Lecture 8A

BT 203

Biochemistry

3-0-0-6

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Key Concepts

- What is fatty acid oxidations?
- What is the route for fatty acid oxidation?
- What are the different steps of fatty acid oxidation?
- What is Fatty acyl –CoA dehydrogenase?
- What are ketone bodies?

Fatty Acid Oxidation

Fatty acid (FA) activation before oxidation

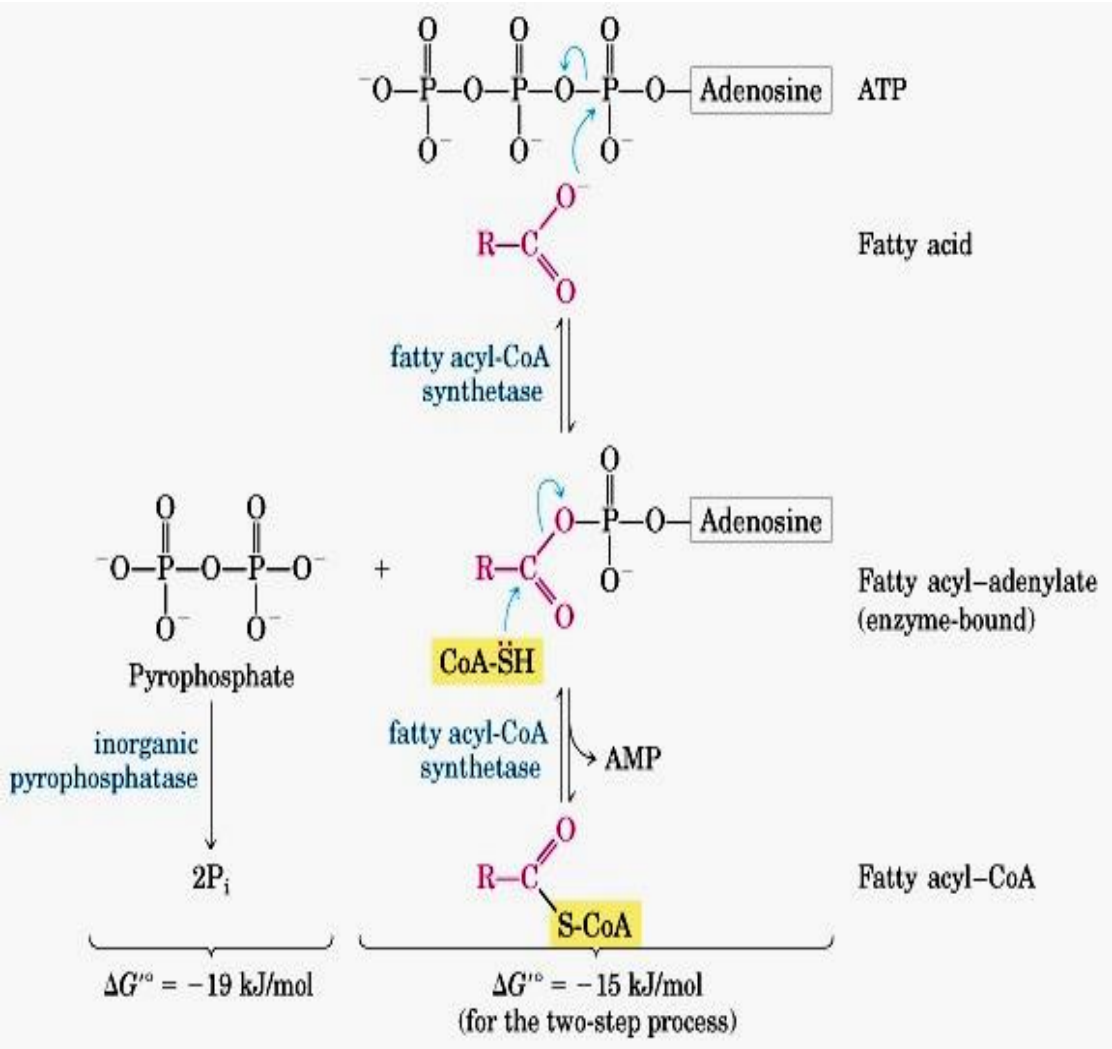
All the enzymes involved in oxidation of FA are present in mitochondria. The free FA obtained from blood cannot enter mitochondia.

