Lecture 19
Q&A

Ahmed Salem, MD, MSc, PhD, FRCR

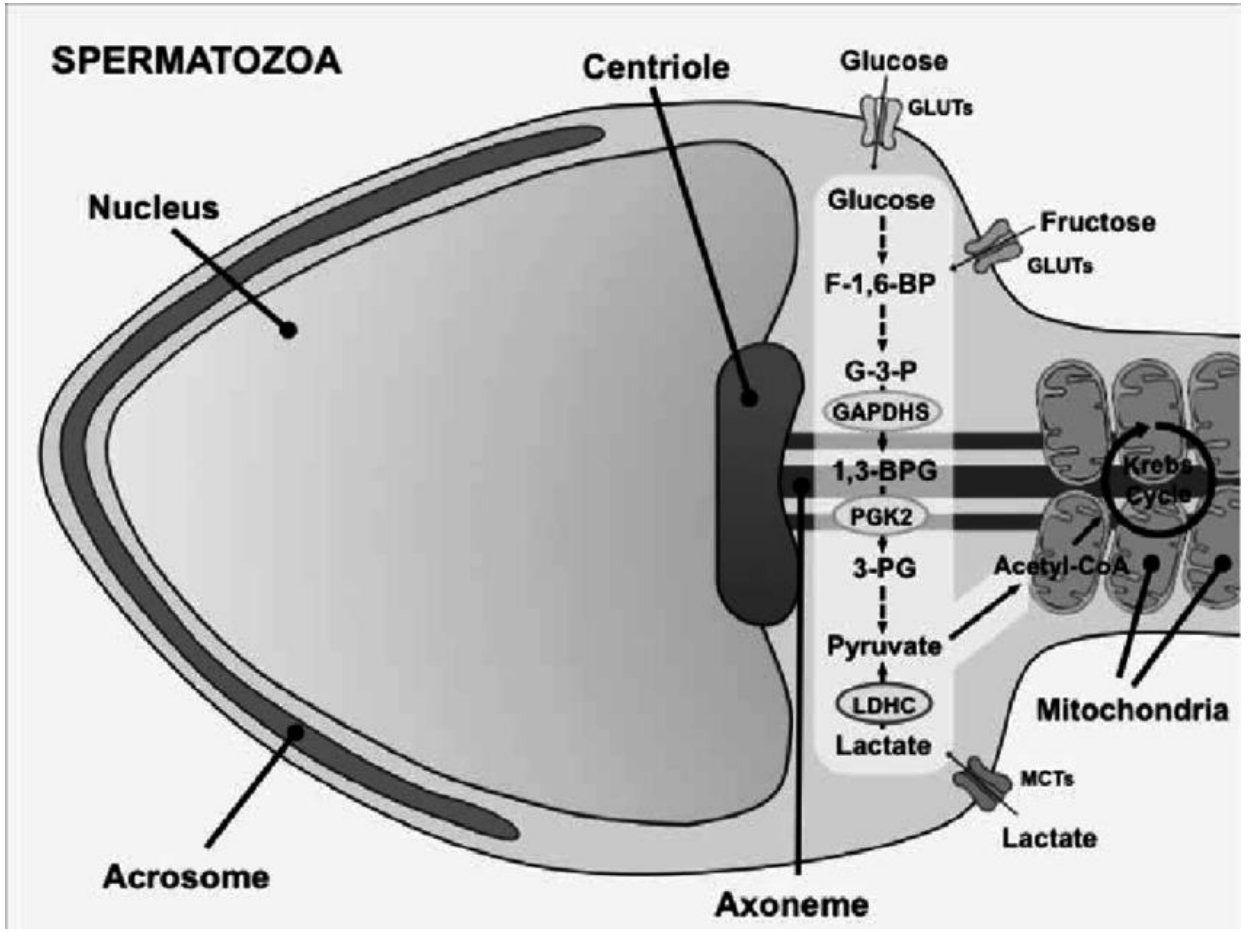
1. Which of the following is **NOT** considered a cell fuel?

A. Glucose
B. Fructose
C. Palmitic acid
D. Cholesterol
E. Acetyl coA

Answer: D

TABLE 8.3: Major fuels in different organs

	Brain	*Skeletal muscle*	*Cardiac muscle*	*Adipose tissue*
After a meal	Glucose	Glucose, Fatty acids	Glucose, pyruvate	Fatty acids; glucose
Fasting (short-term)	Glucose	Fatty acids	Fatty acids	Fatty acids
Fasting (long-term)	Glucose; ketone bodies	Ketone bodies; Branched chain aa	Ketone bodies	Fatty acids; ketone bodies
Exercise		Glycogen	Fatty acids	



2. Fatty acids are **NOT** used as cell fuel by?

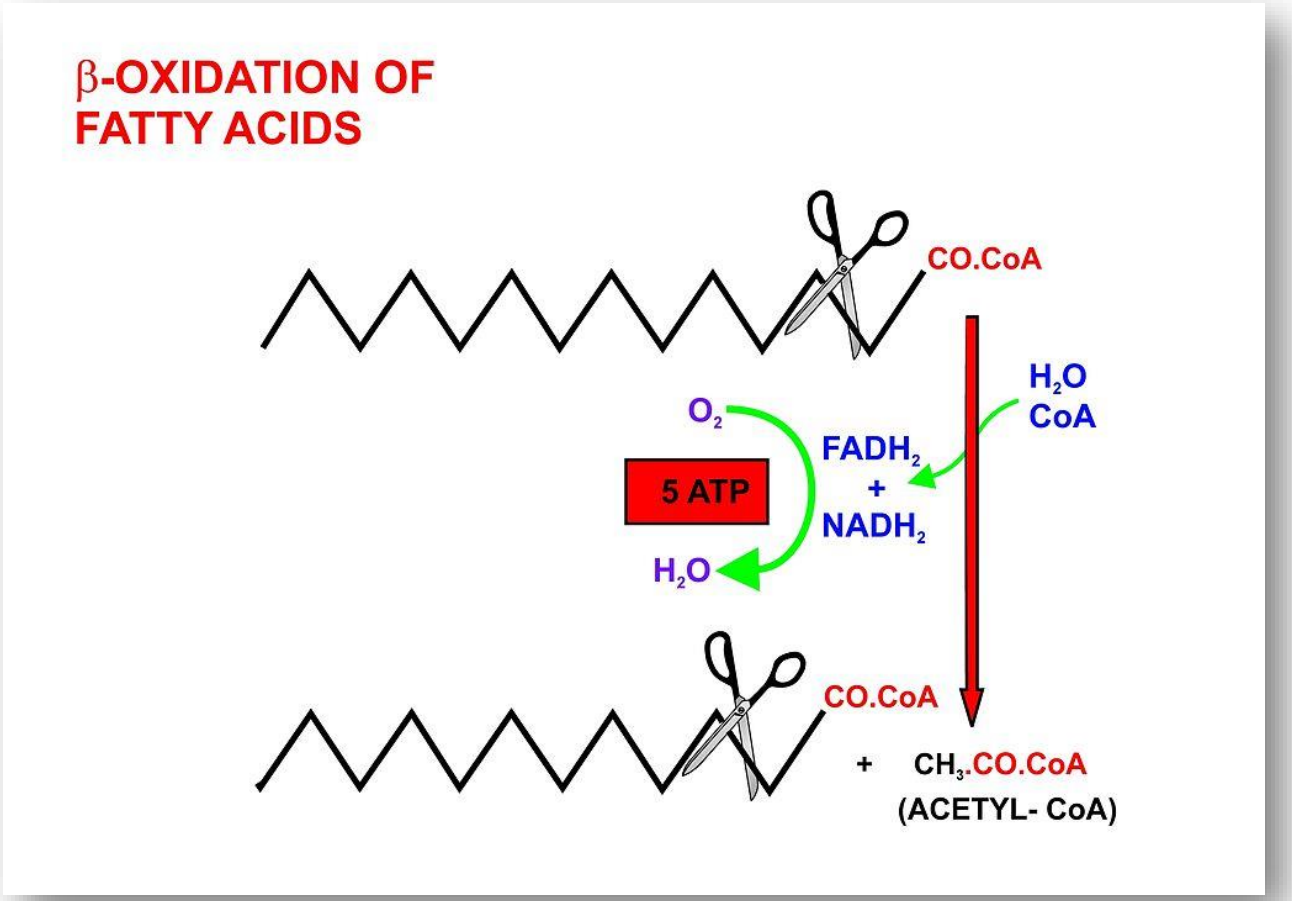
A. Liver cells
B. Adipose tissue cells
C. Muscle and heart
D. Brain and red blood cells

Answer: D

3. Which of the following is true about beta oxidation

A. It degrades fatty acids into acetyl coA
B. It goes aerobically and anaerobically
C. Beta oxidation is an excellent source of energy for the brain
D. Fatty acids cannot be used as an energy source during fasting
E. Beta oxidation is an excellent source of energy for RBCs

Answer: A

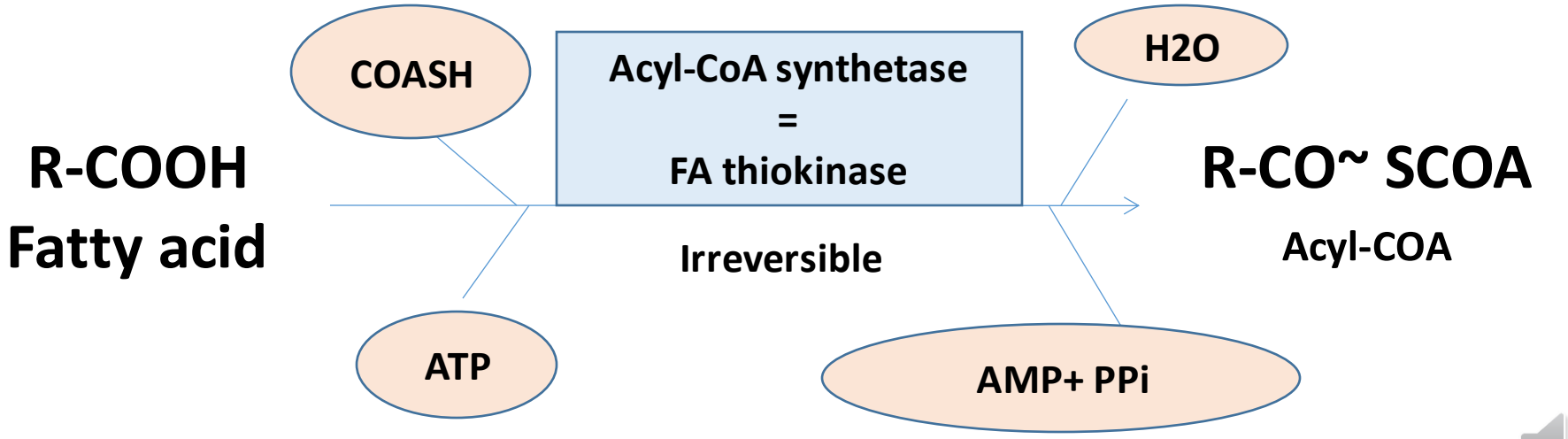

β-OXIDATION OF
FATTY ACIDS
CO.CoA
H_2O
CoA
O_2
$FADH_2$
+
$NADH_2$
5 ATP
H_2O
CO.CoA
+ CH_3.CO.CoA
(ACETYL- CoA)

4. Acyl coA is formed by:

A. Acyl coA synthetase
B. Carnitine acyltransferase II
C. Both A and B
D. Neither A nor B

1- Activation of FA

Answer: C



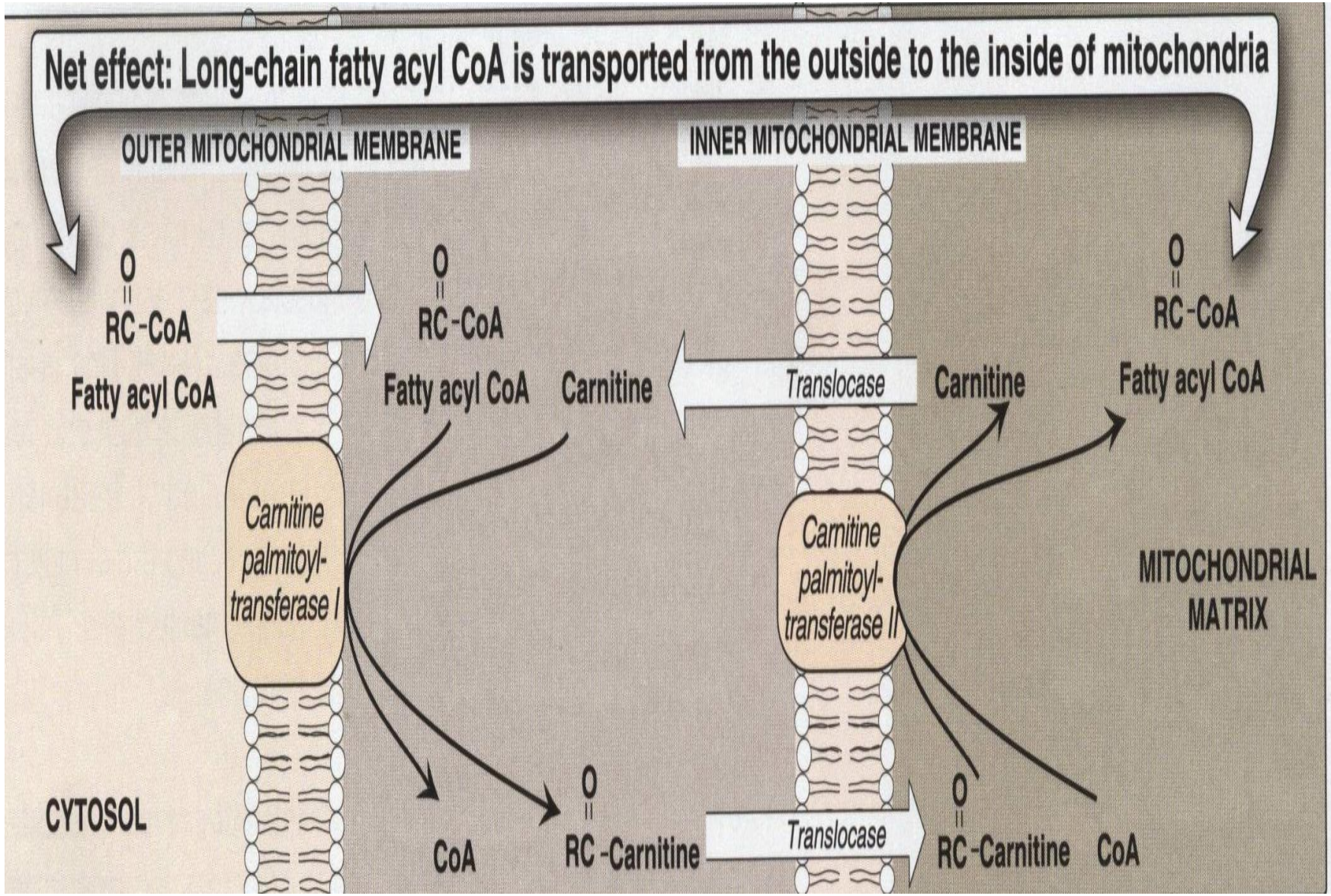
Coenzyme required: CoASH

Energy required:

