PIPADOR REVISION

MRCOG Part 1 Revision Notes

Carbohydrates: TCA Cycle

BIOCHEMISTRY • LECTURE 216

VISUAL EXAMINATION REVISION NOTES

2026 Edition

216

MRCOG PART 1 REVISION NOTES | BIOCHEMISTRY

Carbohydrates: TCA Cycle

The link reaction, Krebs/citric acid cycle, oxidative phosphorylation and ATP yield, regulation and clinical correlates

Matrix	3 NADH	Isocitrate DH	≈ 30–32
Mitochondrial location	+ 1 $FADH_2$ + 1 GTP + 2 CO_2 per turn	Rate-limiting enzyme	ATP per glucose (total, aerobic)

■ **KEY FACTS: Learning objectives**

- Describe the reactions, enzymes, products and regulation of the TCA cycle.
- Describe the link reaction (pyruvate dehydrogenase) and vitamin cofactors.
- Describe oxidative phosphorylation and total ATP yield.
- Describe the TCA cycle as a hub (amphibolic) and clinical correlates.

216.1 The link reaction

Pyruvate enters mitochondria and is oxidatively decarboxylated by the **pyruvate dehydrogenase (PDH) complex**: pyruvate + CoA + NAD^+ → **acetyl-CoA** + CO_2 + NADH. Irreversible — **acetyl-CoA cannot be converted back to glucose** (hence fatty acids are not gluconeogenic). Cofactors: **thiamine pyrophosphate (B1), lipoic acid, CoA (B5), FAD (B2), NAD^+ (B3)**. Activated by insulin, ↓ by its products (acetyl-CoA, NADH) and by phosphorylation. Acetyl-CoA also comes from **β-oxidation of fatty acids** and ketogenic amino acids.

