Fatty Acid and Triacylglycerol Metabolism 3

β oxidation of fatty acids 3

Lippincott's Chapter 16

3rd Lecture

- Oxidation of unsaturated Fatty Acids
- Oxidation of FA with odd number of carbons

- Oxidation of Very Long Chain Fatty Acids

- α Oxidation of Fatty Acids
- Ketone Bodies

Oxidation of unsaturated F.A additional enzyme(s)

Oleic acid is an example of monounsaturated, it Is 18 carbon fatty acid with one double at carbon 9

$CH3 – (CH_2)_7\text{-}CH = CH\ (CH_2)_7\text{-}CO\sim CoA$

18:cis Δ^9

3 Cycles of β oxidation

3 Acetyl CoA

The First three cycles proceed as in case of saturated
So what is the intermediate produced after the 3rd cycle
Hint: 6 carbons are removed from the carboxyl end

Oxidation of unsaturated fatty acids occur as that of the saturated but one or two additional enzymes are requiredC

$CH3 – (CH_2)_7\text{-}CH = CH\text{-}CH_2\text{-}CO\sim CoA$

12:cis Δ^3

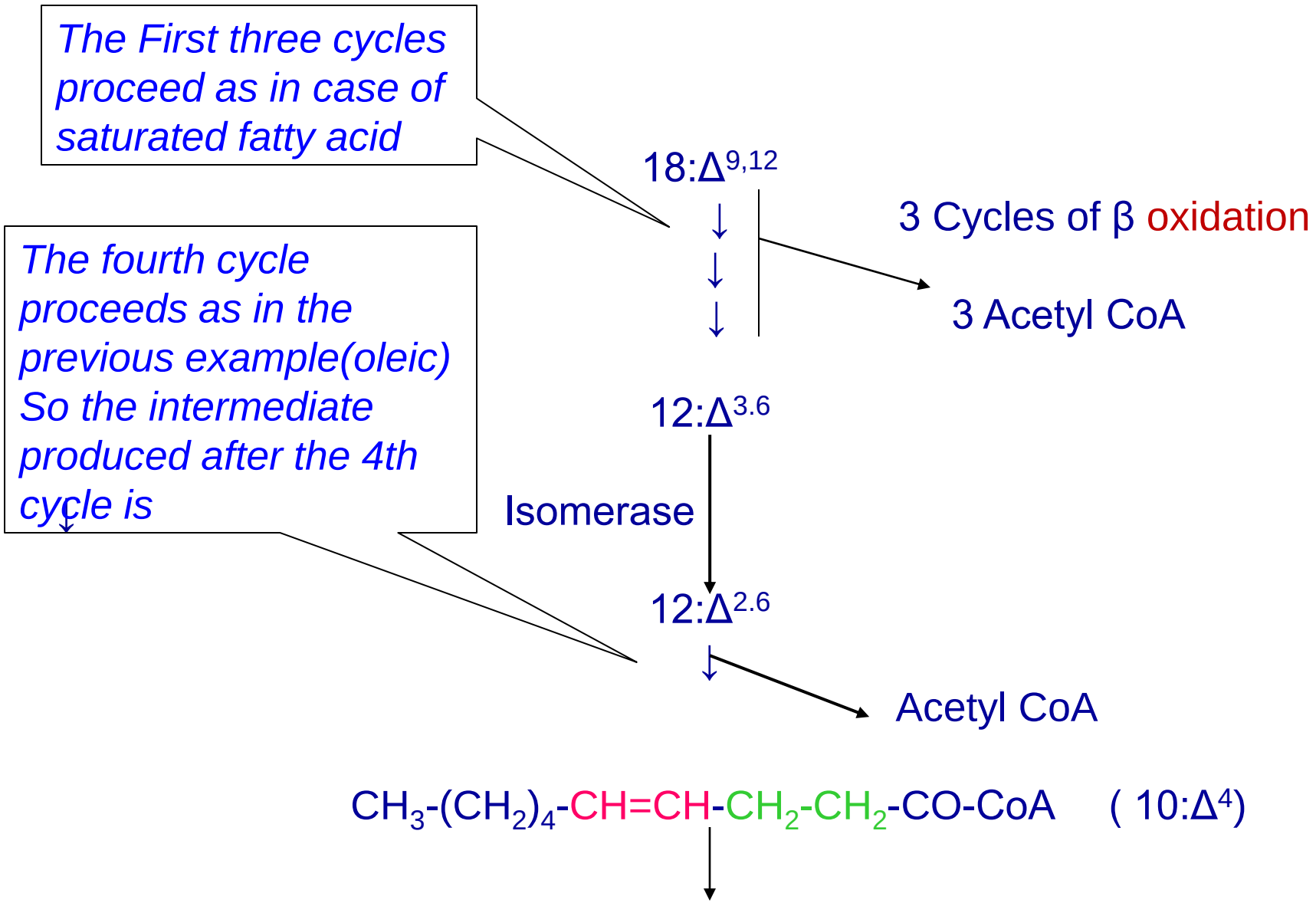
isomerase

$CH3\ (CH_2)_7\ CH_2\text{-}CH{=}CH\text{-}CO\sim CoA$

12:trans Δ^2

the intermediate produced after the 3rd cycle has a double bond between carbon 3&4
No other double bond will be introduced at carbon 2,
So the next reaction in this case just changing the laocation& cofiguration of the (cis ➔ trans) double bond

Oxidation of Unsaturated F.A: Linoleic Acid



Oxidation of Unsaturated F.A: Linoleic Acid(Cont.)

CH_3-$(CH_2)_4$-CH=CH-CH_2-CH_2-CO-CoA (10:Δ^4)

Dehydrogenase ↓

CH_3-$(CH_2)_4$-CH=CH-CH=CH-CO-CoA

Reductase

The 5th cycle starts by introduction of double bond between C2 &C3 as in case of saturated
So what is the intermediate produced by acyl CoA dehydrogenase?

