Lipid Metabolism

BCH 100 — Introductory Biochemistry · Dr. Radi

By the end of this unit, you can…

- Describe lipoproteins (chylomicrons, VLDL, LDL, HDL) and how fat and cholesterol move through the blood
- Trace fat mobilization — lipolysis to glycerol + free fatty acids, activation to acyl-CoA, and the carnitine shuttle into the mitochondrion
- Walk the four steps of β-oxidation with its enzymes and $FADH_2$/NADH/acetyl-CoA yield, and calculate the ATP from oxidizing a fatty acid
- Explain ketone-body synthesis and use as a fasting fuel, and distinguish physiological ketosis from diabetic ketoacidosis
- Outline fatty-acid synthesis (acetyl-CoA carboxylase, fatty acid synthase, the citrate shuttle) and the reciprocal regulation that keeps synthesis and breakdown from running at once

Today's route

1. Lipoproteins: Fat in the Blood
2. Getting Fat Ready to Burn
3. β-Oxidation
4. Ketone Bodies
5. Building Fat

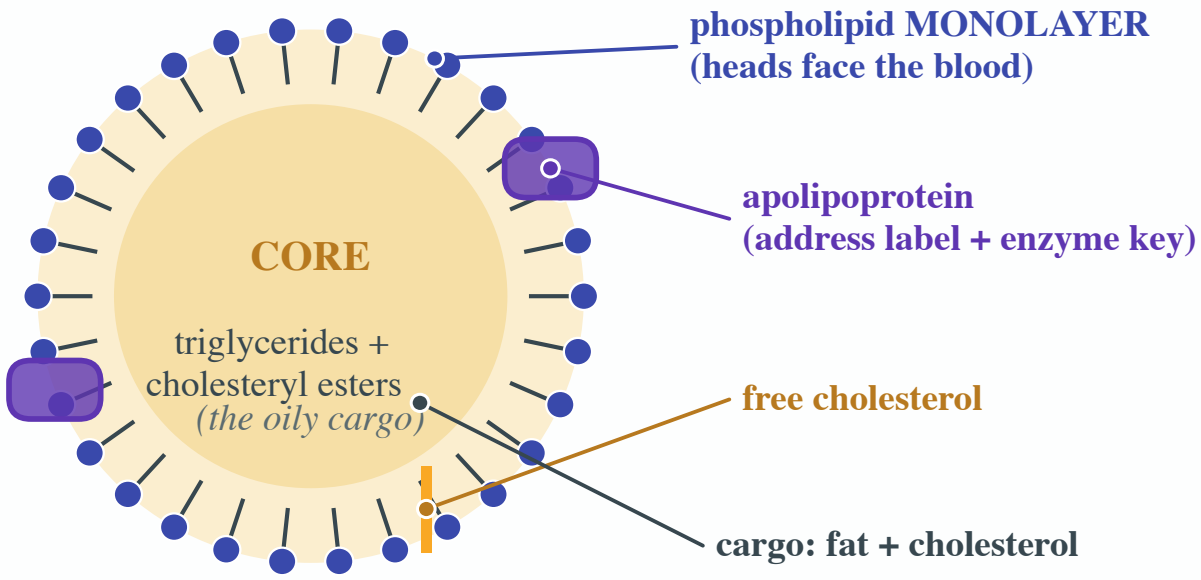
1 · Lipoproteins: Fat in the Blood

"Fat and water don't mix – so how does a greasy meal travel through watery blood? In tiny cargo ships called lipoproteins."

Fat can't swim — so it takes a boat

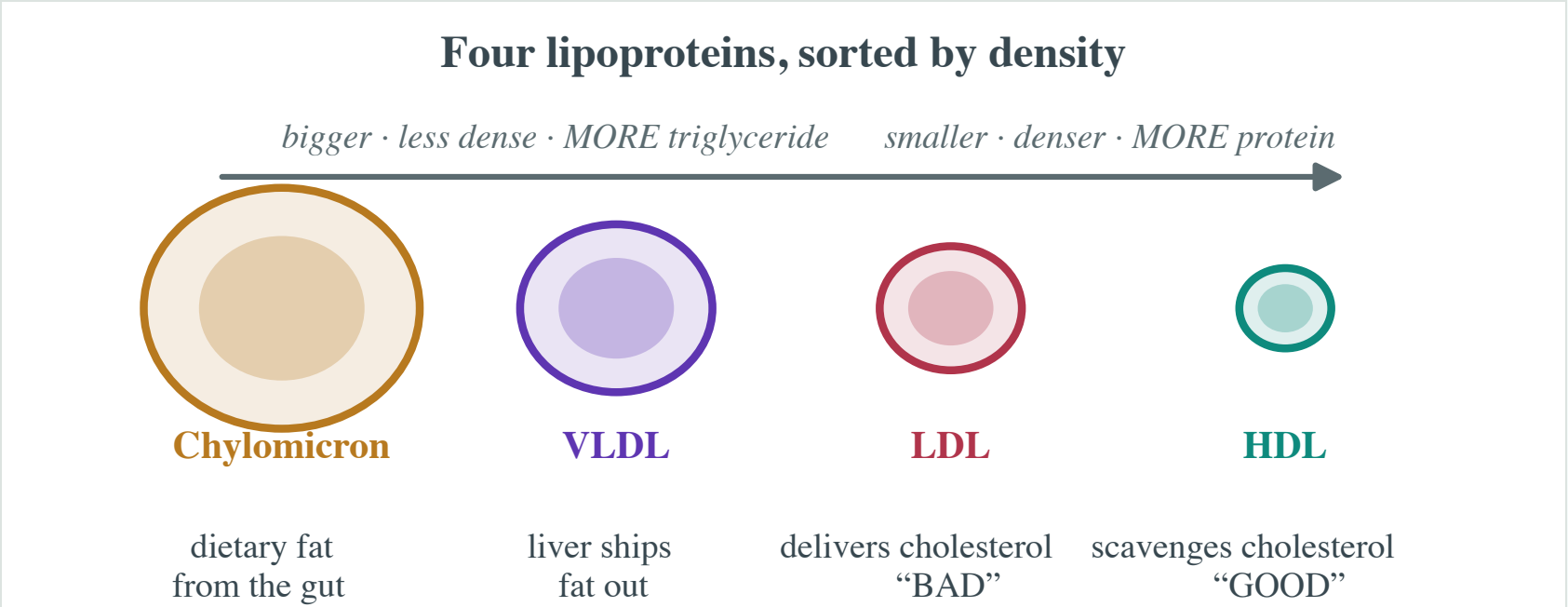
You just ate a greasy meal. Now that fat has to cross your **watery blood** to reach your muscles and fat stores — and **oil doesn't dissolve in water**. The fix is a **lipoprotein**: a little droplet of **oily cargo** (triglycerides + cholesteryl esters) wrapped in a **single layer of phospholipids** — heads out, facing the water — plus some **cholesterol** and **apolipoproteins**. Those apoproteins are the **address labels** that tell each particle where to dock.

