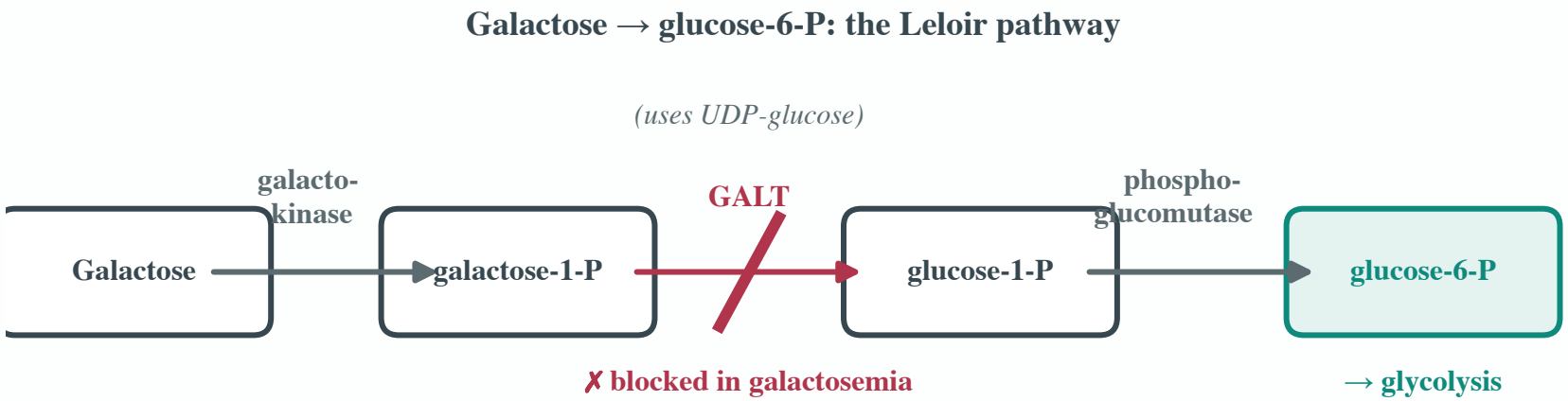
Glucose isn't the only sugar you eat

You eat plenty of **galactose** (from milk) and **fructose** (from fruit and — a lot — from soda). Neither can run glycolysis directly. The trick: the cell **converts each one into a glycolysis intermediate**, then lets the main pathway take over.



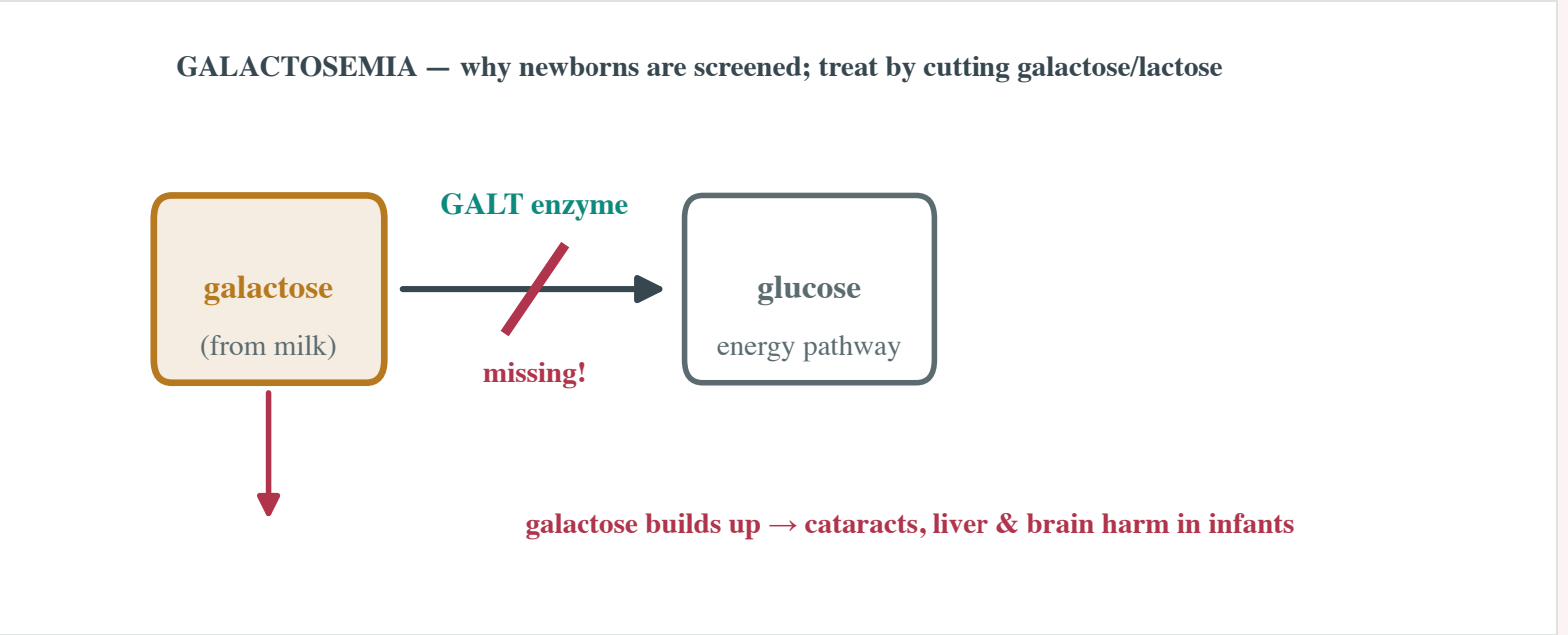
Galactose: the Leloir pathway

Galactose gets a phosphate, then swaps places with a glucose using the enzyme **GALT** (and a UDP-glucose helper), ending up as **glucose-6-phosphate** — right in the middle of glycolysis. Three little steps and it's just glucose again.



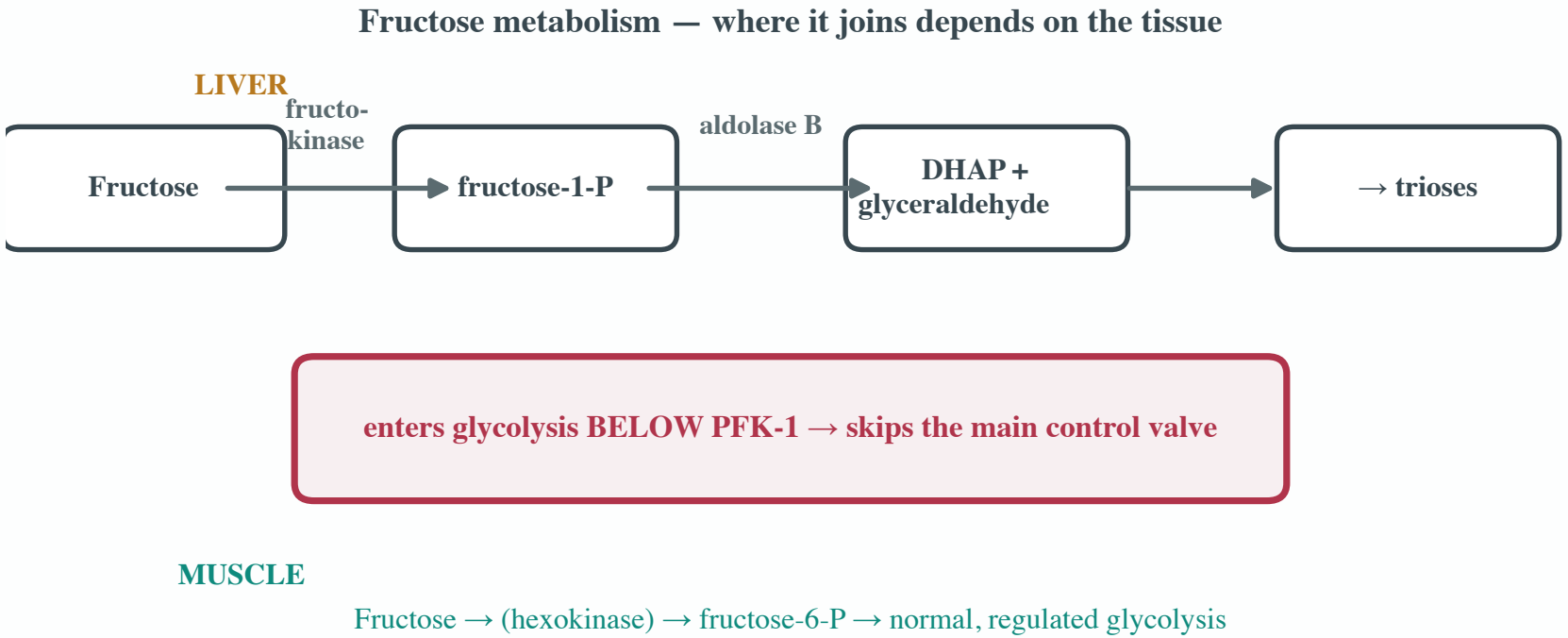
When galactose can't get through: galactosemia

