

Lipid Metabolism

From palmitate's seven-turn spiral down to acetyl-CoA, back up through the fatty acid synthase cycle, and out into ketone bodies, membrane lipids, cholesterol, fat stores, and the lipoprotein fleet that carries it all through blood.

β & ω -Oxidation

FA Biosynthesis

Ketone Bodies

Triglycerides

Phospholipids

Cholesterol

Adipose Tissue

Lipoproteins

β -Oxidation

ω -Oxidation

FA Biosynthesis

Ketone Bodies

Triglycerides

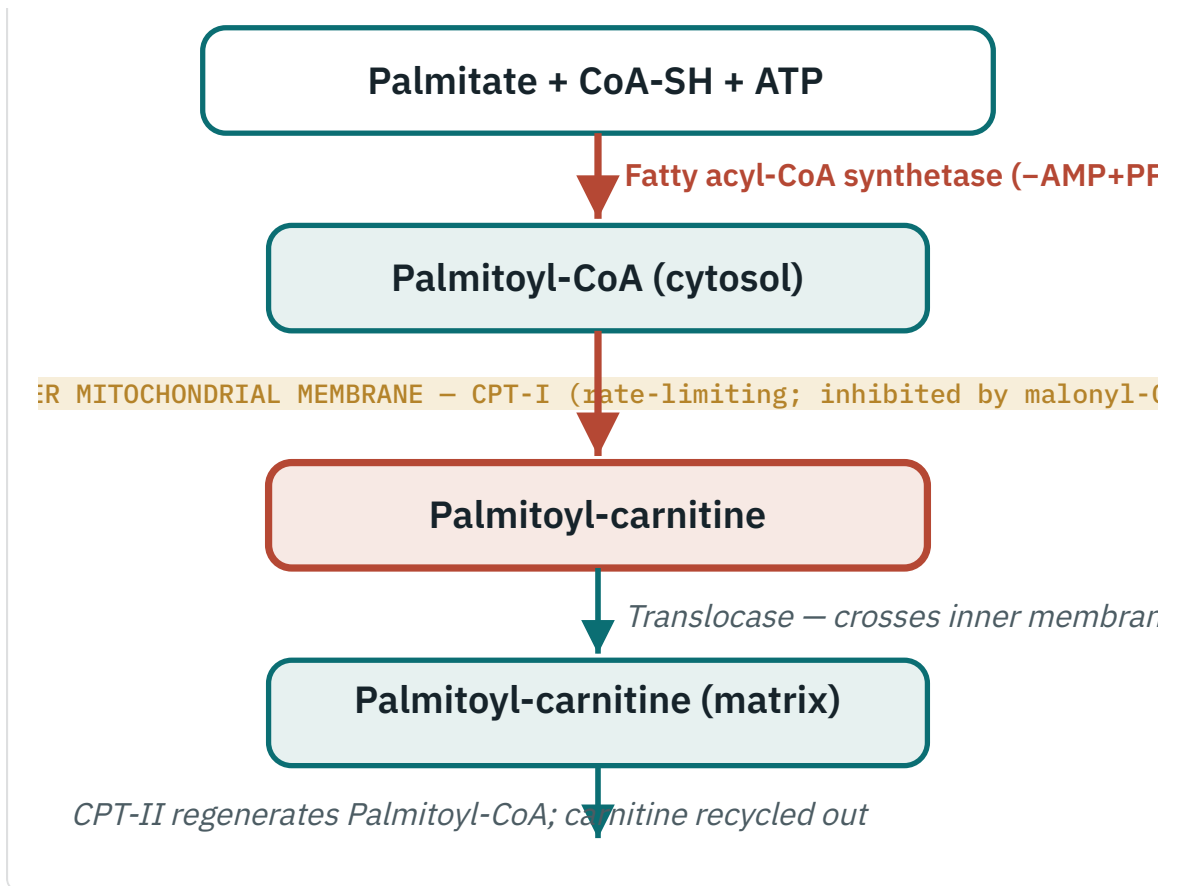
PL

1 **β -Oxidation of Palmitic Acid**

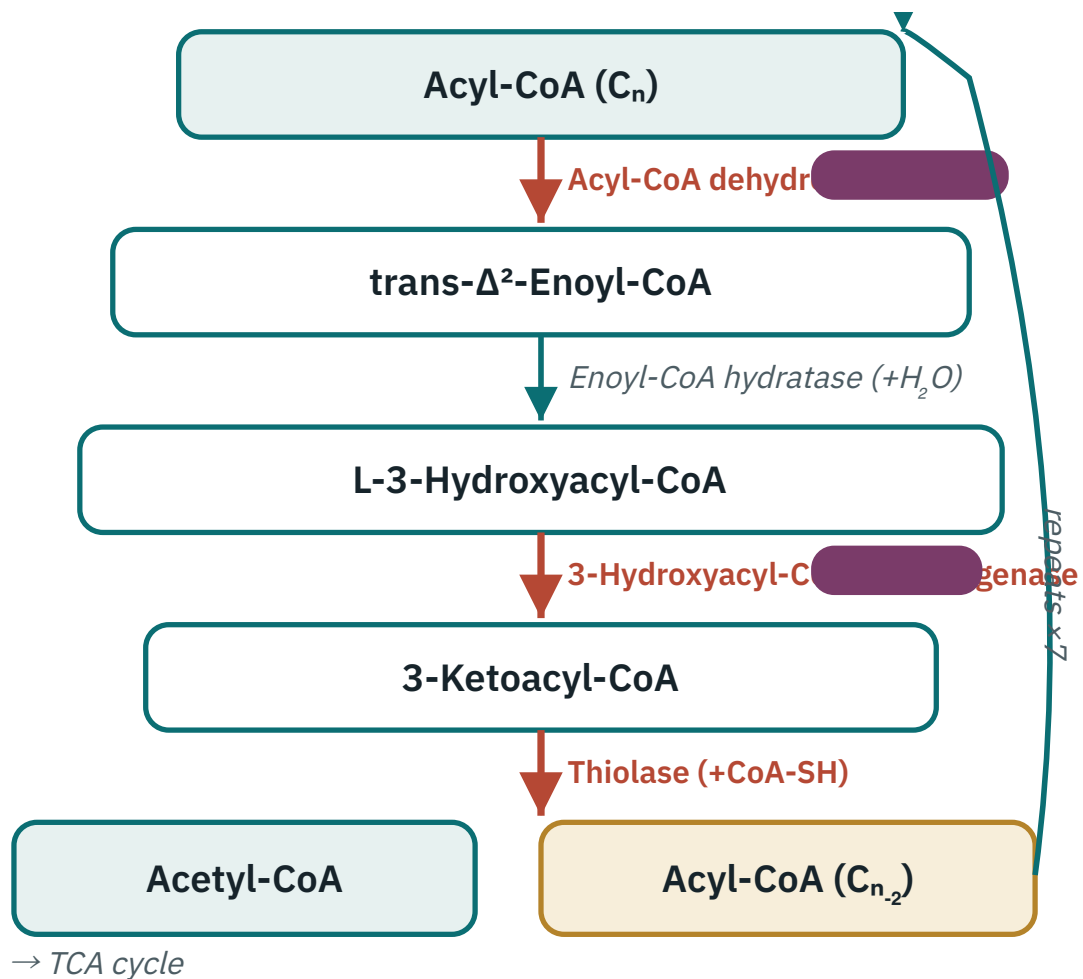
Mitochondrial matrix · the C16 saturated fatty acid, one spiral at a time

Palmitate is activated in the cytosol, ferried into the mitochondrion by the carnitine shuttle, then stripped of two carbons at a time by a four-step spiral that repeats seven times.