ATP which converted into AMP & PPi (pyrophosphate)

The PPi is hydrolyzed by inorganic pyrophosphatase with the loss of further high-energy phosphates

So, **the total loss, two "high" energy phosphates**.


Net effect: Long-chain fatty acyl CoA is transported from the outside to the inside of mitochondria
OUTER MITOCHONDRIAL MEMBRANE
INNER MITOCHONDRIAL MEMBRANE
O
RC-CoA
Fatty acyl CoA
O
RC-CoA
Fatty acyl CoA
Carnitine
Translocase
Carnitine
O
RC-CoA
Fatty acyl CoA
Carnitine palmitoyl-transferase I
Carnitine palmitoyl-transferase II
MITOCHONDRIAL MATRIX
CYTOSOL
CoA
O
RC-Carnitine
Translocase
O
RC-Carnitine
CoA

5. Fatty acid oxidation is inhibited by

A. Insulin
B. Glucagon
C. Fatty acyl coA
D. Acetyl coA
E. Reduced ATP level

Answer: A

6. Insulin indirectly inhibits carnitine acyl transferase I by increasing the synthesis of:

A. Acetyl coA
B. Malonyl coA
C. Fatty acyl coA
D. Acylcarnitine

Answer: B

Regulation of beta oxidation

- **Rate limiting step** of beta oxidation is formation of fatty acyl carnitine (catalysed by CAT1)
- Malonyl coA (1st intermediate of synthesis of FA) allosterically inhibits CAT1
- **In fed state:**
  - ↑ insulin/glucagon ratio → fatty acid synthesis is promoted in liver (insulin activates acetyl coA carboxylase) → ↑ malonyl coA → inhibition of CAT1 → ↓ beta oxidation
- **In starvation:**
  - ↓ insulin/glucagon ratio → glucagon inhibits acetyl coA carboxylase → ↓ malonyl coA → release inhibition of CAT1 → ↑ beta oxidation
- Hormone sensitive lipase is activated by phosphorylation (glucagon)
  - Its activity is low when insulin levels are high

Notes:

- Oxidation of FA supplies **NADH** and **ATP** **required for gluconeogenisis** and supplies **excess acetyl CoA.**

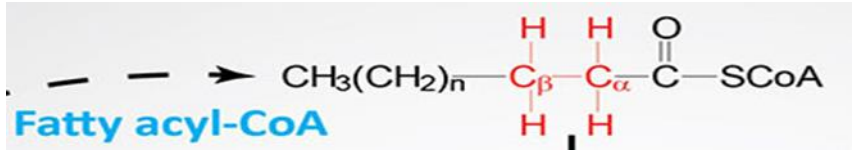
- Acetyl CoA allosterically activates pyruvate carboxylase and inhibits pyruvate dehydrogenase. **This directs pyruvate towards gluconeogenesis rather than oxidation.**

- **If FA oxidation is inhibited, gluconeogenesis is inhibited.**

7. Which of the following best describes beta oxidation of FA

A. Repetition of 3-step cycles, each producing 1 acetyl coA
B. Production of 2 acetyl coA by the last cycle
C. Reduction of 2 NAD+ by each cycle
D. Production of 2 FADH2 by each cycle
E. Production of 2 FADH2 and 1 NADH by each cycle

Answer: B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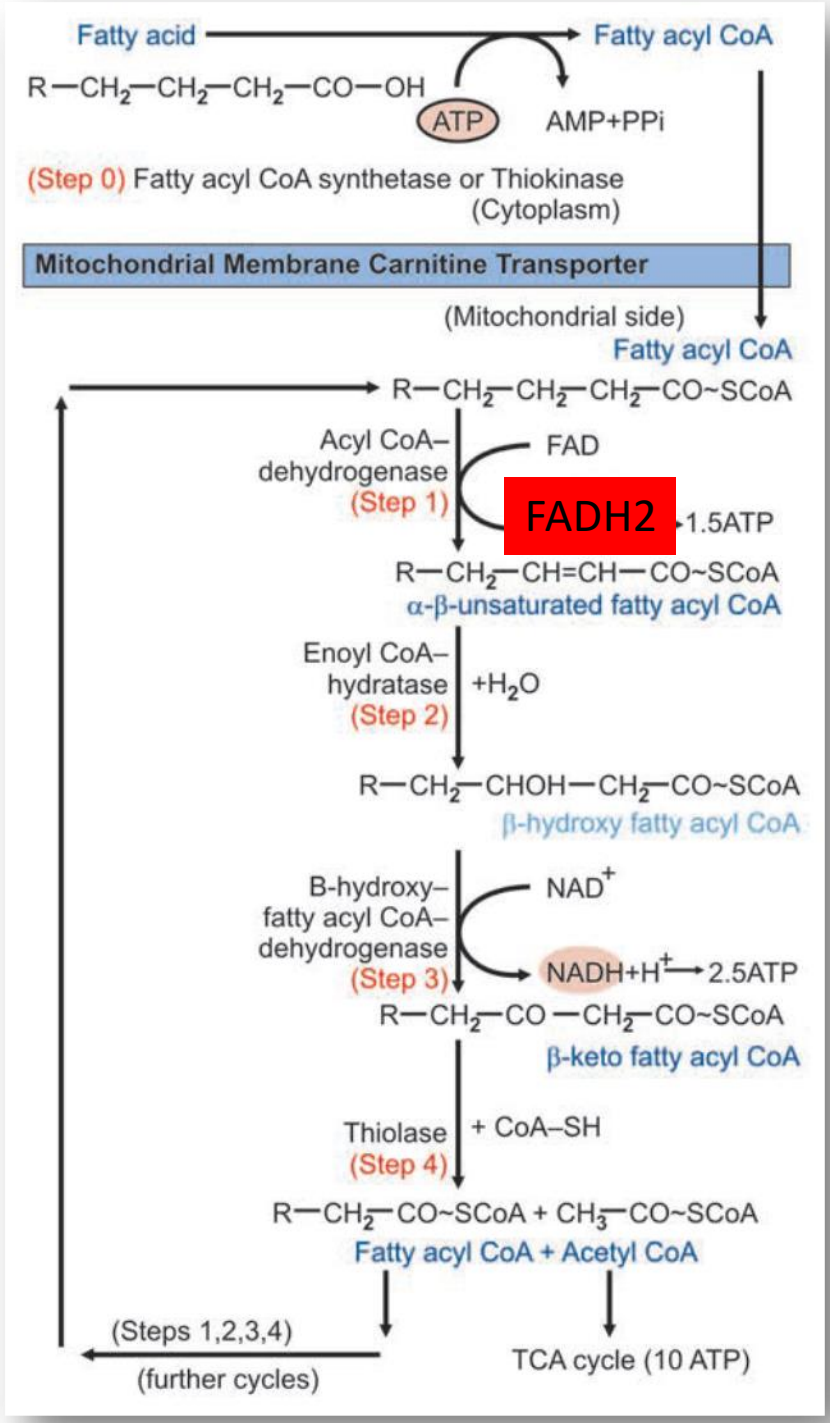
Cβ
Cα
SCoA
Fatty acyl-CoA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Fatty acyl CoA
R—CH2—CH2—CH2—CO—OH
ATP
AMP+PPi
(Step 0) Fatty acyl CoA synthetase or Thiokinase
(Cytoplasm)
Mitochondrial Membrane Carnitine Transporter
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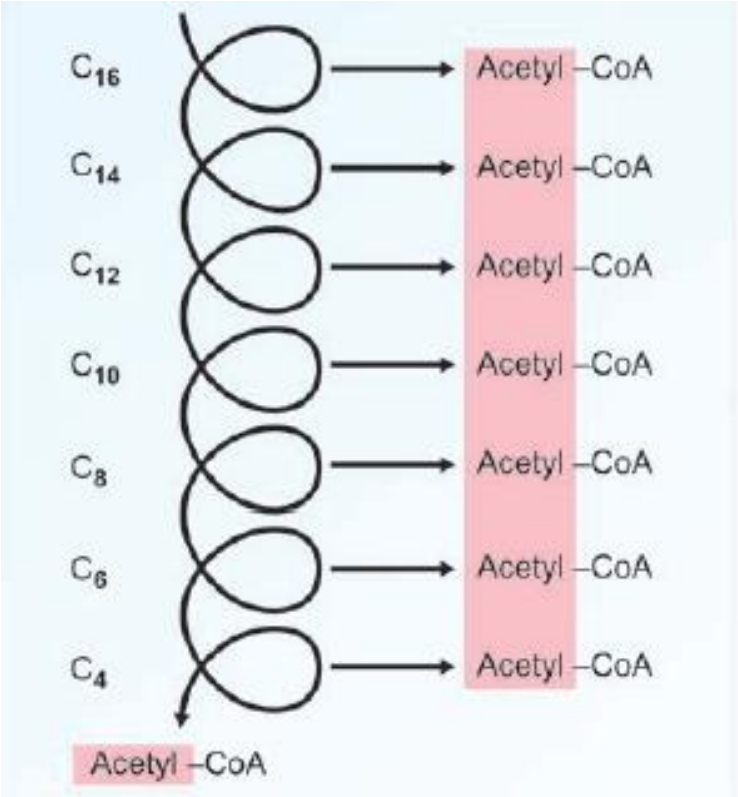
Acyl CoA–
dehydrogenase
(Step 1)
FAD
FADH2
1.5ATP
R—CH2—CH=CH—CO~SCoA
α-β-unsaturated fatty acyl CoA
Enoyl CoA–
hydratase
(Step 2)
+H2O
R—CH2—CHOH—CH2—CO~SCoA
β-hydroxy fatty acyl CoA
B-hydroxy–
fatty acyl CoA–
dehydrogenase
(Step 3)
NAD+
NADH+H+
2.5ATP
R—CH2—CO —CH2—CO~SCoA
β-keto fatty acyl CoA
Thiolase
(Step 4)
+ CoA–SH
R—CH2—CO~SCoA + CH3—CO~SCoA
Fatty acyl CoA + Acetyl CoA
(Steps 1,2,3,4)
(further cycles)
TCA cycle (10 ATP)

When one molecule of palmitate undergoes beta-oxidation, the net reaction is:

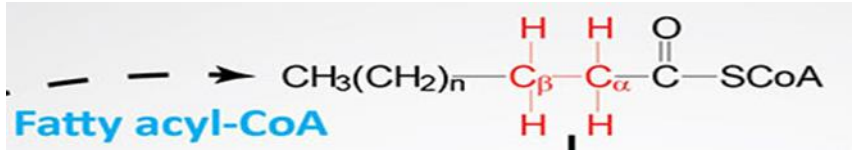
Palmitoyl CoA		8 Acetyl CoA
+ 7FAD		+ $7FADH_2$
+ $7NAD^+$	→	+ 7NADH
+ $7H_2O$		+ $7H^+$
+ 7HSCoA		



8. Which of the following is the correct sequence of beta oxidation steps

A. Dehydrogenase, hydratase, dehydrogenase, thiolase
B. Dehydrogenase, dehydrogenase, hydratase, thiolase
C. Dehydrogenase, thiolase, hydratase, dehydrogenase
D. Dehydrogenase, hydratase, thiolase, dehydrogenase