A lipoprotein: an oil droplet in a water-friendly coat



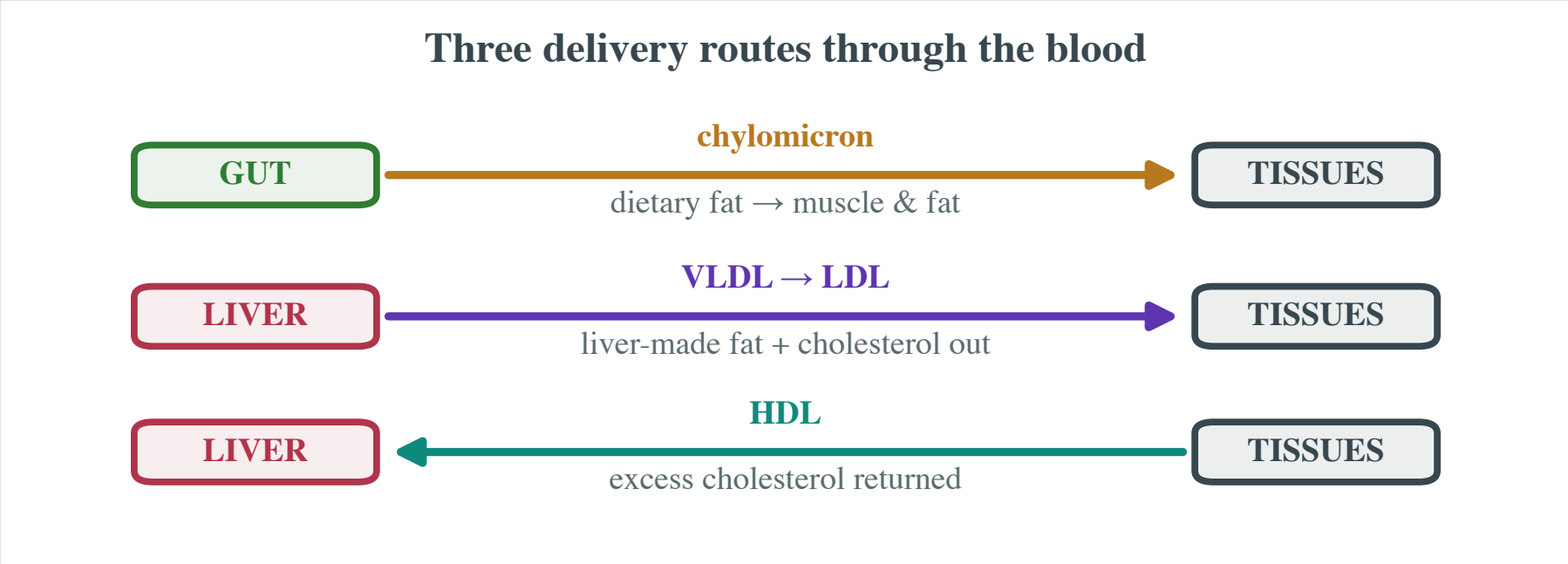
Four ships, sorted by density

There isn't one lipoprotein — there are **four**, and the way to keep them straight is **density**. The more **fat** a particle carries, the **bigger and lighter** it is; the more **protein**, the **smaller and denser**. **Chylomicrons** are huge, greasy, and light (dietary fat). **VLDL** is the liver's fat-export truck. **LDL** is denser and delivers cholesterol. **HDL** is the smallest and densest. Their names literally **are** their densities — Very-Low, Low, and High-Density Lipoprotein.



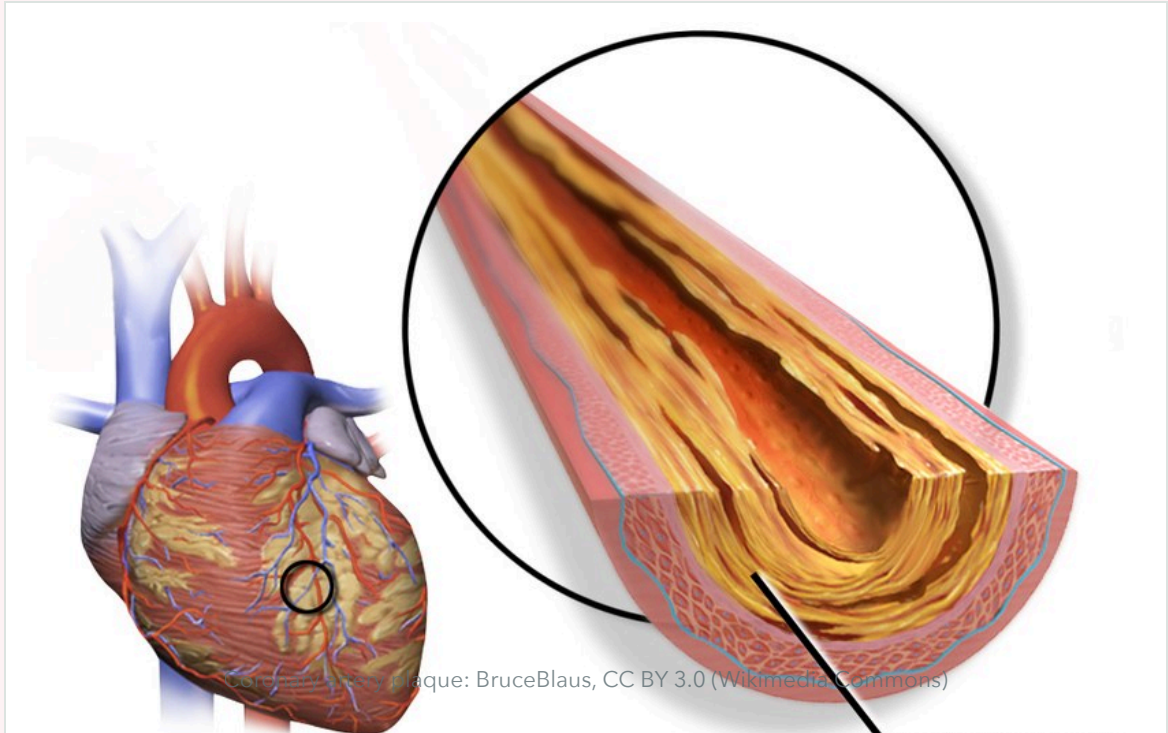
Where it all goes: three routes

Follow the fat and it makes sense. **Route 1 (dietary):** your **gut** packs a meal's fat into **chylomicrons** and ships it to muscle and fat tissue. **Route 2 (liver's own):** your **liver** loads fat and cholesterol into **VLDL**, which sheds triglyceride and shrinks into **LDL** as it delivers cholesterol around the body. **Route 3 (cleanup): HDL** cruises the tissues picking up **excess cholesterol** and carries it **back** to the liver — the only route running in reverse.



"Good" cholesterol vs "bad"

Now the famous part. **LDL** drops cholesterol **off** in your tissues — and when there's too much, it seeps into **artery walls**, where it's oxidized, triggers inflammation, and builds a **plaque** that narrows the vessel (**atherosclerosis**, shown here). That's why LDL is the **"bad"** cholesterol. **HDL** does the opposite — it hauls cholesterol **away** to the liver, so it's the **"good"** one. Same molecule, cholesterol; the difference is **which direction it's traveling**.



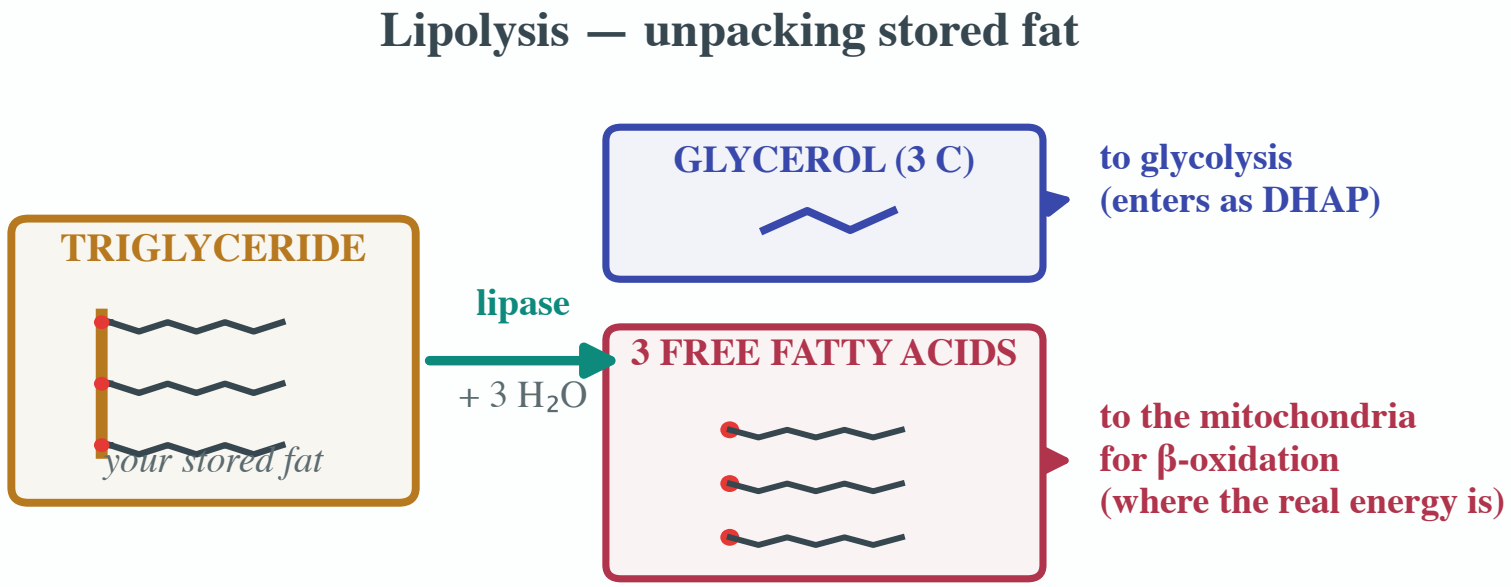
Coronary artery plaque: BruceBlaus, CC BY 3.0 (Wikimedia Commons)

2 · Getting Fat Ready to Burn

"Before a fatty acid can be burned it has to be released, tagged with CoA, and smuggled into the mitochondrion. Three gates before the fire."