216.2 The cycle

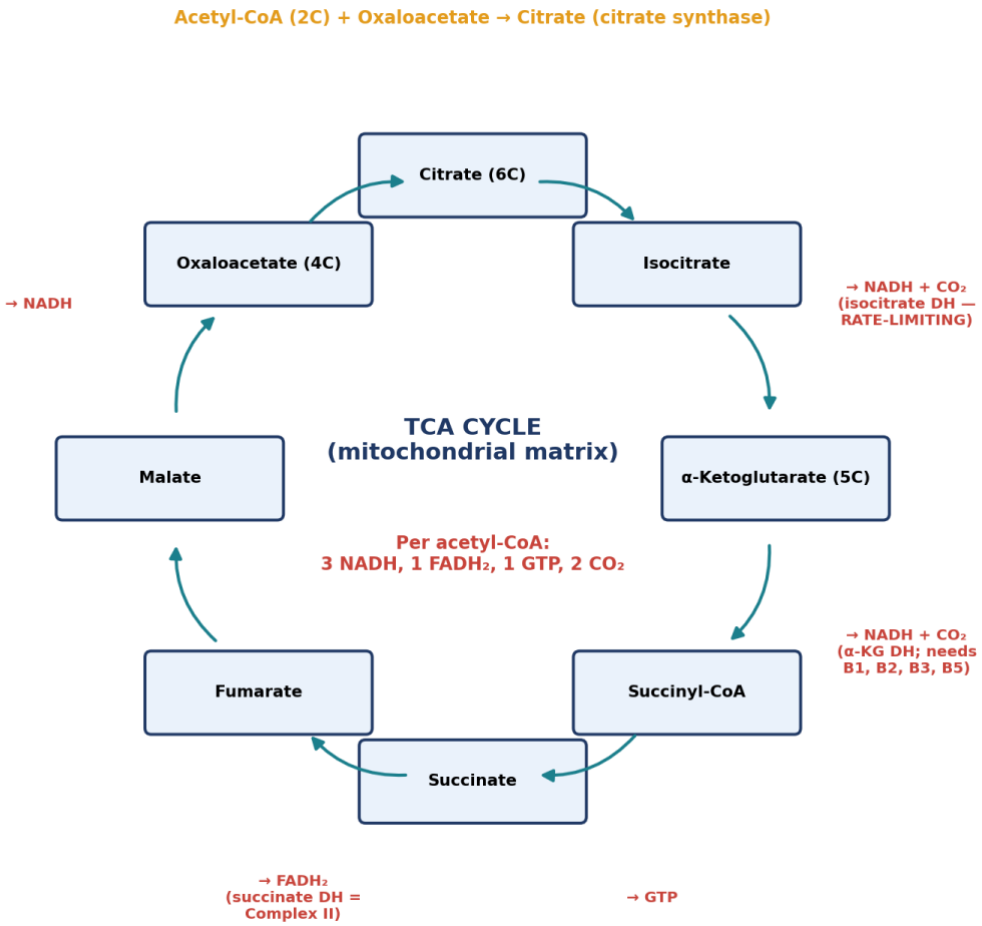


Figure 216.1 — The tricarboxylic acid (Krebs/citric acid) cycle

Step	Enzyme	Product / notes
Acetyl-CoA + oxaloacetate → citrate	Citrate synthase	Inhibited by ATP, NADH, succinyl-CoA, citrate
Citrate → isocitrate	Aconitase	Inhibited by fluoroacetate (rodenticide)
Isocitrate → α-ketoglutarate	Isocitrate dehydrogenase (rate-limiting)	NADH + CO_2; ↑ ADP, Ca^{2+}; ↓ ATP, NADH. IDH1/2 mutations in gliomas, AML
α-KG → succinyl-CoA	α-Ketoglutarate dehydrogenase (like PDH)	NADH + CO_2; same cofactors as PDH (B1, B2, B3, B5, lipoate); arsenic inhibits
Succinyl-CoA → succinate	Succinyl-CoA synthetase	GTP (substrate-level); succinyl-CoA also used for haem synthesis
Succinate → fumarate	Succinate dehydrogenase (= Complex II)	$FADH_2$; SDH mutations → paraganglioma/phaeochromocytoma
Fumarate → malate	Fumarase	FH mutations → hereditary leiomyomatosis (multiple uterine fibroids) and renal cell cancer
Malate → oxaloacetate	Malate dehydrogenase	NADH; oxaloacetate regenerated

216.3 Oxidative phosphorylation and ATP yield

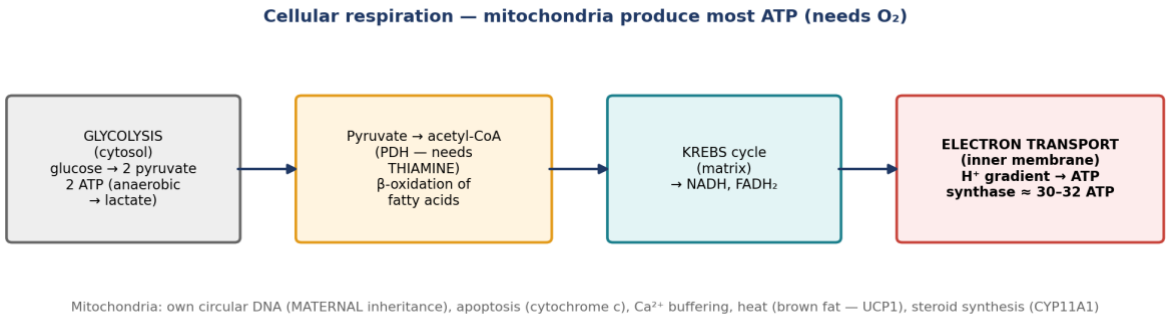


Figure 216.2 — From glucose to ATP

- **Electron transport chain** (inner mitochondrial membrane): NADH → Complex I; $FADH_2$ → Complex II → ubiquinone → Complex III → cytochrome c → **Complex IV (cytochrome oxidase) → O_2 → H_2O**. Proton pumping creates a gradient driving **ATP synthase** (chemiosmosis).
- ≈ **2.5 ATP per NADH** and **1.5 per $FADH_2$**; cytosolic NADH from glycolysis enters via the malate–aspartate (≈ 2.5) or glycerol-phosphate (≈ 1.5) shuttle.
- **Inhibitors**: cyanide and **carbon monoxide** (Complex IV), rotenone (I), antimycin (III), oligomycin (ATP synthase); **uncouplers**: UCP1 (brown fat — neonatal thermogenesis), 2,4-dinitrophenol, aspirin overdose (fever).

