THE OXIDATION OF FAs IN MAMMALS

FAs are derived from TGs by lipases.

TG $\xrightarrow[\text{(Cytosolic)}]{\text{Lipases}}$ 3 FAs (95%) + Glycerol (5%) → To the liver

Nutrient	Energy content Kcal/g
1. TG	> 9.0
2. CHO	4.2
3. Protein	4.3
* 4. Alcohol (ethanol)	7.1

↑ CHO intake → ↑ TG synthesis for storage

β-Oxidation

1. FAs are activated and oxidized in mitochondria.
2. Oxidation involves successive loss of 2-Carbon fragments in which the β-carbon of the FA is oxidized to yield a β-ketoacid. The ketoacid is cleaved by CoA-SH to form Acetyl CoA and a FA chain shorter by 2 Carbon atoms.

3. ATP is necessary to activate or prime a FA. This involves esterification of the -COOH group of FA with the -SH group of CoA - and all subsequent intermediates of FA are thioesters of CoA.

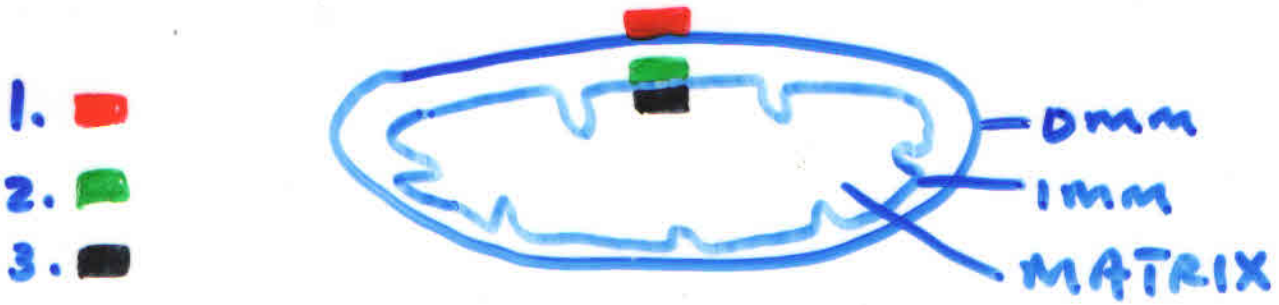
Q. FAs are found in the cytosol. How do they enter the mitochondria for oxidation?

A. FAs enter mit. by a 3-step process.

Enzymatic process

e.g. Liver

FAs + Serum albumin $\xrightarrow{\text{via blood}}$ Liver cell (cytosol)



1ST REACTION

This is activation of a FA to a Fatty-AcylCoA. Catalyzed by enzymes (AcylCoA synthetases) located on the outer side of the OMM (Cytosolic side).

Cytosolic side of the OMM.

$$R\text{-}C(=O)\text{-}O^- + ATP \rightleftharpoons R\text{-}C(=O)\text{-}AMP + PP_i$$

$$R\text{-}C(=O)\text{-}AMP + CoA\text{-}SH \rightleftharpoons R\text{-}C(=O)\text{-}S\text{-}CoA + AMP$$

NET

$$RCOOH + ATP + CoA\text{-}SH \rightleftharpoons R\text{-}C(=O)\text{-}S\text{-}CoA + AMP + PP_i$$

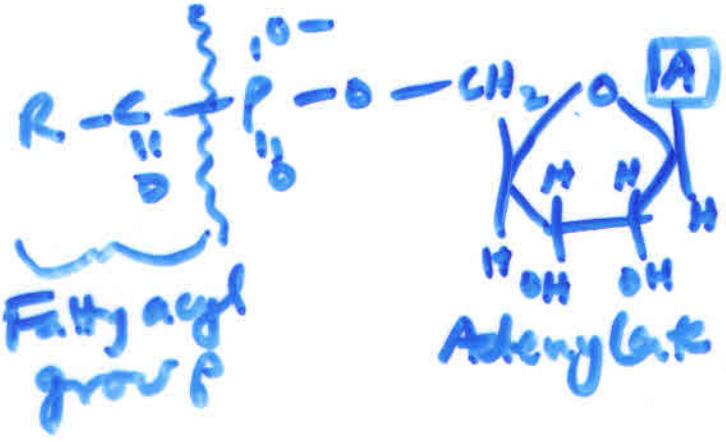
Coupled to:

$$H_2O + PP_i \longrightarrow 2\,P_i$$

Overall

$$RCOOH + ATP + CoA\text{-}SH + H_2O \rightleftharpoons R\text{-}C(=O)\text{-}S\text{-}CoA + AMP + 2\,P_i$$

Fatty acyl adenylate = Fatty acyl Adenosine 5'-monophosphate



$$R\text{-}C(=O)\text{-}S\text{-}CoA$$

Thioester linkage.

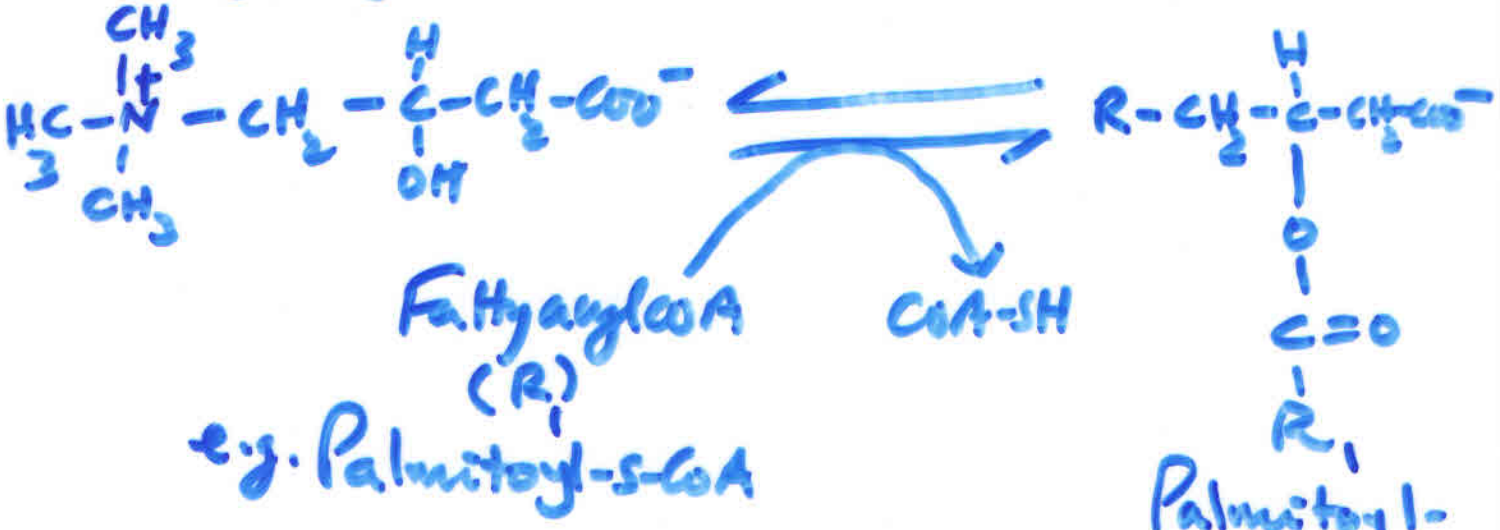
Fatty acyl CoA are high energy thioesters.