Answer: A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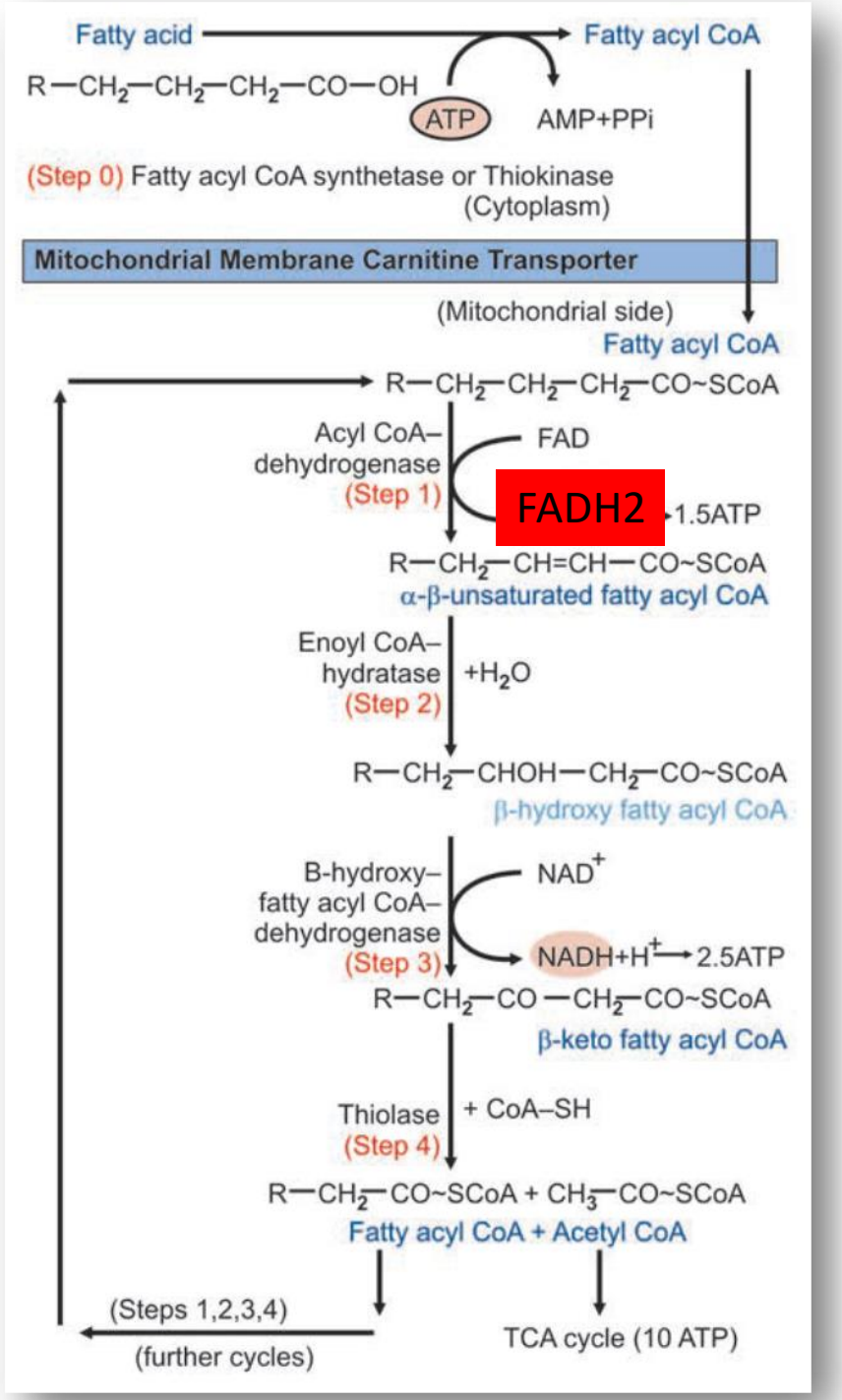
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R—CH2—CH=CH—CO~SCoA
α-β-unsaturated fatty acyl CoA
Enoyl CoA–
hydratase
(Step 2)
+H2O
R—CH2—CHOH—CH2—CO~SCoA
β-hydroxy fatty acyl CoA
B-hydroxy–
fatty acyl CoA–
dehydrogenase
(Step 3)
NAD+
NADH+H+
2.5ATP
R—CH2—CO—CH2—CO~SCoA
β-keto fatty acyl CoA
Thiolase
(Step 4)
+ CoA–SH
R—CH2—CO~SCoA + CH3—CO~SCoA
Fatty acyl CoA + Acetyl CoA
(Steps 1,2,3,4)
(further cycles)
TCA cycle (10 ATP)

9. Propionyl coA is metabolised in the mitochondria to:

A. Malonyl coA
B. Methmalonyl coA then succinyl coA
C. Ketone bodies
D. Glucose

Answer: B

Oxidation of FA with an odd number of C atoms:

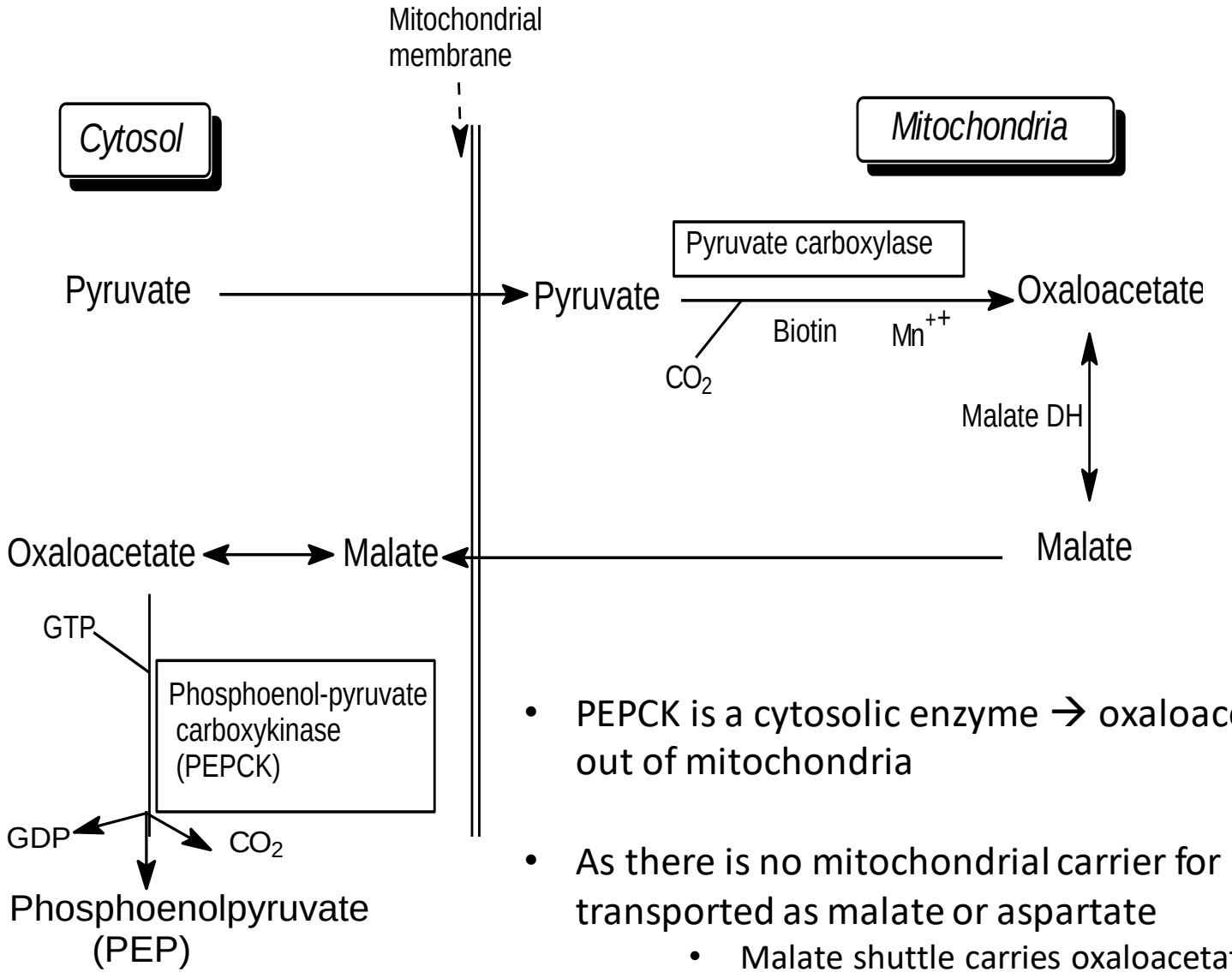
- Odd chain FA are oxidized by β oxidation producing acetyl-CoA but only at the last step one **propionyl-CoA** is produced

- Propionyl CoA can be converted to methyl malonyl CoA which is converted to succinyl-CoA → citric acid cycle → oxaloacetate → glucose

This is the only mechanism by which Fatty acids are converted to glucose

- 3 C units from odd chain FA are glucogenic

- Cow's milk contains significant quantity of odd chain FAs



- PEPCK is a cytosolic enzyme → oxaloacetate must be transported out of mitochondria
- As there is no mitochondrial carrier for oxaloacetate, it is transported as malate or aspartate
  - Malate shuttle carries oxaloacetate and reducing equivalents
  - Aspartate shuttle does not require preliminary reduction step, depends of availability of glutamate and α ketoglutartae

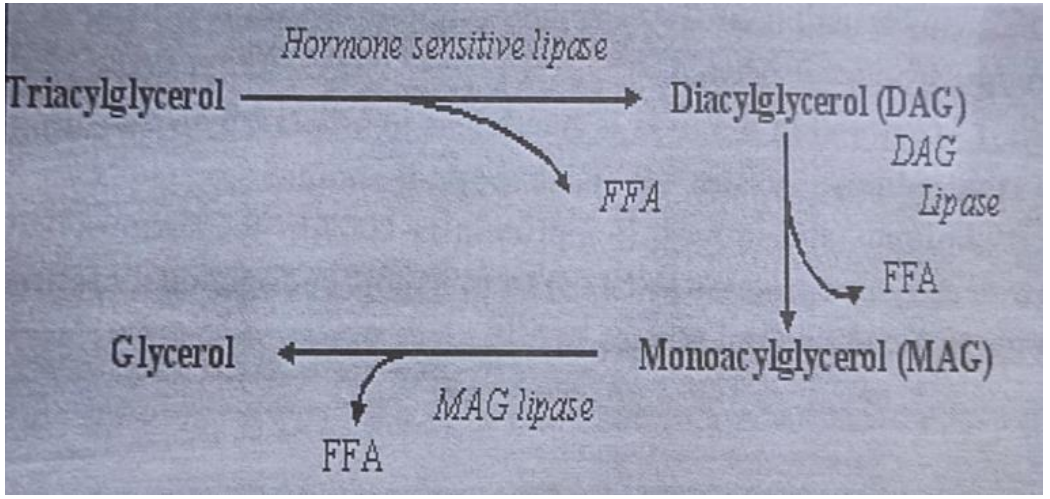
10. Lipolysis in fat cells requires:

A. TAG lipase
B. DAG lipase
C. MAG lipase
D. All of the above

Answer: D

Process of mobilization of stored fats

- **Lipolysis:** process of appearance of FAs in blood during fasting is due to mobilization of fat stores
- This is via hydrolytic release of FAs from glycerol in TAG
- Initiated by hormone sensitive lipase (removes FAs from carbon 1 and/or carbon 3 of TAG)
- Additional lipases remove the remaining FAs from diacylglycerol or monoacylglycerol



11. Energy required for gluconeogenesis is obtained by oxidation of:

A. Ketone bodies
B. Fatty acids
C. Amino acids
D. Glucose

Answer: B

Notes:

- Oxidation of FA supplies **NADH** and **ATP** **required for gluconeogenisis** and supplies **excess acetyl CoA.**

- Acetyl CoA allosterically activates pyruvate carboxylase and inhibits pyruvate dehydrogenase. **This directs pyruvate towards gluconeogenesis rather than oxidation.**