In the first step, FA are converted to fatty acyl CoA on the outer mitochodrial membrane by an ezyme called Fatty acyl CoA synthase (also called thiokinase).

This reaction is coupled with ATP hydrolysis to AMP, and 2Pi.

There are different isoforms of Fatty acyl CoA synthase specific for different kind of FAs.

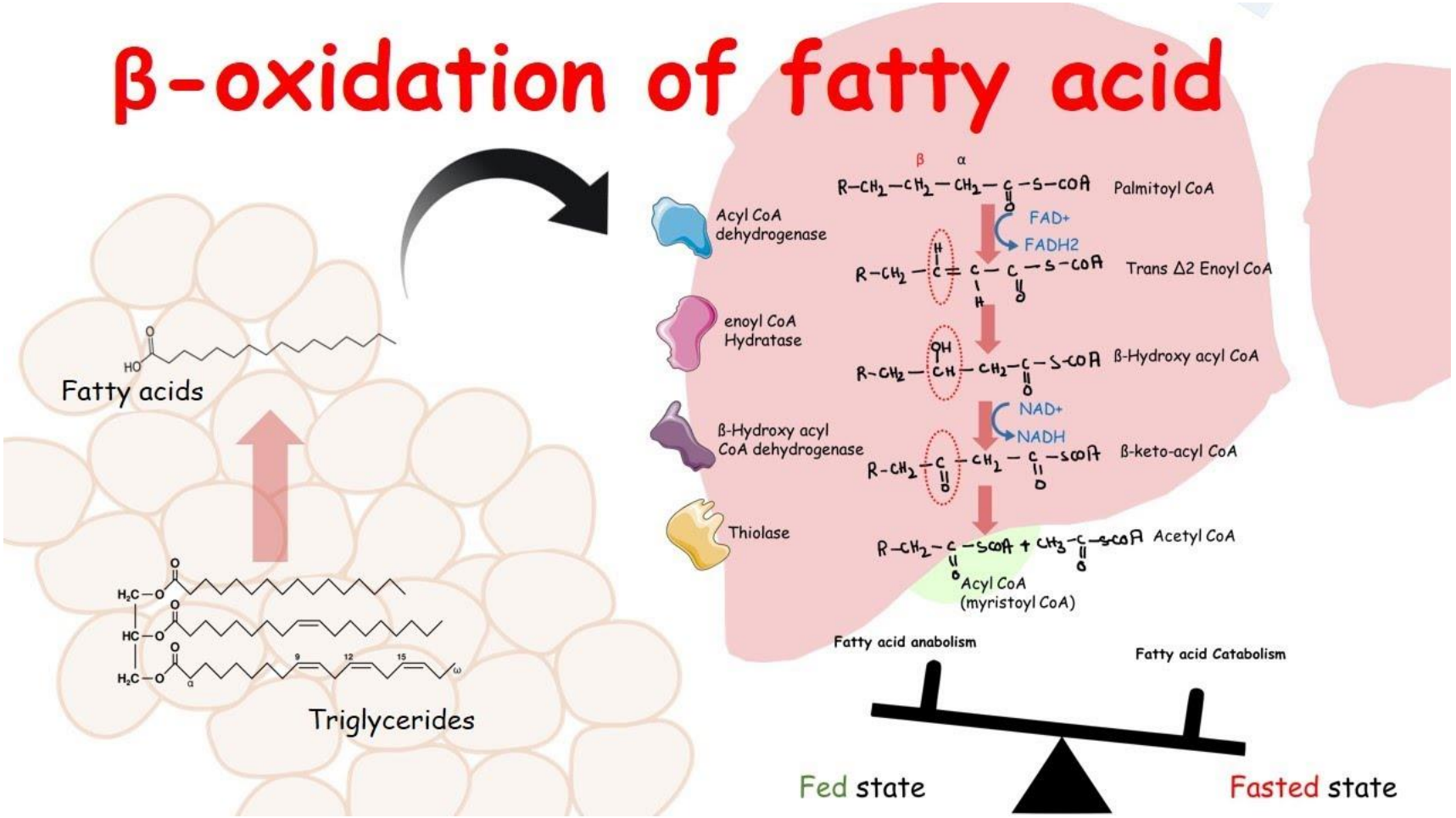
This is the regulatory step of FA oxidation pathway.