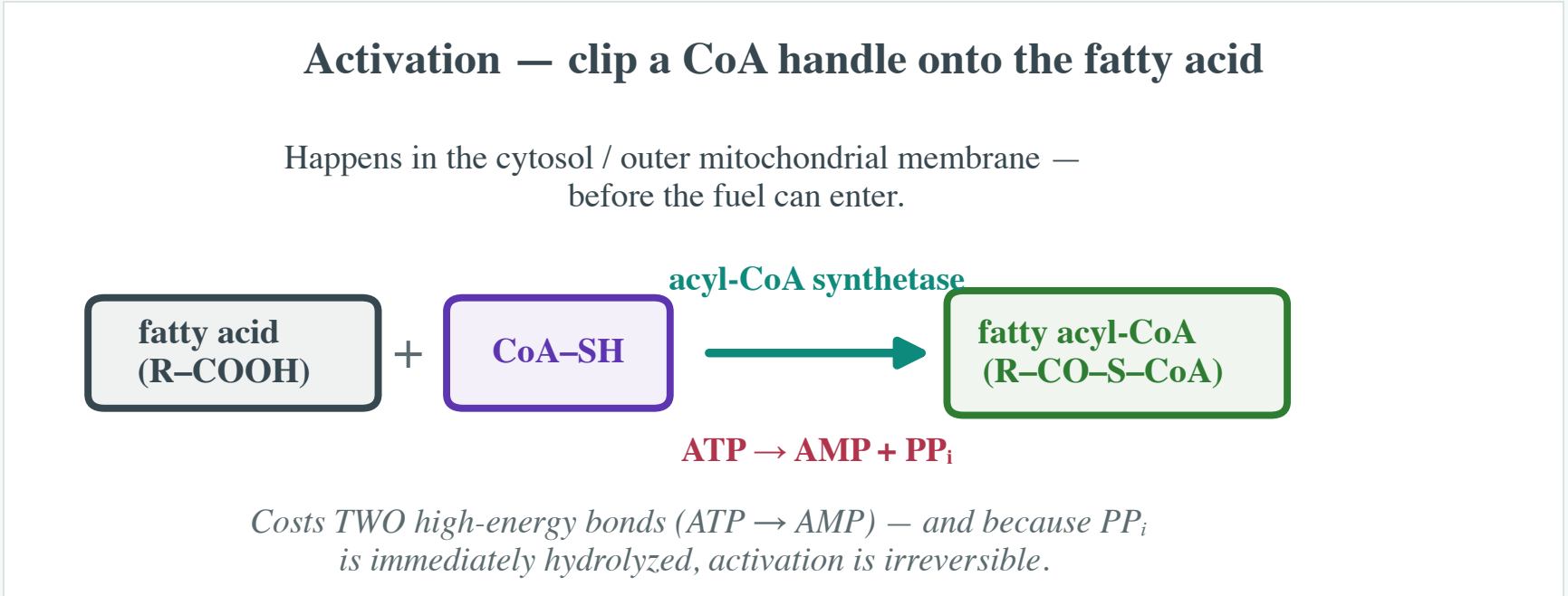
Step one: unlock the fat

Fat is the body's **biggest fuel tank** — pound for pound it stores **more than twice** the energy of carbohydrate, and you carry far more of it. But it's locked away as **triglyceride** in your fat cells. To use it, an enzyme called **lipase** hydrolyzes each triglyceride into **glycerol** + **three free fatty acids**. The **glycerol** slips into **glycolysis** (as DHAP). The **fatty acids** — where nearly all the energy is — head for the **mitochondria** to be burned.



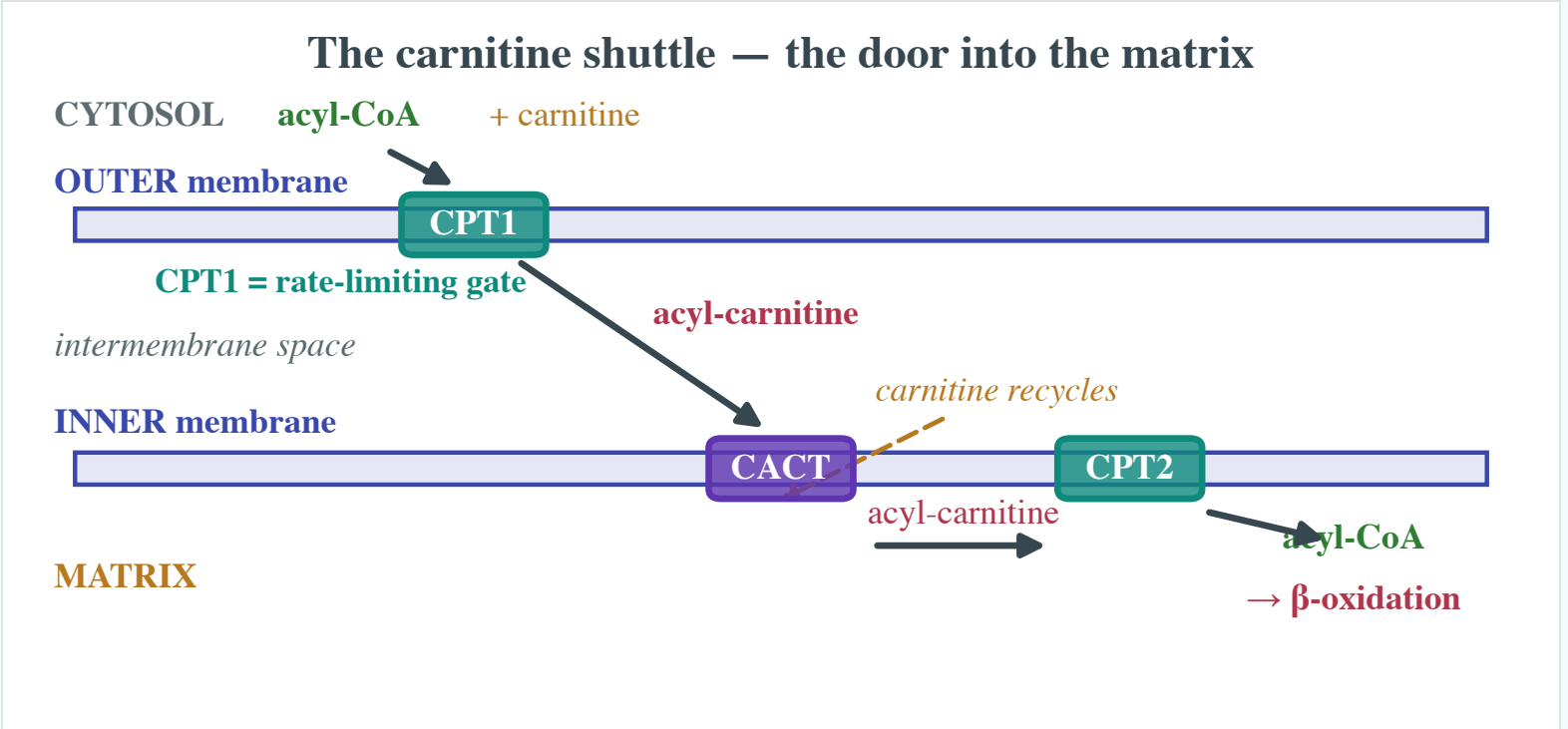
Step two: clip on a CoA handle

A free fatty acid is **unreactive** — the cell can't do anything with it until it's **activated**. The enzyme **acyl-CoA synthetase** attaches **coenzyme A**, turning the fatty acid into a **fatty acyl-CoA**. This costs **one ATP — but broken all the way to AMP + PP_i**, so it's really **two high-energy bonds**. And because the PP_i is immediately hydrolyzed, activation is **irreversible**: once you've committed a fatty acid, there's no going back.



Step three: the carnitine shuttle

Now a problem: **long-chain acyl-CoA can't cross the inner mitochondrial membrane**. So the cell ferries it: **CPT1** swaps CoA for **carnitine** (→ acyl-carnitine), a **translocase** carries it across, and **CPT2** swaps carnitine back for **CoA** — regenerating **acyl-CoA in the matrix**, right where β-oxidation happens. **CPT1 is the rate-limiting gate**: the cell's main control point for burning fat.



Why this is the marathoner's engine

This whole pathway is what powers **endurance**. In a long run, once the quick sugar is gone, your muscles switch to **burning fat** — which means running fatty acids through activation, the **carnitine shuttle**, and β-oxidation, hour after hour. It's also why the shuttle matters clinically: people with **CPT II deficiency** can't move fat into the mitochondria, so **prolonged exercise or fasting** triggers **muscle pain and breakdown** — their cells simply can't reach their biggest fuel tank.