- **If FA oxidation is inhibited, gluconeogenesis is inhibited.**

12. Ketone bodies are formed from:

A. Beta keto acyl coA
B. Acetyl coA
C. Cytosolic HMG coA
D. Ketosugars

Answer: B

13. How is acetoacetate formed from aceto-acetyl coA

A. Directly by a hydratase action
B. Directly by lyase
C. Through formation of HMG coA
D. By thiolase

Answer: C

14. Which of the following is true about HMG coA

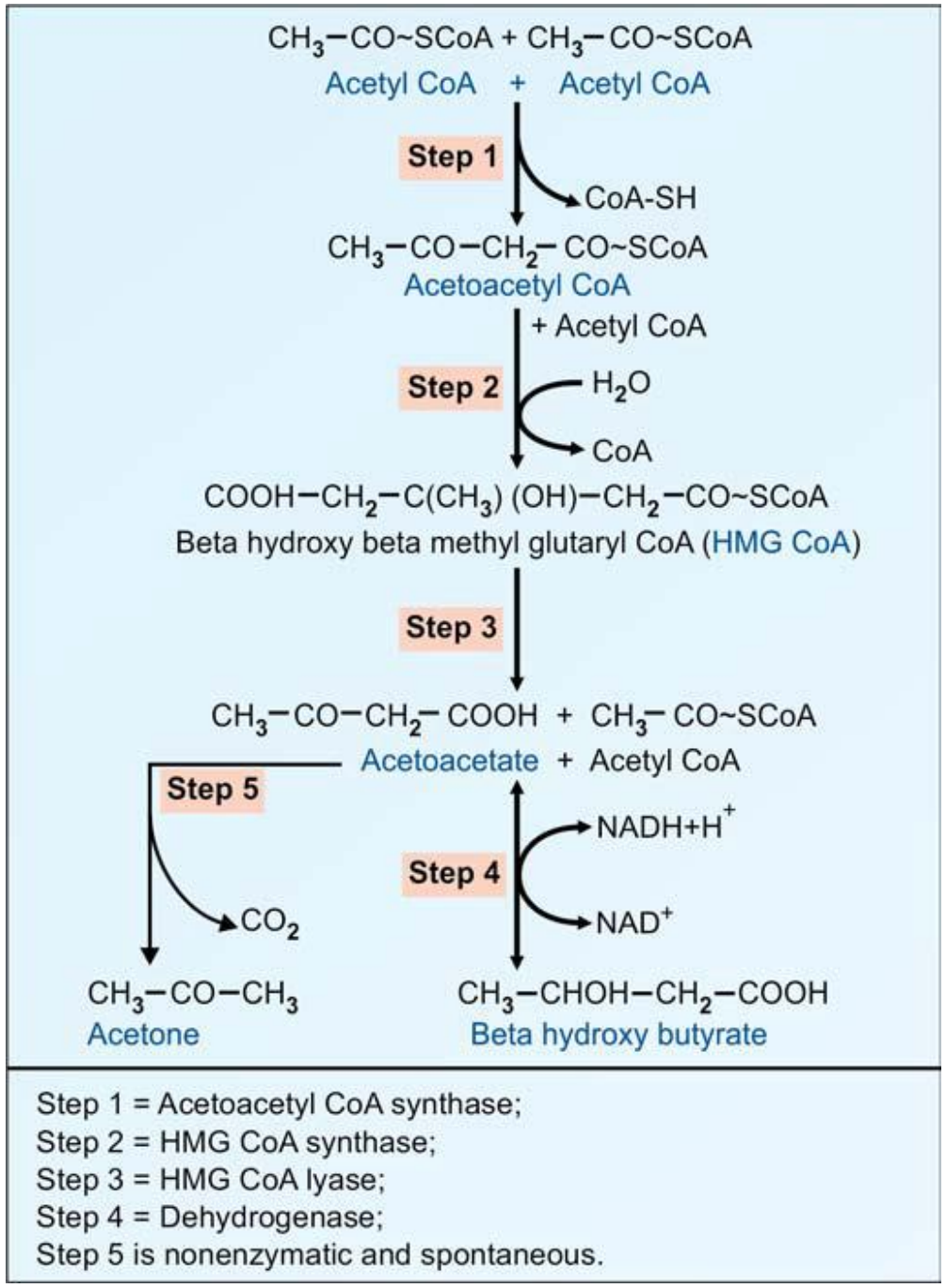
A. It is formed by reaction of acetoacetyl coA with acetyl coA
B. In the cytosol, it is the precursor of ketone bodies
C. In the mitochondria, it the precursor of cholesterol
D. All of the above

Answer: A

Ketogenesis

- Acetoacetate is primary ketone body
- Synthesised **exclusively** in liver **mitochondria**
- 4 Steps:
  - Condensation
  - Production of HMG coA
  - Lysis
  - Reduction
  - Spontaneous decarboxylation

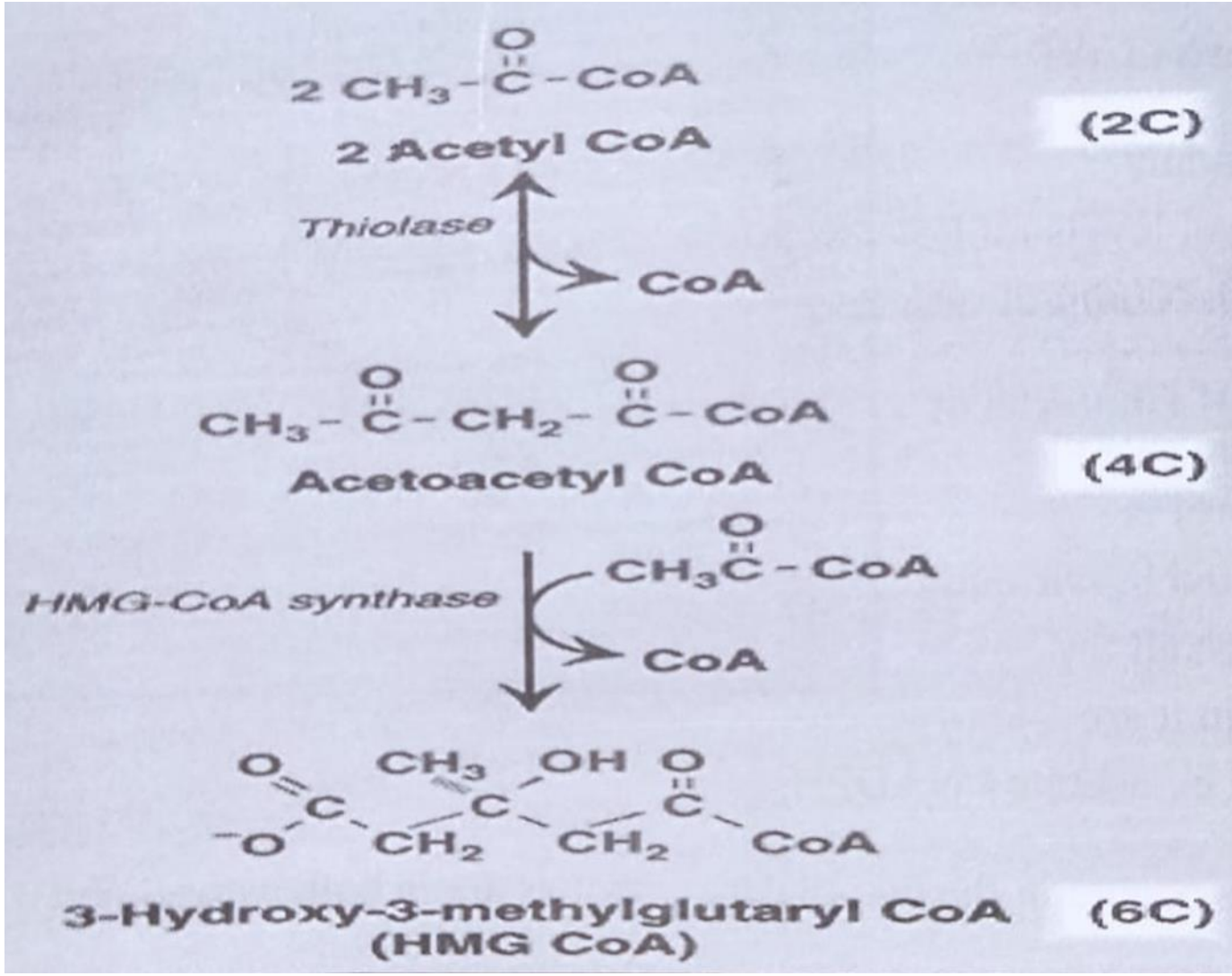
HMG coA synthase is rate limiting step in synthesis of ketone bodies and is present in significant quantities only in liver



Step 1 = Acetoacetyl CoA synthase;
Step 2 = HMG CoA synthase;
Step 3 = HMG CoA lyase;
Step 4 = Dehydrogenase;
Step 5 is nonenzymatic and spontaneous.

Synthesis of HMG coA from acetyl coA

- **Isoenzymes of HMG co synthase**
  - Cytosolic enzyme → cholesterol synthesis
  - Mitochondrial enzyme → ketone body synthesis



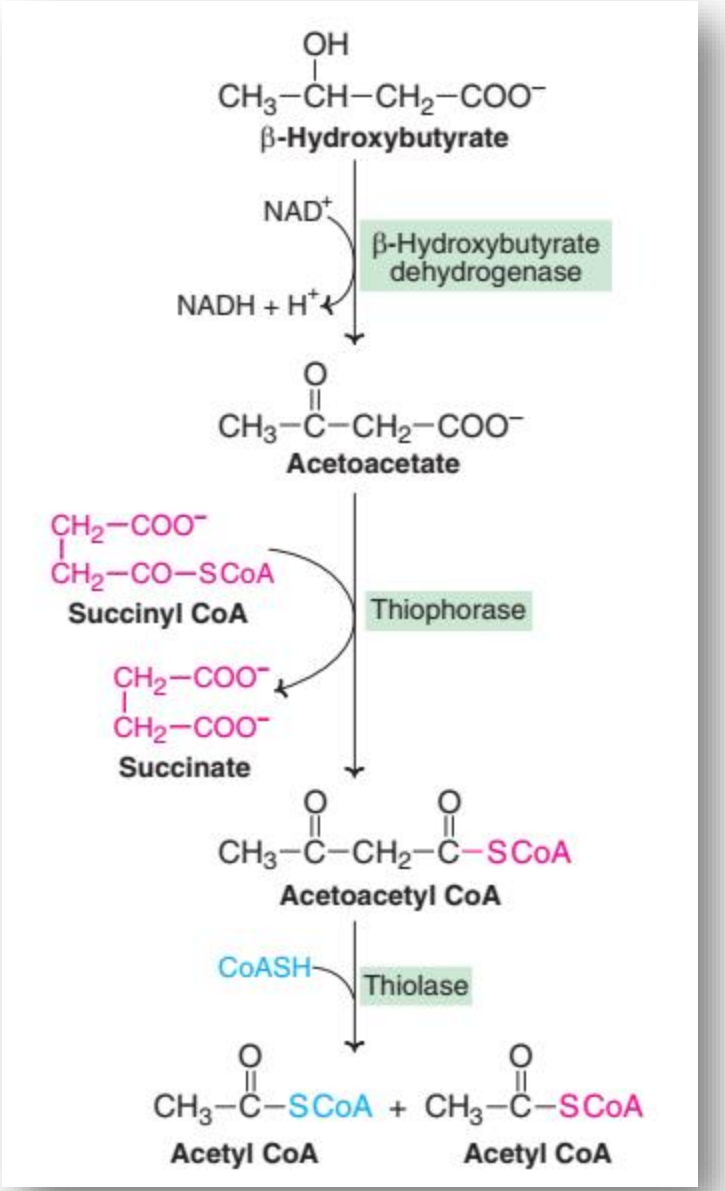
15. Where does ketolysis occur?

A. Liver cell mitochondria
B. Liver cell cytosol
C. Mitochondria of extra-hepatic tissues
D. All tissues except muscle and heart

Answer: C

Ketolysis

- Ketone bodies are formed in liver but utilized in extrahepatic tissues
- Heart muscle, renal cortex sometimes prefer ketone bodies to glucose as fuel
- Muscle can also utilize ketone bodies



16. The product of the key enzyme of ketolysis is metabolised by:

A. Thiolase producing acetyl coA
B. Acyl coA dehydrogenase, producing enoyl coA
C. Citrate cycle producing CO2
D. Carboxylase producing malonyl coA

Answer: A

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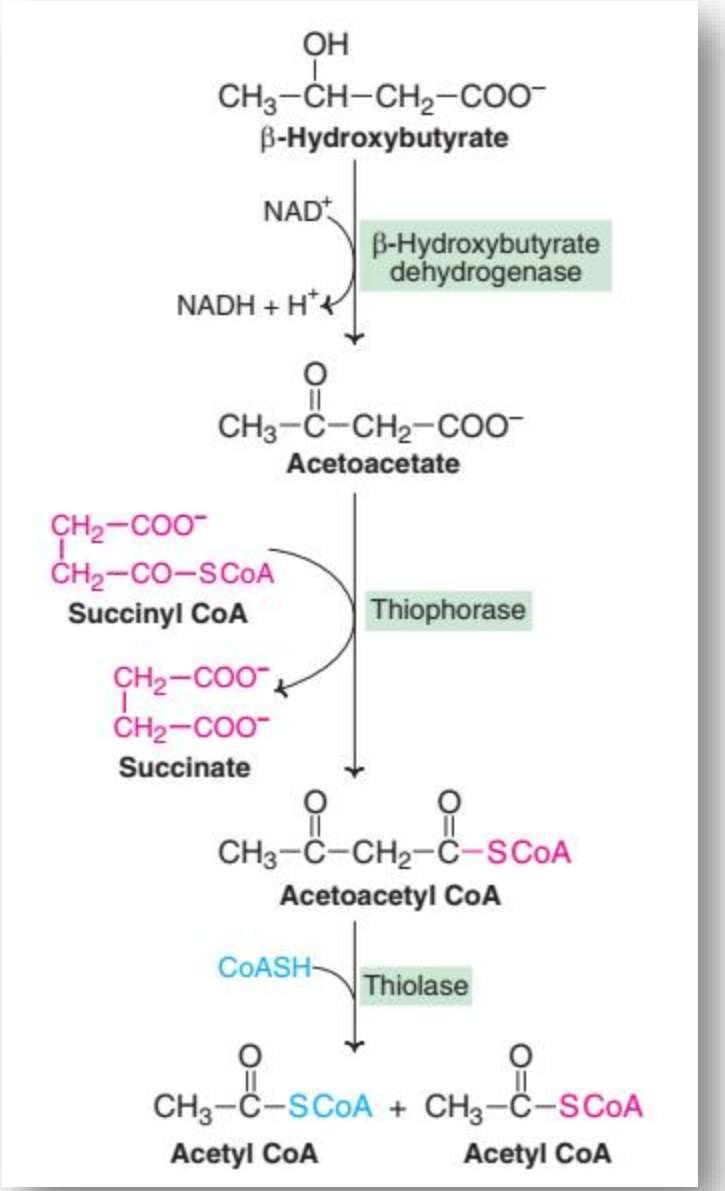