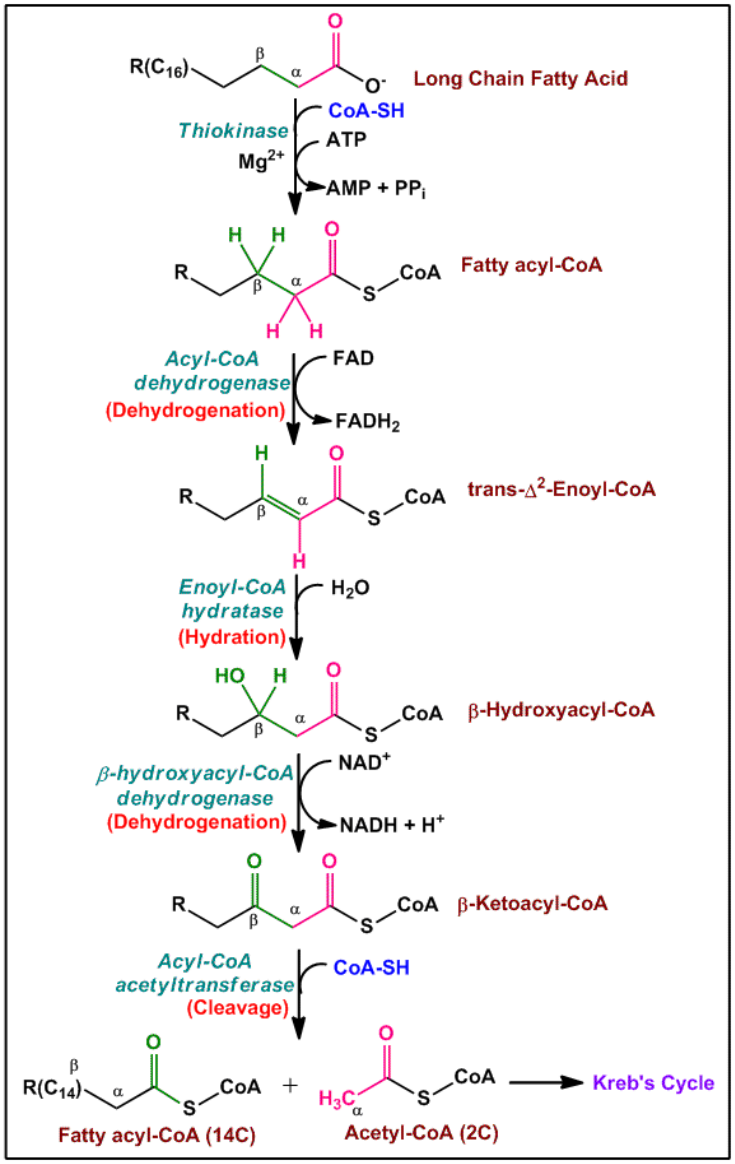
FA + ATP + CoA-SH = Fatty acyl-CoA + AMP + 2Pi