Babies born without **GALT** can't process the galactose in **milk** — so it **backs up** and becomes toxic. The result: **jaundice, an enlarged liver, and cataracts**. This is why every newborn is **screened**; the treatment is simply a **galactose-free (lactose-free) diet**.



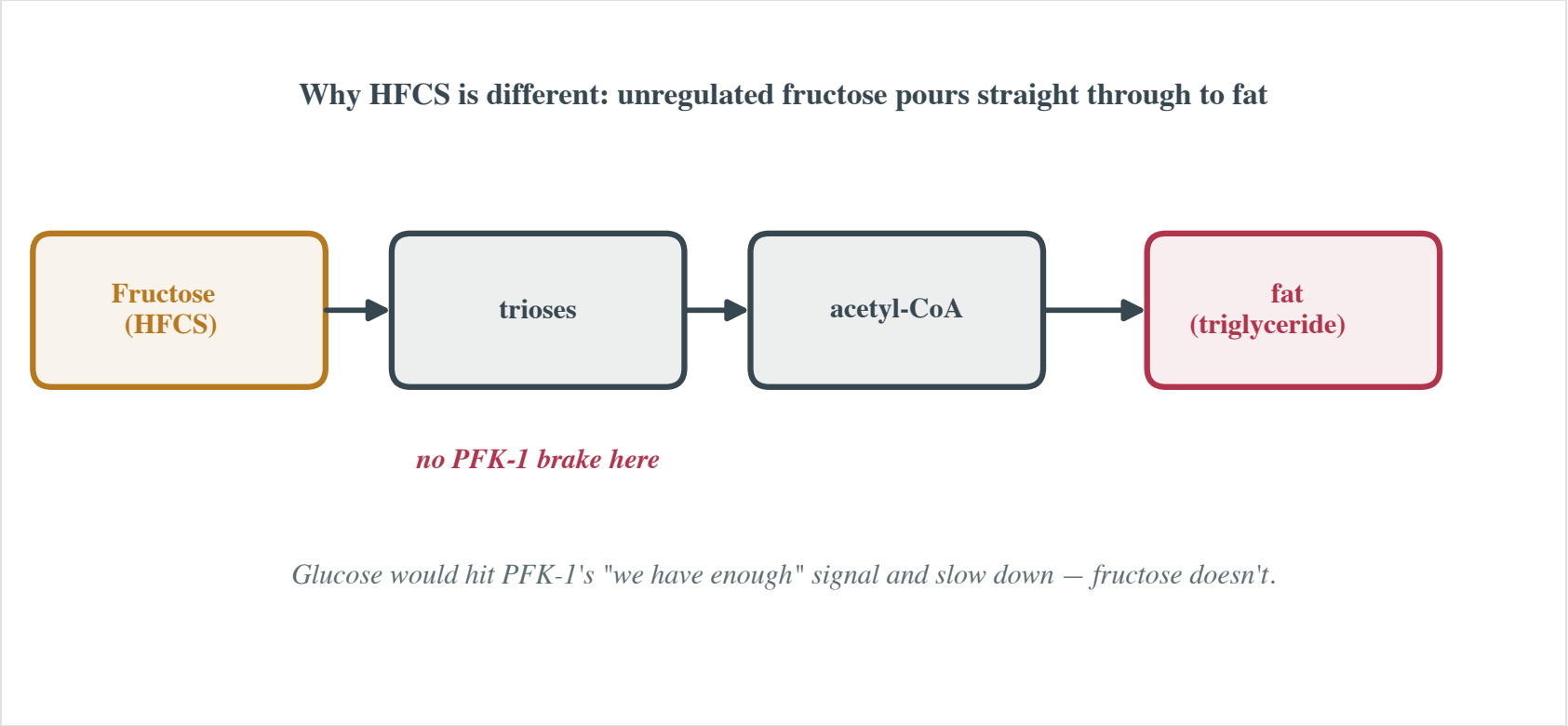
Fructose: a shortcut past the guard

In the **liver**, fructose takes a **different door**: fructokinase and aldolase B chop it straight into **trioses** – dropping it into glycolysis **below PFK-1**. Remember, PFK-1 is the main control valve – so fructose **skips the regulation** entirely. (Muscle plays it safe: fructose → fructose-6-P.)



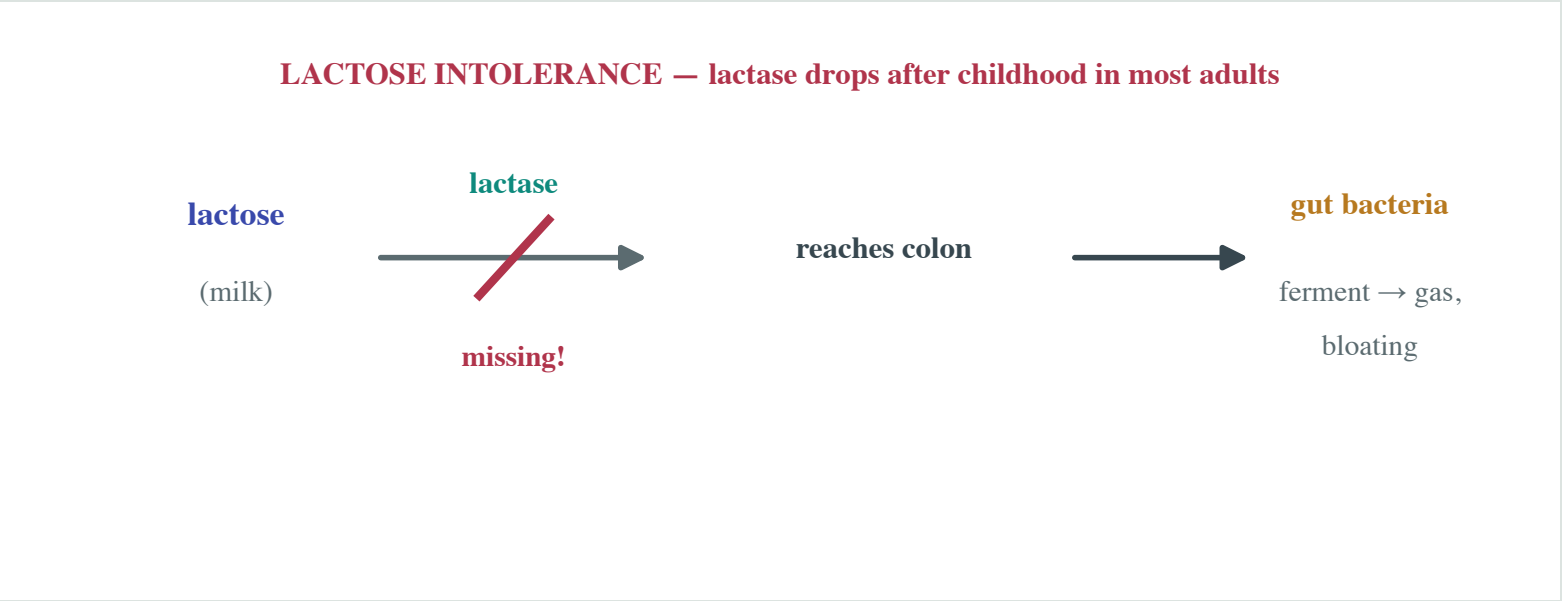
Why HFCS hits different

Here's the catch. Glucose that piles up trips PFK-1's **"we have enough — slow down"** signal. Fructose **never sees that brake**, so a big dose of **high-fructose corn syrup** pours straight through to **acetyl-CoA** and gets stashed as **fat**. Same calories, very different metabolic ride.