Activation & carnitine shuttle



One turn of the spiral (×7 for C16 → 8 Acetyl-CoA)



NET PER PALMITATE (C_{16})

7 cycles → 7 $FADH_2$ + 7 NADH + 8 Acetyl-CoA

$7 \times 1.5 + 7 \times 2.5 + 8 \times 10 = 108$ ATP

– 2 ATP (activation cost) = **~106 ATP net**

(older texts, using $FADH_2=2$ & $NADH=3$, give ~129 ATP)

Last cycle yields 2 Acetyl-CoA directly – no further split

THE MALONYL-COA CHECKPOINT

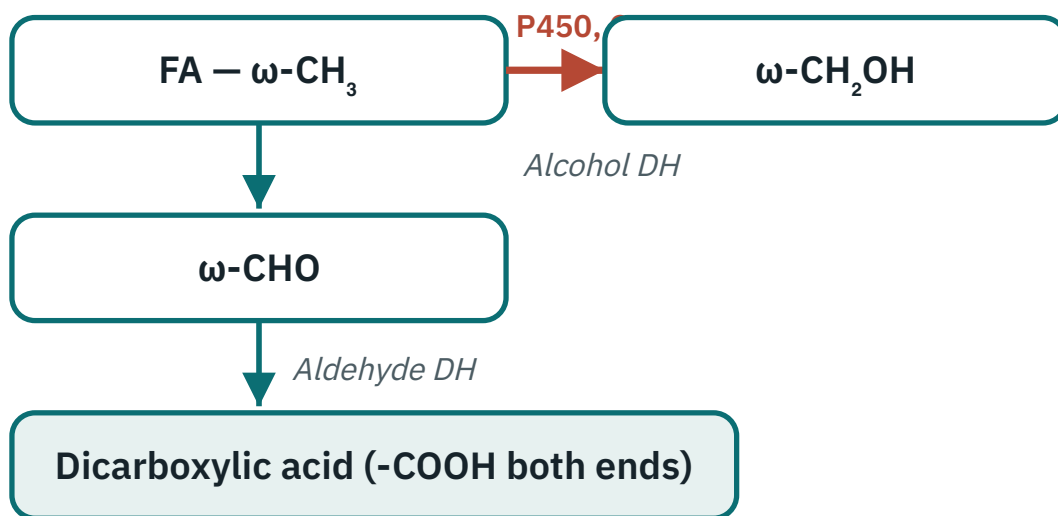
Malonyl-CoA – the first committed intermediate of fatty acid *synthesis* – allosterically inhibits CPT-I. This single switch prevents newly made fatty acids from being immediately re-oxidised, so synthesis and β -oxidation are never fully active at the same time.

