Gluconeogenesis ANSWER KEY

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Name _____ Date _____

Read top to bottom. Counts are per glucose made (2 pyruvate in).

Pyruvate
mitochondria

↓ **1 Pyruvate carboxylase** BYPASS
in **2 ATP, 2 CO_2**
out **2 ADP**

Oxaloacetate
mitochondria

OAA exits the mitochondrion as malate

↓ **2 PEP carboxykinase (PEPCK)** BYPASS
in **2 GTP**
out **2 GDP, 2 CO_2**

Phosphoenolpyruvate (PEP)
cytosol

↓ **Glycolysis enzymes, run in reverse**
in **2 ATP, 2 NADH**
out **2 ADP, 2 NAD^+**

Fructose 1,6-bisphosphate

↓ **3 Fructose-1,6-bisphosphatase** BYPASS
in **H_2O**
out **P_i**

Fructose 6-phosphate

↓ **Phosphoglucose isomerase (shared)**

Glucose 6-phosphate

↓ **4 Glucose-6-phosphatase** BYPASS
in **H_2O**
out **P_i**

Glucose
leaves the ER

Where the carbons come from

Lactate becomes **pyruvate (LDH, Cori cycle)**

Alanine becomes **pyruvate (ALT, transamination)**

Glycerol enters as **DHAP (triose level)**

Odd-chain fatty acids give **propionyl-CoA → succinyl-CoA**

Cannot be used **even-chain fatty acids**

Why not? **PDH is irreversible; acetyl-CoA can't make net OAA**

Know it

Main organs **liver (also kidney)**

Rate-limiting enzyme **fructose-1,6-bisphosphatase**

Activated by **ATP, citrate**

Inhibited by **AMP, fructose 2,6-bisphosphate**

Hormones that turn it on **glucagon, cortisol**

Pyruvate carboxylase activator **acetyl-CoA**

Pyruvate carboxylase cofactor **biotin**

Fed or fasted? **fasted**

Total cost per glucose **4 ATP + 2 GTP + 2 NADH**

Glycolysis steps it bypasses **hexokinase, PFK-1, pyruvate kinase**

The fructose 2,6-bisphosphate switch

High F2,6-BP (fed, insulin) : glycolysis **on**

High F2,6-BP: gluconeogenesis **off**

Glucagon makes F2,6-BP go **down**

Connect it

Why does acetyl-CoA from fat oxidation push gluconeogenesis forward? **it activates pyruvate carboxylase, filling OAA**

Why can't muscle release glucose made from its glycogen? **no glucose-6-phosphatase**

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Glycogen Metabolism ANSWER KEY

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SYNTHESIS (GLYCOGENESIS)

Glucose

↓ Hexokinase / glucokinase
in **ATP**
out **ADP**

Glucose 6-phosphate

↓ Phosphoglucomutase

Glucose 1-phosphate

↓ UDP-glucose pyrophosphorylase
in **UTP**
out **PP_i**

UDP-glucose

↓ Glycogen synthase **RATE-LIMITING**
in **UDP-glucose**
out **UDP**

Glycogen (linear chains) — bond made: **α-1,4**

↓ Branching enzyme
bond made: **α-1,6**

Glycogen (branched)

BREAKDOWN (GLYCOGENOLYSIS)

Glycogen

↓ Glycogen phosphorylase **RATE-LIMITING**
in **P_i**
out **G1P (cuts α-1,4)**

Glucose 1-phosphate

↓ Phosphoglucomutase

Glucose 6-phosphate

→ **Glucose (to blood)** — liver only

Glucose-6-phosphatase
in **H_2O**
out **P_i**

→ **Glycolysis** — muscle

Muscle keeps it: no **glucose-6-phosphatase**

→ **Free glucose**

Debranching enzyme
cuts at **α-1,6** branch points

Know it

- Main storage organs **liver and skeletal muscle**
- Liver glycogen is for **keeping blood glucose up**
- Muscle glycogen is for **the muscle's own glycolysis**
- Chain bond / branch bond **α-1,4 / α-1,6**
- Insulin: synthase / phosphorylase **on / off**
- Glucagon or epinephrine **phosphorylase on, synthase off**
- Glucagon / epinephrine act through **PKA (phosphorylation)**
- Phosphorylation turns synthase **off**
- Allosteric activator of synthase **glucose 6-phosphate**
- Activate muscle phosphorylase **AMP, Ca^{2+}**
- Glucagon acts on **liver only (not muscle)**
- Fed or fasted (synthesis / breakdown) **fed / fasted**