One more: lactose intolerance

Lactose (milk sugar) is glucose + galactose — but you need the enzyme **lactase** to split it. Most adults **lose lactase** after childhood, so lactose sails on to the **colon**, where gut bacteria **ferment** it into gas (CH_4 + H_2) — cue the bloating.

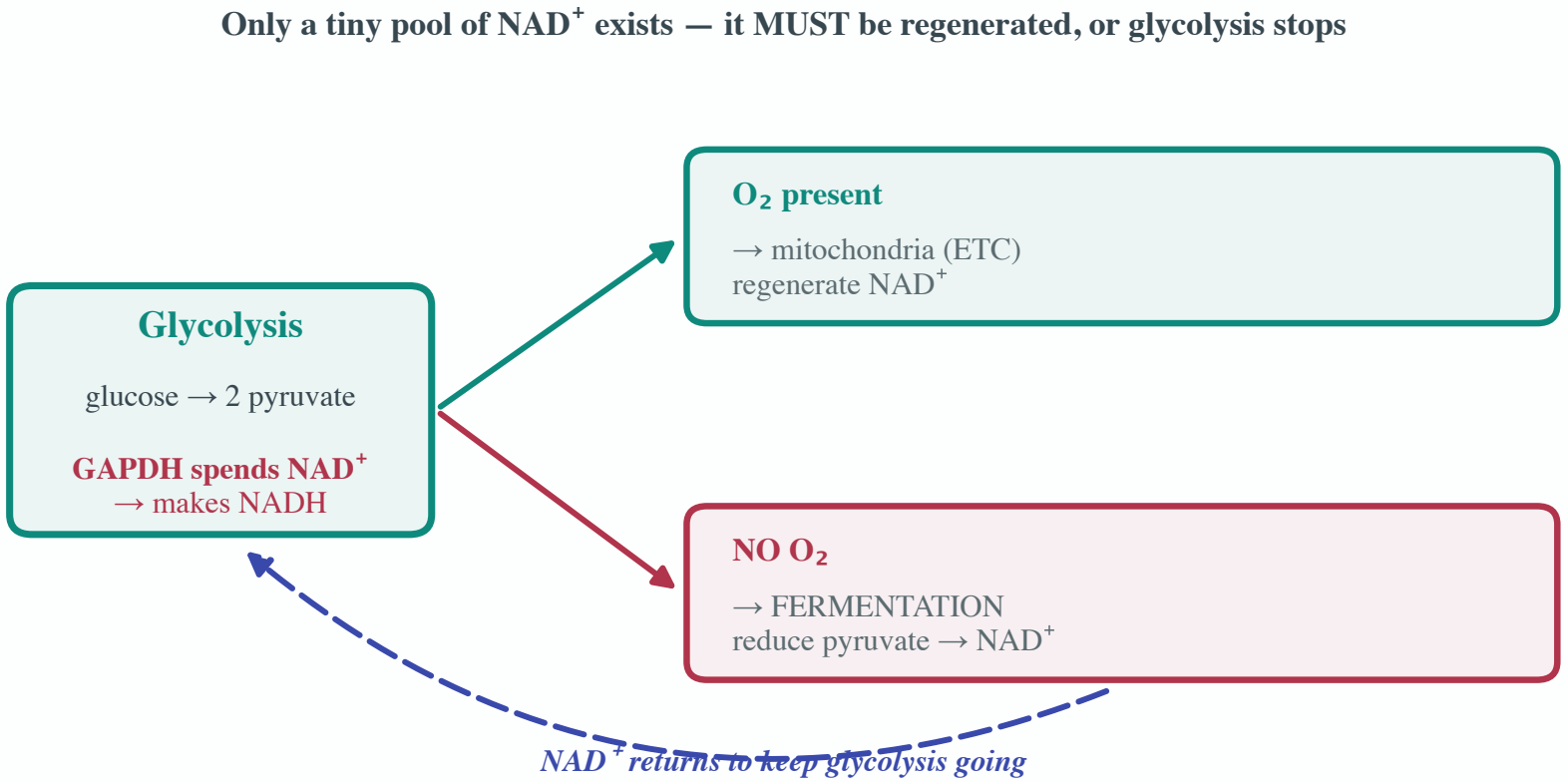


4 · Fermentation & the Cori Cycle

"No oxygen? No problem. See how fermentation keeps glycolysis alive by recycling NAD^+ — and how the liver bails out your sprinting muscles."

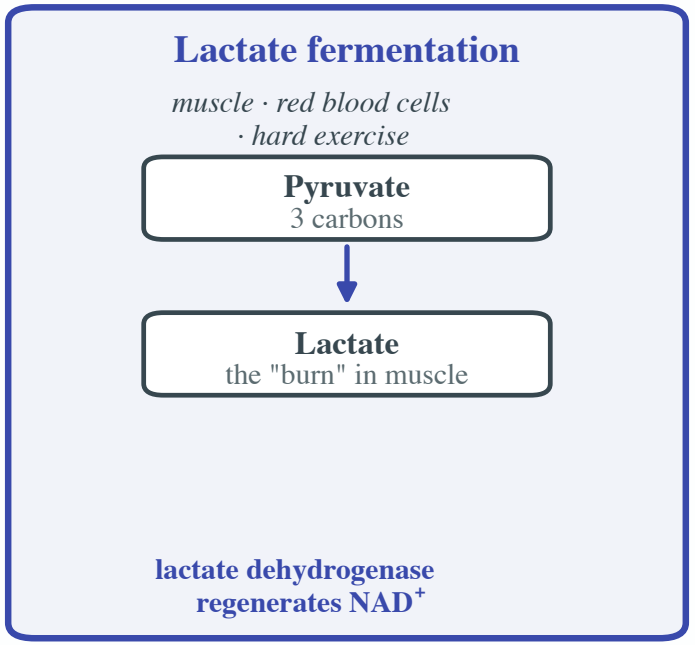
Pyruvate is a crossroads – and there's a catch

Pyruvate can go three ways: with **oxygen**, into the mitochondria as **acetyl-CoA** to feed the **citric acid cycle**; without it, to **lactate** or **ethanol**. Why the detour? Glycolysis **spends NAD⁺** at step 6 (GAPDH) – and there's barely any. If we don't **get NAD⁺ back**, glycolysis grinds to a halt.