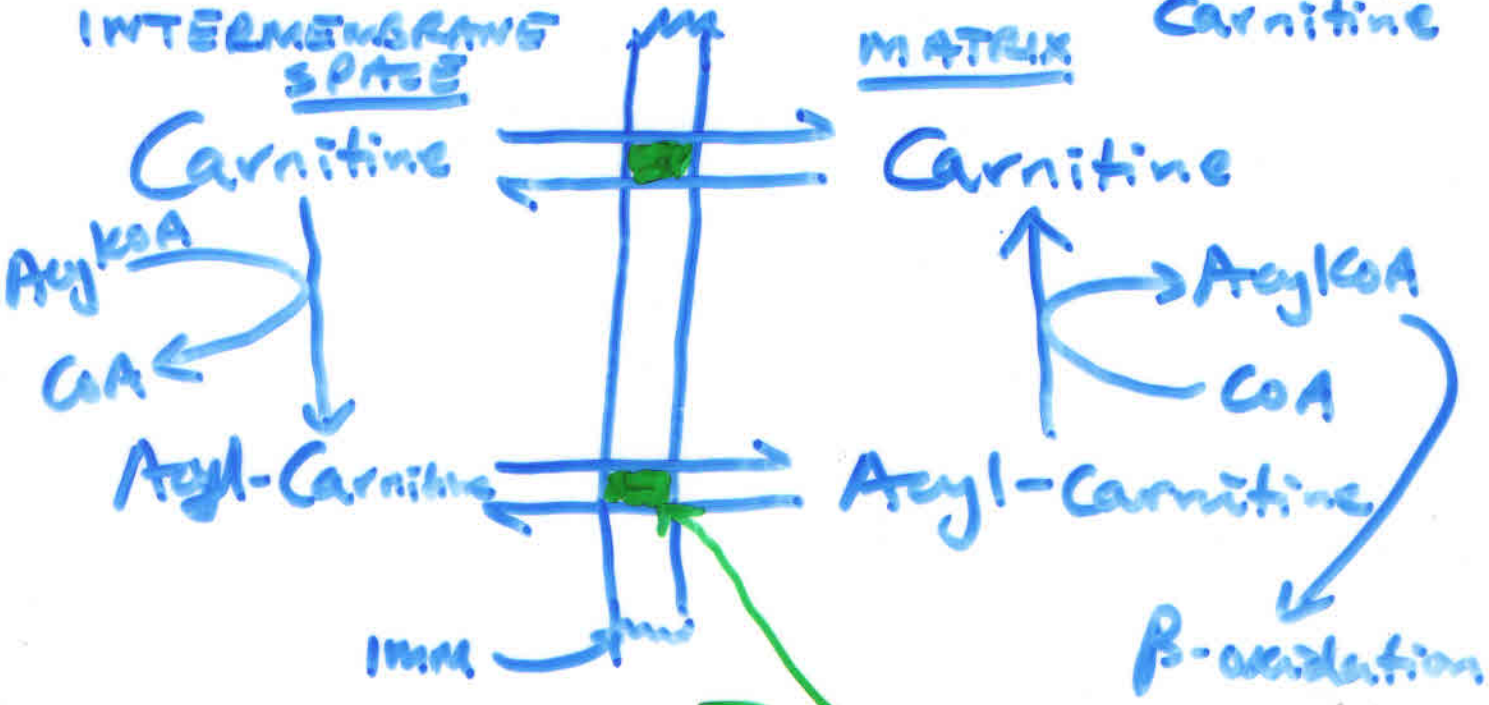
2ND REACTION

The Fatty acyl-CoA is unable to pass thru the IMM. The enzyme Carnitine acyltransferase I (CAT I) catalyses the reaction between the thioester and Carnitine.

CAT I - located on outer surface of IMM.

Fatty acyl CoA + Carnitine $\overset{\text{CAT I}}{\rightleftharpoons}$ Fatty acyl-Carnitine + CoA-SH





Translocase
= Acyl-Carnitine/
Carnitine transporter

3RD REACTION

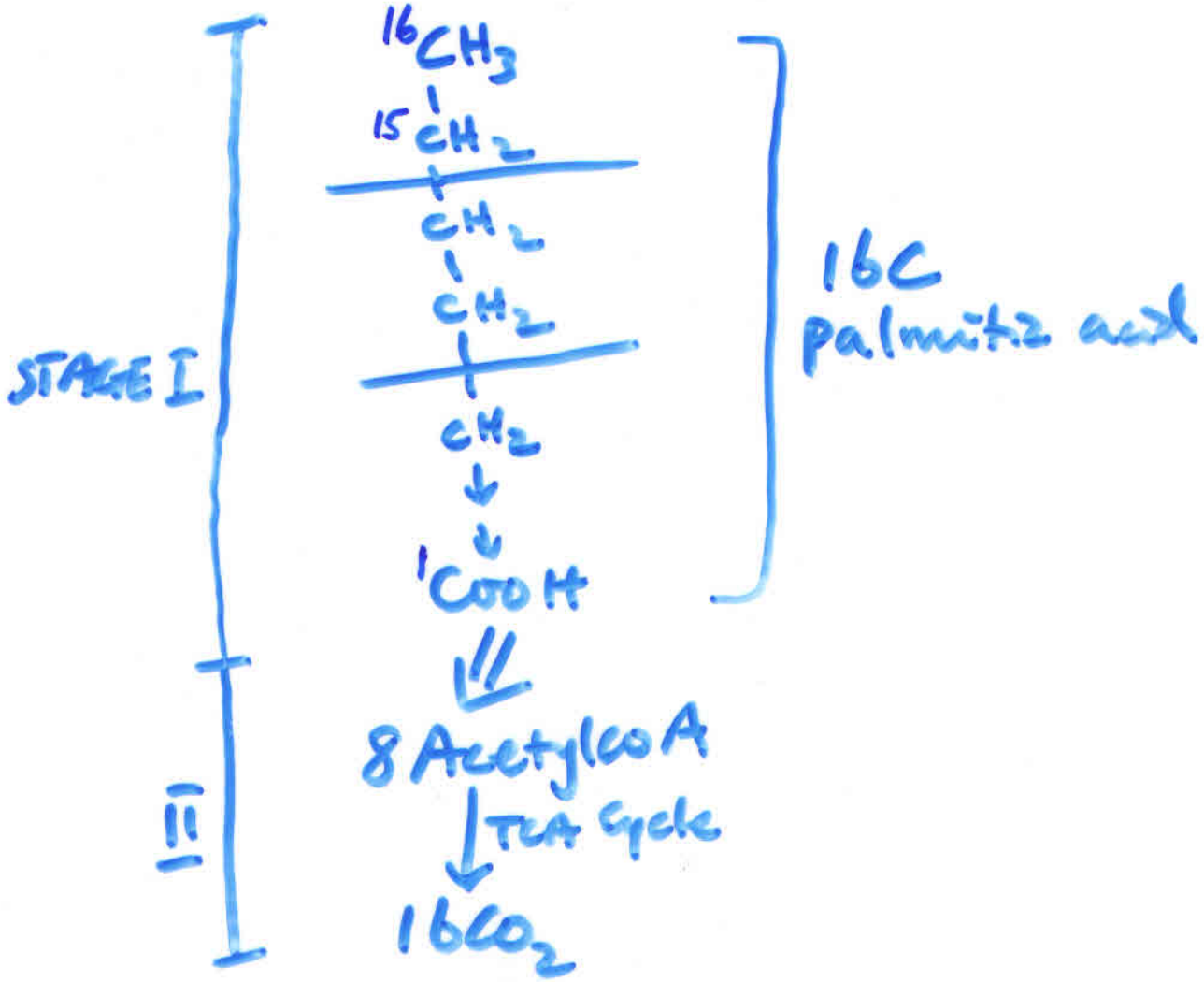
Fatty acyl-Carnitine + CoA-SH (mit.) $\overset{\text{CAT II}}{\rightleftharpoons}$ Fatty acyl CoA + Carnitine (recycled)