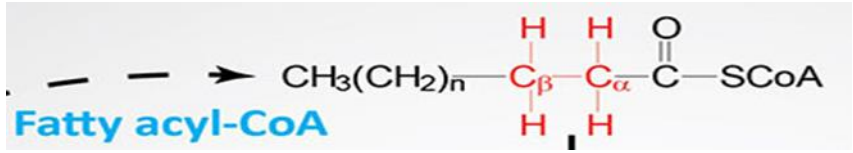
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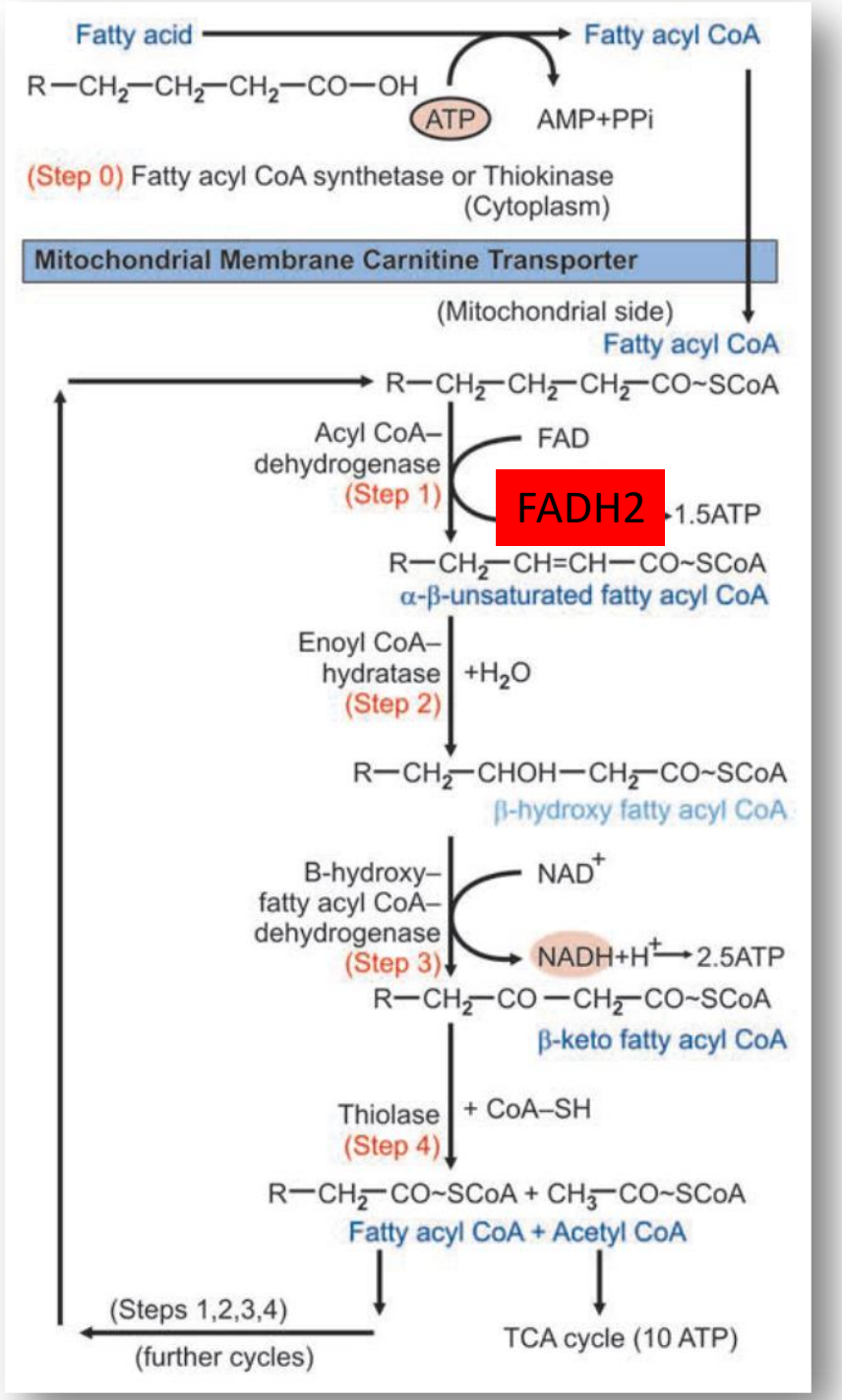
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R—CH2—CO~SCoA + CH3—CO~SCoA
Fatty acyl CoA + Acetyl CoA
(Steps 1,2,3,4)
(further cycles)
TCA cycle (10 ATP)

17. The net energy yield of beta hydroxybutyrate oxidation is:

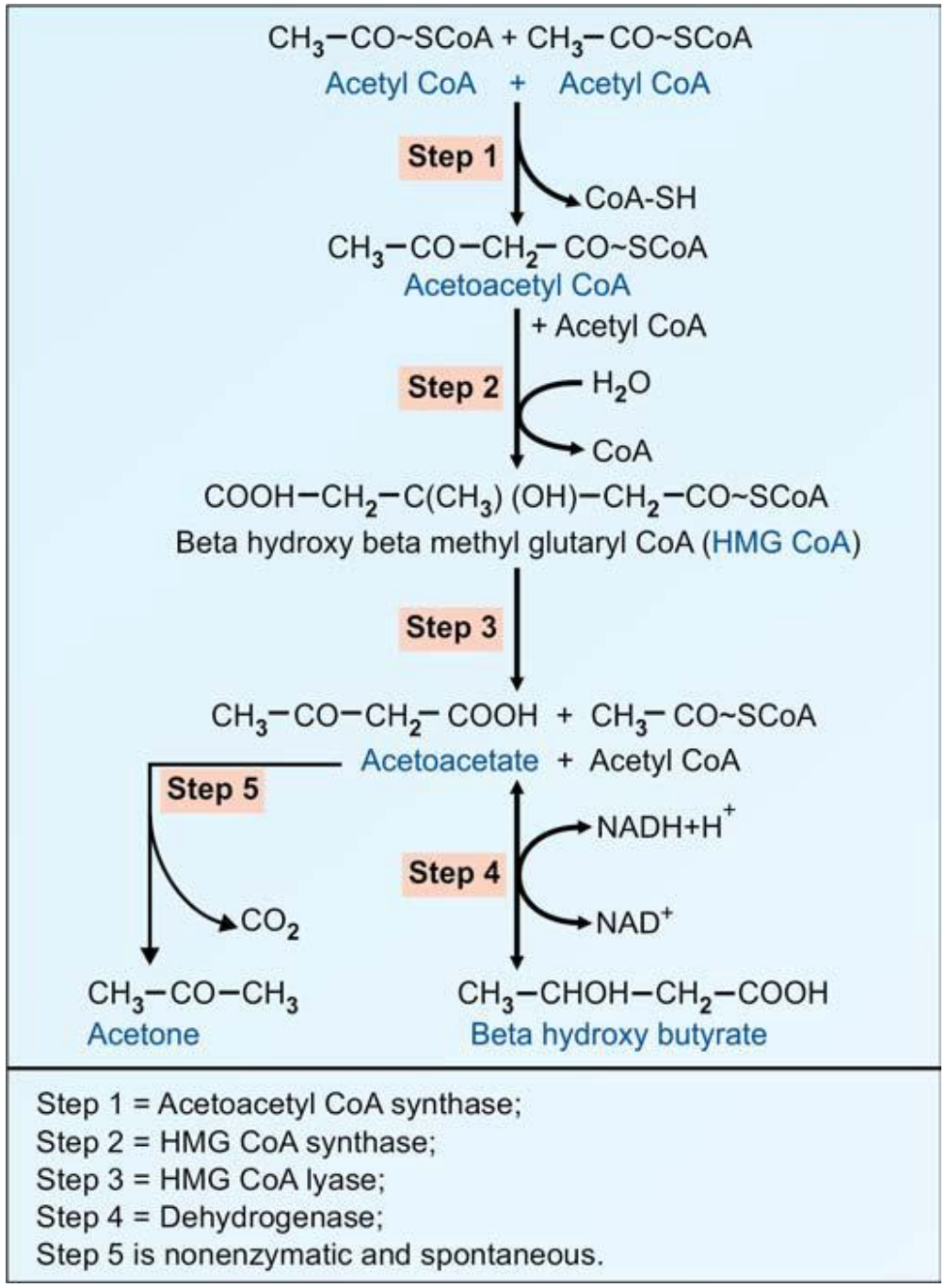
A. Similar to that of acetone
B. Similar to that of acetoacetate
C. 2.5 ATP more that acetoacetate
D. 2.5 ATP less than acetoacetate

Answer: C

Ketogenesis

- Acetoacetate is primary ketone body
- Synthesised **exclusively** in liver **mitochondria**
- 4 Steps:
  - Condensation
  - Production of HMG coA
  - Lysis
  - Reduction
  - Spontaneous decarboxylation

HMG coA synthase is rate limiting step in synthesis of ketone bodies and is present in significant quantities only in liver



Step 1 = Acetoacetyl CoA synthase;
Step 2 = HMG CoA synthase;
Step 3 = HMG CoA lyase;
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Step 5 is nonenzymatic and spontaneous.

the breakdown of

- β-hydroxybutyrate yields 1 NADH and 2 acetyl-CoA (= 22.5 ATP)
- acetoacetate yields only 2 acetyl-CoA and no NADH (= 20 ATP)

18. Ketolysis by the brain spares glucose through:

A. Indirect allosteric inhibition of glycolysis by acetyl coA

B. Inhibition of insulin activated glucose transporters

C. Activation of glycogenolysis

D. Inhibition of the citrate cycle

Answer: A

Regulation of the 3 irreversible reactions

- **Induction and Repression of the key enzymes:** Insulin induces (increases) the synthesis of these enzymes, while glucagon and adrenaline inhibit their synthesis

- **Allosteric regulation:**

- ***GK (Glucokinase)***: No regulation
- Hexokinase is allosterically inhibited by G-6-P.

N.B. hexokinase is present in all cells except liver and pancreatic islets/ glucokinase is present only in liver and pancreatic islets.

- ***PFK (Phosphofructokinase):***

- Allosterically activated by fructose-2,6-bis-phosphate, AMP& ADP
- Allosterically inhibited by ATP & Citrate and low pH

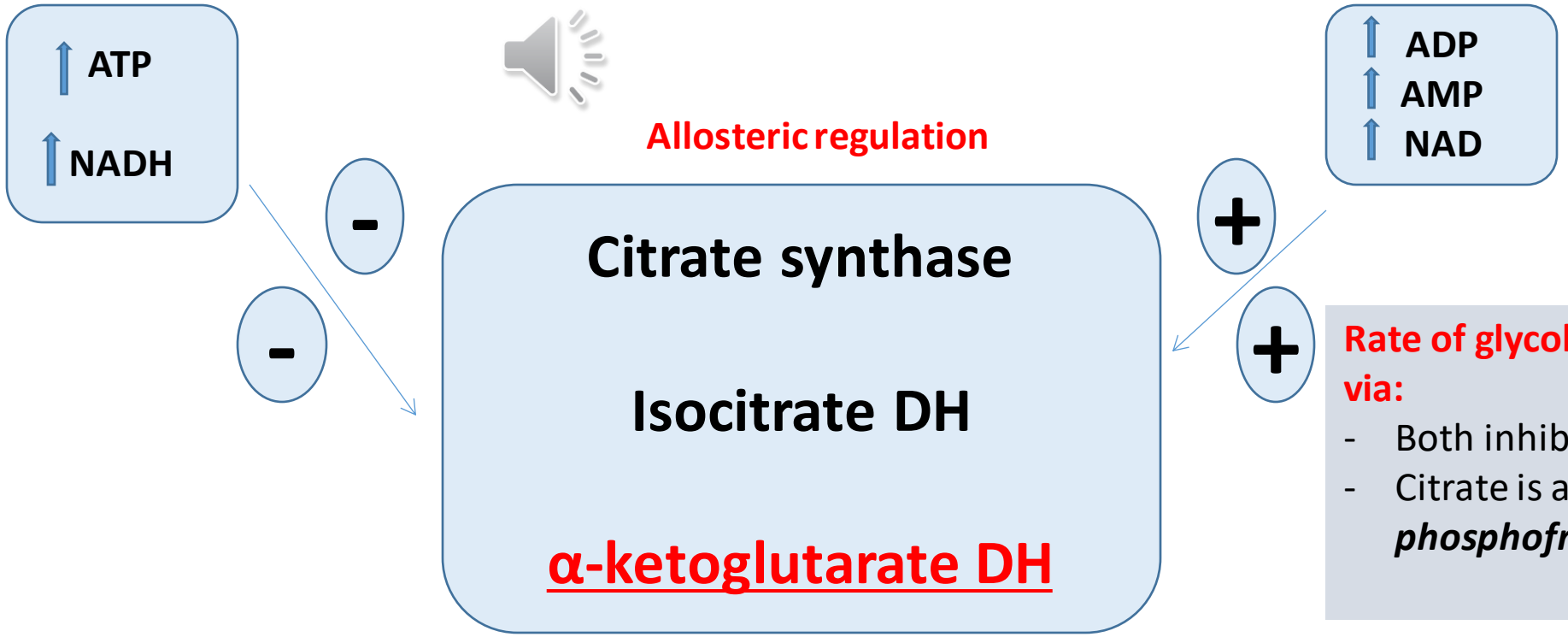
Fructose-2, 6-Bisphosphate: [F-2, 6–BP] is formed by phosphorylation of F-6-P by the enzyme phosphofructokinase–2 (PFK-2)

- ***PK (Pyruvate kinase):***

-Allosterically activated by Fructose-1,6- bis-phosphate, AMP

-Allosterically inhibited by ATP

A possible explanation for the acid- induced protein catabolism and increased amino acid oxidation is that impairment of glycolysis by low pH restricts the pyruvate supply to mitochondria, leading to catabolism of amino acids from protein as an alternative metabolic fuel.