2 ω -Oxidation

Endoplasmic reticulum · a minor back-up route

Instead of attacking the carboxyl (α) end, ω -oxidation hydroxylates the terminal methyl (ω) carbon, converting the fatty acid into a dicarboxylic acid that can then be shortened from both ends.

Terminal-carbon oxidation



WHY IT MATTERS

Normally a very minor pathway, ω -oxidation becomes clinically important when mitochondrial β -oxidation is impaired (e.g. **MCAD deficiency**) — the resulting dicarboxylic aciduria is a useful diagnostic clue on urine organic acid analysis.

3 Biosynthesis of Palmitate (C16)

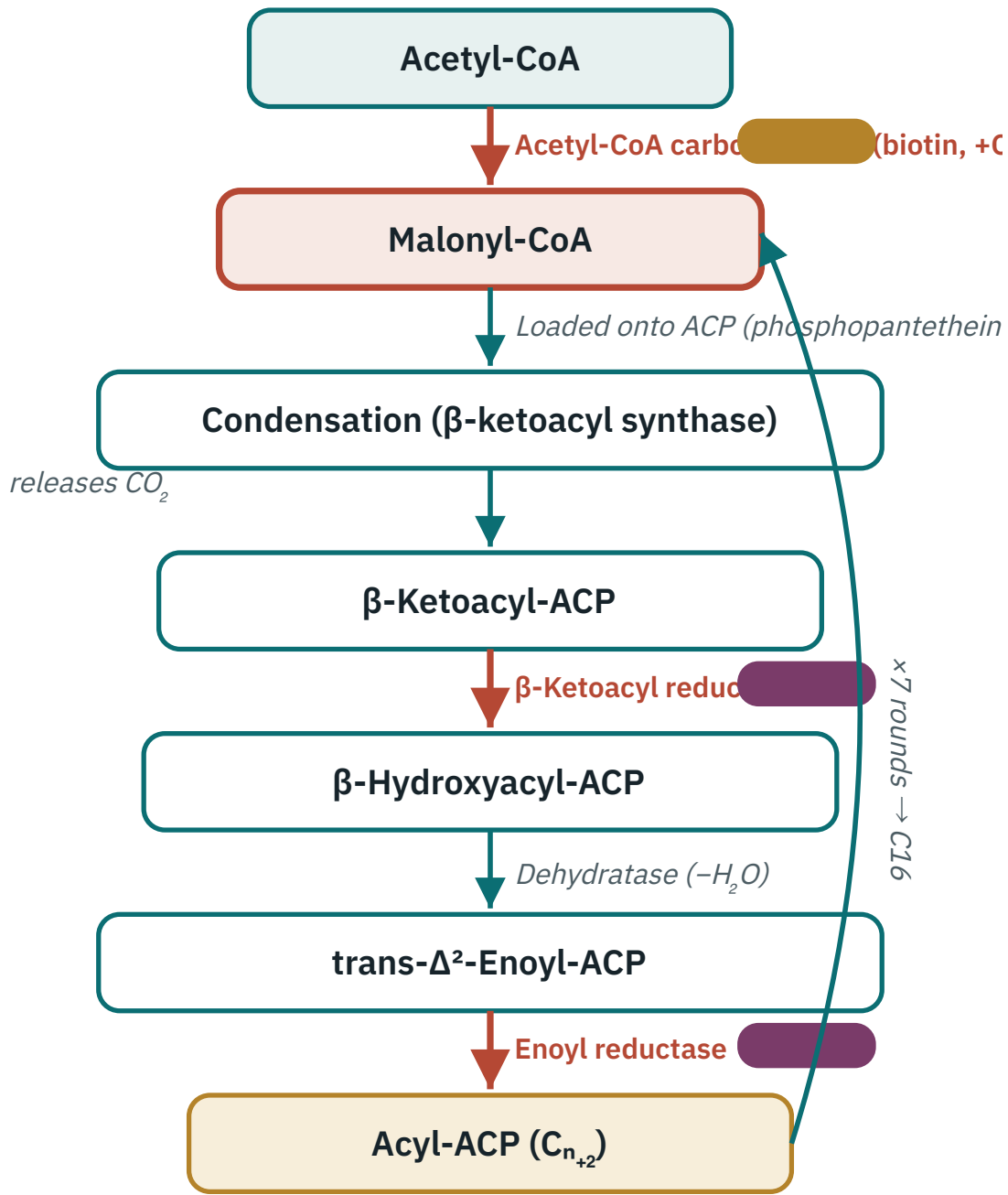
Cytosol · liver, adipose & lactating mammary gland

Fatty acid synthesis is β -oxidation's mirror image in almost every respect — cytosolic instead of mitochondrial, NADPH-driven instead of NAD⁺/FAD-driven, and building two carbons at a time instead of removing them.