CAT II - Located on the inner surface of IMM.

FAs are oxidized in 2 stages;

1st = β-oxidation ⟶ AcetylCoA

2nd = AcetylCoA ⟶ CO_2 (TCA cycle)



∴ 16C Palmitic acid undergoes 7 passes (cycles) + AcetylCoA (C15 and C16).

Each 2-carbon unit removed ⟶ 4 H (2 pairs) atoms produced by the action of DHs.

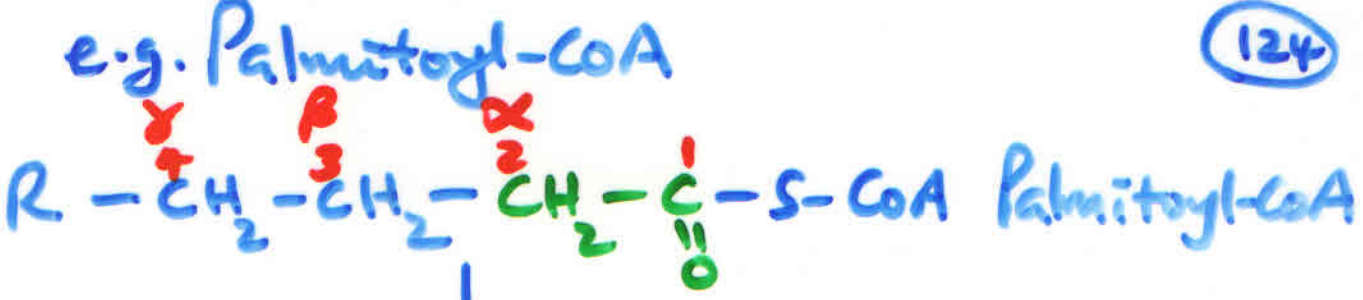
ETC ⟶ H_2O

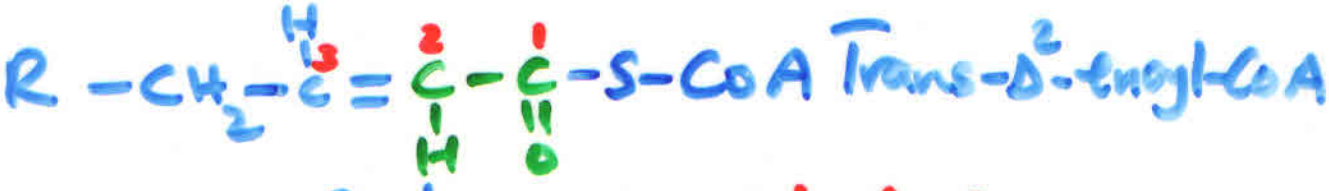
ETC ⟶ ATP

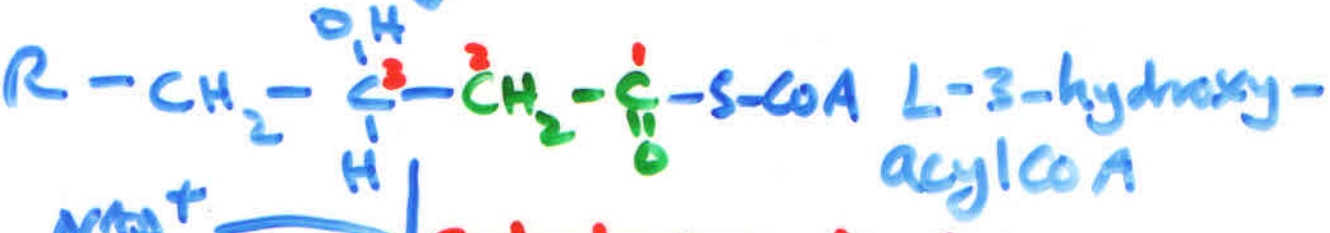
STAGE I

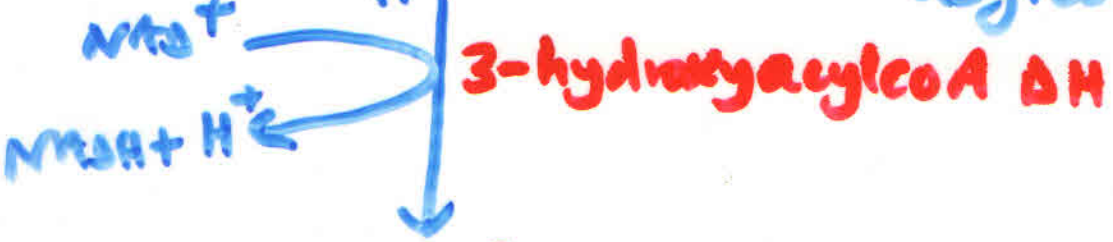
Removal of a single 2-C fragment (AcetylCoA) involves 4 steps e.g. Palmitic Acid (Saturated FA)