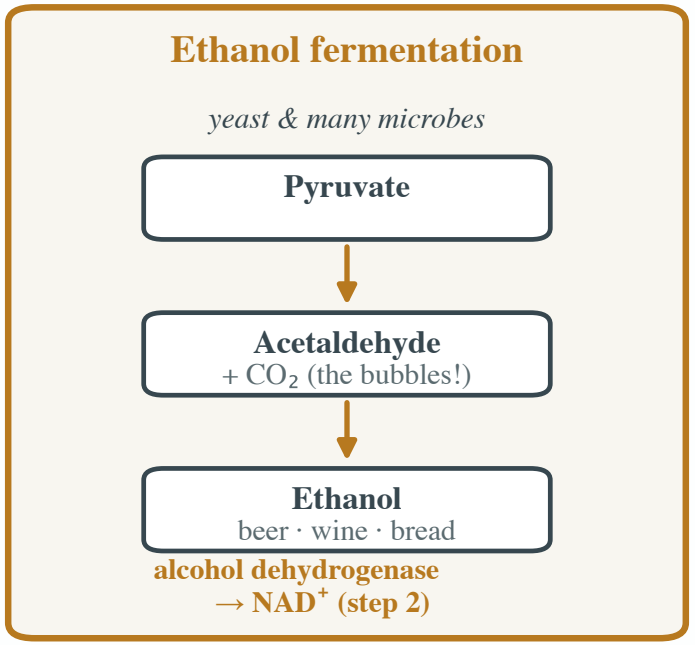
Lactate fermentation

When your muscles outrun their oxygen supply, they take the shortcut: **pyruvate + NADH → lactate**, run by **lactate dehydrogenase**. The whole point isn't the lactate — it's **regenerating NAD⁺** so glycolysis (and that quick 2 ATP) can keep going. Your **red blood cells** do this **all the time**.



Ethanol fermentation

Yeast solves the same NAD^+ problem differently — in **two steps**. **Pyruvate decarboxylase** knocks a **CO_2** off pyruvate to make acetaldehyde (those are the **bubbles**!), then **alcohol dehydrogenase** reduces it to **ethanol**, regenerating **NAD^+** on that second step. Humanity has been exploiting this for **beer, wine, and bread** for millennia.



Lactate vs ethanol: same goal, different exit

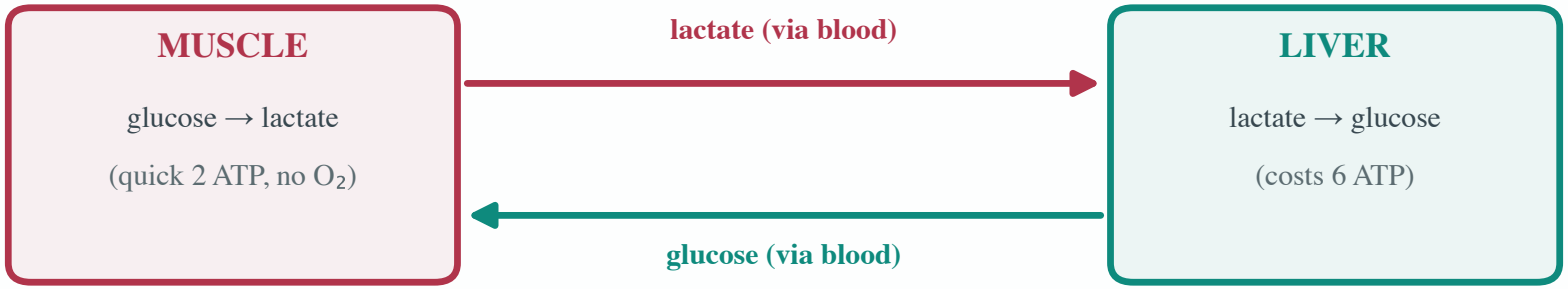
Both fermentations exist for **one reason: regenerate NAD^+**. They just dump the electrons onto different molecules. **We** (and lactic-acid bacteria) make **lactate**; **yeast** makes **ethanol + CO_2**. Neither one makes **extra** ATP — the payoff is simply **keeping glycolysis running**.

	LACTATE	ETHANOL
who?	muscle, RBCs, us	yeast, microbes
steps	1 (lactate dehydrogenase)	2 (+ CO_2 released)
product	lactate (3C)	ethanol (2C) + CO_2
the point	**regenerate NAD^+**	**regenerate NAD^+**

The Cori cycle: the liver has your back

That lactate from your muscles doesn't just sit there. It rides the **blood to the liver**, which spends **6 ATP** to turn it **back** into glucose (gluconeogenesis) and ships it out again. Your muscle got a quick **2 ATP**; the **liver eats the cost**. The liver really is the most giving organ!

The Cori cycle — muscle borrows, the liver pays it back



The liver shoulders the energy cost so tired muscle can keep sprinting.

Fermentation, in a glass

That "reduce pyruvate to regenerate NAD^+" trick is doing **real work** every time yeast turns grape sugar into **wine** — the alcohol and the fizz are literally **ethanol and CO_2** from glycolysis running without oxygen. Same chemistry as the burn in your legs, just a tastier product.

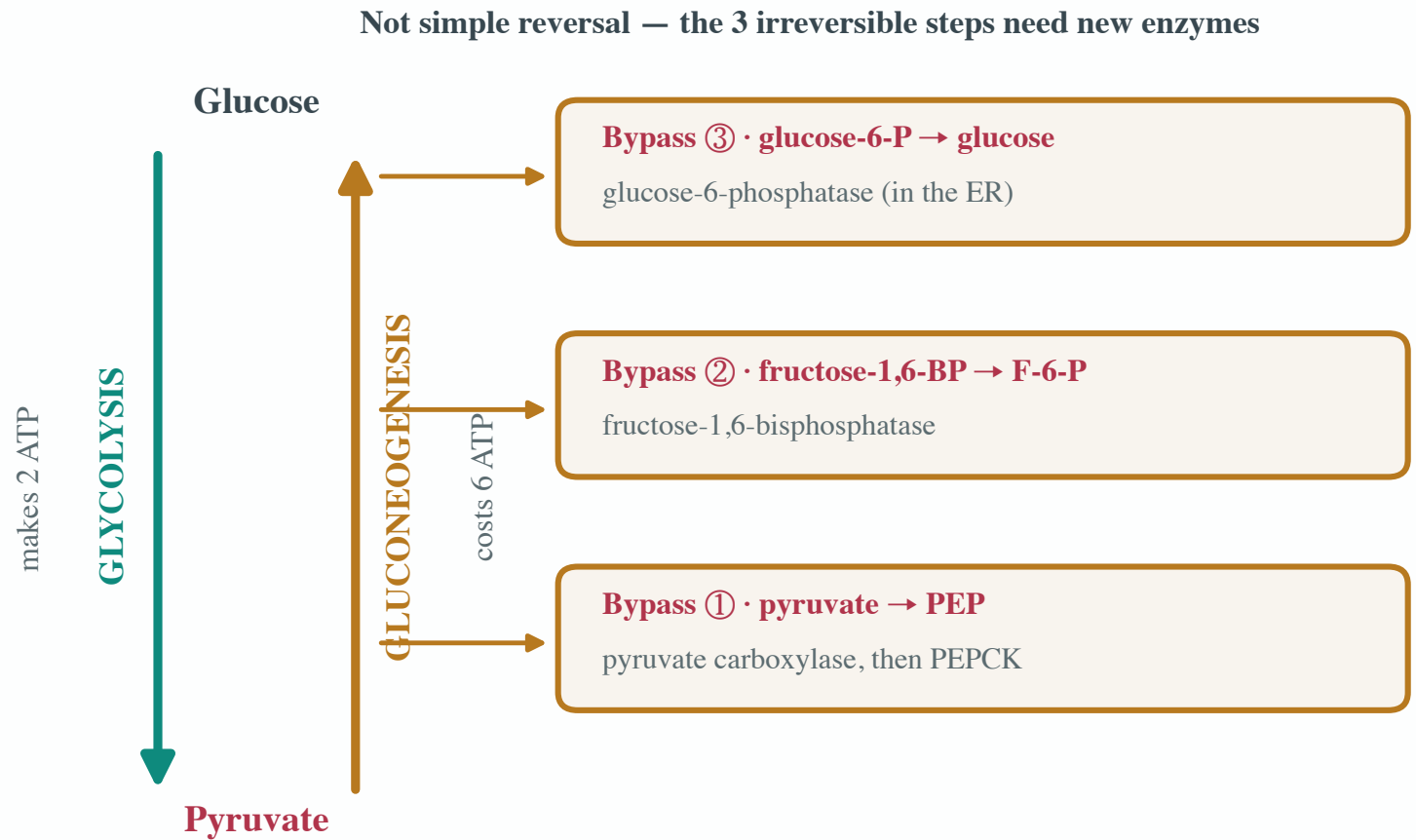
Red wine: André Karwath, CC BY-SA 3.0 (Wikimedia Commons)

5 · Gluconeogenesis — Making Glucose

"Run glycolysis backward to make new glucose — but three steps won't reverse, so four special enzymes bypass them."