Now: the second additional enzyme catalyzes the reduction of the two double bonds into one double bond between C3 & C4

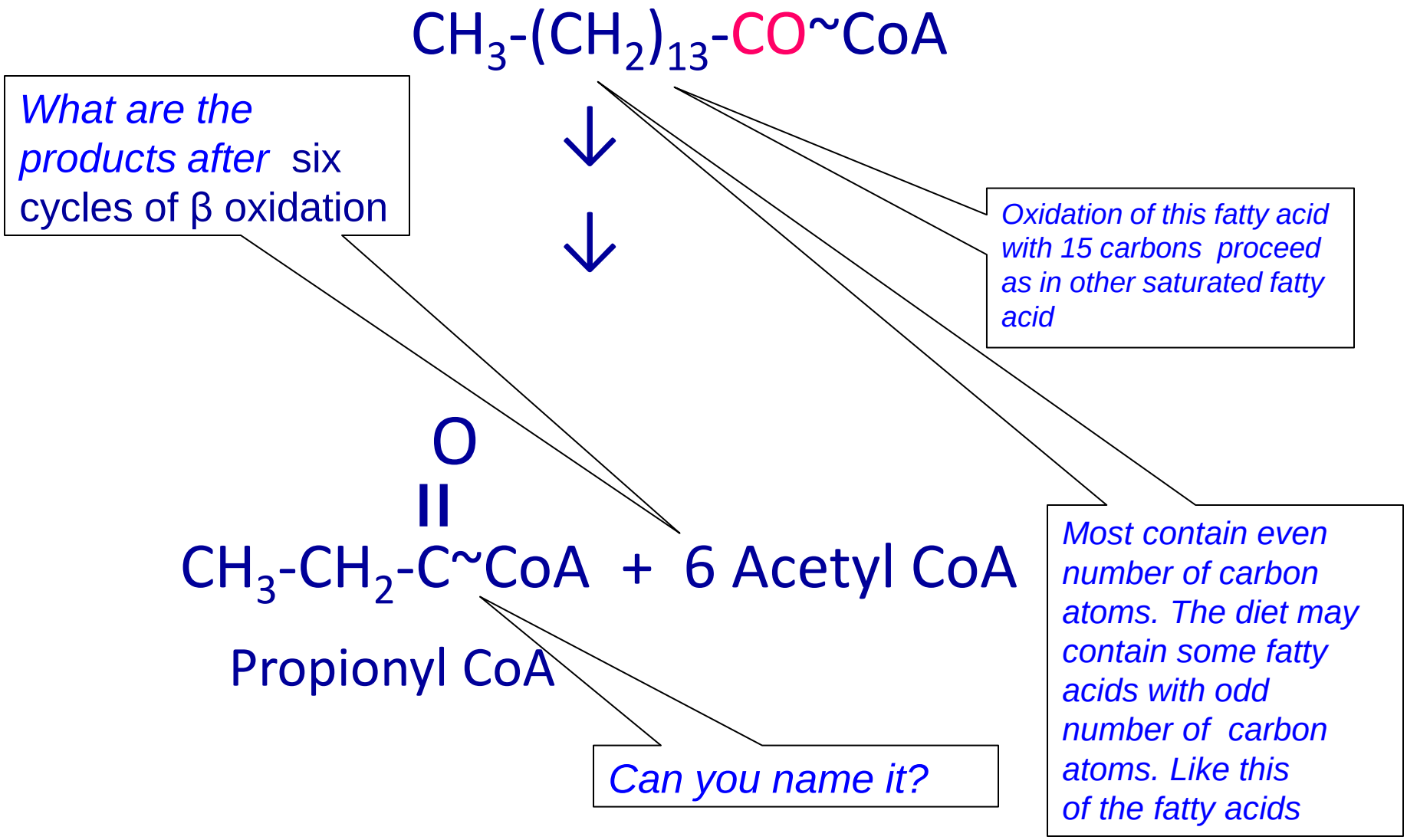
CH_3-$(CH_2)_4$-CH_2-CH=CH-CH_2-CO-Co

Now: You should know what is the next step

↓

Take home message
One or two additional enzymes are needed for oxidation of unsaturated fatty acids

Oxidation of FA with odd number of carbons



Metabolism of Propionyl CoA

The first step is addition of carboxyl group at the α carbon

carboxylation reaction is catalyzed by ?