GETTING ACETYL-CoA OUT OF THE MITOCHONDRION

Mitochondrial acetyl-CoA condenses with OAA to form **citrate**, which crosses into the cytosol and is cleaved by ATP-citrate lyase back to acetyl-CoA + OAA. The OAA returns to pyruvate via malate, generating bonus NADPH through malic enzyme along the way.

Commitment step, then the FAS cycle (×7)



Thioesterase releases free Palmitate at C16

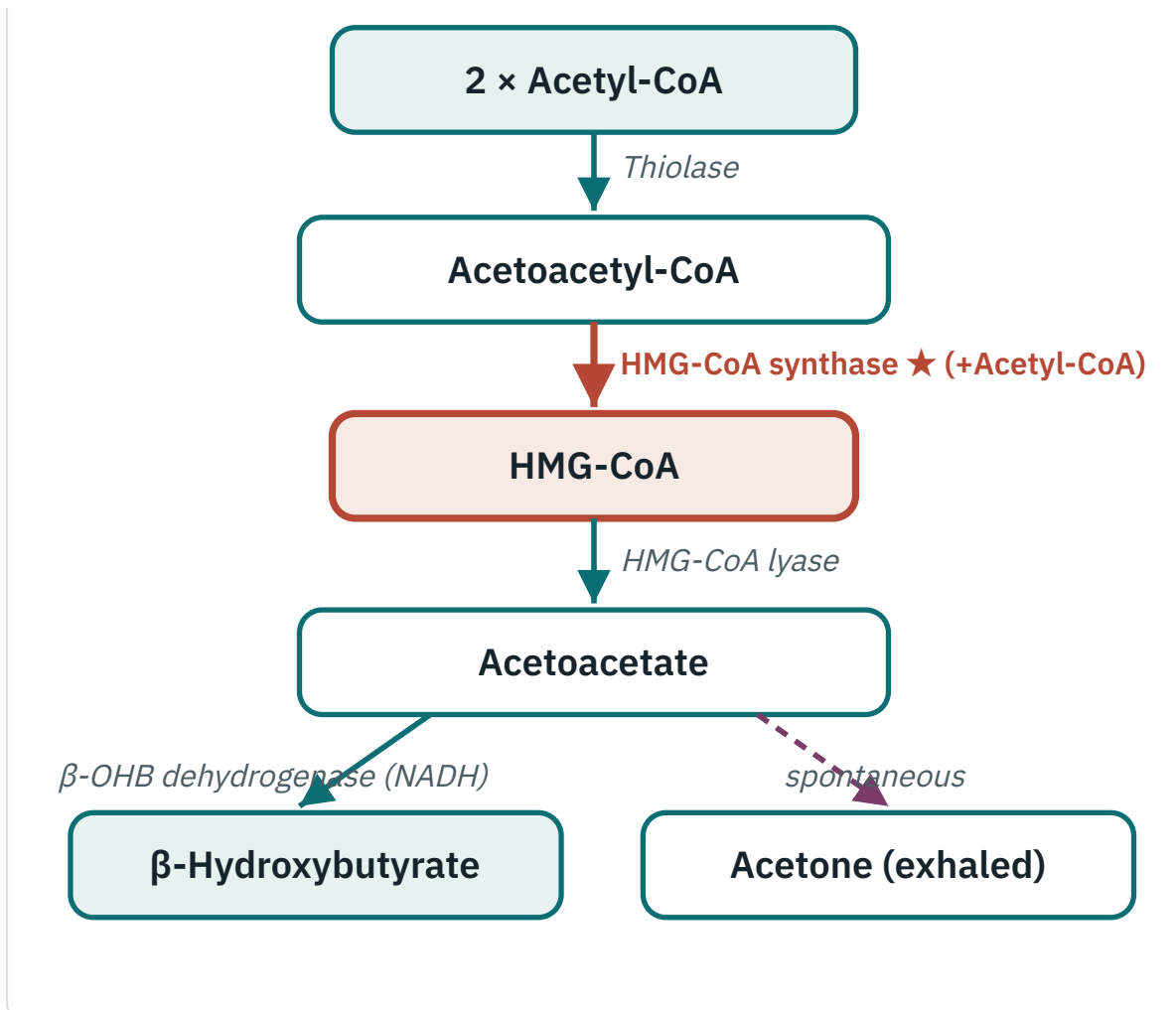
Feature	β -Oxidation	FA Biosynthesis
Site	Mitochondrial matrix	Cytosol
Redox coenzyme	FAD, NAD ⁺ (oxidise)	NADPH (reduce)
Acyl carrier	Coenzyme A	Acyl carrier protein (ACP)
Rate-limiting enzyme	CPT-I	Acetyl-CoA carboxylase
2-carbon donor	— (released as acetyl-CoA)	Malonyl-CoA

4 Formation & Fate of Ketone Bodies

Liver mitochondria make them; peripheral tissues burn them

When fasting or unchecked lipolysis floods the liver with acetyl-CoA faster than the (gluconeogenesis-depleted) TCA cycle can absorb it, the surplus is packaged into water-soluble ketone bodies for export.