δG = -34 KJ/mole

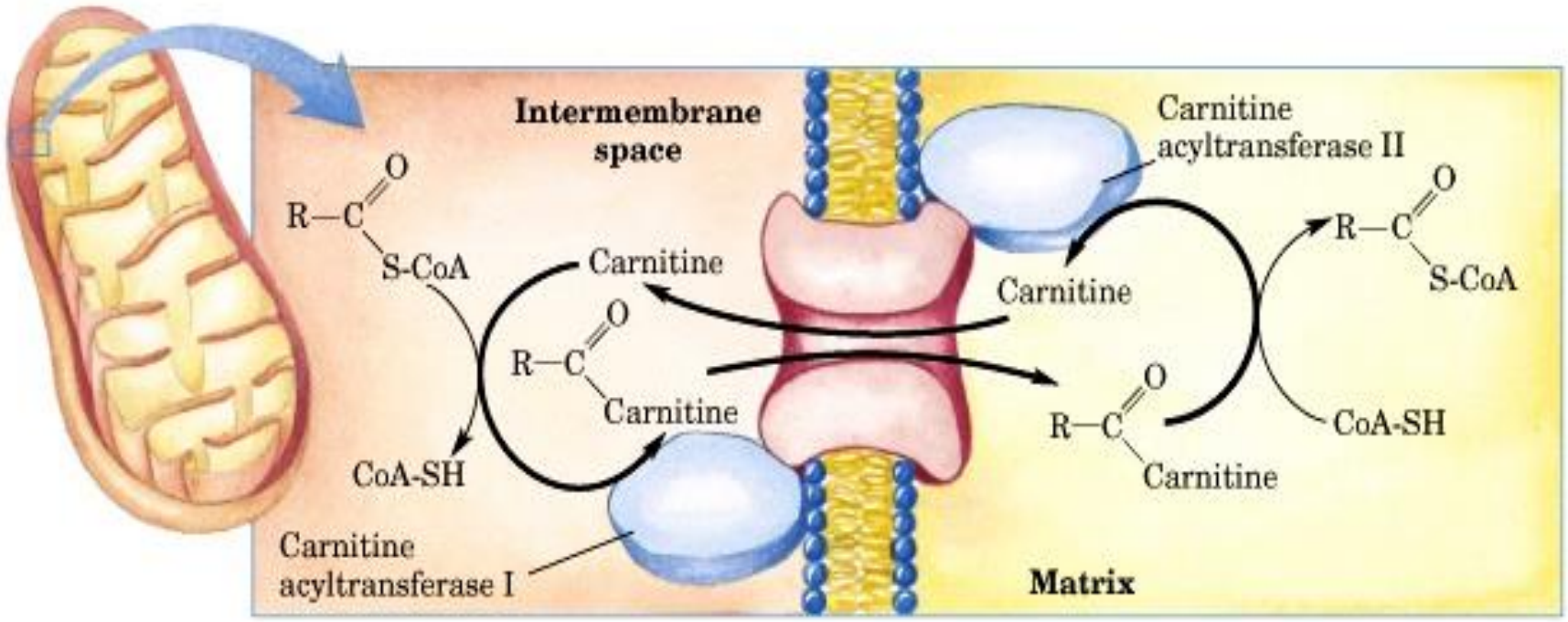
Fatty Acid Oxidation



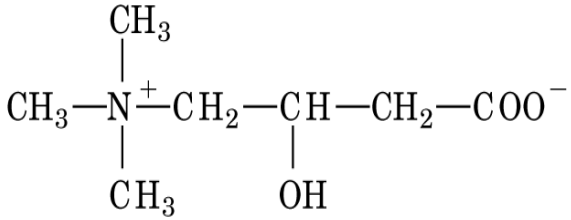
Fatty Acid Oxidation



Routes of FA entry



FA entry into mitochondria via Fatty acyl-carnitine-carnitine transporter: Fatty acyl CoA ester formed on outer mitochondrial membrane do not enter directly in mitochondria. 1.The FA is transferred to OH gp of carnitine by Carnityl acyl transferase I (CAT-I), then the fatty acyl-Carnitine ester is transported in the mitochondra. 2. In mitochondria, FA is transferred to mitochondral CoA by CAT-II, and the Fatty acyl-CoA thus formed is ready for oxidation pathway.



Carnitine

Cytosolic and mitochondrial CoA pools have different functions; for biosynthetic and catabolic reaction respectively.

FA oxidation- Steps

Once in mitochondria, the fatty acyl CoA is subjected to beta oxidation.