Rate of glycolysis and Krebs cycle are matched via:

- Both inhibited by high levels of ATP & NADH
- Citrate is an important allosteric inhibitor of ***phosphofructokinase 1***

Substrate availability is required for Krebs cycle:

- **NAD and FAD:** NADH+H and FADH2 must be re-oxidised via active respiratory chain
  - Active respiratory chain needs high oxygen and high ADP concentrations
- **Acetyl coA** (via glucose oxidation, FA & KB oxidation and catabolism of ketogenic AA)
- **Oxaloacetate** (from malate, aspartate and pyruvate)

19. Infection or trauma may precipitate an episode of ketoacidosis by:

A. Increase in cortisol or epinephrine

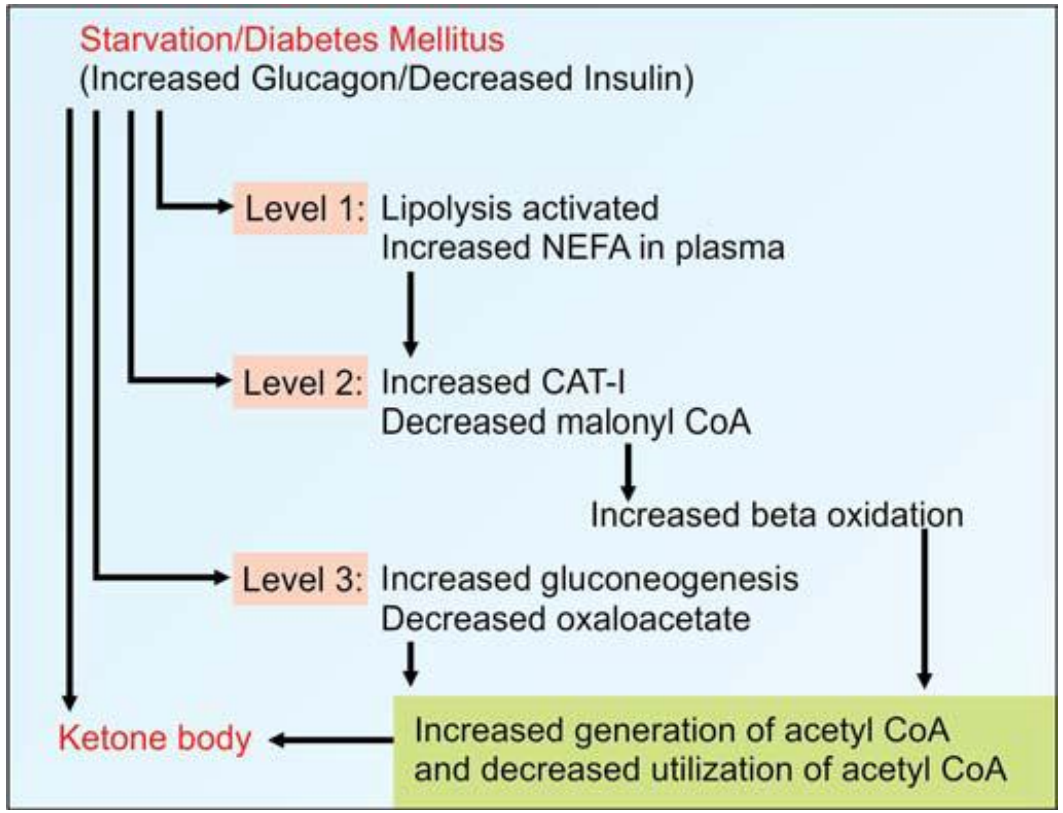
B. Inhibition of fat cell lipase

C. Decreased consumption of ketone bodies

Answer: A

D. Decreased fatty acid oxidation by the liver

Ketosis



Salient Features of Ketosis

1. **Metabolic acidosis.** Acetoacetate and beta-hydroxy butyrate are acids. When they accumulate, metabolic acidosis results. (see Chapter 29).
2. **Reduced buffers.** The plasma bicarbonate is used up for buffering of these acids.
3. **Kussmaul's respiration.** Patients will have typical acidotic breathing (see Chapter 24) due to compensatory hyperventilation.
4. **Smell of acetone** in patient's breath.
5. **Osmotic diuresis** induced by ketonuria may lead to dehydration.
6. **Sodium loss.** The ketone bodies are excreted in urine as their sodium salt, leading to loss of cations from the body.
7. **Dehydration.** The sodium loss further aggravates the dehydration.
8. **Coma.** Hypokalemia, dehydration and acidosis are contributing for the lethal effect of ketosis.

Regulation of beta oxidation

- **Rate limiting step** of beta oxidation is formation of fatty acyl carnitine (catalysed by CAT1)
- Malonyl coA (1st intermediate of synthesis of FA) allosterically inhibits CAT1
- **In fed state:**
  - ↑ insulin/glucagon ratio → fatty acid synthesis is promoted in liver (insulin activates acetyl coA carboxylase) → ↑ malonyl coA → inhibition of CAT1 → ↓ beta oxidation
- **In starvation:**
  - ↓ insulin/glucagon ratio → glucagon inhibits acetyl coA carboxylase → ↓ malonyl coA → release inhibition of CAT1 → ↑ beta oxidation
- Hormone sensitive lipase is activated by phosphorylation (glucagon)
  - Its activity is low when insulin levels are high

20. Fatty acids are synthesised from:

A. Acetyl coA resulting from CHO and amino acid oxidation

B. Ketone bodies

C. Glycerol

Answer: A

D. HMG coA

Biosynthesis of FAs

- Pathway is called **Lynen's pathway** (Feodor Lynen → Nobel prize)
- Glucose by glycolysis → pyruvate (cytosol)
- Pyruvate by PDH→ acetyl-CoA (mitochondria)

Acetyl – CoA derived from glucose & others is used for synthesis of FA by:

1) **The extramitochondrial (cytosolic) system (site of FA synthesis)**
2) The mitochondrial system
3) The microsomal system

FA elongation

21. Which of the following is **NOT** true about *de novo* fatty acid synthesis:

A. The reactions are the reverse of beta oxidation

B. The acetate moiety added in each cycle is provided by malonyl coA

C. Reducing equivalents are provided by FADH2 and NADH

Answer: C

D. Lipogenic enzymes are induced by feeding

Steps of de novo FA synthesis:

1. The initial step of FA biosynthesis including carboxylation of acetyl CoA to produce malonyl CoA

This step needs **biotin**, Mn^{2+}, and an enzyme; **ACC** *(acetyl CoA carboxylase)* *and biocarbonate*

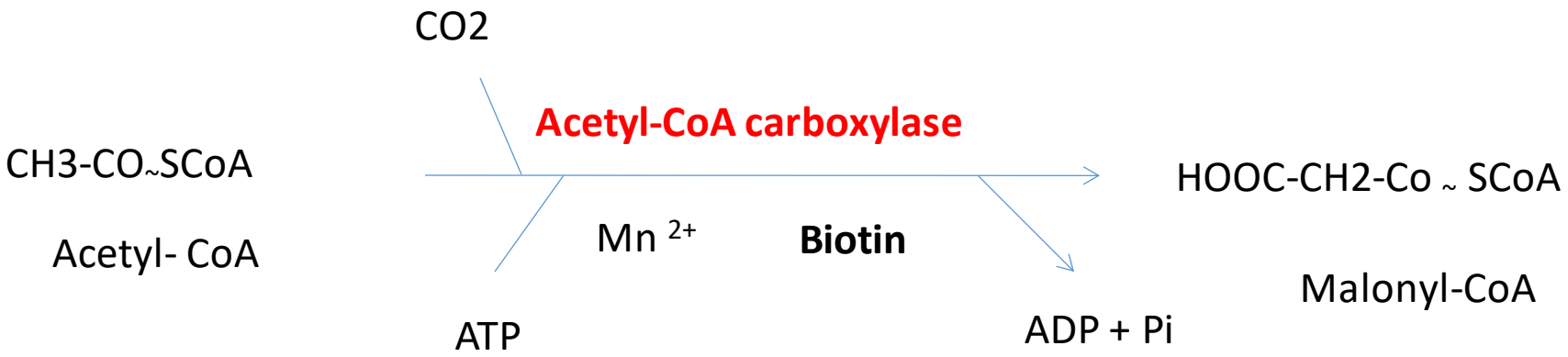
Rate limiting step of FA synthesis

The enzyme is allosterically regulated, the major effectors being:

→citrate (positive)

→ palmitoyl CoA (negative)

- 8 acetyl-CoA (C2) → 1 palmitic acid (C16)
- 7 of these 8 acetyl-CoA are converted to malonyl-CoA (2C)



Steps 3-5

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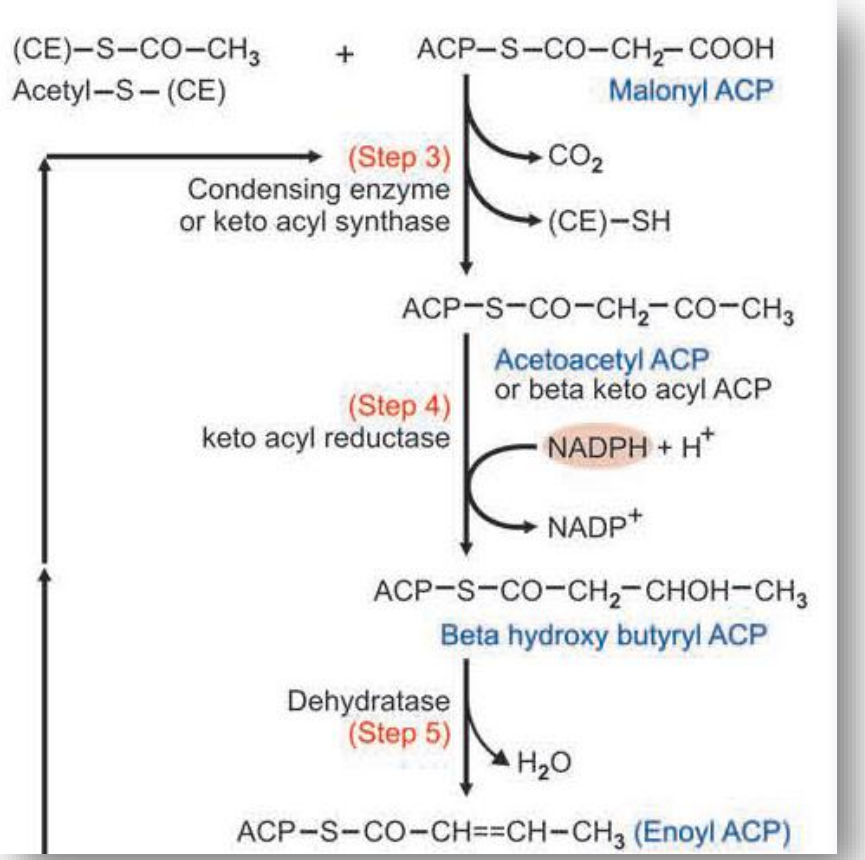

Step 6 and cycling

- **Step 6 (2nd reduction):** The enoyl ACP is again reduced by enoyl reductase (ER) utilizing a 2nd molecule of NADPH to form butyryl ACP

- **Cycling of Reactions:**
  - The butyryl group (4C) is now transferred to the SH group of the condensing enzyme on the other monomer and;
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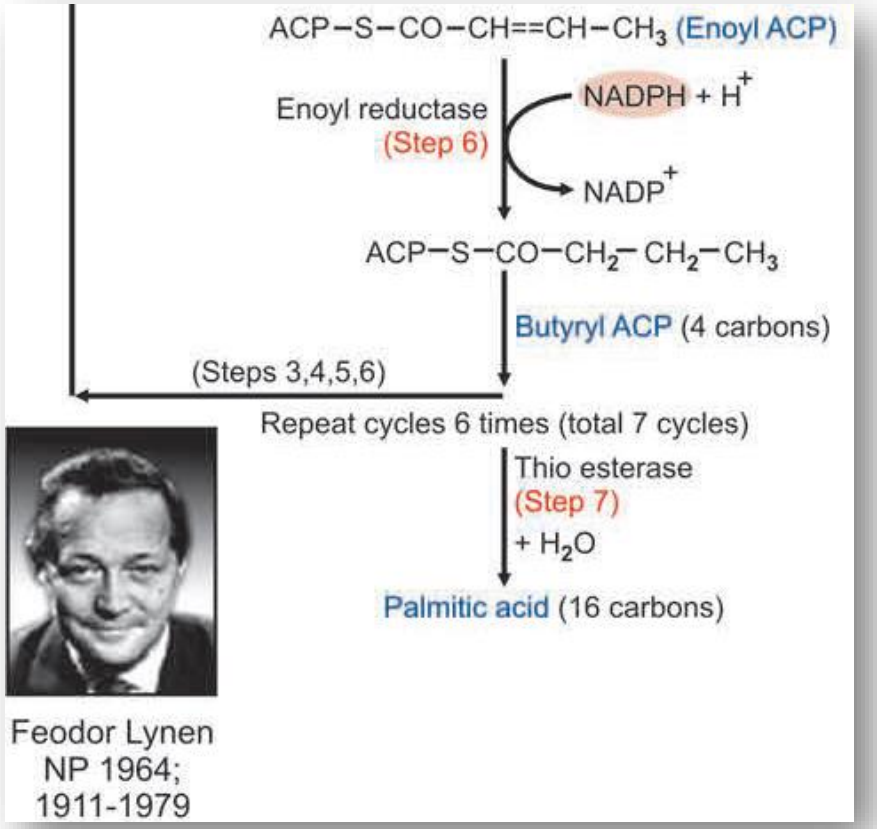
    - The sequence of reactions (steps 3,4,5,6) are repeated
    - The cycles are repeated a total of 7 times, till the 16-carbon palmitic acid is formed



Feodor Lynen
NP 1964;
1911-1979

3. Acetyl –CoA carboxylase (ACC):

The active form is the dephosphorylated:

- Insulin, suppresses cAMP, so it activates acetyl CoA carboxylase
- Adrenaline and glucagon have the reverse effect (phosphorylate or inactivate ACC)
- ACC is inactivated by AMP activated protein kinase (AMPK)
    - AMPK is allosterically activated by rise in AMP relative to ATP

- Feeding status:

CHO feeding stimulates insulin secretion which induces the synthesis of acetyl-coA.