Ketogenesis



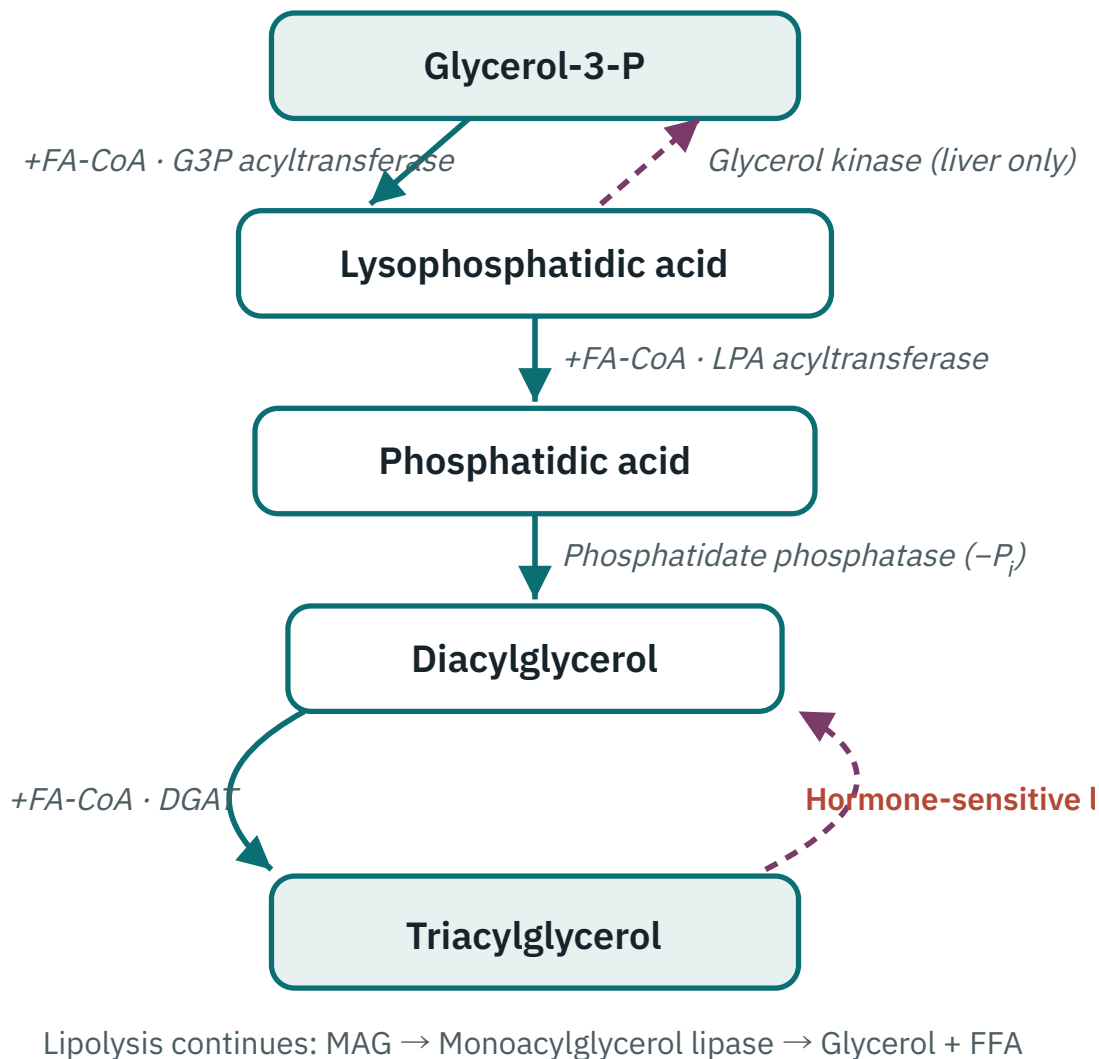
FATE IN PERIPHERAL TISSUES

Muscle, kidney, and — after ~2–3 days of starvation — brain, take up β-hydroxybutyrate, reoxidise it to acetoacetate, and activate it with **thiophorase** (succinyl-CoA: 3-ketoacid CoA transferase, using succinyl-CoA) to acetoacetyl-CoA → 2 acetyl-CoA → TCA cycle.

THE LIVER CANNOT USE ITS OWN KETONES

Hepatocytes lack thiophorase entirely — the liver is a ketone *producer*, never a consumer. In uncontrolled diabetes, unrestrained lipolysis and ketogenesis overwhelm peripheral uptake, causing diabetic ketoacidosis: metabolic acidosis, Kussmaul breathing, and the classic fruity (acetone) breath odour.