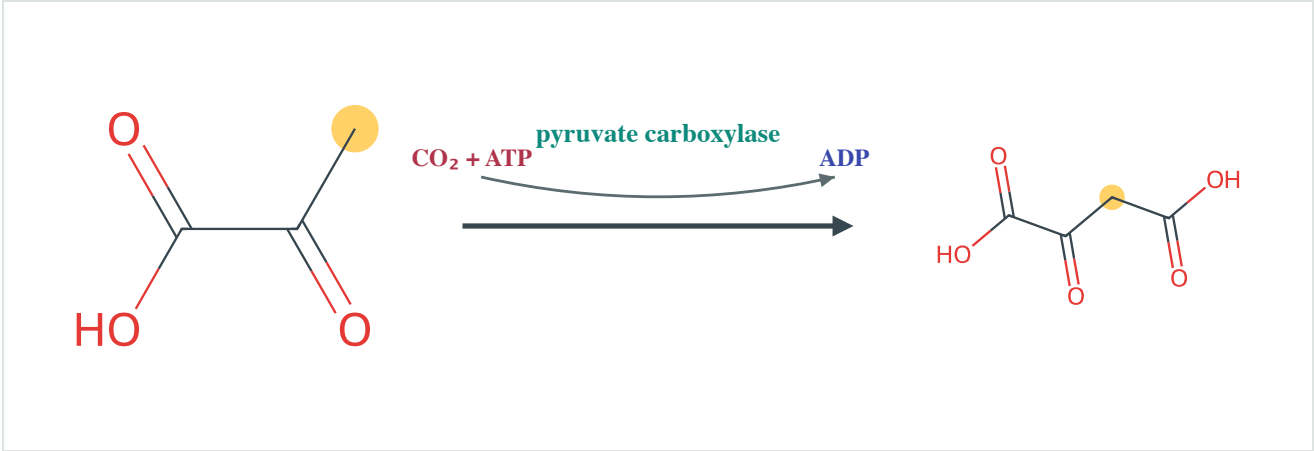
Making glucose from scratch

Your **brain** and **red blood cells** run on glucose — so when you're **fasting**, the **liver** makes fresh glucose from pyruvate, lactate, and amino acids. It's **mostly** glycolysis run in reverse… but **three steps are irreversible** and simply won't back up. Gluconeogenesis needs **four special enzymes** to go around them.



Bypass 1, part 1: Pyruvate carboxylase

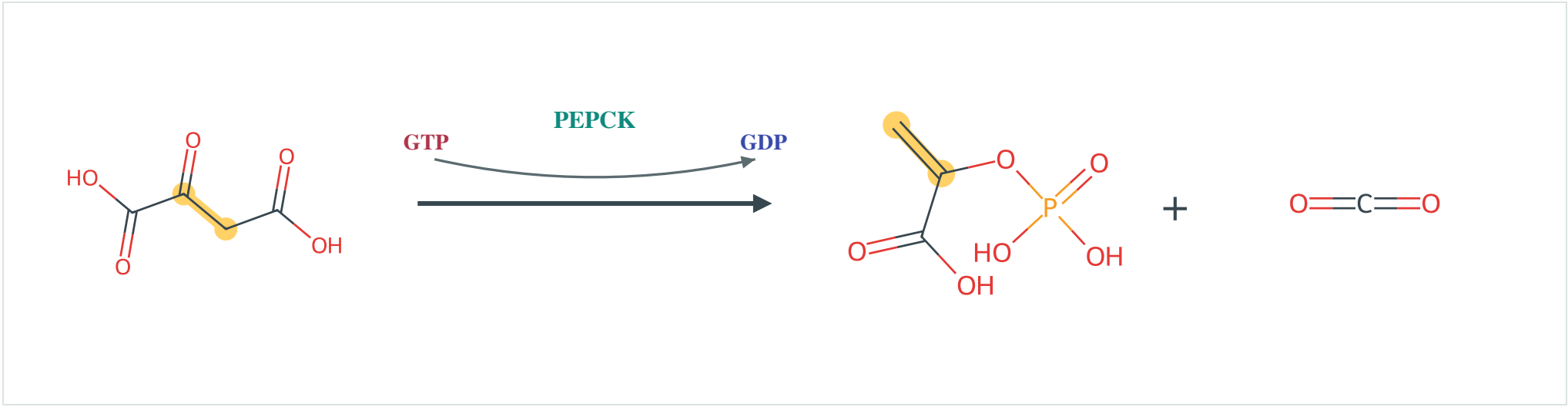
Pyruvate + CO_2 → oxaloacetate. We can't push pyruvate straight back to PEP, so we take a **detour through oxaloacetate**. This happens in the **mitochondrion**, costs an **ATP**, and needs the vitamin cofactor **biotin** to carry the CO_2.



−1 ATP · + CO_2 · needs biotin · in the mitochondrion

Bypass 1, part 2: PEPCK

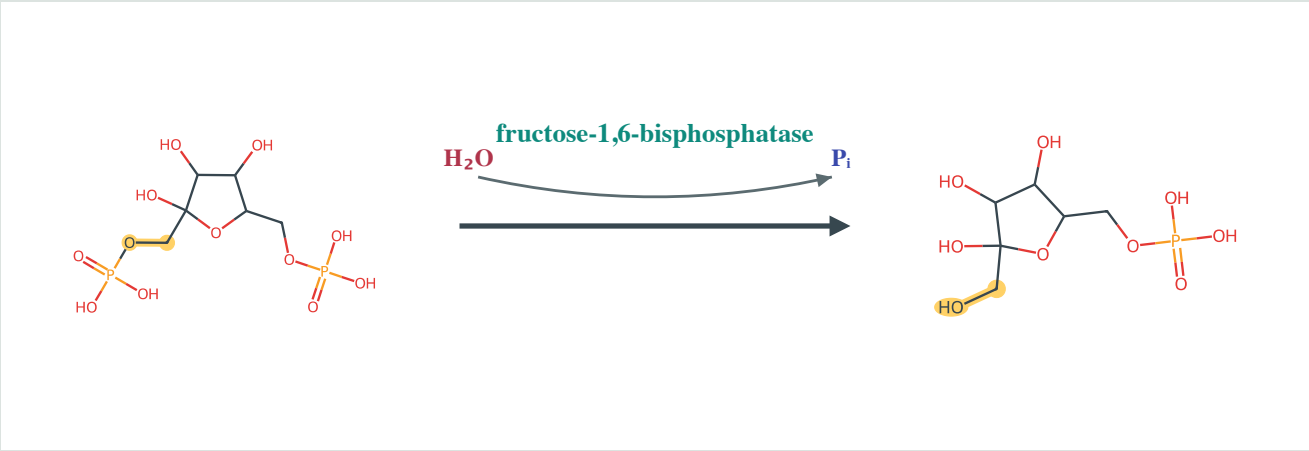
Oxaloacetate → phosphoenolpyruvate + CO_2. Now **PEPCK** pops that CO_2 back off and adds a phosphate (using **GTP**) to make **PEP** — finally past the pyruvate-kinase roadblock. Two enzymes, one bypass.