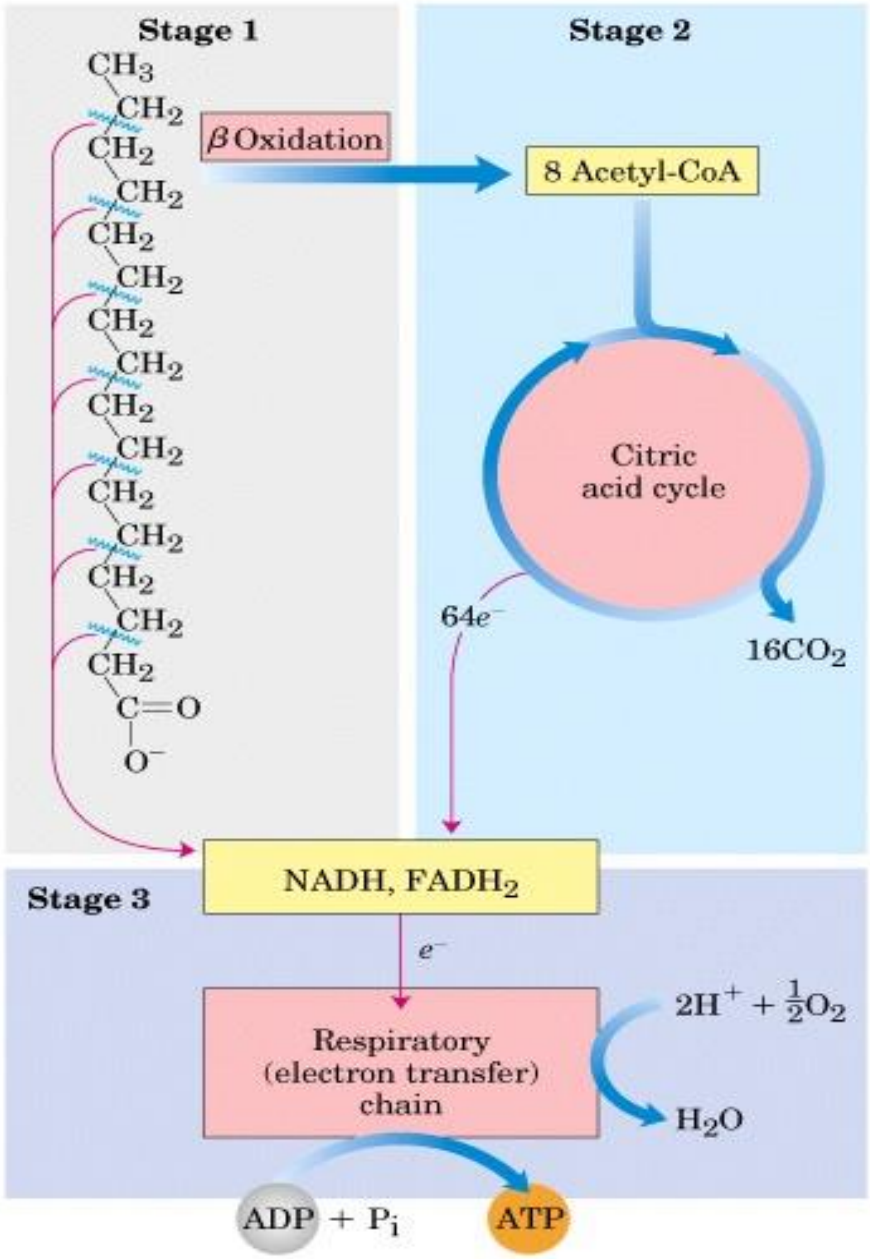
Utilization of FA for oxidation and generation of ATP is achieved in the following three steps;

1. beta-oxidation of fatty acid chain yielding acaty-CoA.

2. Entry of actyl-CoA in citric acid cycle yielding NADH, FADH2 and GTP.

3. Utilization of NADH and FADH2 in oxidative phosphorylation generating ATP.

The first Fatty acyl-CoA dehydrogenase enzyme of β-oxidation pathway is linked to ETC and it directly transfers the electrons to Coenzyme Q in ETC via FADH2.