Synthesis (down) and lipolysis (reverse, up)



HORMONAL CONTROL OF LIPOLYSIS

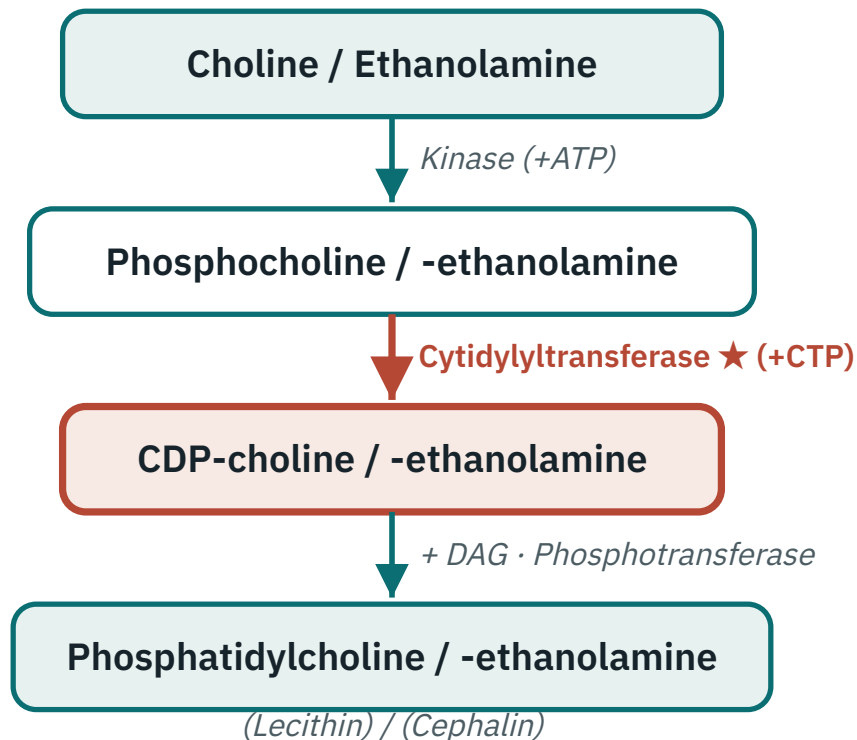
Glucagon, epinephrine, cortisol and GH raise cAMP → PKA phosphorylates perilipin and hormone-sensitive lipase → lipolysis accelerates. Insulin does the opposite — it dephosphorylates HSL and lowers cAMP, favouring storage.

Adipose and muscle lack glycerol kinase, so the glycerol released must travel to the **liver** to re-enter gluconeogenesis.

6 Lecithin, Cephalin & Sphingomyelin

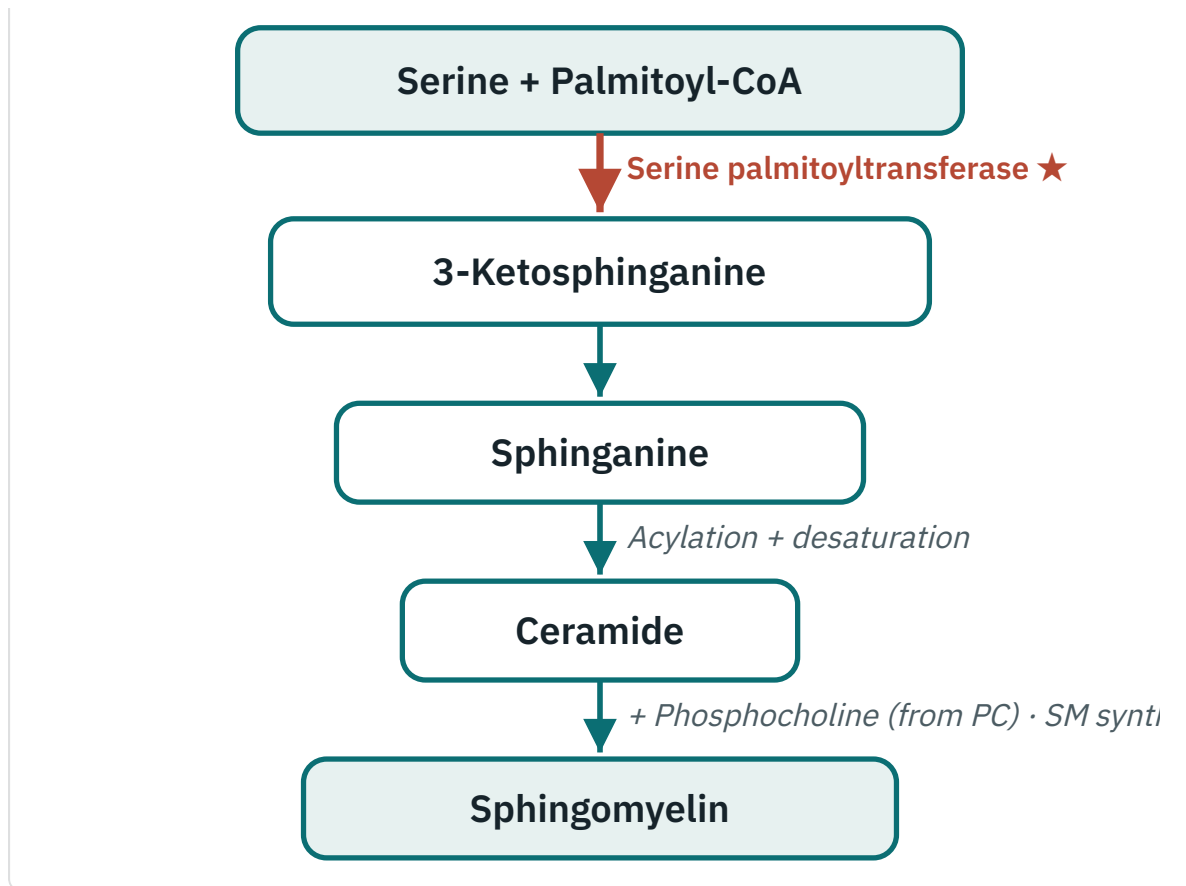
Membrane phospholipids — Kennedy pathway & sphingolipid synthesis