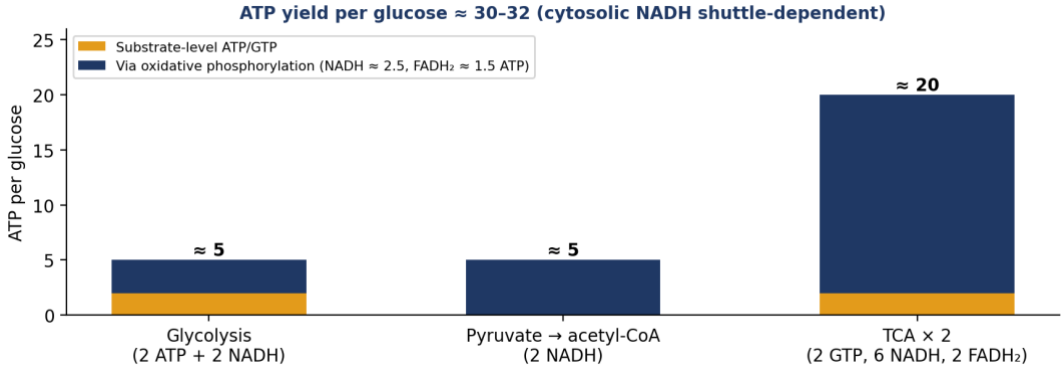


Figure 216.3 — ATP accounting per glucose

216.4 Regulation and the cycle as a metabolic hub

Topic	Key points
Regulation	Driven by energy demand: ↑ ADP, Ca^{2+} (muscle contraction); ↓ ATP, NADH; NAD^+ availability depends on O_2 (hypoxia stops the cycle)
Amphibolic (catabolic + anabolic)	Citrate exported → fatty acid & cholesterol synthesis (→ steroid hormones); α-KG/oxaloacetate → amino acids; succinyl-CoA → haem; oxaloacetate → gluconeogenesis
Anaplerosis	Replenishment of intermediates — pyruvate carboxylase (biotin) → oxaloacetate
Ketogenesis link	In fasting/diabetes, oxaloacetate is diverted to gluconeogenesis → acetyl-CoA accumulates → ketone bodies (DKA; accelerated starvation of pregnancy)

■ CLINICAL CORRELATION

- **Thiamine deficiency** (hyperemesis gravidarum, alcohol, refeeding) blocks PDH and α-KG dehydrogenase → lactic acidosis, **Wernicke's encephalopathy** — give **thiamine before glucose**.
- **Fumarate hydratase deficiency** (HLRCC): early-onset **multiple uterine leiomyomas** and type 2 papillary renal cancer — consider in young women with many fibroids/family history.
- **Mitochondrial disease**: maternal inheritance; ETC defects → lactic acidosis, myopathy (Lecture 204).

216.5 Must-know summary

■ EXAM TIP

- PDH: pyruvate → acetyl-CoA (irreversible; **B1, B2, B3, B5, lipoate**).
- Per turn: **3 NADH, 1 $FADH_2$, 1 GTP, 2 CO_2**; isocitrate DH rate-limiting; succinate DH = Complex II.
- Total ≈ **30–32 ATP/glucose**; NADH ≈ 2.5, $FADH_2$ ≈ 1.5 ATP.
- Amphibolic: citrate → fatty acids/steroids; succinyl-CoA → haem; oxaloacetate → glucose.
- Clinical: thiamine (Wernicke's), **FH mutations → fibroids + renal cancer**, SDH → paraganglioma, CO/cyanide block Complex IV.

■ MNEMONIC / MEMORY AID

TCA intermediates — 'Citrate Is Krebs' Starting Substrate For Making Oxaloacetate': Citrate, Isocitrate, α-Ketoglutarate, Succinyl-CoA, Succinate, Fumarate, Malate, Oxaloacetate.

PDH cofactors — 'Tender Loving Care For Nancy': Thiamine, Lipoate, CoA, FAD, NAD^+.