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Fatty Acid β-Oxidation ANSWER KEY

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1 · ACTIVATE AND TRANSPORT

Fatty acid
cytosol

↓ Acyl-CoA synthetase
in ATP, CoA-SH
out AMP + PP_i

Fatty acyl-CoA
cytosol

↓ Carnitine acyltransferase I (CPT-I) RATE-LIMITING
in carnitine
out CoA-SH

Fatty acylcarnitine
intermembrane space

↓ Translocase, then CPT-II
in CoA-SH
out carnitine

Fatty acyl-CoA
matrix

2 · ONE ROUND (IN THE MATRIX)

Fatty acyl-CoA (C_n)

↓ Oxidation
in FAD
out $FADH_2$

trans-Δ^2-Enoyl-CoA

↓ Hydration
in H_2O
out none

3-Hydroxyacyl-CoA

↓ Oxidation
in NAD^+
out NADH

3-Ketoacyl-CoA

↓ Thiolysis (cleavage)
in CoA-SH
out acetyl-CoA

Acyl-CoA (C_{n-2}) + Acetyl-CoA

repeat with the shorter chain

Step types (oxidation, hydration…) go on the enzyme lines.

Worked example: palmitate (C16)

Rounds of β-oxidation **7**

Acetyl-CoA made **8**

$FADH_2$ / NADH made **7 / 7**

8 acetyl-CoA × 10 ATP **80**

7 $FADH_2$ × 1.5 **10.5**

7 NADH × 2.5 **17.5**

Minus activation cost **2**

Net ATP **~106**

Know it

Location **mitochondrial matrix**

Rate-limiting enzyme **CPT-I**

CPT-I inhibited by **malonyl-CoA**

Fed or fasted? **fasted (glucagon, epinephrine)**

Fat released from adipose by **hormone-sensitive lipase**

Odd-chain end product **propionyl-CoA → succinyl-CoA**

Can odd-chain carbons make glucose? **yes (succinyl-CoA)**

Liver's acetyl-CoA in fasting goes to **ketone bodies**

Unsaturated fatty acids need **an extra isomerase**

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Fatty Acid Synthesis ANSWER KEY

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Acetyl-CoA can't cross the inner membrane, so it travels as citrate.

Acetyl-CoA
mitochondria

↓ Citrate synthase
in **oxaloacetate**
out **CoA-SH**

Citrate
mitochondria

↓ Citrate shuttle (transporter)

Citrate
cytosol

↓ ATP-citrate lyase
in **ATP, CoA-SH**
out **OAA, ADP**

Acetyl-CoA
cytosol

↓ Acetyl-CoA carboxylase
RATE-LIMITING
in **ATP, CO_2**
out **ADP**

Malonyl-CoA
cytosol

↓ Fatty acid synthase
in **7 malonyl-CoA, 14 NADPH**
out **7 CO_2, 14 $NADP^+$**

Palmitate (C16)
cytosol

One fatty acid synthase cycle

Step 1 **condensation**
Step 2 **reduction**
Step 3 **dehydration**
Step 4 **reduction**
Carbons added per cycle **2**
NADPH used per cycle **2**
Cycles to make palmitate **7**
Growing chain is carried on **acyl carrier protein (ACP)**

Where the NADPH comes from

Main source **pentose phosphate pathway**
Second source **malic enzyme (malate → pyruvate)**

Know it

Location **cytosol (liver, adipose)**
Fed or fasted? **fed**
Activated by **citrate, insulin**
Inhibited by **palmitoyl-CoA, glucagon, epinephrine**
ACC cofactor **biotin**
Longest chain FA synthase makes **C16**
Malonyl-CoA also blocks **CPT-I (no futile cycle)**

COMPARE: BREAKDOWN VS. SYNTHESIS

	β-Oxidation	Fatty acid synthesis
Location	mitochondrial matrix	cytosol
Fed or fasted	fasted	fed
Rate-limiting enzyme	CPT-I	acetyl-CoA carboxylase
2-carbon unit	released as acetyl-CoA	added from malonyl-CoA
Electron carriers	FAD, NAD^+ (reduced)	NADPH (oxidized)
Acyl carrier	CoA	ACP

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PPP & Ketone Bodies ANSWER KEY