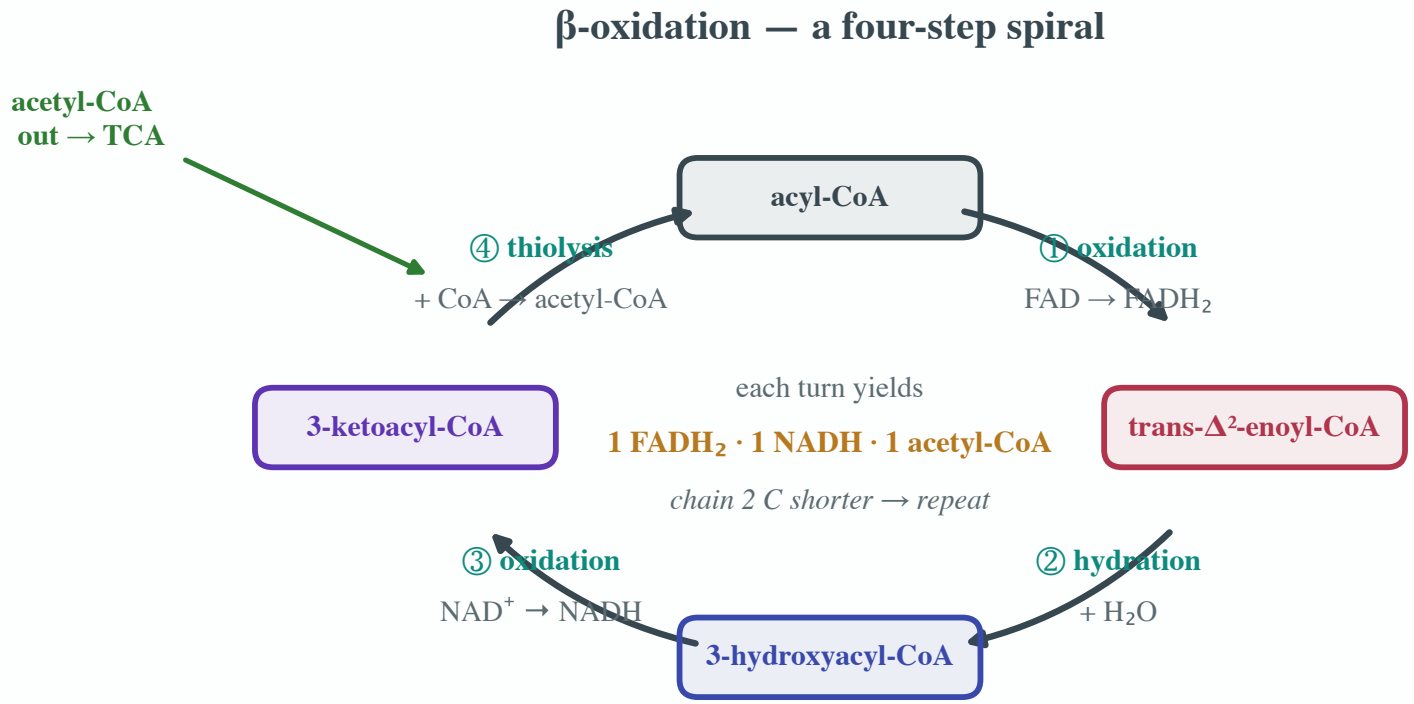
Marathon finisher: Shixart1985, CC BY 2.0 (Wikimedia Commons)

3 · β-Oxidation

"Now the fire. A fatty acid is chewed off two carbons at a time — the same four reactions, over and over — pouring out NADH, $FADH_2$, and acetyl-CoA."

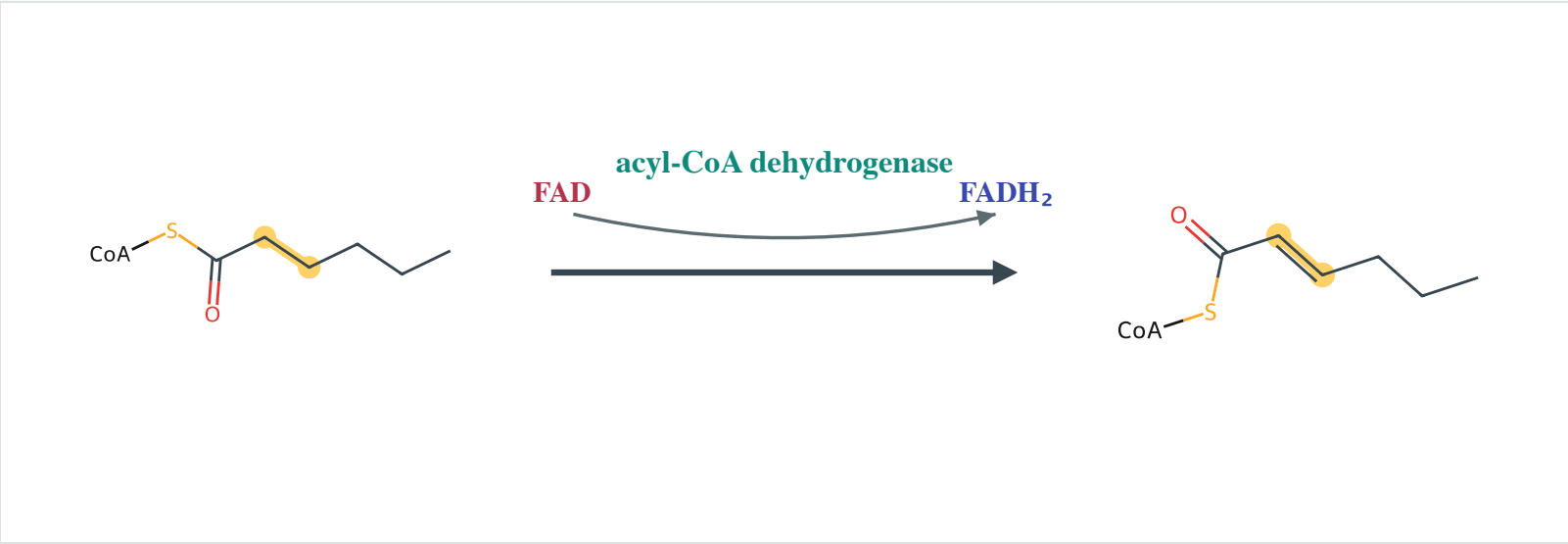
The spiral that eats a fatty acid

Once a fatty acyl-CoA is in the matrix, it's burned by **β-oxidation** — named because the action happens at the **β-carbon** (the third carbon, counting the carbonyl as one). It's a **spiral**: the same **four reactions — oxidize, hydrate, oxidize, cut** — run over and over. Each lap **clips off the last two carbons as acetyl-CoA** and hands you **one $FADH_2$ and one NADH**, leaving a fatty acid two carbons shorter to go around again.



Step ①: oxidation → makes $FADH_2$

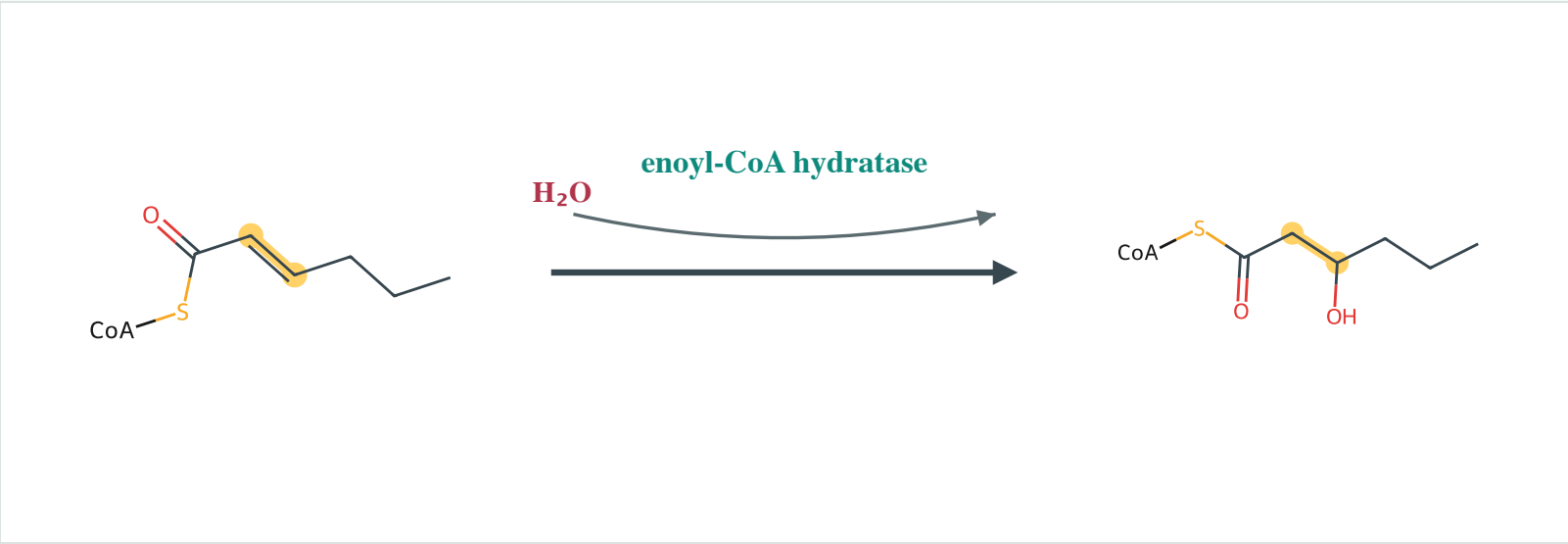
First, **acyl-CoA dehydrogenase** pulls two hydrogens off the α- and β-carbons, creating a **trans double bond** between them (a **trans**-Δ^2 -enoyl-CoA). Those electrons are caught by **FAD**, making **$FADH_2$** – worth ~1.5 ATP downstream. This is the step that MCAD (medium-chain) does; keep an eye on it – it comes back at the end of the lecture.