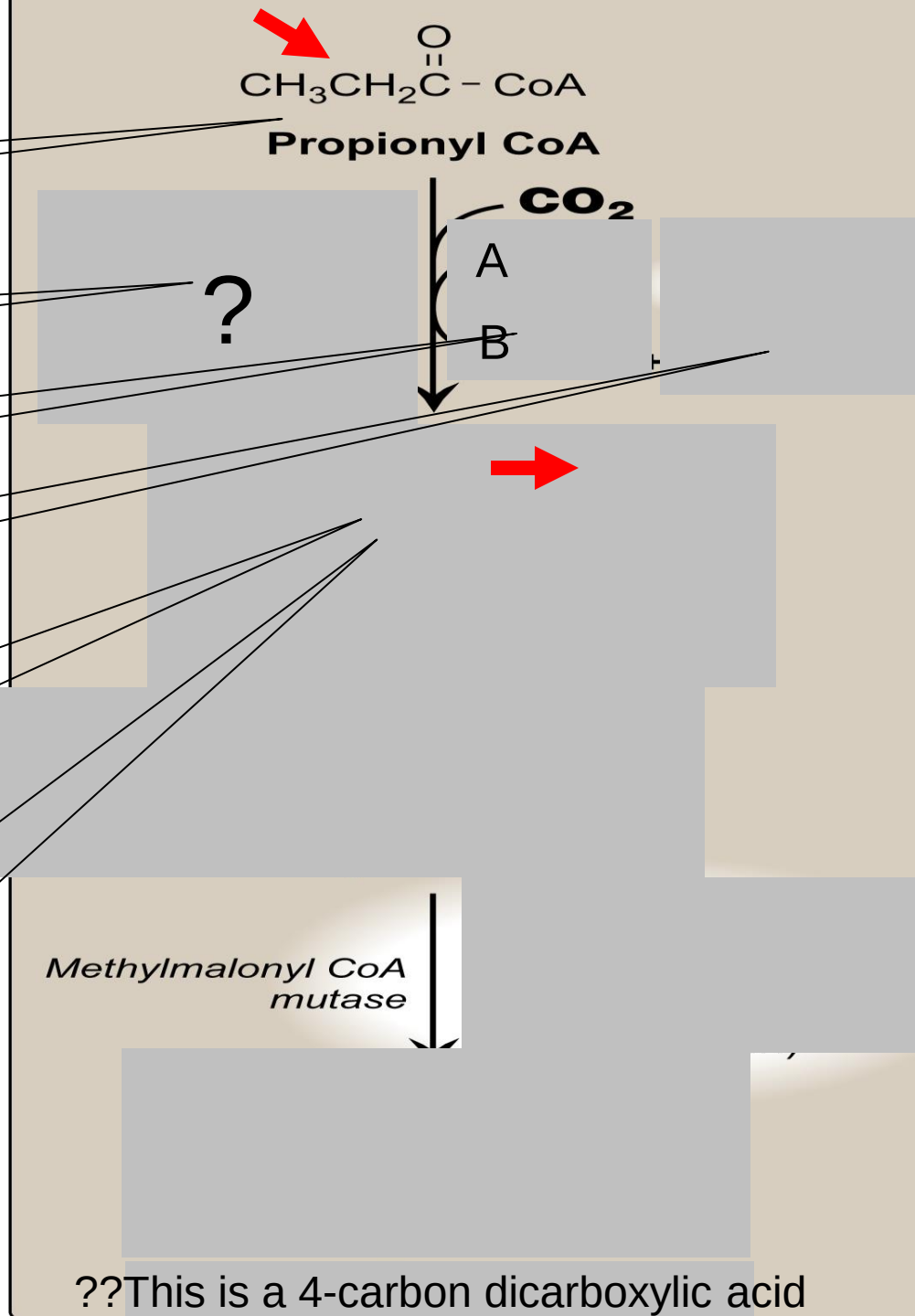
*carboxylation reaction Requires source of energy (A) what are A & **B***

carboxylase requires a cofactor

Malonic acid is a 3-carbon dicarboxylic acid; in methylmalonyl a methyl group is attached to the middle carbon

methylmalonyl (asymmetric molecule) is isomerized from D to L

Then the COO- is transferred to the adjacent carbon (mutase)