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PENTOSE PHOSPHATE PATHWAY · CYTOSOL

Glucose 6-phosphate

↓ Glucose-6-phosphate dehydrogenase (G6PD) **RATE-LIMITING**
in **2 $NADP^+$**
out **2 NADPH, CO_2**

OXIDATIVE · IRREVERSIBLE

Ribulose 5-phosphate

NON-OXIDATIVE · REVERSIBLE
Transketolase, transaldolase

Ribose 5-phosphate
→ nucleotides

Fructose 6-P + G3P
→ back to glycolysis

Know it

- Rate-limiting enzyme **G6PD**
- Activated by **$NADP^+$ (insulin)**
- Inhibited by **NADPH**
- NADPH is used for **FA synthesis, glutathione**
- Ribose 5-P is used for **nucleotides**
- Transketolase cofactor **thiamine (TPP)**

KETONE BODIES · LIVER MITOCHONDRIA

2 Acetyl-CoA

↓ Thiolase
in **none**
out **CoA-SH**

Acetoacetyl-CoA

↓ HMG-CoA synthase **RATE-LIMITING**
in **acetyl-CoA**
out **CoA-SH**

HMG-CoA

↓ HMG-CoA lyase
in **none**
out **acetyl-CoA**

Acetoacetate

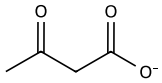
↓ β-HB dehydrogenase
in **NADH**
out **NAD^+**

β-Hydroxybutyrate

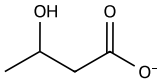
↘ Spontaneous
in **none**
out **CO_2**

Acetone
exhaled

Acetoacetate



β-Hydroxybutyrate



Acetone



Draw each one. Which isn't really a ketone? **β-hydroxybutyrate**

Know it

- Made when **fasting, low insulin**
- Made in **liver mitochondria**
- Used by **brain, heart, skeletal muscle**
- Liver can't use them because it lacks **thiophorase (SCOT)**
- Back to fuel: acetoacetate → **acetoacetyl-CoA → 2 acetyl-CoA**
- Fed or fasted? **fasted**

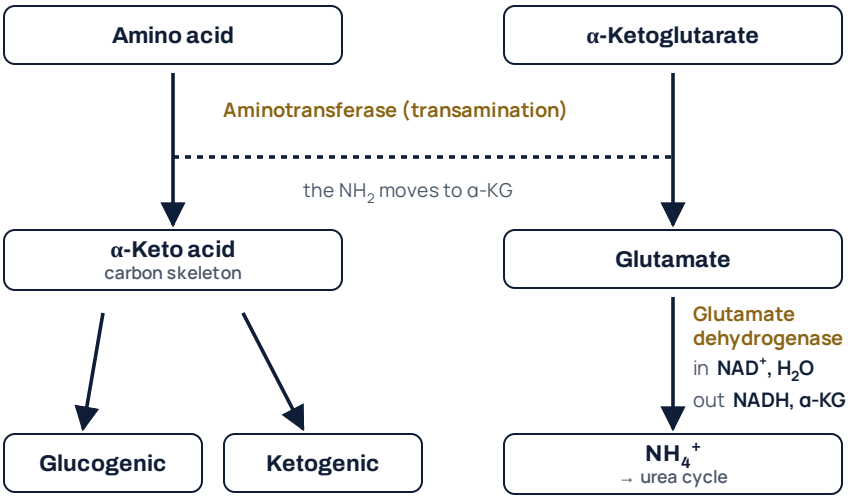
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Amino Acids & Urea ANSWER KEY