−1 GTP · − CO_2 · makes PEP

Bypass 2: Fructose-1,6-bisphosphatase

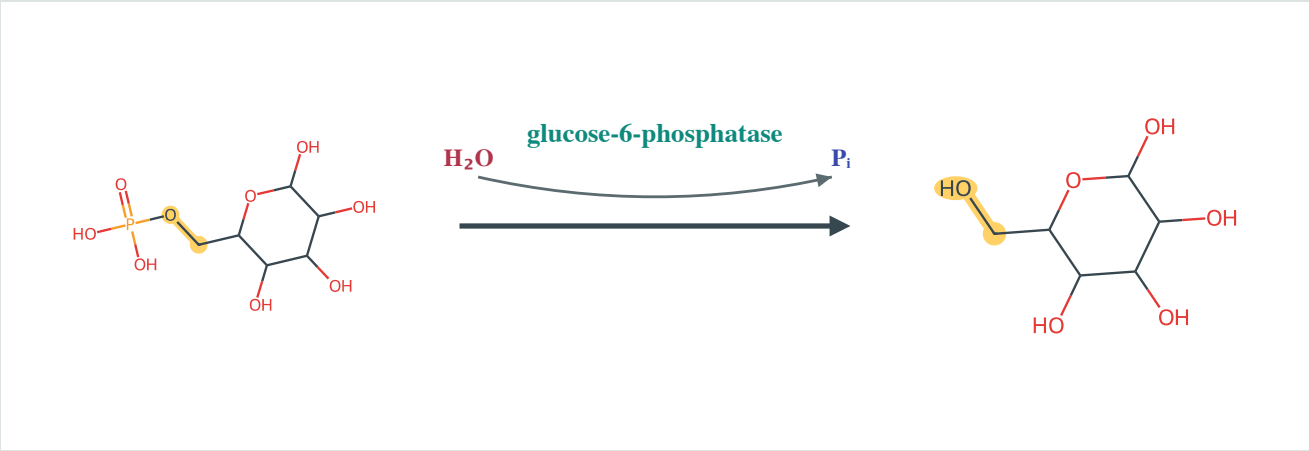
Fructose-1,6-bisphosphate → fructose-6-P + P_i. PFK-1 was irreversible, so we don't run it backward — instead we just **hydrolyze the phosphate off** with a phosphatase. No ATP made, no ATP spent — the phosphate simply leaves as **P_i**.



releases P_i · reciprocal with PFK-1 (never both at once)

Bypass 3: Glucose-6-phosphatase

Glucose-6-P → glucose + P_i. The last hurdle: hexokinase had **trapped** glucose by phosphorylating it, so to release **free glucose** we hydrolyze that phosphate. This enzyme lives in the **ER**, mostly in **liver and kidney** — the body's glucose exporters.



releases P_i · mainly liver & kidney · glucose → blood

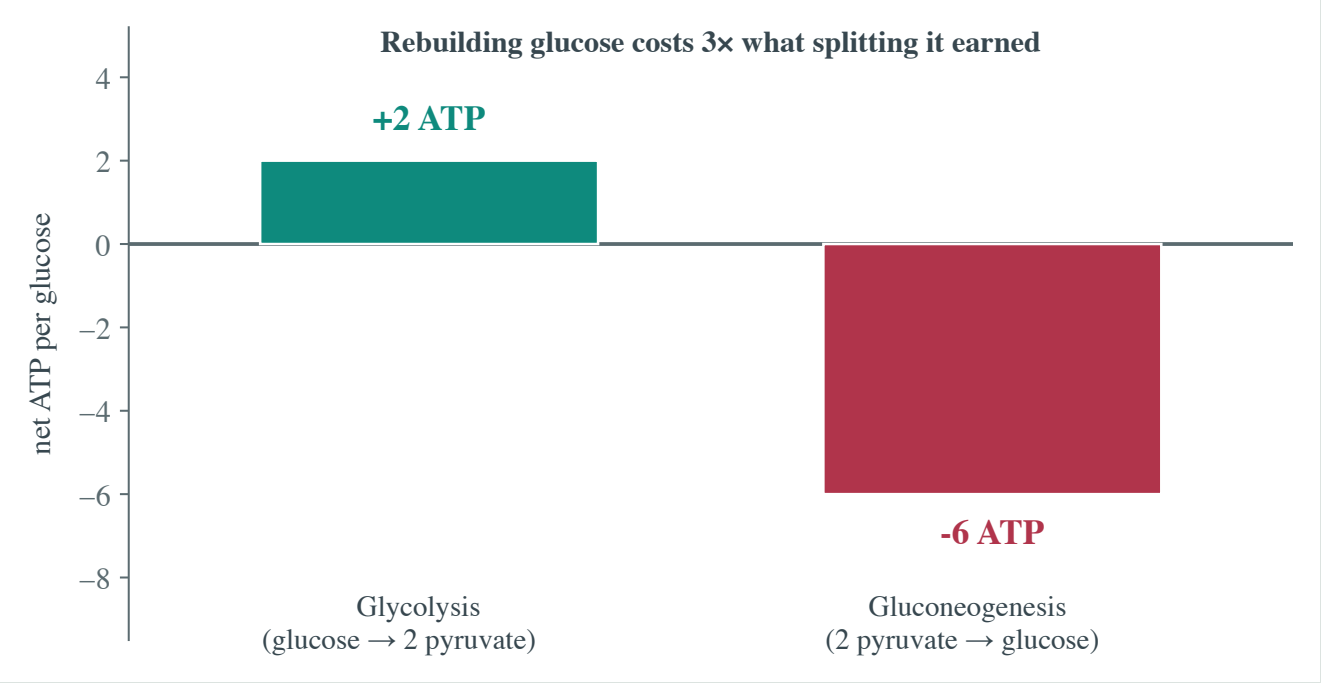
One on, the other off

Glycolysis and gluconeogenesis are **opposite directions** — running both at once would just **burn ATP in a circle**. So they're **reciprocally regulated**: **glucagon** and **cortisol** (fasting) turn gluconeogenesis **on**, **insulin** (fed) turns it **off**, and **fructose-2,6-bisphosphate** flips the two in opposite directions at PFK-1 / FBPase-1.

Reciprocal: fructose-2,6-bisphosphate turns one ON as it turns the other OFF — you never waste ATP running both directions at once.

The cost — and why the liver pays it

Gluconeogenesis is **expensive**: **6 high-energy phosphates** (ATP + GTP) to build one glucose, versus the 2 ATP glycolysis got from splitting one. That's why it's a **fasting** program, run when blood sugar dips — and why the liver's ability to do it keeps your **brain fueled** through the night.

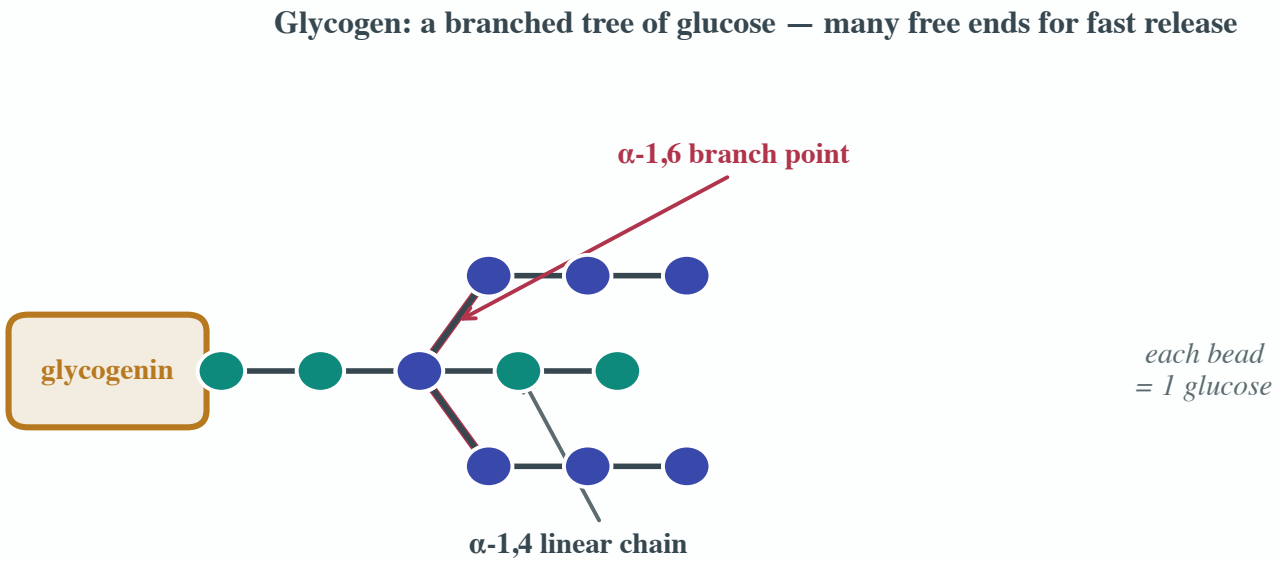


6 · Glycogen — Storing & Mobilizing Glucose

"Meet glycogen — your glucose battery. Build it, break it, and see how one phosphate flips the whole thing between store and spend."