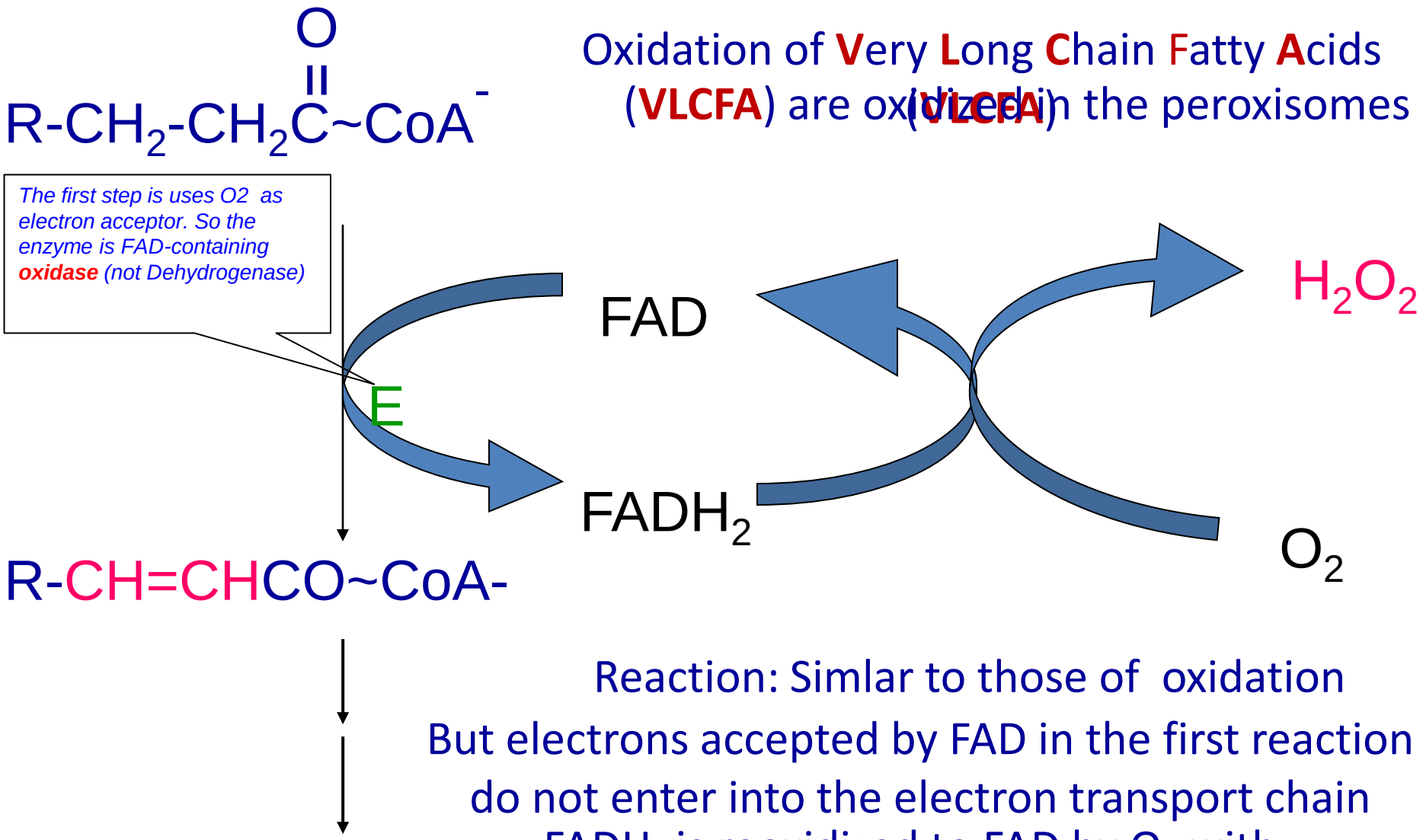
??This is a 4-carbon dicarboxylic acid

Significance of Methylmalonyl CoA Mutase

- This enzyme is one of two enzymes only that require a cofactor made from Vit. B_{12} (cobalamine)

- Vitamine B_{12} deficiency inhibits the reaction catalyzed by the enzyme causing accumaltion of methylmalonic acid.
- Measurent of methylmalonic acid in the plasma used to be the method for assesment of Vit. B12

Oxidation of **V**ery **L**ong **C**hain **F**atty **A**cids (**VLCFA**) are oxidized in the peroxisomes



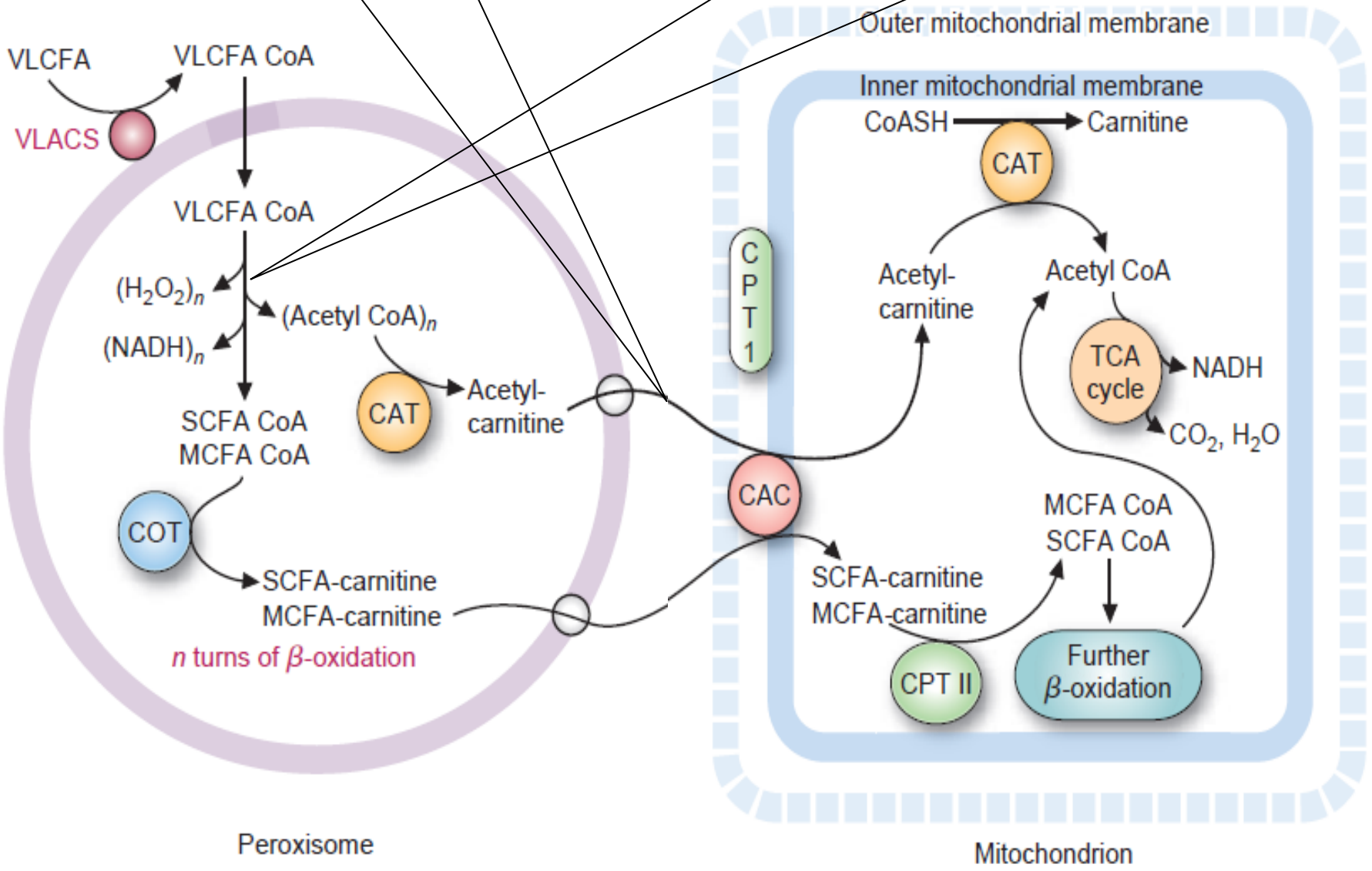
Reaction: Simlar to those of oxidation

But electrons accepted by FAD in the first reaction do not enter into the electron transport chain