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REMOVING THE NITROGEN



Know it

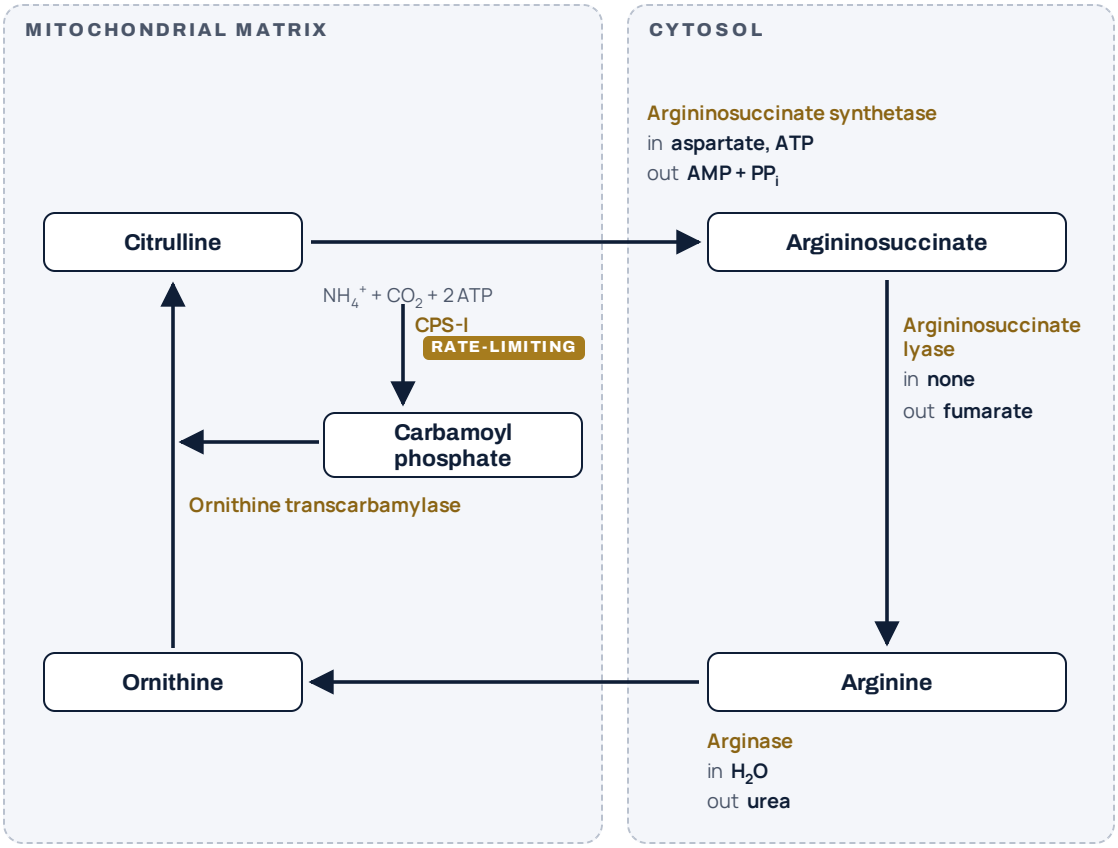
Transamination cofactor
PLP (vitamin B_6)

Usual NH_2 acceptor
α-ketoglutarate

Purely ketogenic amino acids
leucine, lysine

Muscle ships N to liver as
alanine, glutamine

UREA CYCLE · LIVER



Know it

Rate-limiting
CPS-I

Activator
N-acetylglutamate

Organ
liver

Two N sources
NH_4^+, aspartate

ATP used
3 (4 high-energy bonds)

Link to TCA
fumarate

Urea leaves via
kidneys

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Regulation at a Glance ANSWER KEY

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Fill in the control point for every pathway in Parts 1 and 2. Hormones count as activators or inhibitors.

Pathway	Rate-limiting enzyme	Activated by	Inhibited by	Fed or fasted
Glycolysis	PFK-1	AMP, F2,6-BP, insulin	ATP, citrate, glucagon	fed
Gluconeogenesis	Fructose-1,6-bisphosphatase	ATP, glucagon, cortisol	AMP, F2,6-BP, insulin	fasted
Pyruvate dehydrogenase	PDH complex	ADP, pyruvate, insulin	acetyl-CoA, NADH, ATP	fed
Citric acid cycle	Isocitrate dehydrogenase	ADP, Ca^{2+}	ATP, NADH	both
Glycogen synthesis	Glycogen synthase	G6P, insulin	glucagon, epinephrine	fed
Glycogen breakdown	Glycogen phosphorylase	AMP, Ca^{2+}, glucagon, epinephrine	ATP, G6P, insulin	fasted
Pentose phosphate	G6PD	$NADP^+$, insulin	NADPH	fed
Fatty acid synthesis	Acetyl-CoA carboxylase	citrate, insulin	palmitoyl-CoA, glucagon	fed
β-Oxidation	CPT-I	glucagon (low malonyl-CoA)	malonyl-CoA	fasted
Ketogenesis	HMG-CoA synthase	glucagon, high acetyl-CoA	insulin	fasted
Urea cycle	CPS-I	N-acetylglutamate	—	high protein / fasted

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