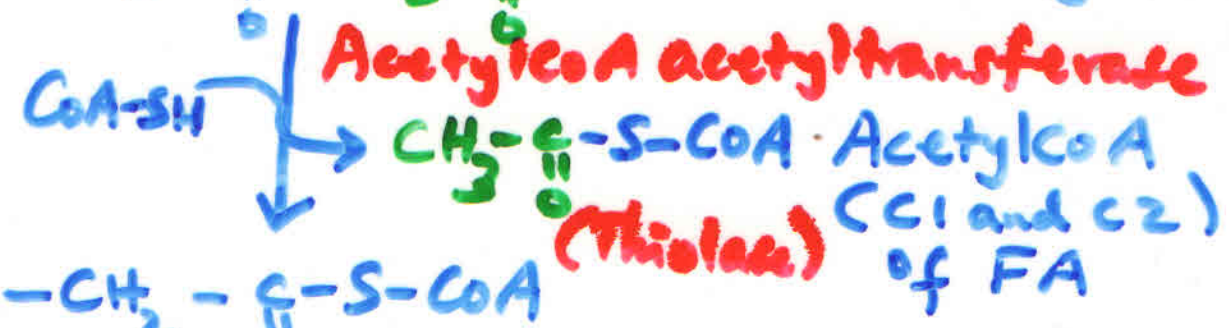
e.g. Palmitoyl-CoA

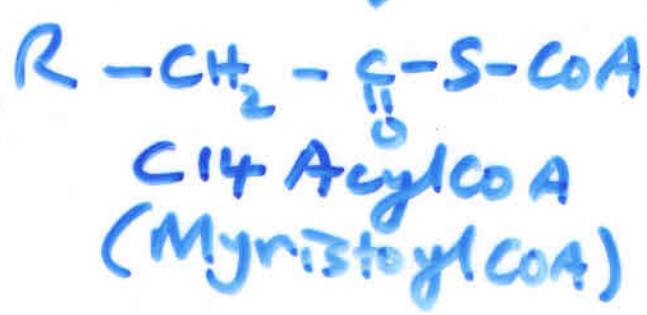












Overall reaction;

1 Pass:

$$\text{Palmitoyl-S-CoA} + \text{CoA-SH} + \text{FAD} + \text{NAD}^+ + H_2O \longrightarrow$$
$$\text{Myristoyl-S-CoA} + \text{Acetyl-S-CoA} + FADH_2 + NADH + H^+$$

7 Passes:

$$\text{Palmitoyl-S-CoA} \longrightarrow 8\ \text{Acetyl-S-CoA}$$

ETC

$$\text{Palmitoyl-S-CoA} + 7\,\text{CoA-SH} + 7O_2 + 35\,ADP + 35\,P_i \longrightarrow 8\,\text{Acetyl-S-CoA} + 35\,ATP + 4H_2O$$

14?

7 NADH passes × 3 ATPs each = 21 ATPs
7 $FADH_2$ passes × 2 ATPs each = 14 ATPs
Total 35

STAGE II

Acetyl-S-CoA is oxidized via the TCA cycle;

$$8\,\text{Acetyl-S-CoA} + 16O_2 + 96\,ADP + 96\,P_i \longrightarrow$$
$$8\,\text{CoA-SH} + 96\,ATP + 104H_2O + 16CO_2$$

32?

∴ Combining I and II stages;

$$\text{Palmitoyl-S-CoA} + 23O_2 + 131\,ADP + 131\,P_i \longrightarrow$$
$$\text{CoA-SH} + 131\,ATP + 146H_2O + 16CO_2$$

46?

1 Palmitoyl CoA $\longrightarrow CO_2 + H_2O$

	NAD-linked steps	FAD-linked steps	ATP
Acyl-CoA DH	—	7	14
3-Hydroxyacyl CoA DH	7	—	21
Isocitrate DH	8	—	24
α-Kg DH	8	—	24
Succinyl CoA synthetase	—	—	8
Succinate DH	—	8	16
Malate DH	8	—	24
		TOTAL ATP formed =	131

$\Delta G^{0'}$ for Palmitic acid $\longrightarrow CO_2 + H_2O$
= 2340 Kcal/mol

131 ATPs

$131 \times 7.3 = 956$ Kcal/mol

Recovery; $\frac{956}{2340} \times 100 \simeq 41\%$

Under cellular conditions, the recovery is over 80%.

$CH_3(CH_2)_{14}COOH + 23O_2 \longrightarrow 16CO_2 + 16H_2O$

$\Delta G^{0'} = 2340$ Kcal/mol

OXIDATION OF PALMITOYLCoA – SUMMARY

STAGE I

1. PalmitoylCoA + 7 CoASH + 7 FAD + 7 NAD^+ + 7 H_2O → 8 AcetylCoA + 7 $FADH_2$ + 7 NADH + 7 H^+

2. 7 $FADH_2$ + 7 NADH + 7 H^+ + 35 ADP + 35 P_i + 7 O_2 → 7 FAD + 7 NAD^+ + 35 ATP + 14 H_2O

NET:

3. PalmitoylCoA + 7 CoASH + 35 ADP + 35 P_i + 7 O_2 → 8 AcetylCoA + 35 ATP + 14 H_2O

STAGE II

1. 8 AcetylCoA + 96 ADP + 96 P_i + 16 O_2 → 8 CoASH + 96 ATP + 16 CO_2 + 32 H_2O

Combining I and II;

PalmitoylCoA + 131 ADP + 131 Pi + 23 O_2 → CoASH + 131 ATP + 16 CO_2 + 46 H_2O

NET H_2O produced = 46 − 7 = 39

Compare with;

$CH_3(CH_2)_{14}COOH + 23O_2 \rightarrow 16CO_2 + 16H_2O$

OXIDATION OF UNSATURATED FATTY ACIDS

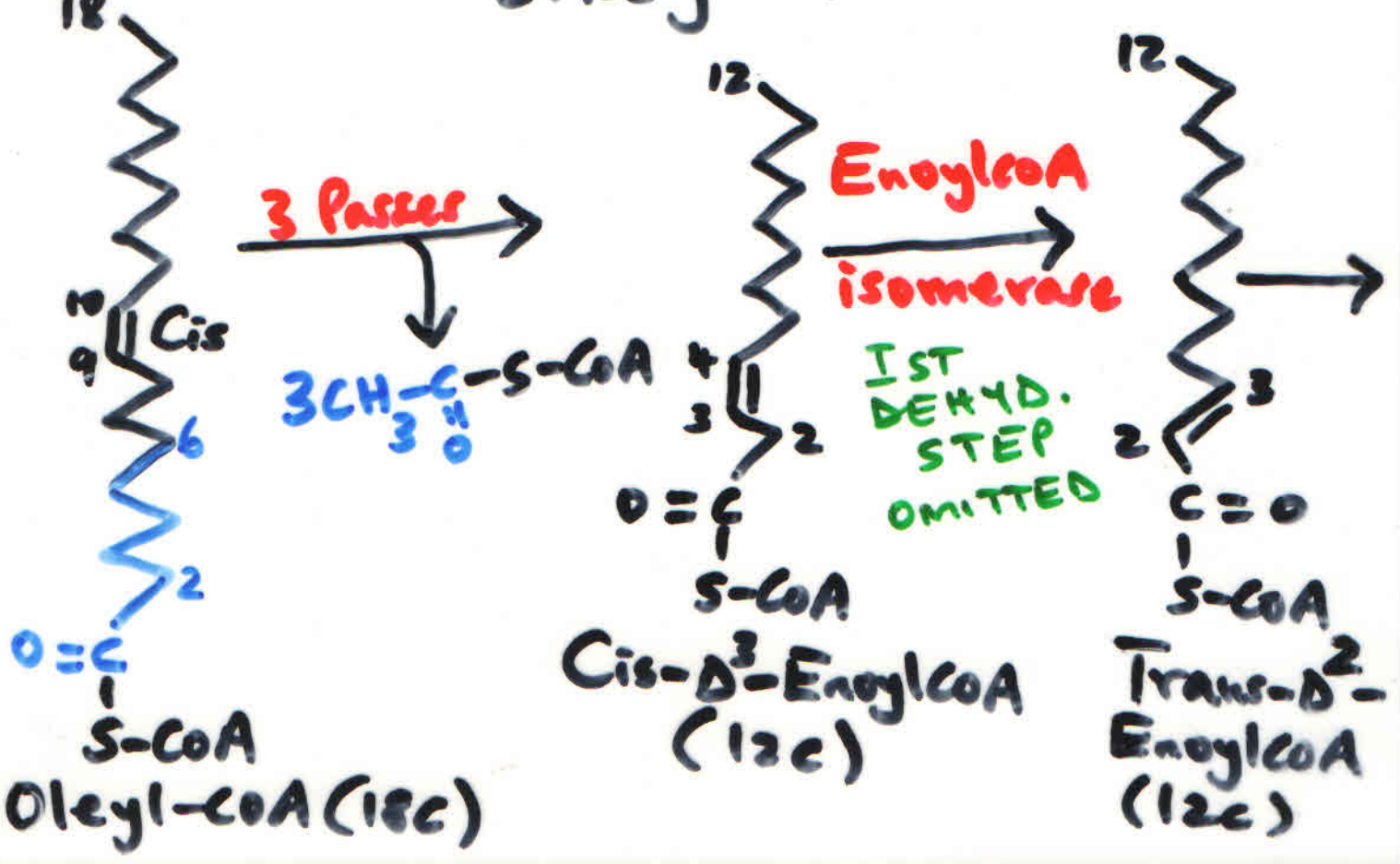
Requires 2 additional enzymes (Isomerase, Epimerase)