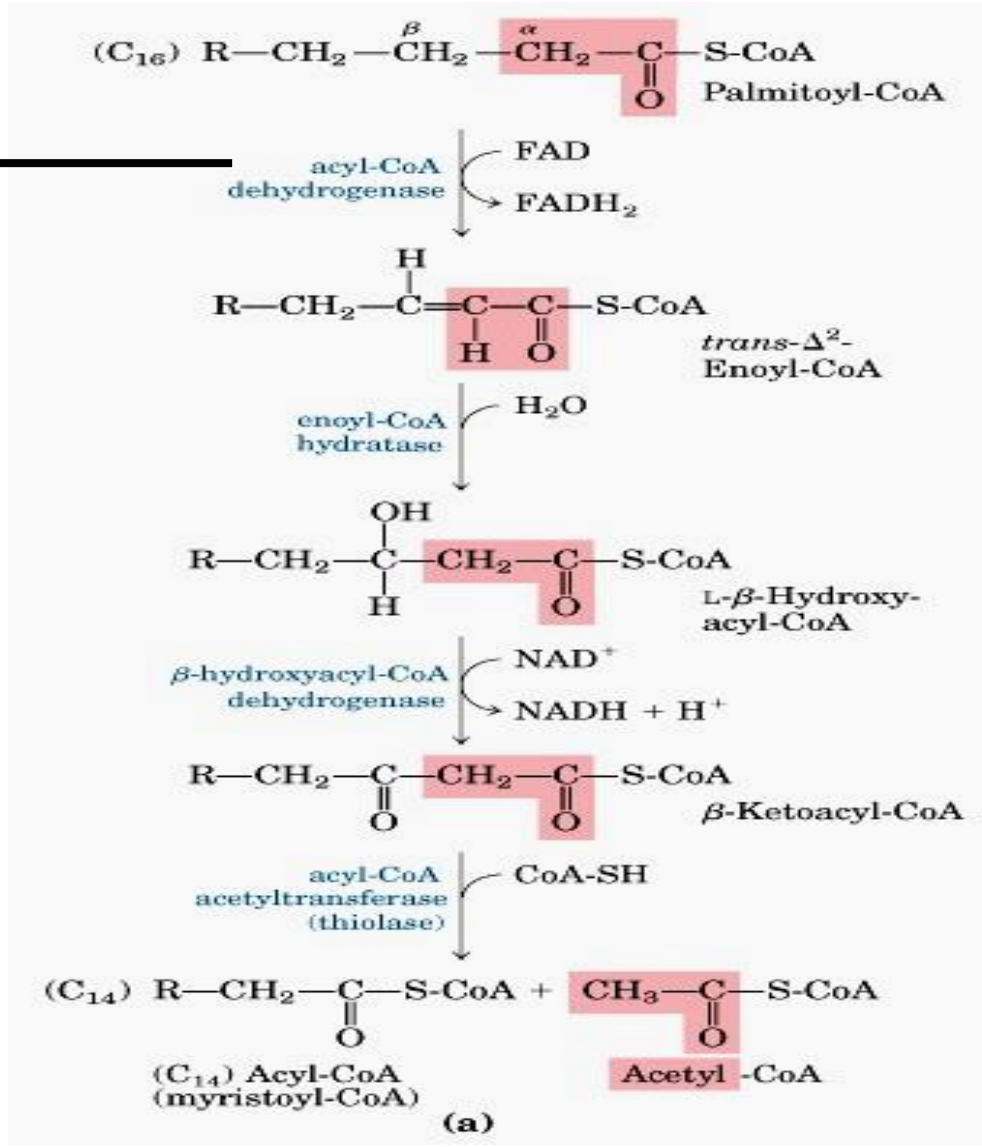
FA oxidation- Steps

The β-Oxidation of fatty acyl-CoA: 1. The first enzyme catalyses the formation of a trans α, β double bond, using FAD as cofactor. This enzyme is linked to electron transport chain via electron transferring flavoprotein see next slide.