This turn so far: 1 $FADH_2$

Step ②: hydration

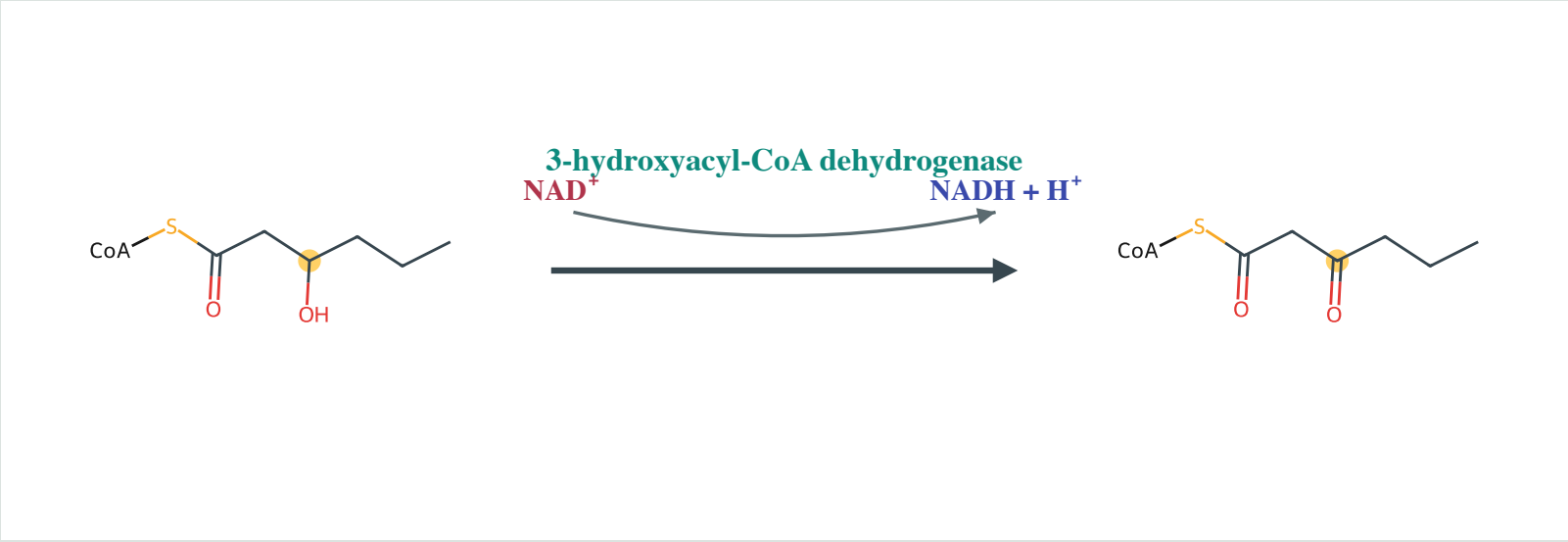
Next, **enoyl-CoA hydratase** adds a molecule of **water** across that new double bond, parking a **hydroxyl group on the β-carbon**. No electrons are harvested here — it's a **setup move**, converting the double bond into a β-hydroxyl so the next enzyme has something to oxidize. The product is **3-hydroxyacyl-CoA**.



This turn so far: 1 $FADH_2$

Step ③: oxidation → makes NADH

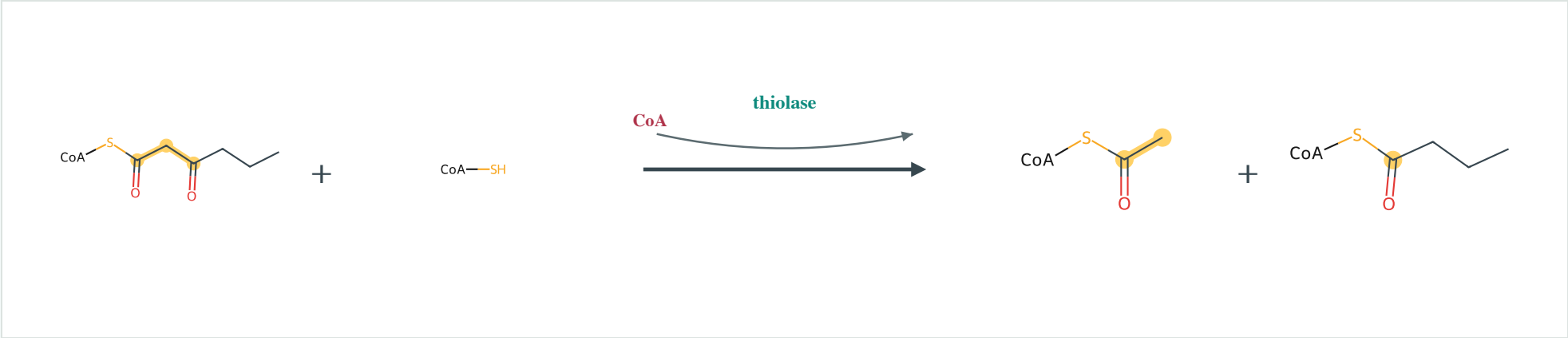
Now **3-hydroxyacyl-CoA dehydrogenase** oxidizes that **β-hydroxyl into a β-keto** group – turning the carbon into a **ketone**. The two electrons go to **NAD^+**, making **NADH** – worth ~2.5 ATP. The molecule is now a **3-ketoacyl-CoA**, primed with a carbonyl exactly where the chain is about to be cut.



This turn so far: 1 $FADH_2$ · 1 NADH

Step ④: thiolysis → releases acetyl-CoA

Finally, **thiolase** breaks the bond between the α- and β-carbons, and a **fresh CoA** grabs the loose end. Out pops **acetyl-CoA** (the two-carbon piece), and what's left is an **acyl-CoA two carbons shorter** — ready to re-enter the spiral at step ①. One lap: **1 $FADH_2$, 1 NADH, 1 acetyl-CoA**.



One full turn: 1 $FADH_2$ · 1 NADH · 1 acetyl-CoA · chain −2 C

Add it up: why fat is such rich fuel

Take **palmitate (C16)**. It goes around **7 times** — producing **8 acetyl-CoA, 7 $FADH_2$, and 7 NADH**. Send the acetyl-CoA through the **TCA cycle** and the carriers through the **electron transport chain**, subtract the **2 ATP** you spent activating it up front, and you clear about **106 ATP** — versus roughly **32** from a glucose. Fat stores more energy **and** releases more of it per molecule.

Cashing in one palmitate (C16)

7 turns of the spiral → 8 acetyl-CoA + 7 $FADH_2$ + 7 NADH

8 acetyl-CoA → TCA cycle	8 × 10	**+80**
7 NADH → ETC	7 × 2.5	**+17.5**
7 $FADH_2$ → ETC	7 × 1.5	**+10.5**
activation (once, up front)	ATP → AMP + PP_i	**– 2**
NET per palmitate		**≈ 106 ATP**

Compare: one glucose ≈ 32 ATP. Gram for gram and molecule for molecule, fat is the richer fuel.

When step ① is broken

That first enzyme comes in chain-length versions — long, medium, and short. **MCAD deficiency** (medium-chain acyl-CoA dehydrogenase) is one of the **most common inherited metabolic disorders**, and it's dangerous precisely because fat is a **backup fuel**: as long as a baby eats often, glucose covers everything. But during a **fast or an illness**, when the body must switch to **burning fat**, an MCAD-deficient infant **can't** — blood sugar crashes and they can become critically ill. That's why nearly every newborn is **screened for it at birth**.