Kennedy pathway — shared logic for PC and PE



Liver alt. route: PE --3× methylation (SAM, PEMT)--> PC

Sphingomyelin synthesis



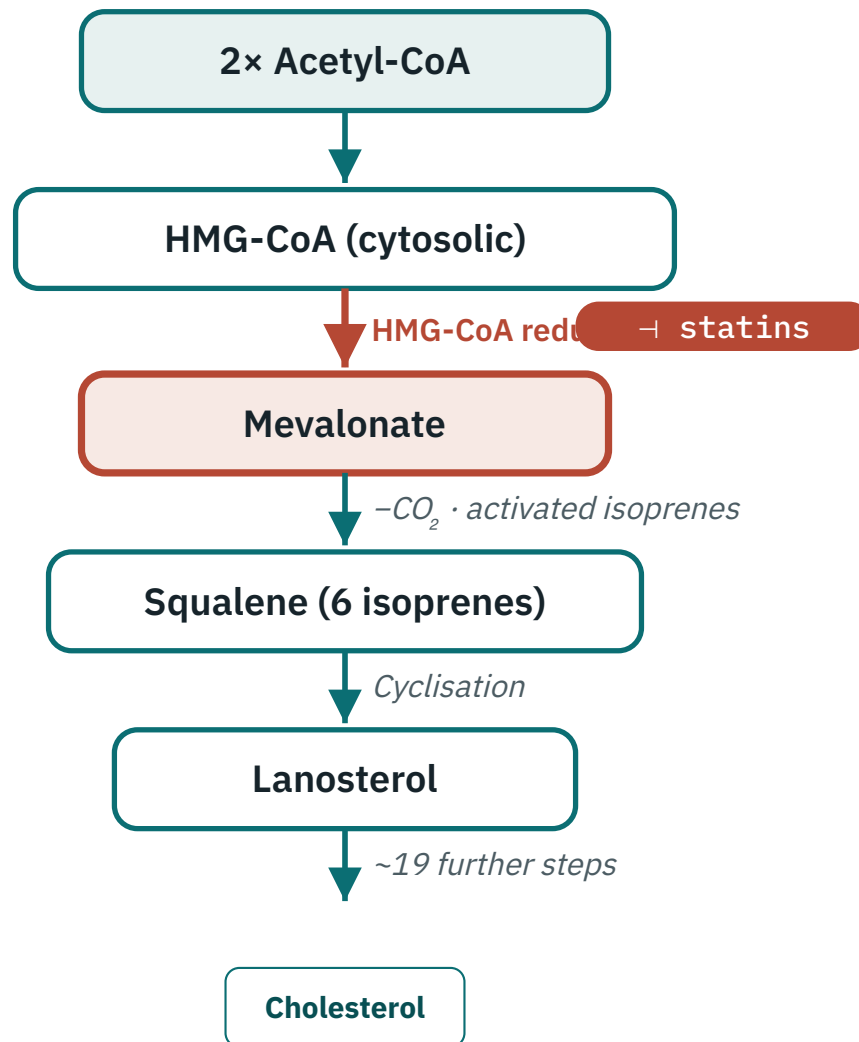
Enzyme	Action	Note
Phospholipase A ₂	Releases arachidonic acid from C2 of glycerol	Eicosanoid precursor; inhibited by corticosteroids
Phospholipase C	Releases DAG + phospho-head group	DAG is a second messenger (PKC activation)
Sphingomyelinase	Sphingomyelin → Ceramide + Phosphocholine	Deficiency (acid SMase) → Niemann–Pick disease

7 Cholesterol Biosynthesis

Mevalonate pathway · cytosol/ER · mainly liver

All 27 carbons of cholesterol trace back to acetyl-CoA, assembled through activated 5-carbon isoprene units — the same rate-limiting enzyme that statins target.

Acetyl-CoA → Cholesterol, in five landmarks



REGULATION

HMG-CoA reductase is feedback-inhibited by cholesterol itself, competitively blocked by statins, activated by insulin (dephosphorylation) and inhibited by glucagon/AMPK (phosphorylation) — with long-term transcriptional control via SREBP sensing cellular sterol levels.