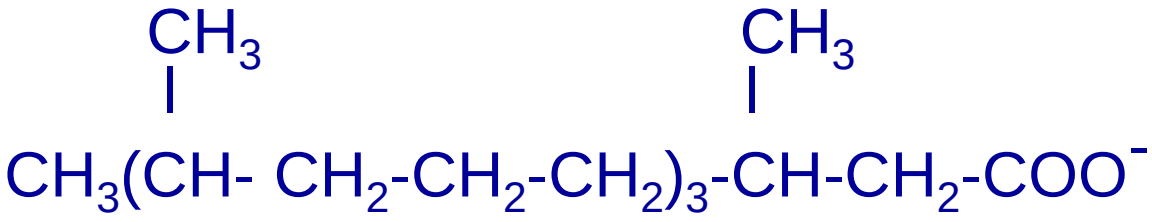
$FADH_2$ is reoxidized to FAD by O_2 with production of H_2O_2

then it is transferred to mitochondria

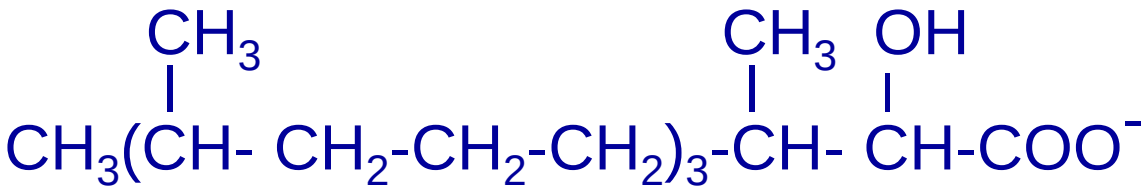
The reactions continue in the peroxisomes untill the fatty acid is shortened to Short (CSFA) or medium chain,

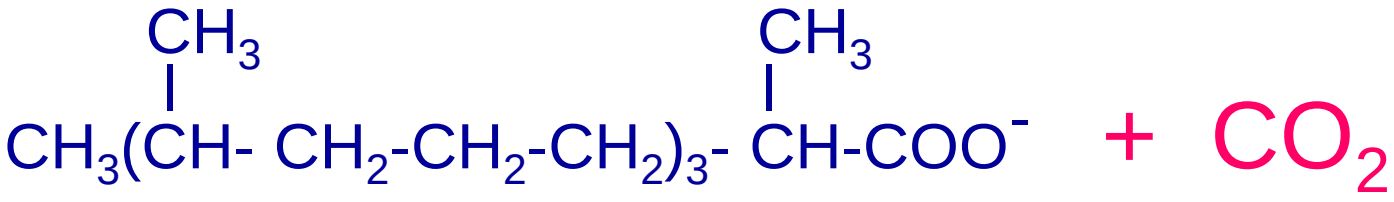


α Oxidation of Fatty Acids



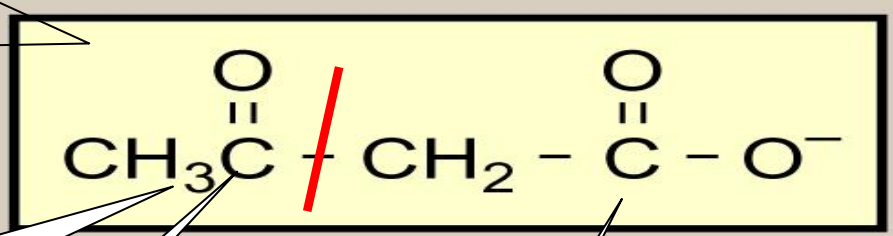
Hydroxylation at α carbon





Ketone Bodies

The ketone bodies are three compounds produced in the body



The first compound is commonly known as acetoacetate, its structure shows as if it is formed from 2 acetate molecules

?

3-Hydroxybutyrate dehydrogenase

NADH + H^+

CO_2

NAD^+

Acetoacetate can be reduecd (ketone group to hydroxyl group) or

or it may udergo non enzymic decarboxylation

??

Ketone Bodies

- Synthesis:

  In Liver

- Precursor:

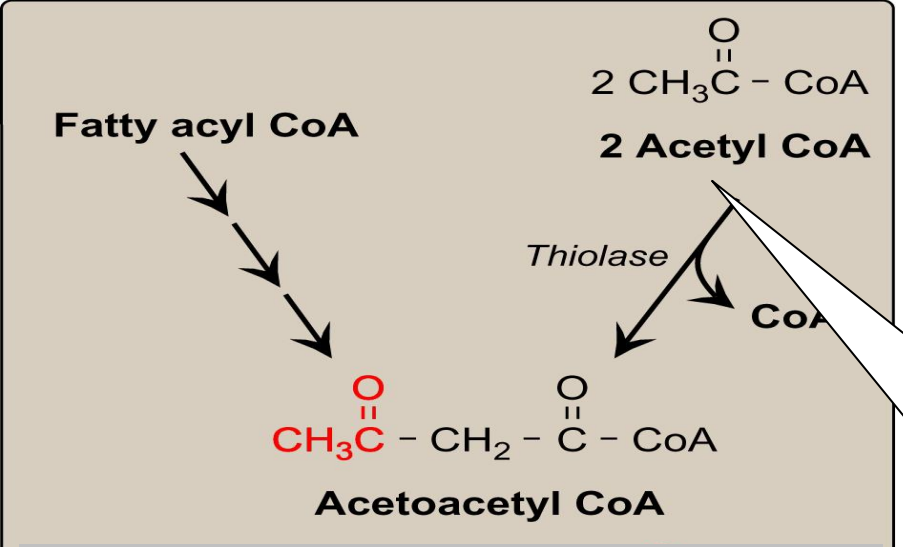
  Acetyl CoA(mainly from β Oxidation)

- At high rate during:

  - Fasting

  - Uncontrolled Diabetes Mellitus

Acetoacetate Synthesis fro Acetyl CoA



Net Reaction ??