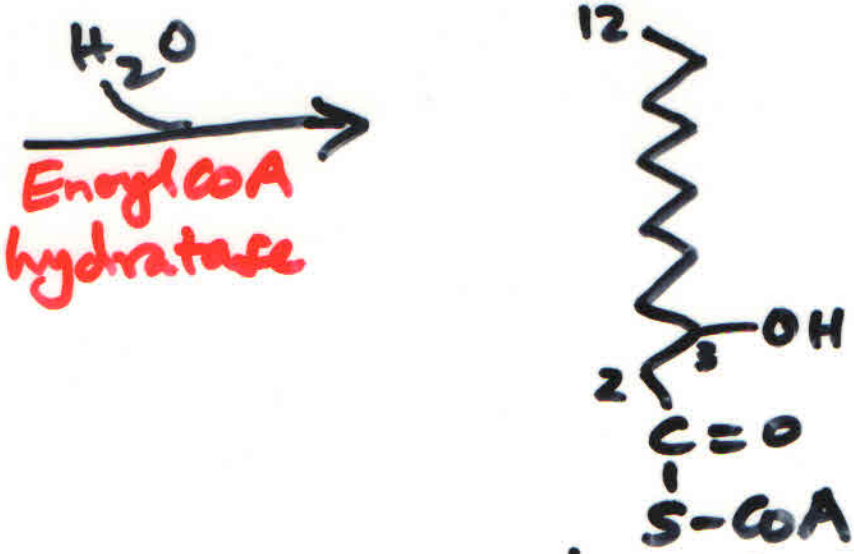
e.g. Oxidation of oleic acid $18:\Delta^9$

1. Oleic acid (cytosol) —Activation→ Oleyl-CoA (cytosol) ⟶

Oleyl-Carnitine ⟶ Oleyl-CoA (Mit.)

2. Oleyl-CoA —3 Passes→ Cis-Δ^3-EnoylCoA (12c) + 3 AcetylCoA





L-3-hydroxyacyl-CoA

→ Acetyl CoA

10C FA ester (saturated)

→ 4 Passes (4 Acetyl CoA)

9 Acetyl CoA = Total

∴ Oleic acid ⟶ 9 Acetyl CoA

4 enzymes + 1 auxiliary enzyme (isomerase)

e.g. Oxidation of Linoleic acid 18: $\Delta^{9,12}$

Linoleyl CoA ⟶ (3 Passes) 3 Acetyl CoA + CoA Ester (12C) with Δ^3 and Δ^6 cis double bonds

Trans-Δ^2-Enoyl CoA ← (Isomerase) ✱

Trans-Δ^2-Enoyl CoA ⟶ (1 pass) Acetyl CoA

10C FA ester with a Δ^4 cis

→ AcetylCoA (1 Pass)

8C Unsaturated FA ester with a Δ^2 Cis

Isomerase *

8C Unsaturated FA ester with a Δ^3 Trans

Enoyl CoA hydratase

D-3-Hydroxyacyl CoA

3-Hydroxyacyl CoA epimerase

L-3-Hydroxyacyl CoA

→ AcetylCoA (1 Pass)

6C saturated FA ester

2 Passes → 2 AcetylCoA

AcetylCoA

∴ Linoleic acid —4 enzymes + 2 auxiliary enzymes→ 9 AcetylCoA

OXIDATION OF LINOLEIC ACID

$18:\Delta^{9,12}$

Linoleyl CoA

3 Passes → 3 Acetyl CoA

Cis-$\Delta^{3,6}$ Enoyl CoA

Isomerase

1ST DEHY. STEP OMITTED

Trans-Δ^{2}, Cis Δ^{6} Enoyl CoA

1 Pass → 1 Acetyl CoA

Cis-Δ^{4} CoA ester

1 Pass → 1 Acetyl CoA

Cis-Δ^{2} CoA ester

Isomerase

1ST DEHY. STEP OMITTED

Trans-Δ^3 CoA ester

↓ Hydratase

D-3-Hydroxyacyl CoA

↓ Epimerase

L-3-Hydroxyacyl CoA

↓ 1 Pass → 1 Acetyl CoA

6C CoA ester (saturated)