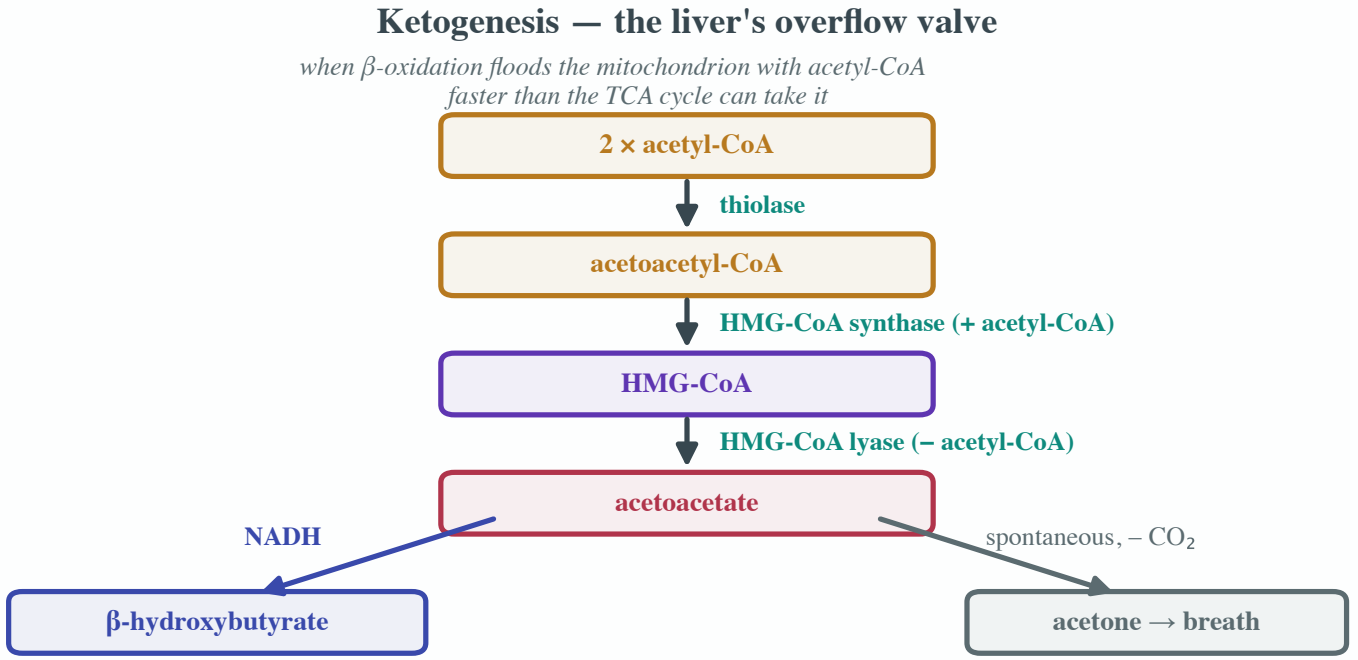
Sleeping newborn: esudroff, CC0 (Wikimedia Commons)

4 · Ketone Bodies

"Burn fat fast enough and acetyl-CoA piles up. The liver packages the overflow into ketone bodies — a water-soluble fuel even your brain can run on."

Plan B for acetyl-CoA

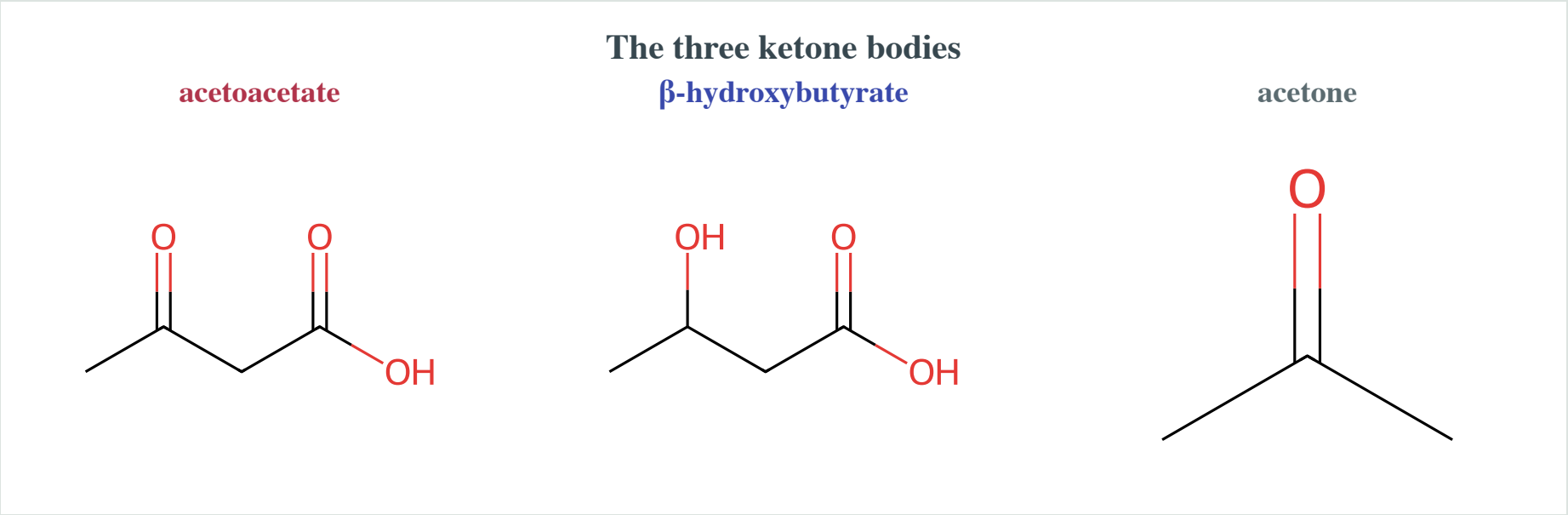
β-oxidation is fast — and in a long **fast** or on a **low-carb** diet, it floods the mitochondrion with **acetyl-CoA faster than the TCA cycle can burn it** (the oxaloacetate it needs is being siphoned off to make glucose). So the **liver** does something clever with the excess: it condenses acetyl-CoA — two at a time, through an **HMG-CoA** intermediate — into **ketone bodies**. It's an overflow valve, turning a traffic jam of acetyl-CoA into a fuel it can ship out.



β-hydroxybutyrate & acetoacetate travel the blood as fuel; acetone is just exhaled.

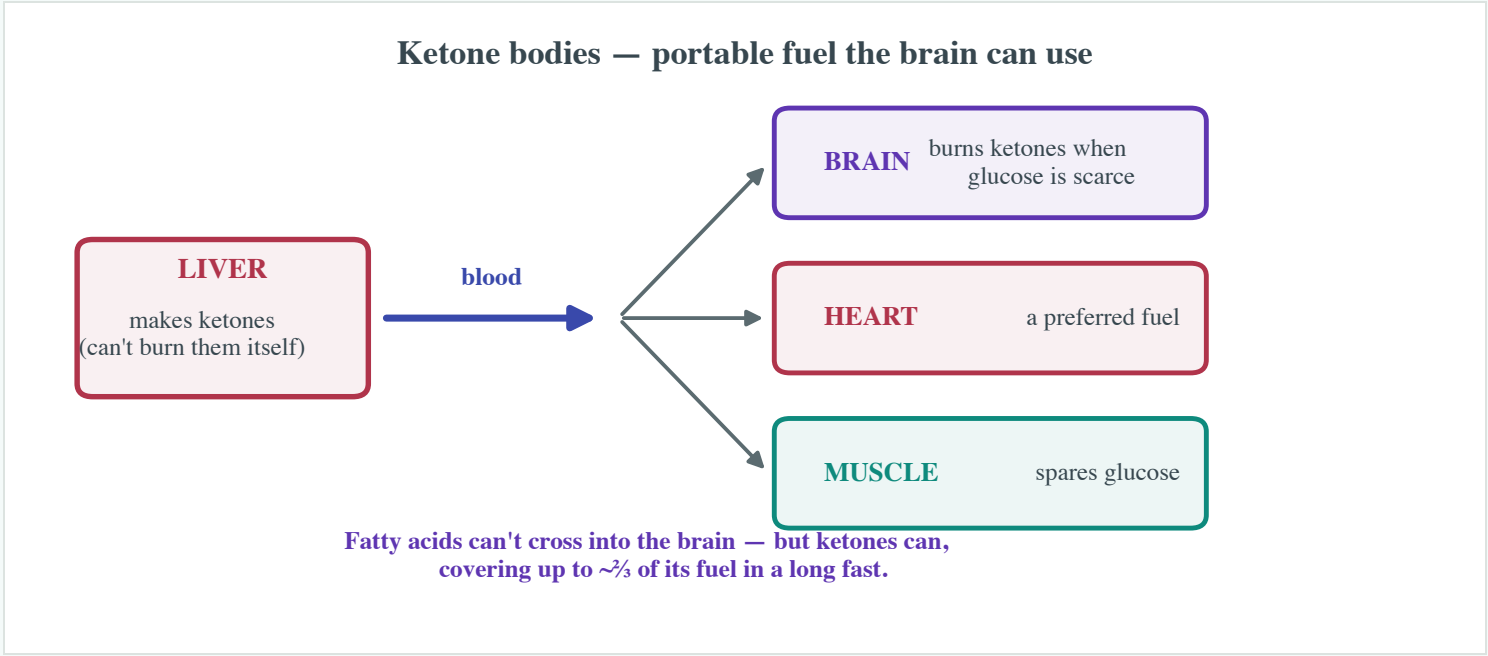
Meet the three ketone bodies

There are **three**, and despite the name only two are truly "keto." **Acetoacetate** is the parent — a simple β-keto acid. Reduce it (using NADH) and you get **β-hydroxybutyrate**, actually the **most abundant** one in blood (and, confusingly, not a ketone at all — it's an alcohol). Let acetoacetate sit and it slowly loses CO_2 to become **acetone** — the one you can't use, so you **breathe it out** (that "fruity" breath).