2 Acetyl CoA →
Acetoacetate + 2 CoA

*The 5 carbon dicarboxylic acid is known as Glutaric acid ; so this is **H**ydroxym **M**ethyl **G**lutaryl CoA (**HMG** CoA)*

The net reaction can be obtained by
all reactants ➔ all products
Any intermediate that is produced by a step and used by another step is ignored

The last reaction is cleavage of acetyl CoA

Net Reaction

2 Acetyl CoA → Acetoacetate + 2 CoA

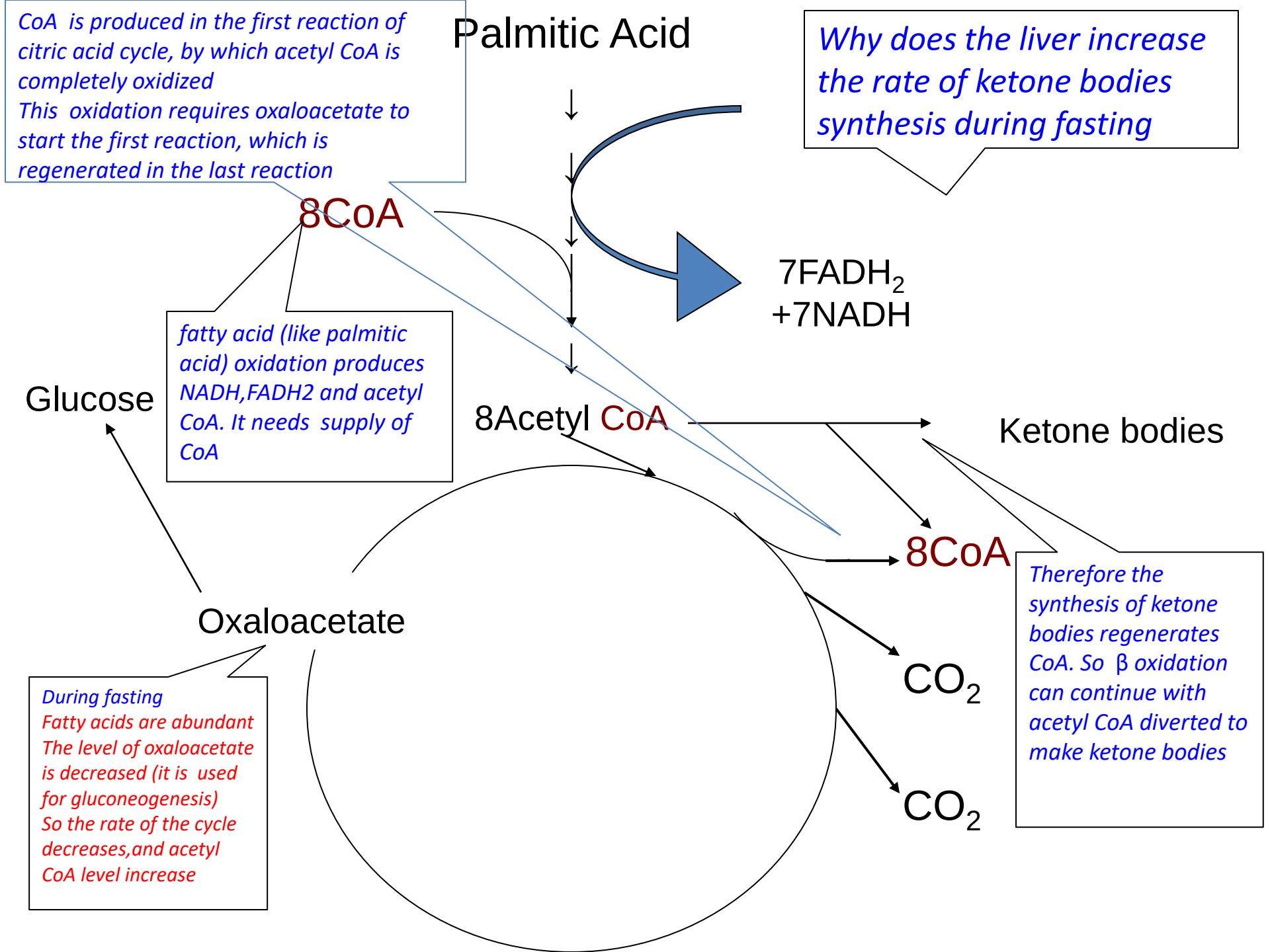
So what is the Advantage (Purpose) ?