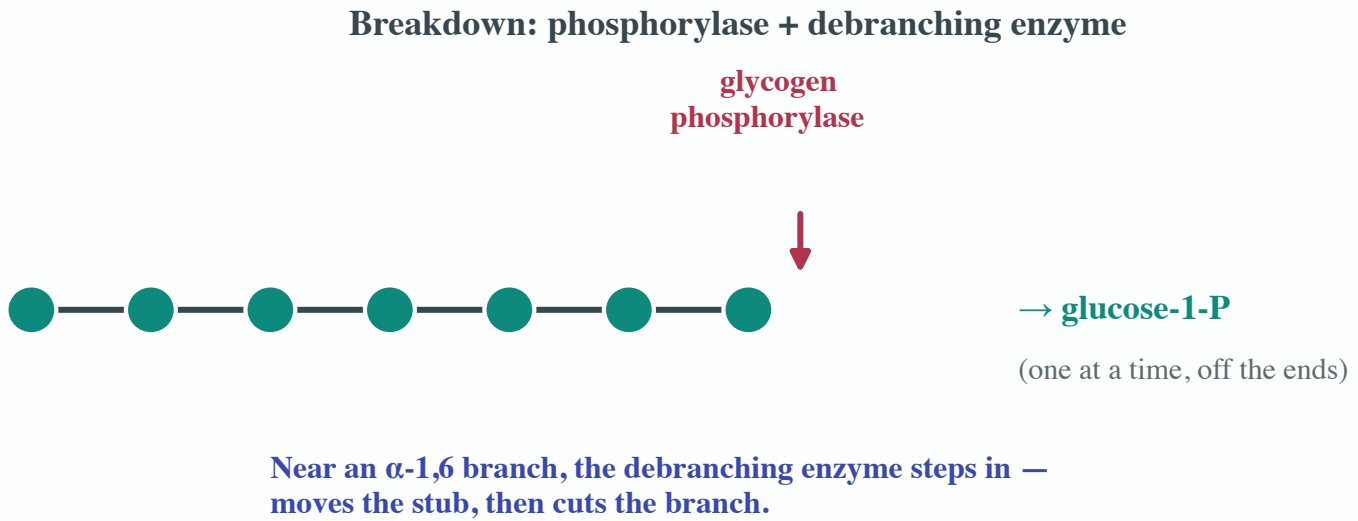
Glycogen: your glucose battery

When glucose is plentiful, you don't leave it floating around — you **store** it as **glycogen**, a big branched polymer of glucose. Straight chains use **α-1,4** bonds; every ~10 residues an **α-1,6** bond starts a **branch**. Why so branched? **Many free ends** means you can release glucose **fast** when you need it.



Breaking it down

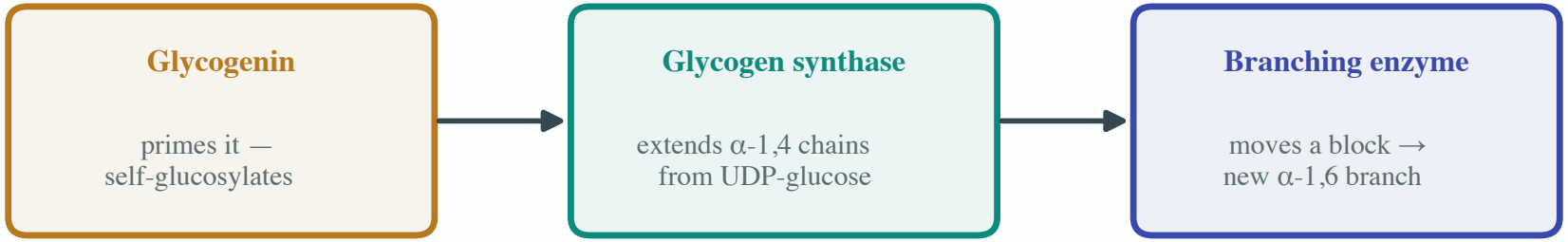
Glycogen phosphorylase chews glucose off the **ends** one at a time — and cleverly uses **phosphate** (not water) so the product comes out already primed as **glucose-1-phosphate → glucose-6-P** (**muscle** burns it in glycolysis; the **liver** frees it as blood glucose). It stops near a branch, where the **debranching enzyme** clears the **α-1,6** knot.



Building it up

Synthesis needs a **primer**: the protein **glycogenin** starts the chain by adding glucose **to itself**. Then **glycogen synthase** extends the **α-1,4** chain — adding glucose delivered as **UDP-glucose**, the activated donor — and a **branching enzyme** relocates a block to make the **α-1,6** branches.

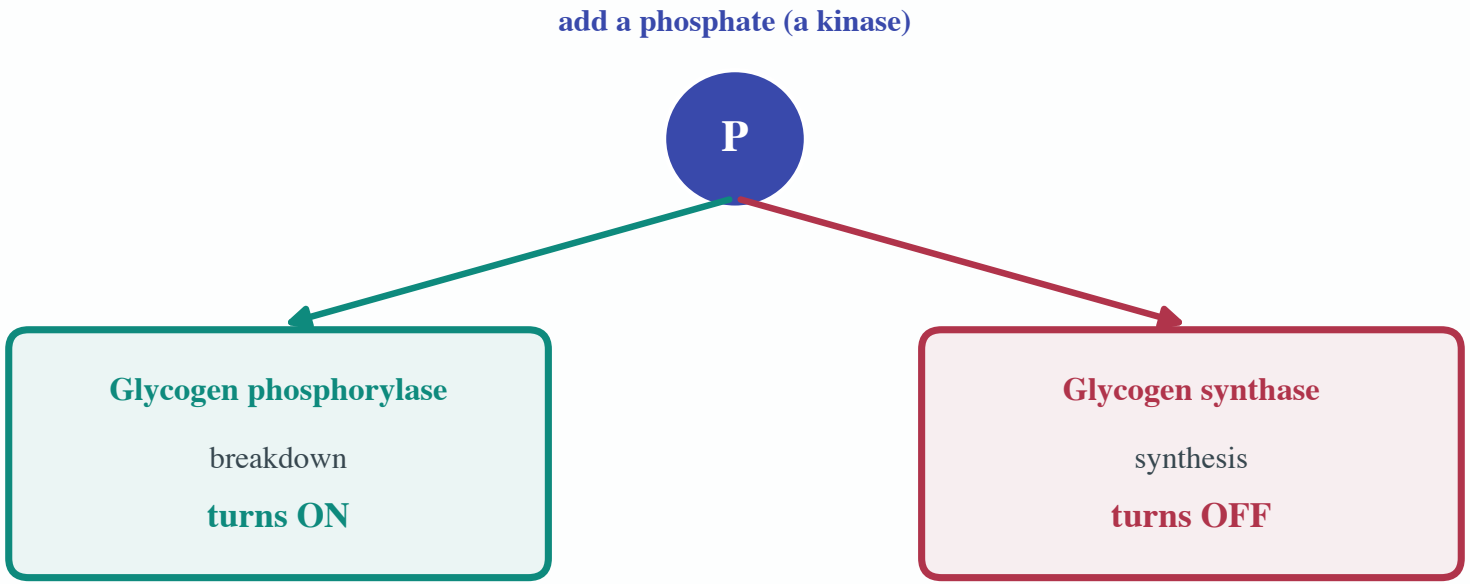
Synthesis: a primer, a chain-builder, and a brancher



Glucose is added as UDP-glucose — the activated donor.