↓ 2 Passes → 2 Acetyl CoA

Acetyl CoA

Q. Compare ATPs formed by complete oxidation of;

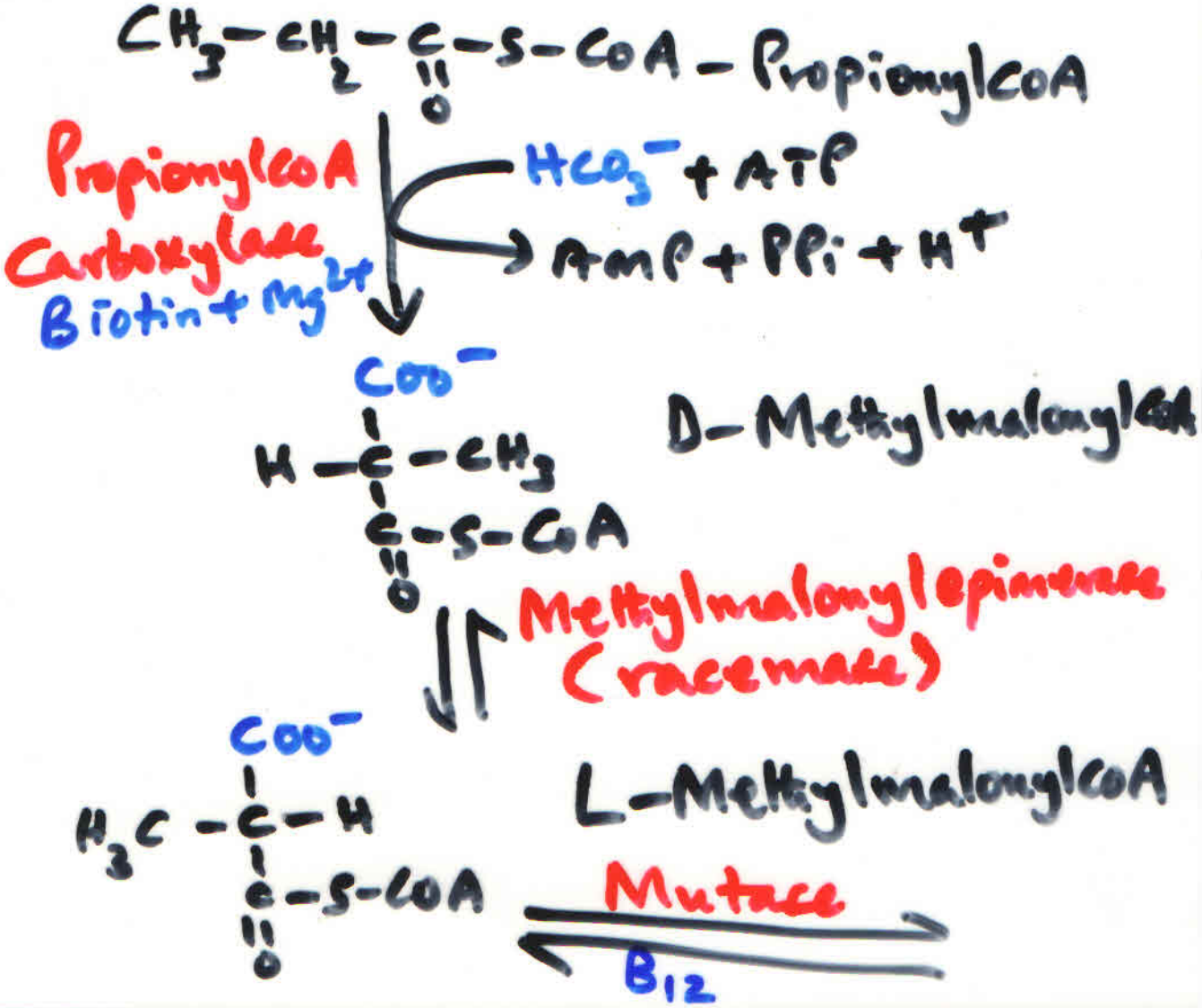
a) Oleic and Linoleic acids 18C
b) Palmitic and Palmitoleic acids 16C
c) Stearic and linoleic acids 18C

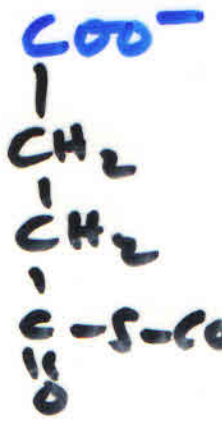
OXIDATION OF FAs WITH AN ODD NUMBER OF CARBON ATOMS

Plants / Marine organisms – Odd no.
Higher animals – Even no.

When odd no. is ingested, they undergo oxidation but the substrate at the last pass is a FA ester with 5C.

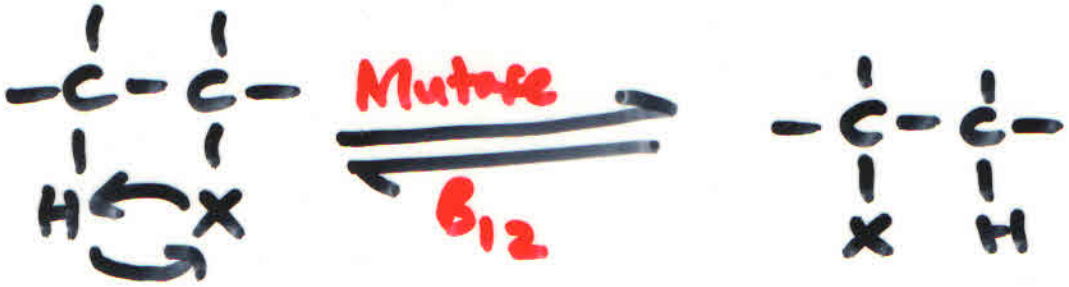
Last pass
Oxidized & cleaved → Acetyl CoA (2c) + Propionyl CoA (3c)



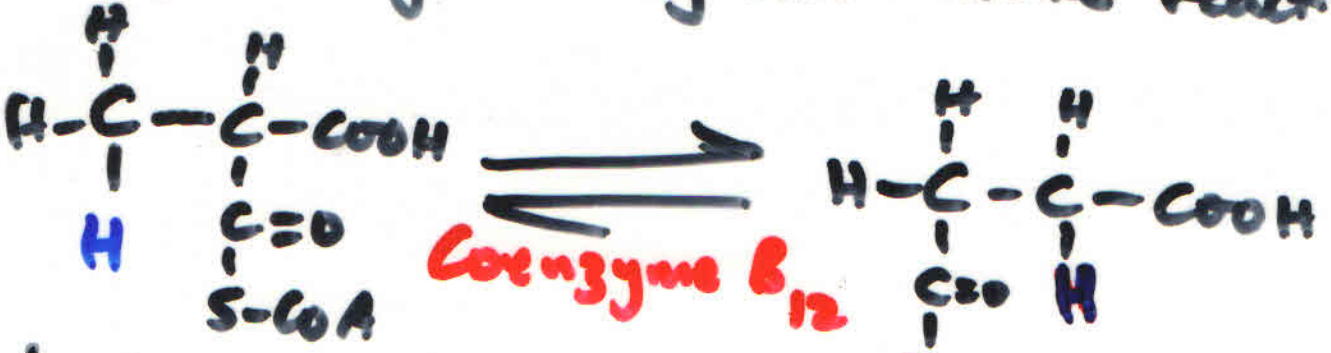


Succinyl CoA ⟶ OAA in the TCA cycle.

Mutase reaction:



e.g. Methylmalonyl CoA mutase reaction:



L-Methylmalonyl CoA ⟶ Succinyl CoA

B_{12} — participates in reactions in which a hydrogen atom and a functional group (e.g. X) on an adjacent carbon are exchanged.