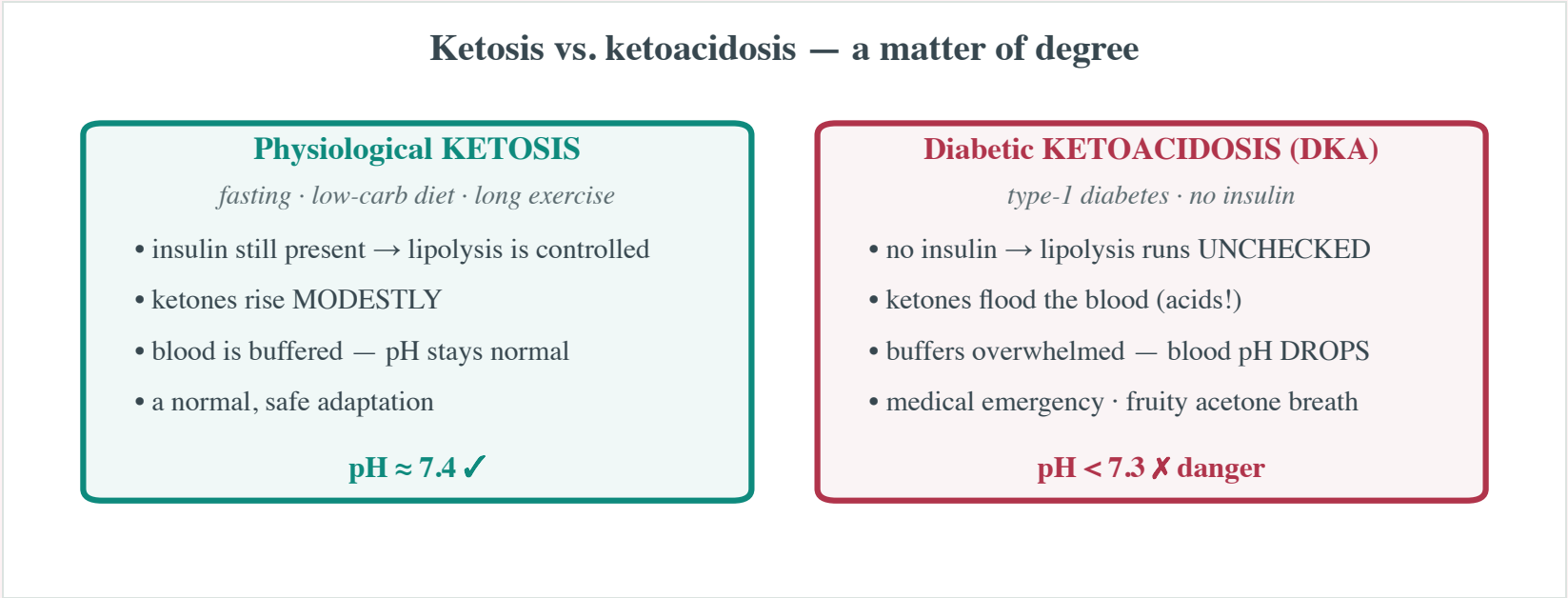
The fuel your brain can actually use

Here's why ketones matter. Your **brain** normally runs on **glucose** and **can't burn fatty acids** — they don't cross into it. So in a long fast, what keeps you thinking? **Ketone bodies.** The liver makes them but **can't burn them itself**; it ships them through the blood to the **brain, heart, and muscle**, which convert them **back to acetyl-CoA** and feed the TCA cycle. In prolonged starvation, ketones can supply up to **two-thirds** of the brain's energy — sparing precious glucose.



Ketosis vs. ketoacidosis

Ketones are **acids**, so the difference between **helpful** and **dangerous** is **how many**. **Physiological ketosis** — from fasting, keto diets, or long exercise — is **controlled**: insulin still reins in fat release, ketones rise modestly, and your blood **buffers** hold pH at 7.4. **Diabetic ketoacidosis (DKA)** is the runaway version: in **type-1 diabetes** with **no insulin**, lipolysis goes unchecked, ketones flood the blood faster than buffers can cope, and **blood pH crashes** — a life-threatening emergency. Same molecules; a matter of **degree**.

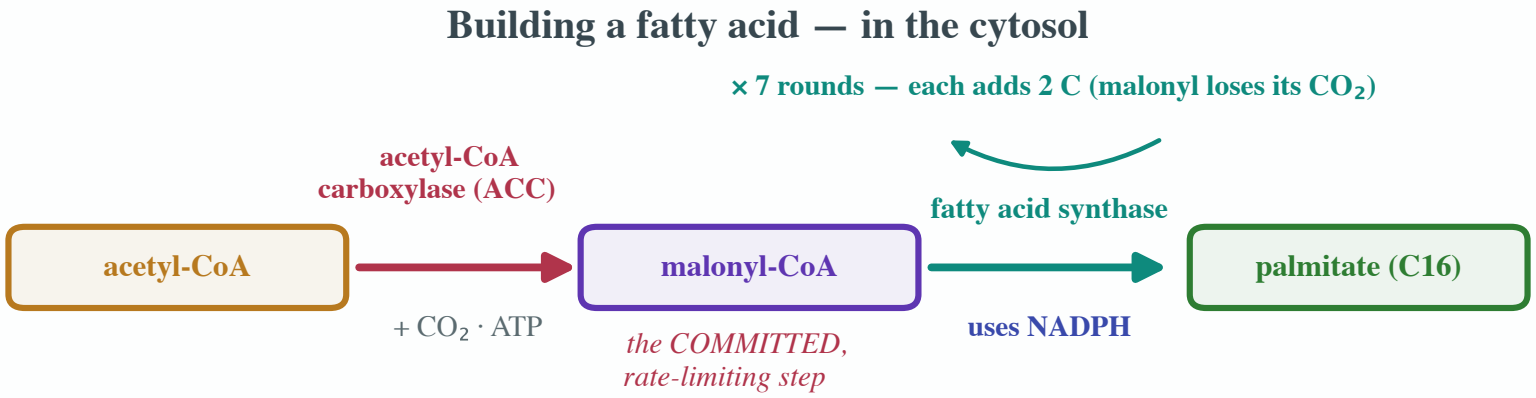


5 · Building Fat

"Making fat is burning it run backwards — different place, different carriers, different cofactor. And a single molecule decides whether you build or burn."

Building fat: the plan

When you have **more fuel than you need**, you store it — and that means **making fatty acids**. The build happens in the **cytosol** (not the mitochondrion), and it needs two things: **carbon**, delivered as **acetyl-CoA**, and **reducing power**, delivered as **NADPH**. The committed step is **acetyl-CoA carboxylase (ACC)**, which spends ATP and CO_2 to make **malonyl-CoA**. Then **fatty acid synthase** adds **two carbons at a time** — seven rounds — to build **palmitate (C16)**.