- For the liver
- For the tissues

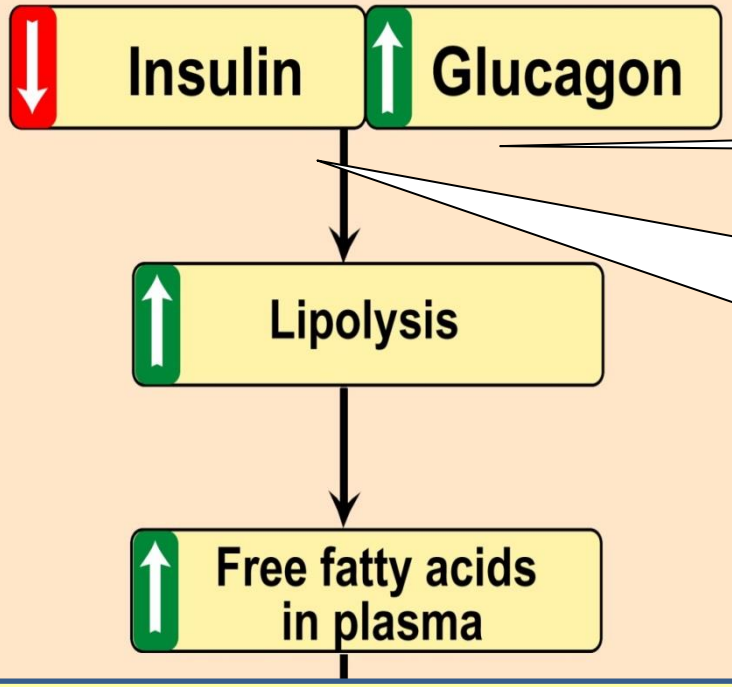
So the net reaction is

Notice that the intermediates are ignored

From the net reaction
One can guess that the purpose is to produce either acetoacetate or Coenzyme A.
We will see that the purpose is to produce CoA; Why!


CoA is produced in the first reaction of citric acid cycle, by which acetyl CoA is completely oxidized
This oxidation requires oxaloacetate to start the first reaction, which is regenerated in the last reaction
Palmitic Acid
Why does the liver increase the rate of ketone bodies synthesis during fasting
8CoA
7FADH2
+7NADH
fatty acid (like palmitic acid) oxidation produces NADH,FADH2 and acetyl CoA. It needs supply of CoA
Glucose
8Acetyl CoA
Ketone bodies
8CoA
Therefore the synthesis of ketone bodies regenerates CoA. So β oxidation can continue with acetyl CoA diverted to make ketone bodies
Oxaloacetate
CO2
CO2
During fasting
Fatty acids are abundant
The level of oxaloacetate is decreased (it is used for gluconeogenesis)
So the rate of the cycle decreases,and acetyl CoA level increase

In Uncontrolled Diabetes Melitus(DM)



Why does the liver increase the rate of ketone bodies synthesis in uncontrolled DM

In uncontrolled DM, the plasma level of inulin is low and glucagon is high

This hormonal state is similar to that during **fasting.**

So the rate of TAG mobilization from adipose tissue is high ➔ ↑ free FA

Gluconeogenesis (active in liver) ➔ ↓ oxaloacetate increase production of ketone bodies(acids)

Increase Excretion of ketone bodies in Urine as

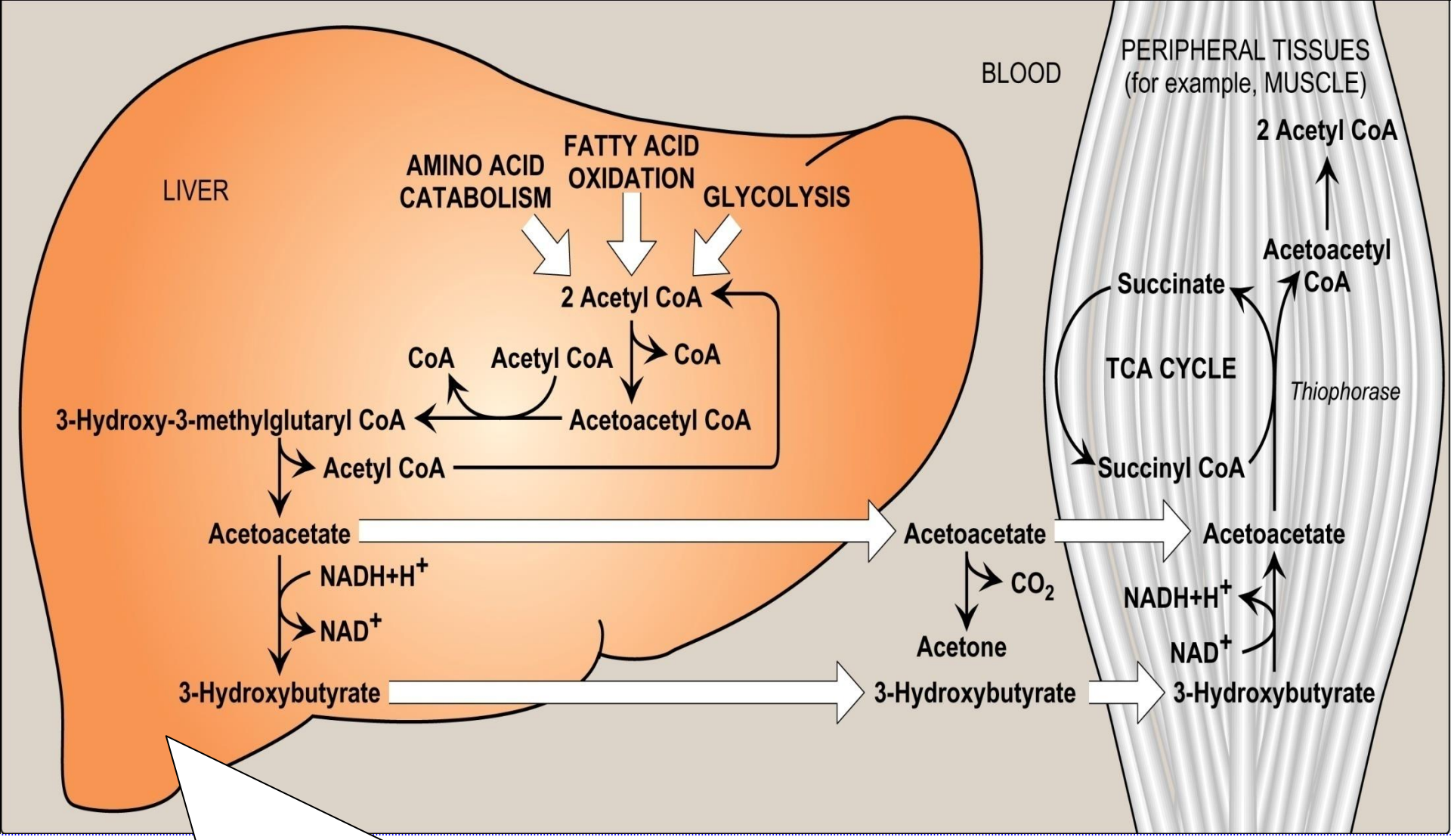
Sodium Salt of

↓

Loss of water

↓

Dehydration



Use of Ketone Bodies by Peripheral Tissues:

Ketone bodies produced by liver and released into the plasma, can be used as source of energy by other tissues like **muscles**

Diabetic Ketoacidosis(DKA)

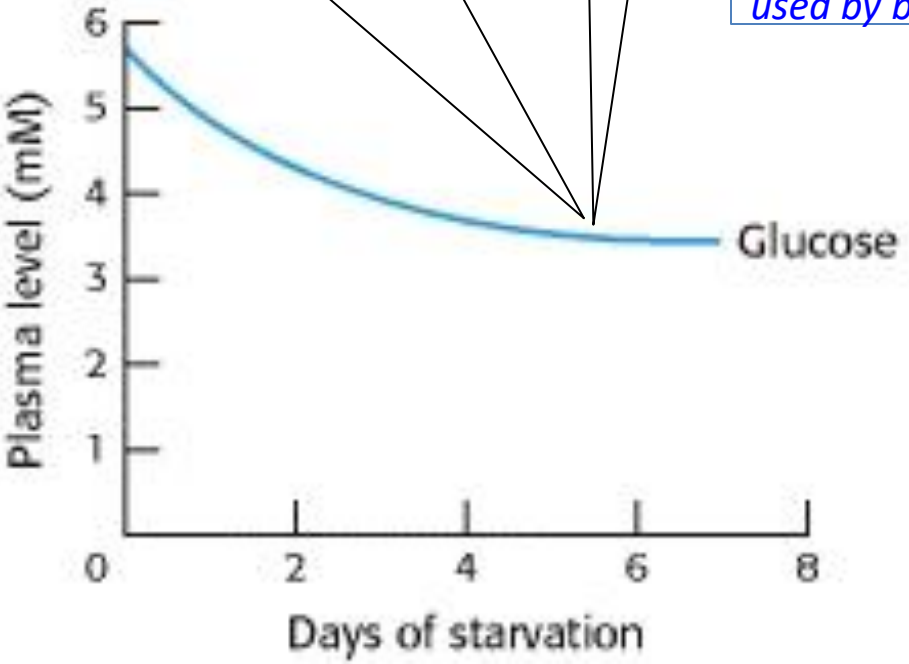
- It is an emergency clinical situation
- Occurs in uncontrolled type 1 diabetes (insulin dependent)
  - High blood glucose
  - high plasma level of ketone bodies
  - Dehydration
  - Coma

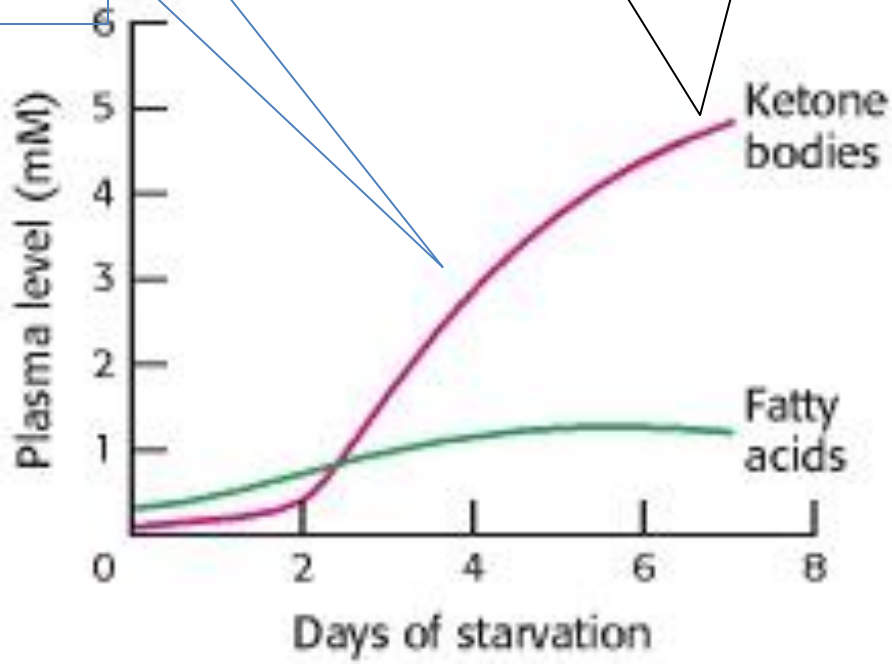
These two curves show the plasma level fuel molecules with time during prolonged fasting (starvation)

It is clear that plasma level of glucose slightly drops, glucogneogenesis is the source of glucose; Amino acids ➔ glucose

This will decrease the conversion of Amino acids to glucose and decrease protein degradation, (muscle and plasma proteins), So Fatty acids ➔ Ketone bodies to be used by brain

At the same time the plasma level of ketone bodies increases which allows the brain cell to use them as source of energy instead of glucose,





Fuel metabolism in starvation

	Amount formed or consumed in 24 hours (grams)	
Fuel exchanges and consumption	**3rd day**	**40th day**
Fuel use by the brain		
Glucose	100	40
Ketone bodies	50	100
All other use of glucose	50	40
Fuel mobilization		
Adipose-tissue lipolysis	180	180
Muscle-protein degradation	75	20
Fuel output of the liver		
Glucose	150	80
Ketone bodies	150	150