Deficiency of B_{12} ⟹ Pernicious anemia

//

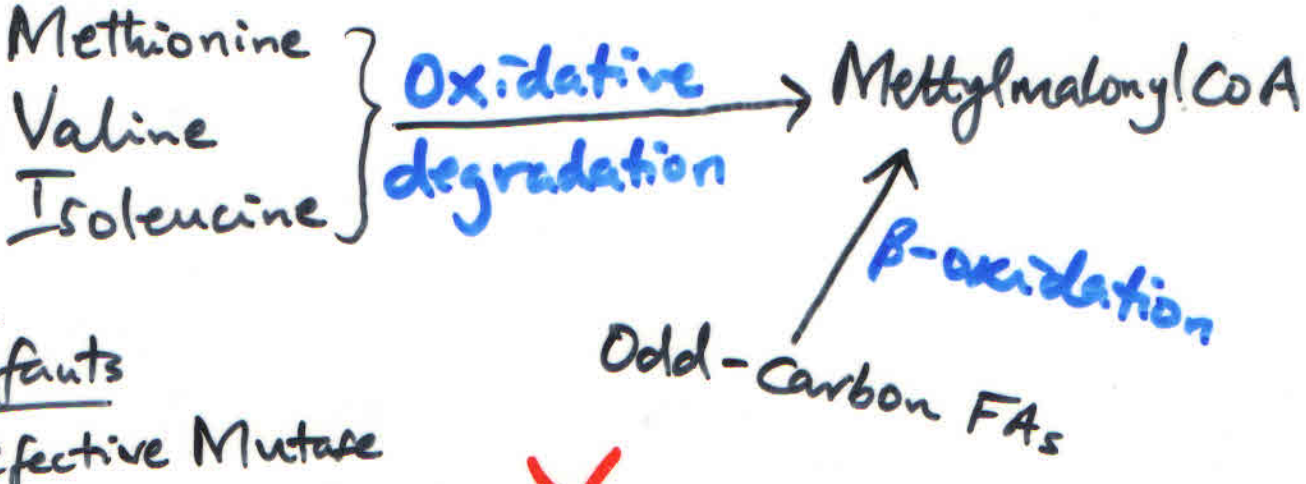
Vitamin B_{12} Malabsorption

Pathology:

1) Reduced production of RBC.
2) Reduced level of Hb.
3) Impairment of the CNS.

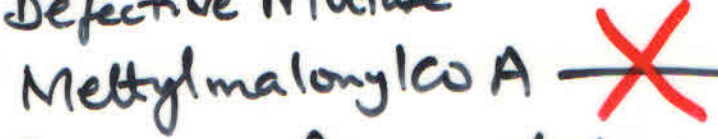
Cause: Not because of lack of B_{12} but due to failure of absorption from intestine. Individuals lack "Intrinsic factor" – a glycoprotein essential to B_{12} absorption.

NB B_{12} not made by both plants and animals but made by a few microorganisms which reside in the intestines.



Infants

Defective Mutase



Results: Accumulation of Methylmalonyl CoA
↑ Methylmalonic acid in blood / Urine
Low PH (blood)

Methylmalonic acidemia

Some patients: Problem is conversion of B_{12} (Cyanocobalamine) to its active form (Deoxyadenosylcobalamine) – Treated by injection of large amounts of B_{12}.

KETONE BODIES

FA

↓ β-oxidation

Acetyl CoA → CO_2 (TCA cycle)

Acetyl CoA → Ketone bodies (Ketone Synthesis)

1. Acetoacetate

$$CH_3-\overset{\overset{O}{\|}}{C}-CH_2-COO^-$$

2. D-β-hydroxybutyrate

$$CH_3-\overset{\overset{OH}{|}}{\underset{\underset{H}{|}}{C}}-CH_2-COO^-$$

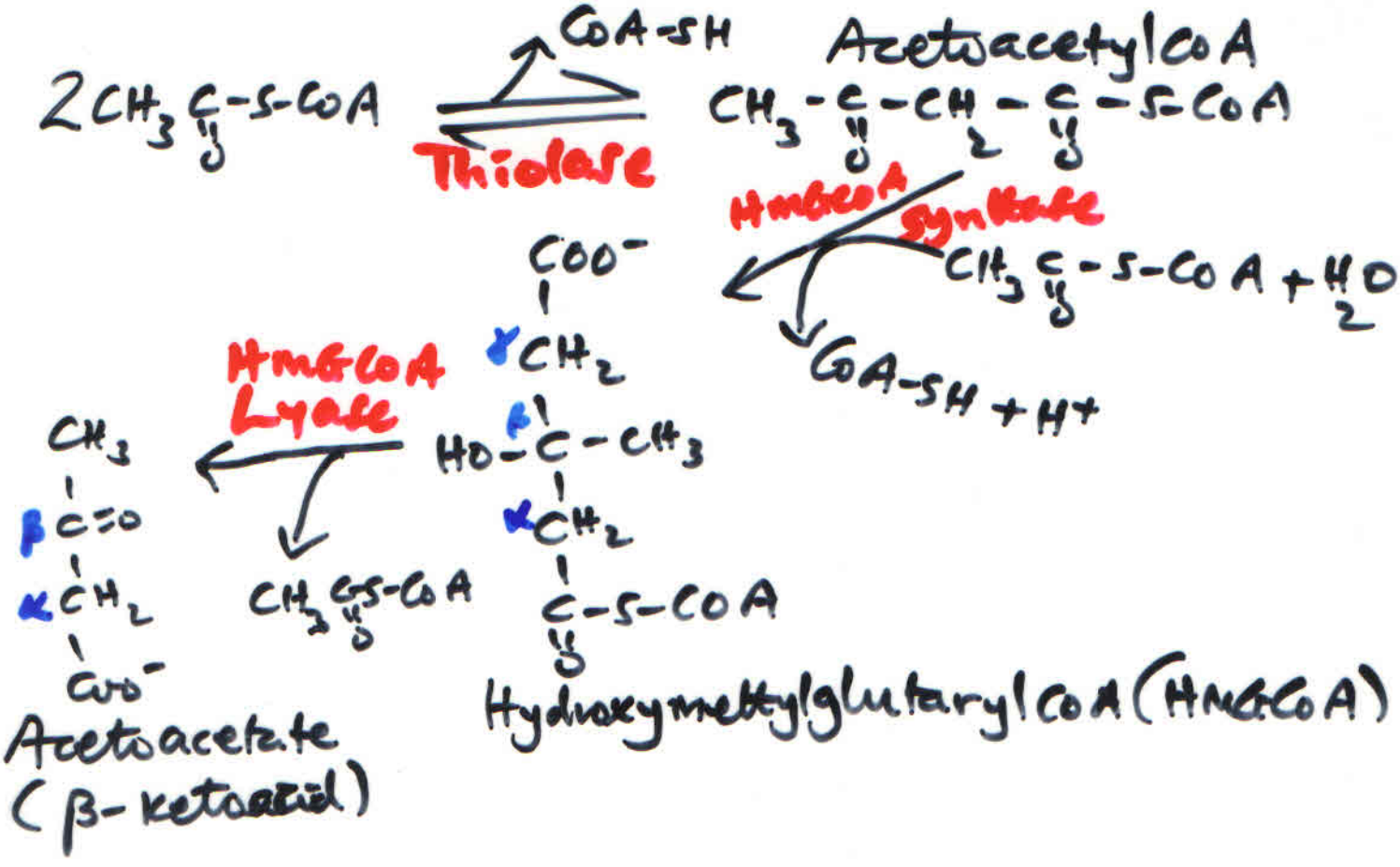
3. Acetone

$$CH_3-\overset{\overset{O}{\|}}{C}-CH_3$$

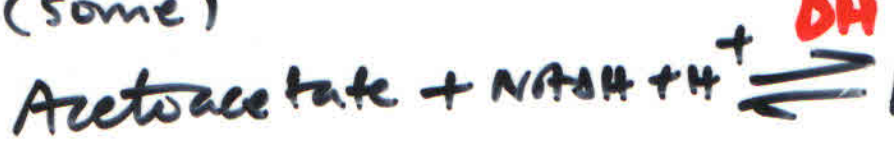
Prolonged Starvation:

75% of brain fuel comes from ketone bodies – particularly acetoacetate. Also used by Heart Muscle and renal cortex instead of glucose.