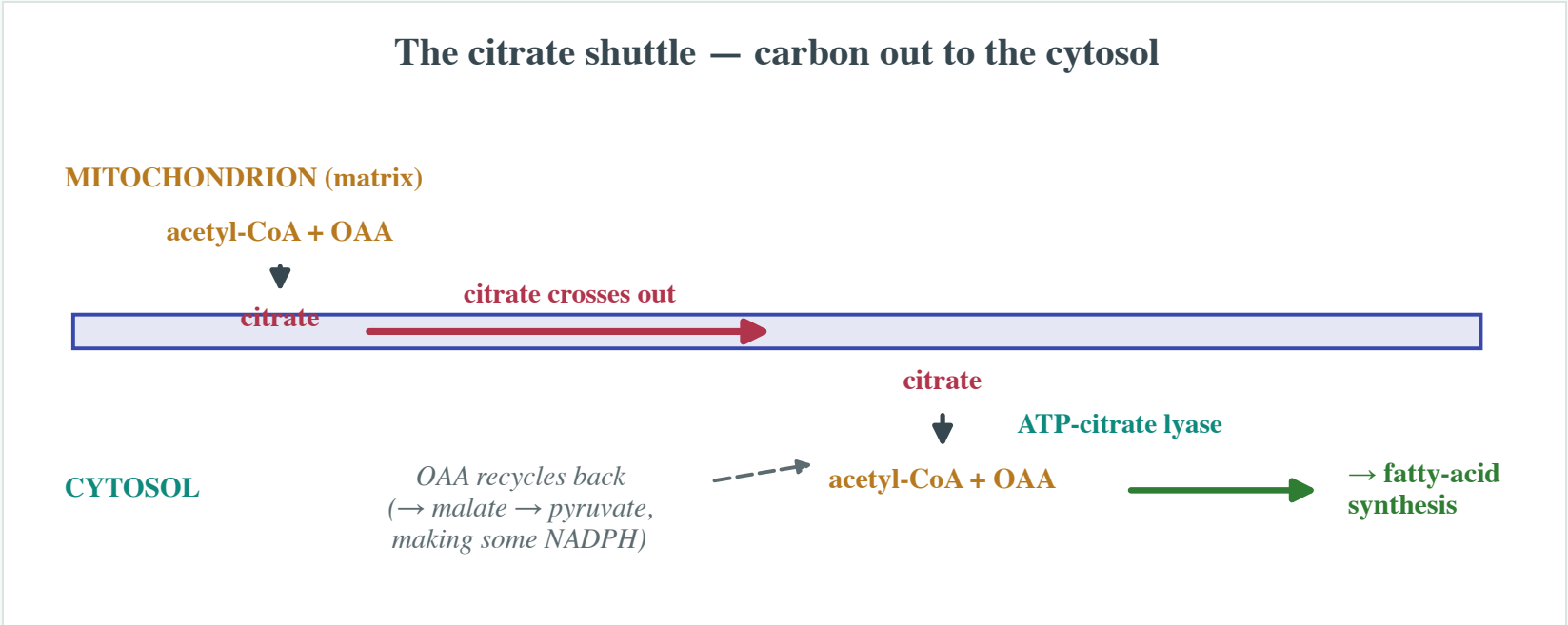


Carbon comes in as acetyl-CoA; the reducing power is NADPH (from the pentose-phosphate pathway).

Note the flip from β-oxidation: this happens in the CYTOSOL — it builds rather than breaks.

Getting the carbon out: the citrate shuttle

There's a logistics problem: acetyl-CoA is made **inside the mitochondrion**, but fat is built **in the cytosol** — and acetyl-CoA **can't cross** the inner membrane. The trick: in the matrix, acetyl-CoA is joined to **oxaloacetate** to make **citrate** (yes, the TCA intermediate), which **can** cross out. In the cytosol, **ATP-citrate lyase** splits citrate **back** into acetyl-CoA + oxaloacetate. The acetyl-CoA feeds synthesis; the oxaloacetate cycles home, generating some **NADPH** on the way.



Burning vs. building: mirror images

Fatty-acid synthesis is not just β-oxidation in reverse gear — but it **rhymes** with it, point for point. Different **compartment** (cytosol vs. mitochondria), different **carrier** (ACP vs. CoA), and — crucially — a different **cofactor**: breakdown **makes NADH and $FADH_2$** to burn for ATP, while synthesis **spends NADPH** to build. One removes acetyl-CoA two carbons at a time; the other adds it (as malonyl-CoA). Learn one and you nearly know the other.

Burning vs. building — mirror images

	β-OXIDATION (burn)	SYNTHESIS (build)
where	**mitochondria**	**cytosol**
carrier	**coenzyme A**	**ACP**
cofactor	**makes NADH + $FADH_2$**	**spends NADPH**
2-C unit	**removes acetyl-CoA**	**adds malonyl-CoA**
chain	**shortens 2 C / turn**	**grows 2 C / round**
key enzyme	**thiolase**	**ACC · fatty acid synthase**

The switch: reciprocal regulation

Building and burning fat at the **same time** would just waste ATP in a **futile cycle** – so the cell makes sure only one runs at a time. The elegant part is the **switch**: **malonyl-CoA**, the very first building block of synthesis, also **blocks CPT1**, the gate into β-oxidation. So when you're **fed** (**insulin**, high citrate), ACC fires, malonyl-CoA rises, synthesis runs, and burning is **shut off**. When you're **fasting** (**glucagon**, epinephrine), ACC is switched off, malonyl-CoA falls, CPT1 opens, and you **burn**.

Reciprocal regulation — never both at once

FED → BUILD fat

insulin · high citrate

- insulin activates ACC
- ACC → makes malonyl-CoA
- **malonyl-CoA BLOCKS CPT1**

→ β-oxidation shut off

synthesis ON · burning OFF

FASTED → BURN fat

glucagon · epinephrine

- glucagon inactivates ACC
- malonyl-CoA falls
- **CPT1 opens**

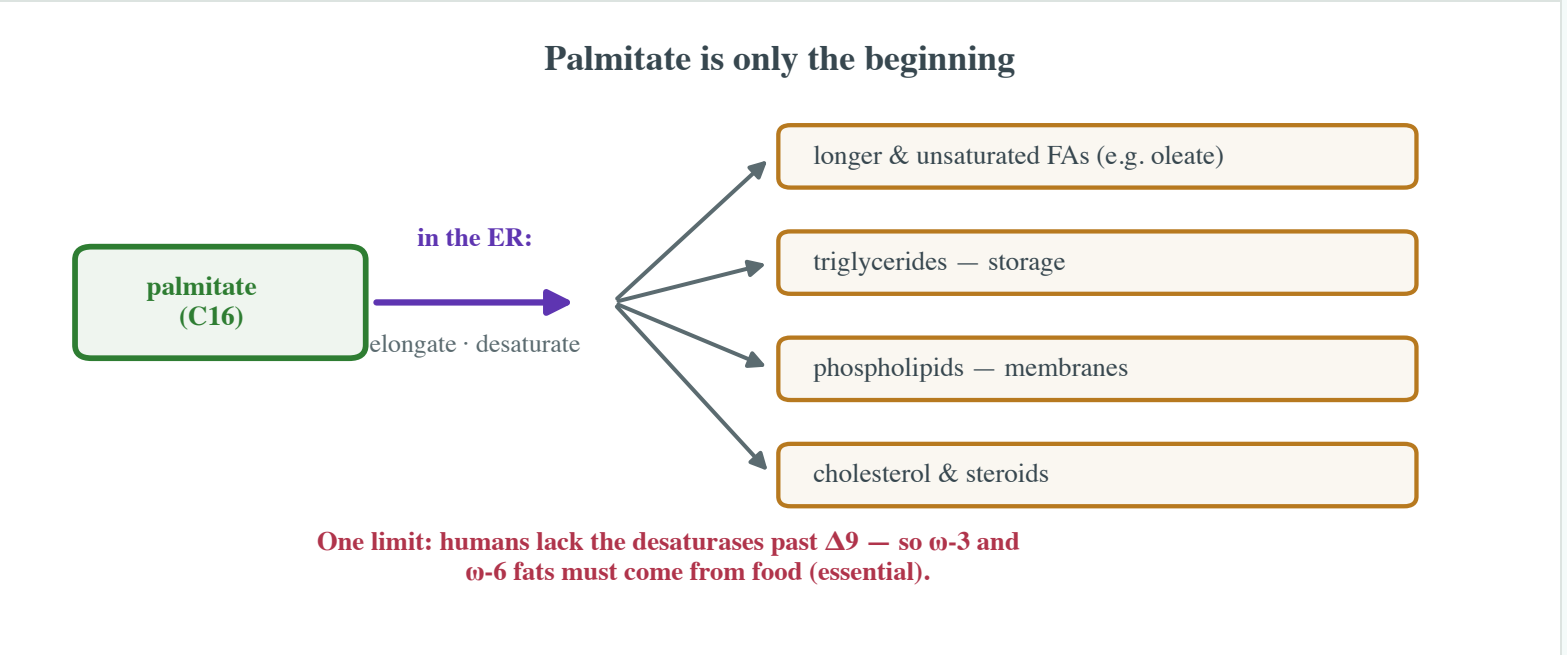
→ β-oxidation runs

burning ON · synthesis OFF

Malonyl-CoA is the switch: it's the first building block AND the off-switch for burning.

Beyond palmitate

Fatty acid synthase only makes **one product — palmitate (C16)**. Everything else is **remodeling**, done mostly in the **endoplasmic reticulum**: enzymes **elongate** the chain and **desaturate** it (adding double bonds, e.g. making oleate). Those tailored fatty acids then get built into **triglycerides**, **phospholipids**, **cholesterol**, and signaling lipids. One catch: humans **can't** add double bonds past the Δ9 position — which is exactly why **ω-3 and ω-6** fats are **essential** and must come from your diet.



Can you…?

- □ describe lipoproteins (chylomicrons, VLDL, LDL, HDL) and how fat and cholesterol move through the blood?
- □ trace fat mobilization — lipolysis to glycerol + free fatty acids, activation to acyl-CoA, and the carnitine shuttle into the mitochondrion?
- □ walk the four steps of β-oxidation with its enzymes and $FADH_2$/NADH/acetyl-CoA yield, and calculate the ATP from oxidizing a fatty acid?
- □ explain ketone-body synthesis and use as a fasting fuel, and distinguish physiological ketosis from diabetic ketoacidosis?
- □ outline fatty-acid synthesis (acetyl-CoA carboxylase, fatty acid synthase, the citrate shuttle) and the reciprocal regulation that keeps synthesis and breakdown from running at once?

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