Fasting → ↓↓ insulin and ↑↑ adrenalin and glucagon→ ↓↓ glucose uptake and utilization, so fasting inhibits FA synthesis.

3. Insulin Favors Lipogenesis

Insulin enhances the uptake of glucose by adipocytes and increases the activity of pyruvate dehydrogenase, acetyl CoA carboxylase and glycerol phosphate acyl transferase (see Table 24.4). Insulin also depresses the hormone sensitive lipase (Fig. 11.16).

Well-fed state	During fasting
Lipogenesis increased Lipolysis inhibited Lipoprotein lipase active Insulin inhibits HS-lipase	Lipogenesis inhibited Lipolysis increased Glucagon activates HS-lipase FFA in blood increased

Synthesis is not the opposite of oxidation

	Beta-oxidation	Fatty acid synthesis
Site	Mitochondria	Cytoplasm
Intermediates	Present as CoA derivatives	Covalently linked to SH group of ACP
Enzymes	Present as inde-pendent proteins	Multienzyme complex
Sequential units	2 carbon units split off as acetyl CoA	2 carbon units added, as 3 carbon malonyl CoA
Co-enzymes	NAD^+ and FAD are reduced	NADPH used as reducing power

22. NADPH is produced by all of the following except:

A. Glucose 6-phosphate dehydrogenase

B. Malate dehydrogenase

C. Malic enzyme

Answer: B

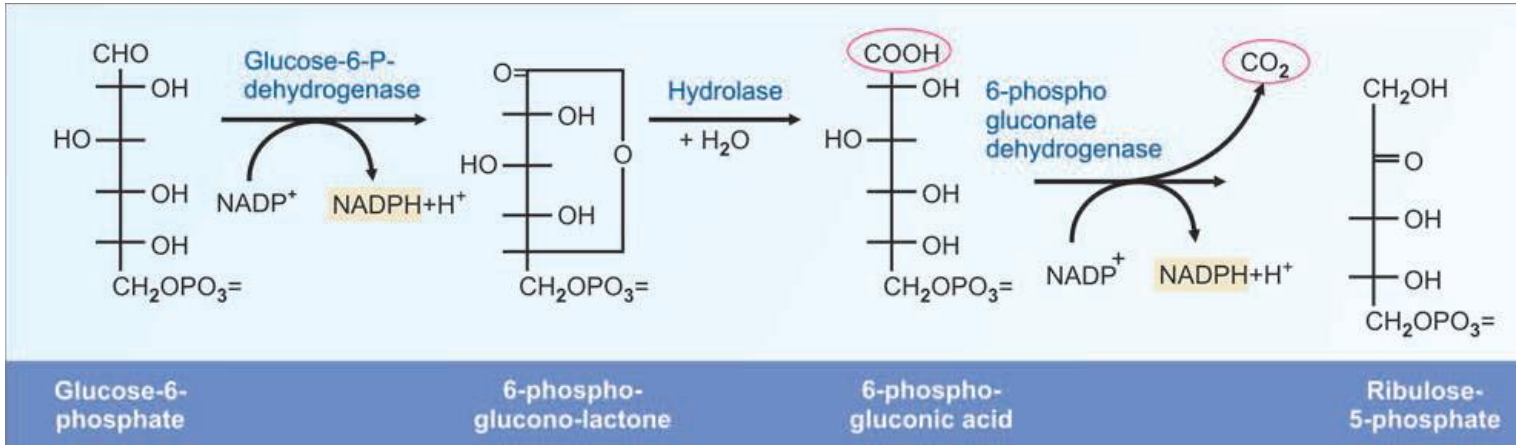
D. 6 phosphogluconate dehydrogenase

Oxidative phase steps

1. Glucose 6-P is oxidized by NADP+ dependent glucose 6-P dehydrogenase → 6-phosphogluconolactone
   - Rate limiting step

2. Lactone is hydrolyzed by gluconolactone hydrolyase → 6-phosphogluconic acid

3. *Decarboxylation of 6-phosphogluconic acid catalyzed by 6-phosphogluconate dehydrogenase →
   - 1 x Ribulose 5-P
   - 2 x NADPH+H
   - 1 x CO2



We start with 3 Glucose 6-P to obtain 3 ribulose 5-P to enter non-oxidative phase

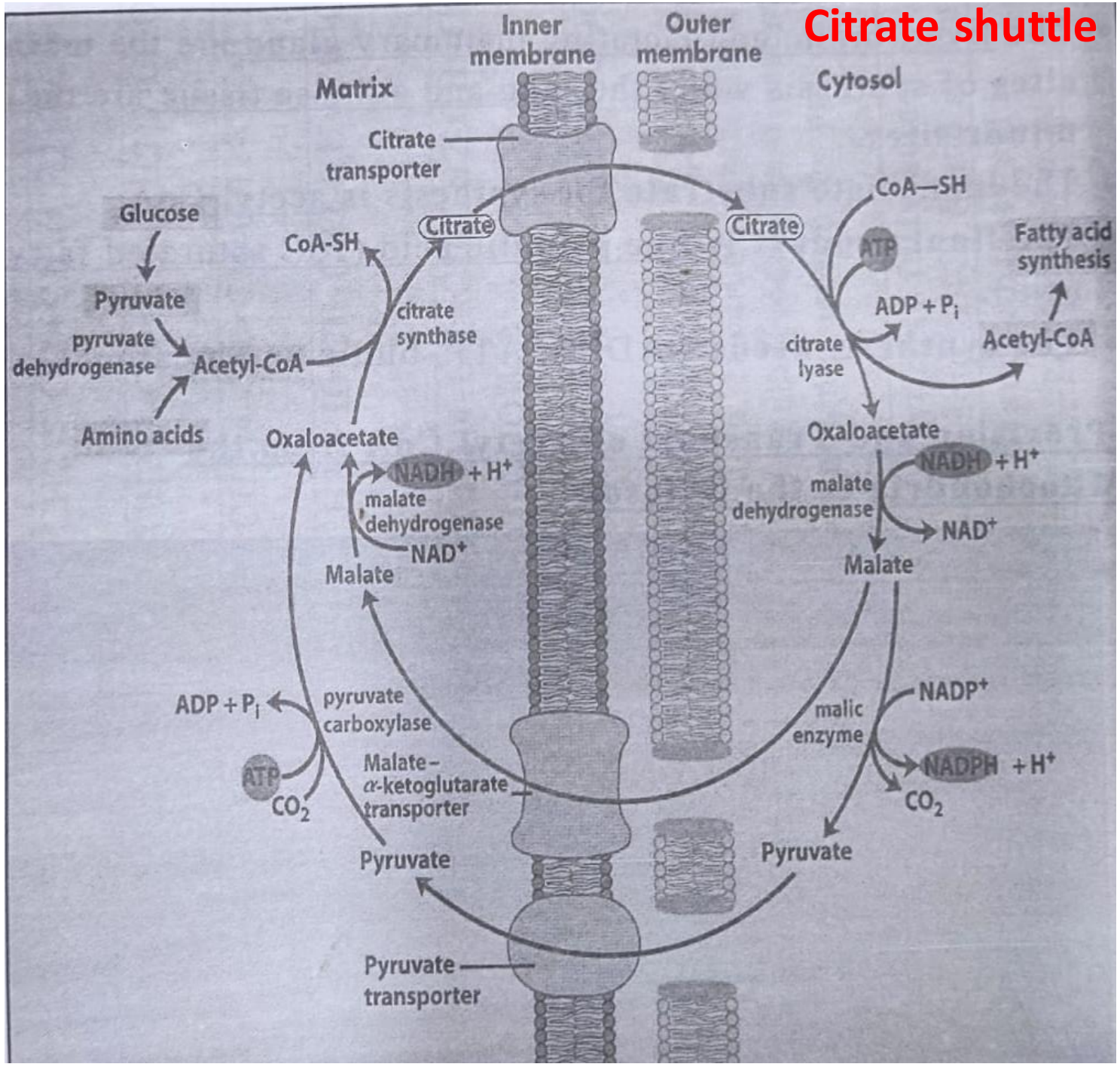
Key facts about FA synthesis

- FA synthesis takes place in cytosol and uses NADP as co-enzyme for redox reactions
- **Citrate shuttle** is responsible for moving acetyl coA from mitochondria to the cytosol
- NADPH is an important co-enzyme for de novo FA synthesis; sources:
  - Main source of NADPH is PPP (both FA synthesis and PPP occur in cytosol; no permeability barrier)
  - Malic Enzyme: The reaction helps to transfer cytoplasmic oxaloacetate to the mitochondria

$$\text{Malate} + \text{NADP}^+ \rightarrow \text{Pyruvate} + \text{CO}_2 + \text{NADPH} + \text{H}^+$$

- The building block for FA synthesis is malonyl coA (3C)
- FA synthesis in each reaction cycle adds 2 carbons that are derived from malonyl coA following decarboxylation
  - Acetyl (2C) coA is used as a primer for C15 and 16 in palmitate → even number FA
  - If propionyl (3C) coA is used as a primer → odd n FA is formed
  - Short chain FA is formed if chain is released before reaching 16 carbons as in mammary glands

Citrate shuttle



23. Which of the following is true about the source of carbons of the newly synthesised fatty acid

A. All of the carbons are from acetyl coA

B. All of the carbons are from CO2

C. Half of the carbons are from acetyl co A and half form CO2

D. Half of the carbons are from acetyl co A and half from biocarbonate

Answer: A

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Steps of de novo FA synthesis:

1. The initial step of FA biosynthesis including carboxylation of acetyl CoA to produce malonyl CoA

This step needs **biotin**, Mn^{2+}, and an enzyme; **ACC** *(acetyl CoA carboxylase)* *and biocarbonate*

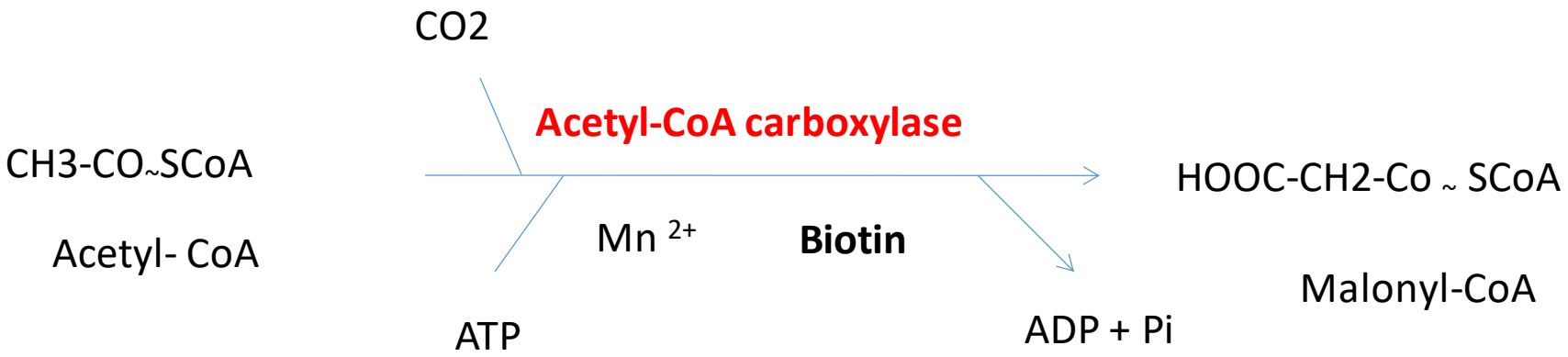
Rate limiting step of FA synthesis

The enzyme is allosterically regulated, the major effectors being:

→citrate (positive)

→ palmitoyl CoA (negative)

- 8 acetyl-CoA (C2) → 1 palmitic acid (C16)
- 7 of these 8 acetyl-CoA are converted to malonyl-CoA (2C)