① SYNTHESIS – In the liver (exclusively)



Acetoacetate reversibly reduced to D-β-hydroxybutyrate (some)



LIVER

Acetoacetate
D-β-hydroxybutyrate

↓ Blood

Peripheral tissues for utilization

Blood of diabetics – sweet odor to the breath).

↓

Some in urine

2. UTILIZATION – In the peripheral tissues

a) D-β-hydroxybutyrate + NAD^+ $\overset{DH}{\rightleftharpoons}$ Acetoacetate + NADH + H^+

b) Acetoacetate + Succinyl CoA $\overset{\text{CoA transferase}}{\rightleftharpoons}$ Succinate + Acetoacetyl CoA

c) Acetoacetyl CoA + CoA-SH $\overset{\text{Thiolase}}{\rightleftharpoons}$ 2 Acetyl CoA → TCA cycle

CoA transferase = 3-ketoacyl CoA transferase

Lacking in liver – So liver unable to utilize ketone bodies.

Q. What is the purpose of ketone body formation?

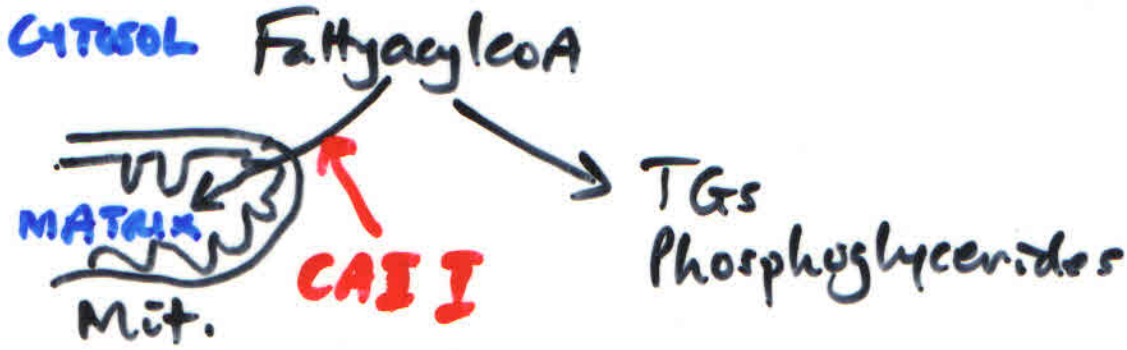
1) To divert excess acetyl CoA from liver to peripheral tissues for oxidation to $CO_2 + H_2O$.
2) Liver uses the pathway to distribute fuel to the rest of the tissues.

"Overflow pathway"

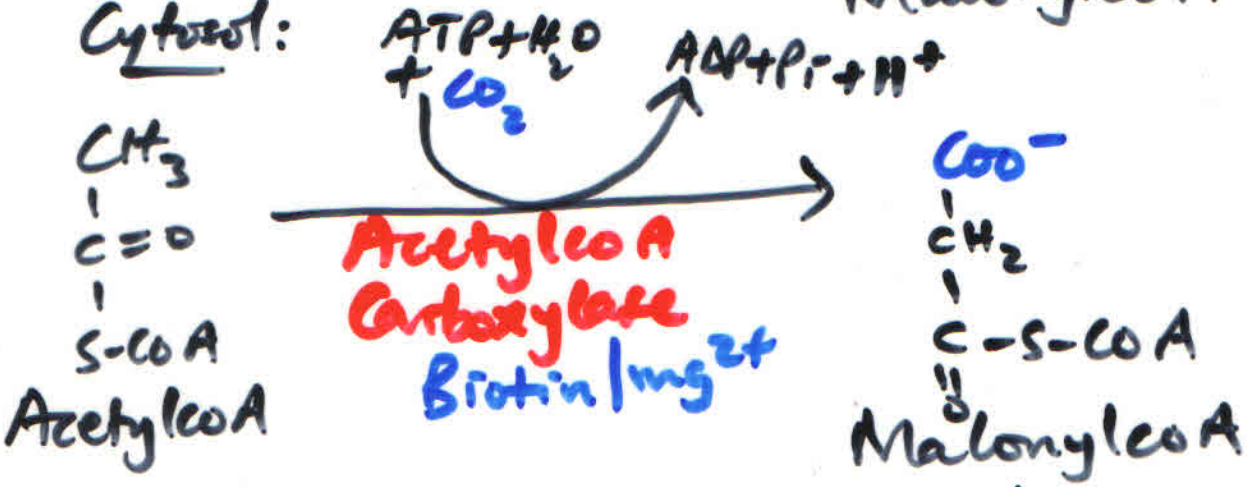
Diabetes / Fasting → ↑[K.B] → Ketosis

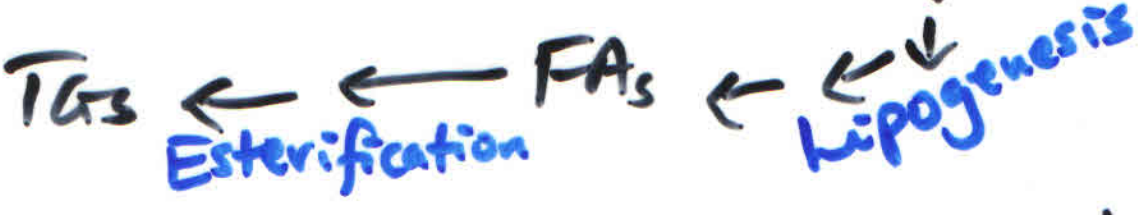
Ketosis – arises from high rate of KB synthesis beyond the rate of KB utilization by the peripheral tissues.
– failure of the tissues to use glucose
∴ Burning more FAs.

Regulation of FA oxidation and KB formation



CAT I – Allosteric – inhibited by Malonyl CoA





↑ CHO intake ⟶ ↑ MalonylcoA ⟶ ↓ FA oxidation

The entry of FaHyacylcoA into the Mit. is put off when the cell has enough CHO (i.e. acetylcoA) as fuel. ⟶ ↓ KBs

↓ CHO intake ⟶ ↑ FA oxidation ⟶ ↑ AcetylcoA

↑ KBs ⟷ TCA cycle