PHYSIOLOGICAL SIGNIFICANCE

Precursor of **bile acids** (fat digestion), **steroid hormones** (cortisol, aldosterone, sex hormones — via pregnenolone), and **vitamin D** (7-dehydrocholesterol → cholecalciferol on UV exposure); an essential structural component that tunes membrane fluidity.

8 Metabolism of Adipose Tissue

Energy reservoir and endocrine organ

	White adipose tissue (WAT)	Brown adipose tissue (BAT)
Main role	Energy storage, insulation, cushioning	Non-shivering thermogenesis
Mitochondria	Few	Abundant — rich in thermogenin (UCP1)
Distribution	Widespread (subcutaneous, visceral)	Interscapular, perirenal — abundant in neonates

Fed vs. fasting adipocyte

FED (↑ Insulin)

LPL hydrolyses chylomicron/VLDL-TAG →
FA uptake → re-esterified & stored as TAG

FASTING (↑ Glucagon/Epinephrine)

HSL + ATGL hydrolyse stored TAG →
FFA + glycerol released into blood

ADIPOSE AS AN ENDOCRINE ORGAN

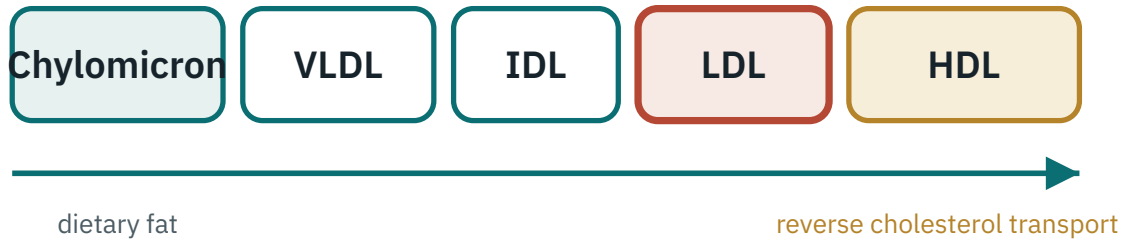
Beyond storage, adipocytes secrete **leptin** (satiety signalling), **adiponectin** (insulin sensitisation), and inflammatory mediators such as **TNF-α** and **IL-6** — linking fat mass directly to whole-body energy balance and insulin resistance.

9 Lipoproteins — Transport & Storage

Packaging hydrophobic lipid for an aqueous bloodstream

Density spectrum & circulatory routes

SIZE / TAG CONTENT → DENSITY / PROTEIN CONTENT



- **Chylomicrons** — carry dietary TAG from intestine (ApoB-48) via lymph to blood; LPL (activated by ApoC-II) strips FFA for tissue uptake; remnants cleared by the liver via ApoE.
- **VLDL** — liver-made (ApoB-100), exports endogenous TAG; LPL action progressively converts it to **IDL** then cholesterol-rich **LDL**.
- **LDL** — delivers cholesterol to peripheral tissues via the LDL receptor (recognises ApoB-100); the "bad cholesterol" when in excess.
- **HDL** — nascent particles (ApoA-I) pick up free cholesterol from tissues; **LCAT** esterifies it, driving reverse cholesterol transport back to the liver — the "good cholesterol."

Apoprotein	Found on	Function
ApoB-48	Chylomicron	Structural
ApoB-100	VLDL, IDL, LDL	Structural; ligand for LDL receptor
ApoC-II	Chylomicron, VLDL	Activates lipoprotein lipase (LPL)
ApoE	Chylomicron/VLDL remnants	Receptor-mediated hepatic uptake
ApoA-I	HDL	Activates LCAT; structural

CLINICAL CORRELATIONS

LDL-receptor defects cause **familial hypercholesterolemia** (markedly raised LDL, premature atherosclerosis). LPL or ApoC-II deficiency causes **Type I hyperlipoproteinemia** (chylomicronemia, eruptive xanthomas, pancreatitis risk). A high LDL/HDL ratio is a key atherogenic risk marker.

10 Exam Corner

Practice question set — end-semester format

B.Sc. Biochemistry — End-Semester Examination

Paper: Lipid Metabolism

Full Marks: 30

Time: 1.5 Hrs

GROUP A — LONG ANSWER (ANSWER ANY TWO)

1. Describe β -oxidation of palmitic acid with a suitable diagram and calculate its net ATP yield. Add a note on the carnitine shuttle. **10**
2. Outline the biosynthesis of a C16 saturated fatty acid, and compare it with β -oxidation under site, cofactor, carrier, and regulation. **10**
3. Describe the formation of ketone bodies in the liver and their utilisation in peripheral tissues. Discuss the biochemical basis of diabetic ketoacidosis. **10**

GROUP B — SHORT NOTES (ANSWER ANY TWO)

- a. ω -Oxidation of fatty acids **5**
- b. Role of lipoproteins in lipid transport **5**
- c. Physiological significance of cholesterol **5**