One phosphate, opposite effects

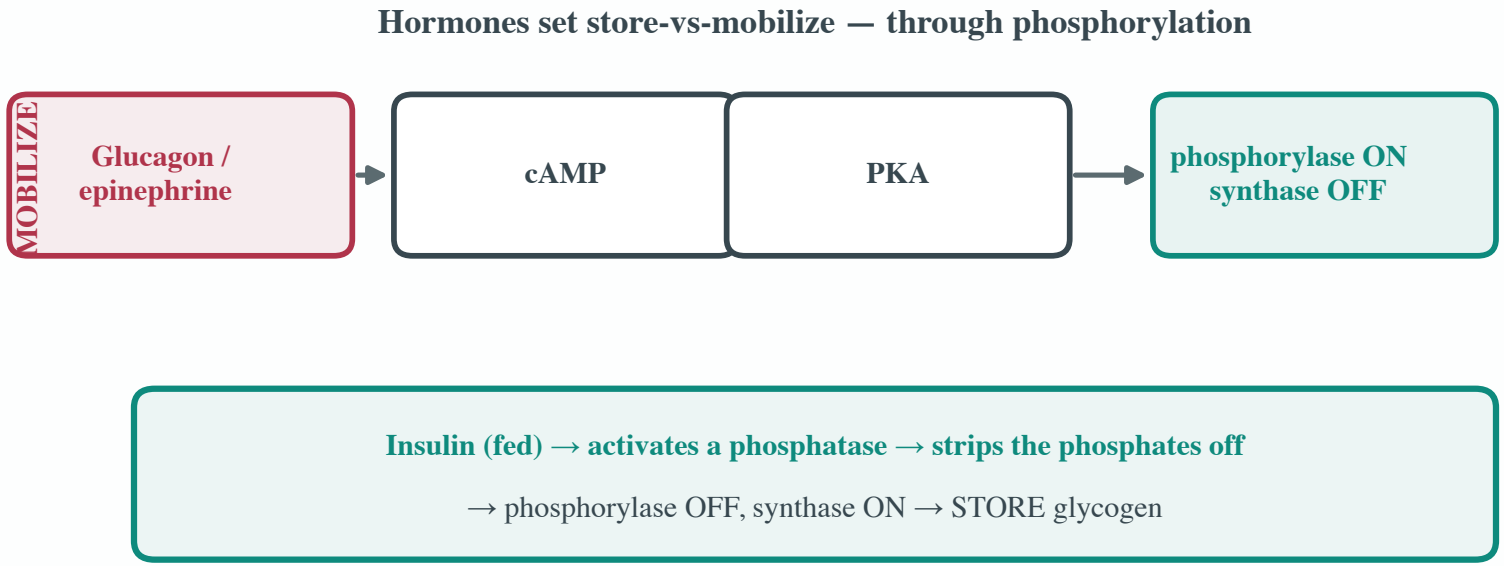
Here's the elegant part: a **single phosphorylation** controls **both** enzymes — but in **opposite directions**. Adding a phosphate turns **phosphorylase ON** (break down) and **synthase OFF** (stop building). So you never waste energy doing both at once. **AMP** (low energy) also flips phosphorylase on; **ATP** and **glucose-6-P** (plenty) turn it off.



Allosteric too: AMP (low energy) turns phosphorylase ON; ATP / glucose-6-P (plenty) turn it OFF.

Hormones: store or mobilize

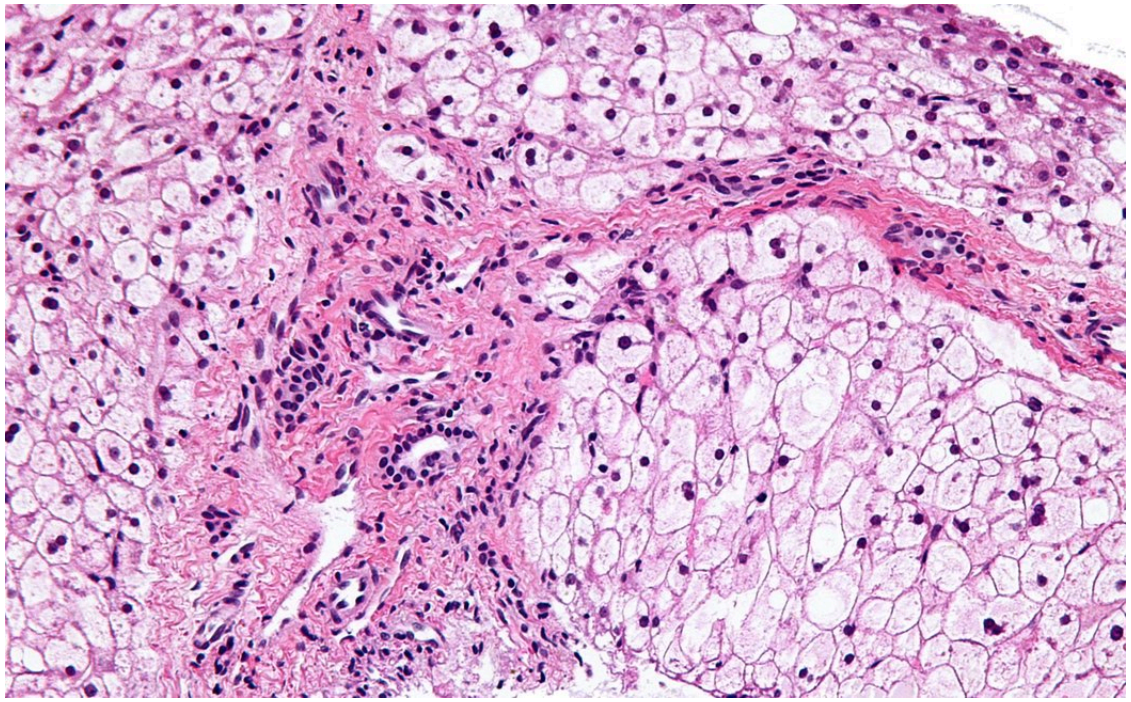
The hormones drive that phosphorylation. **Glucagon** (fasting) and **epinephrine** (stress) fire off a **cAMP → PKA** cascade that **phosphorylates** everything → **breakdown ON**. **Insulin** (fed) activates a **phosphatase** that **strips the phosphates off** → **synthesis ON**. Store when fed, mobilize when stressed.



Epinephrine in muscle: fuel for fight-or-flight. Glucagon in liver: glucose for the blood.

When storage goes wrong

If an enzyme in this cycle is **missing**, glycogen **piles up** where it shouldn't — the **glycogen storage diseases**. In **von Gierke** disease (no glucose-6-phosphatase), the **liver swells** with glycogen and blood sugar crashes between meals. You can see it here: hepatocytes so stuffed with glycogen they look **pale and ballooned**.



Liver histology (glycogen storage disease): Nephron, CC BY-SA 3.0 (Wikimedia Commons)

Can you…?

- □ walk all ten steps of glycolysis — the enzymes, the reactions, and the running ATP/NADH ledger (net 2 ATP + 2 NADH per glucose)?
- □ identify the regulated steps (hexokinase, PFK-1, pyruvate kinase) and the hormonal + fructose-2,6-bisphosphate control of glycolysis?
- □ trace the fates of pyruvate — aerobic oxidation, lactate fermentation, and ethanol fermentation — and the Cori cycle?
- □ explain how galactose and fructose feed into glycolysis, and the diseases when they can't (galactosemia, fructose→fat)?
- □ describe gluconeogenesis and its four bypass enzymes, and how glycogen is built and broken down under hormonal control?

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