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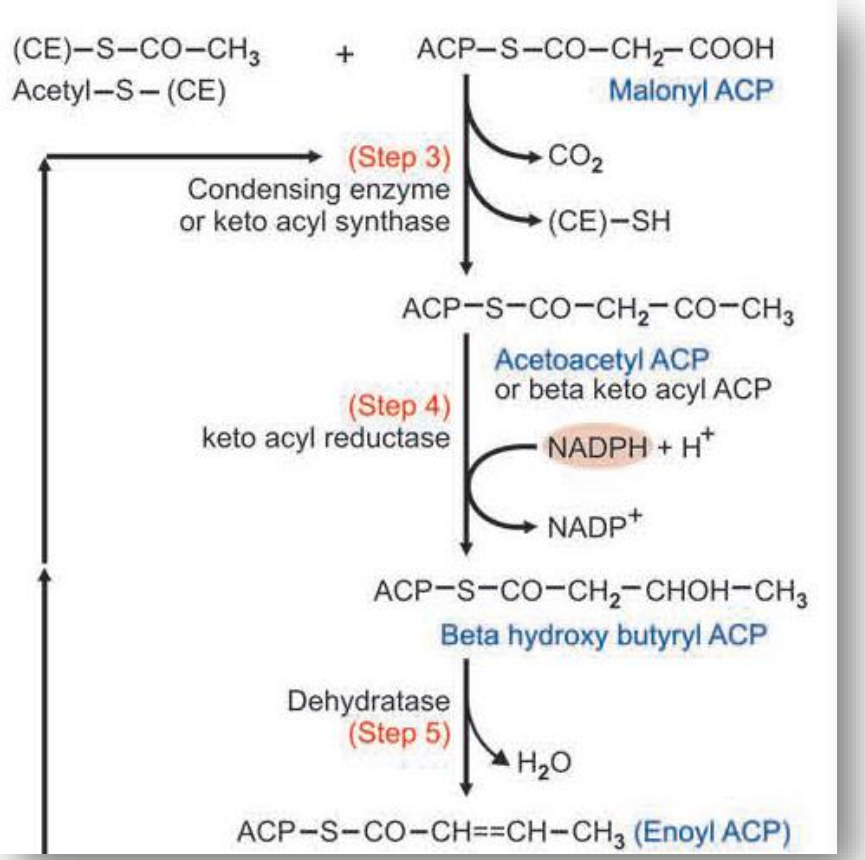

24. The final step of de novo fatty acid synthesis is

A. Thiolase

B. Thioesterase

C. Thiokinase

D. HMG co A synthase

Answer: B

Step 6 and cycling

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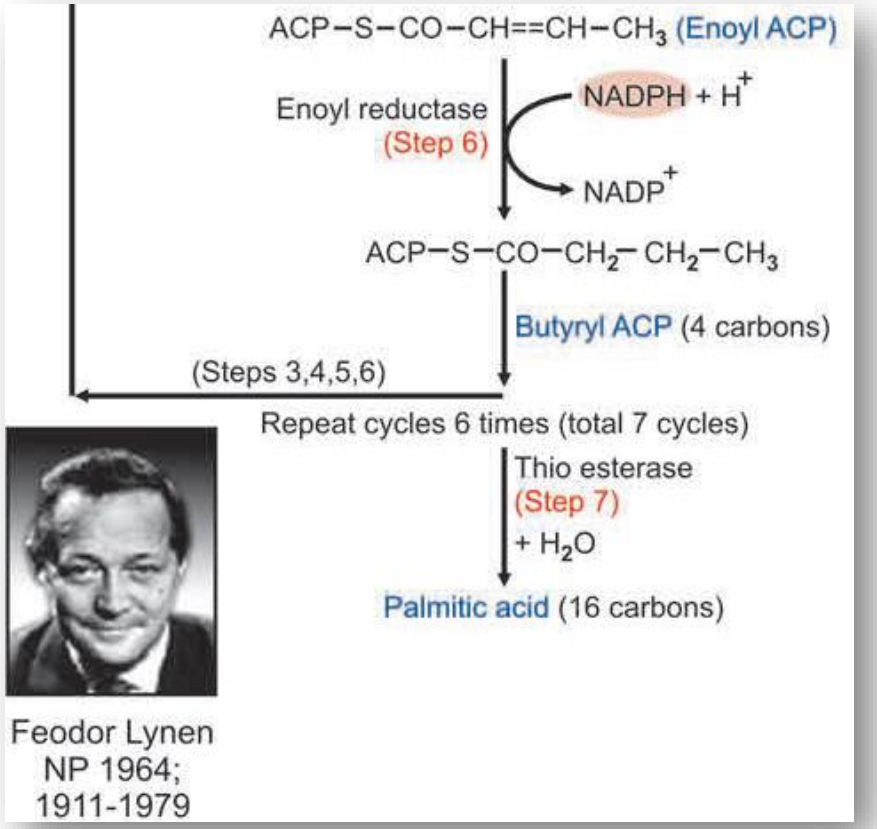

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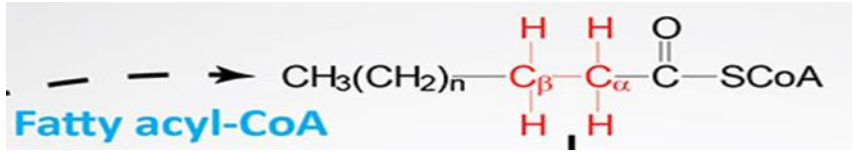
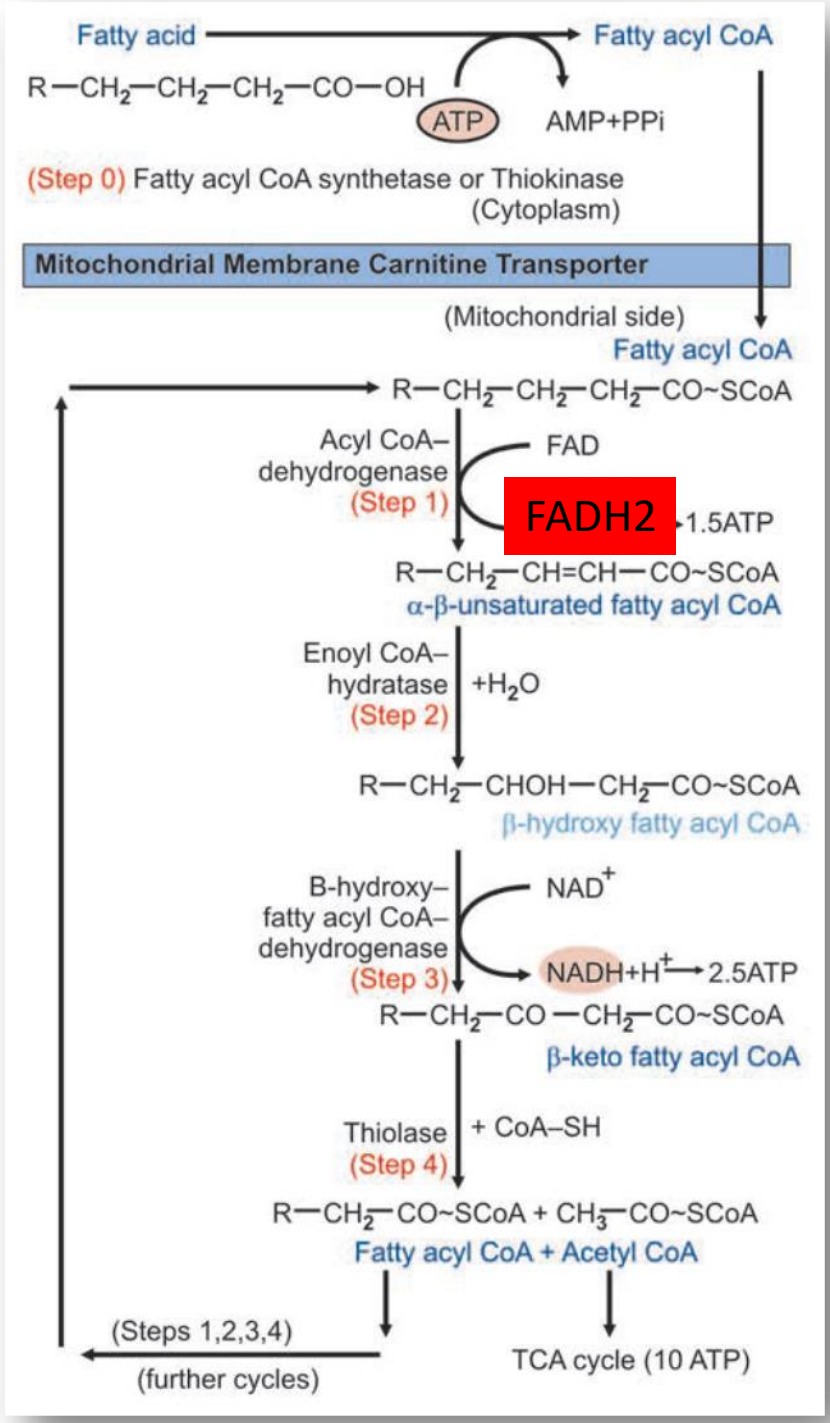


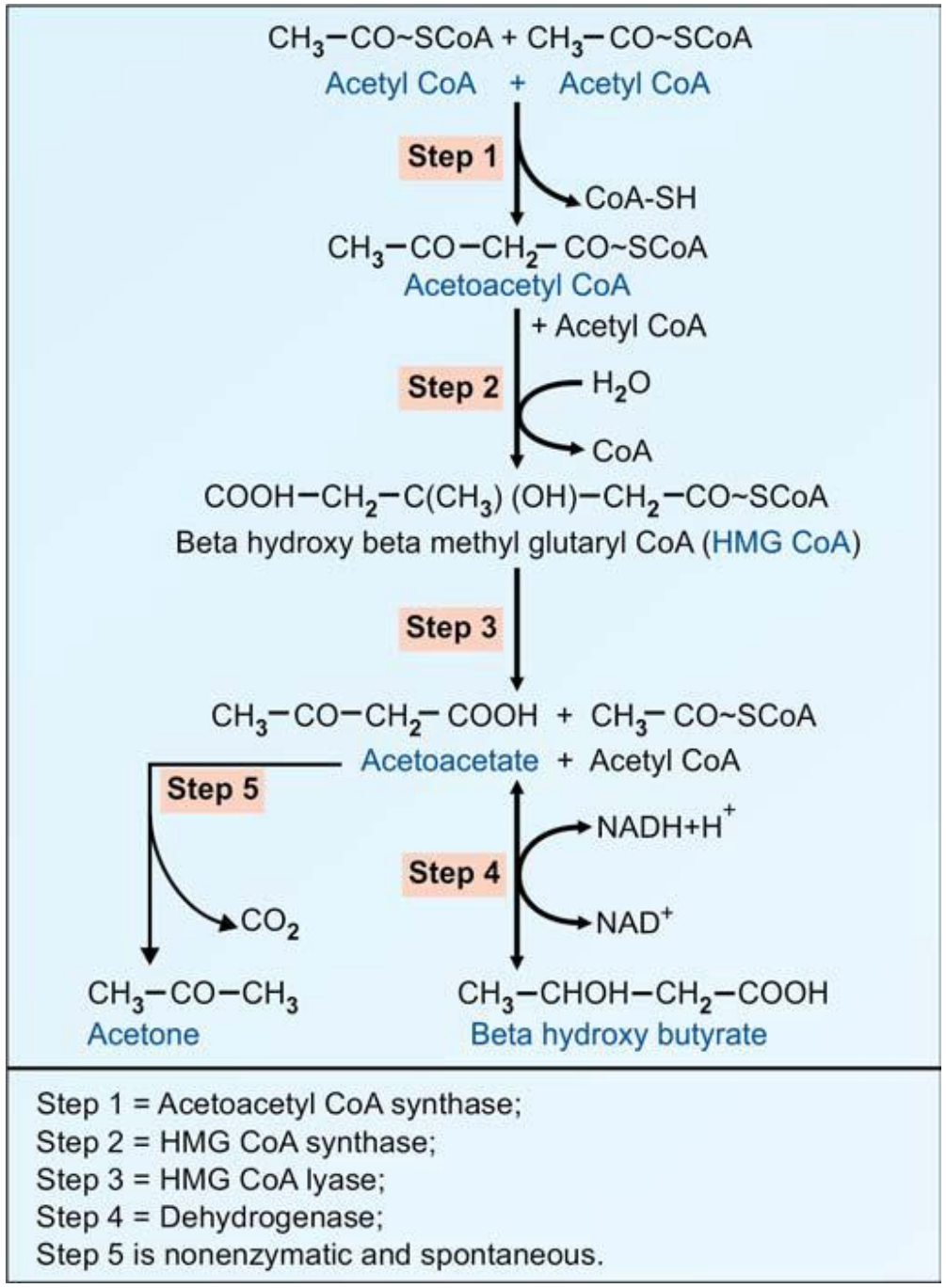
Beta oxidation



Ketogenesis

- Acetoacetate is primary ketone body
- Synthesised **exclusively** in liver **mitochondria**
- 4 Steps:
  - Condensation
  - Production of HMG coA
  - Lysis
  - Reduction
  - Spontaneous decarboxylation

HMG coA synthase is rate limiting step in synthesis of ketone bodies and is present in significant quantities only in liver



Step 1 = Acetoacetyl CoA synthase;
Step 2 = HMG CoA synthase;
Step 3 = HMG CoA lyase;
Step 4 = Dehydrogenase;
Step 5 is nonenzymatic and spontaneous.

25. Which carbons of palmitic acid are the initial 2 carbons attached to fatty acid synthase

A. 1 and 2

B. 8 and 9

C. 15 and 16

D. 1 and 16

Answer: C

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