2. Hydration of the double bond by enoyl-CoA hydratase to form L-β-hydroxyacyl-CoA.

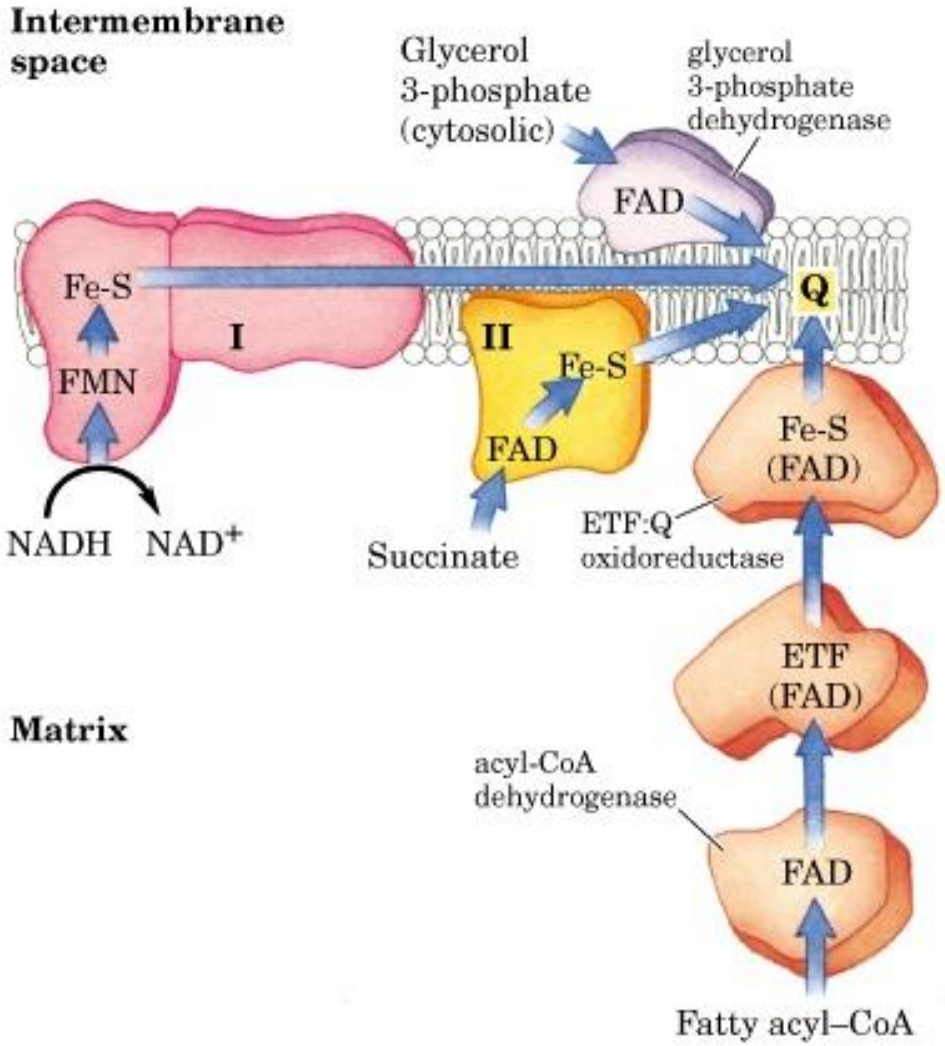
3. NAD^+-dependent dehydrogenation by L-β-hydroxyacyl-CoA dehydrogenase to form β-ketoacyl-CoA.

4. Cα—Cβ cleavage in athiolysis reaction with CoA, catalysed by thiolase, producing acetyl-Coa and a new fatty acyl-CoA with two less carbon units.



Fatty acyl –CoA dehydrogenase

Fatty acyl –CoA dehydrogenase is linked to electron transport chain vis Electron transferring flavoptotrien (ETF) anf ETF-Q oxidoreductase



FA oxidation- Steps

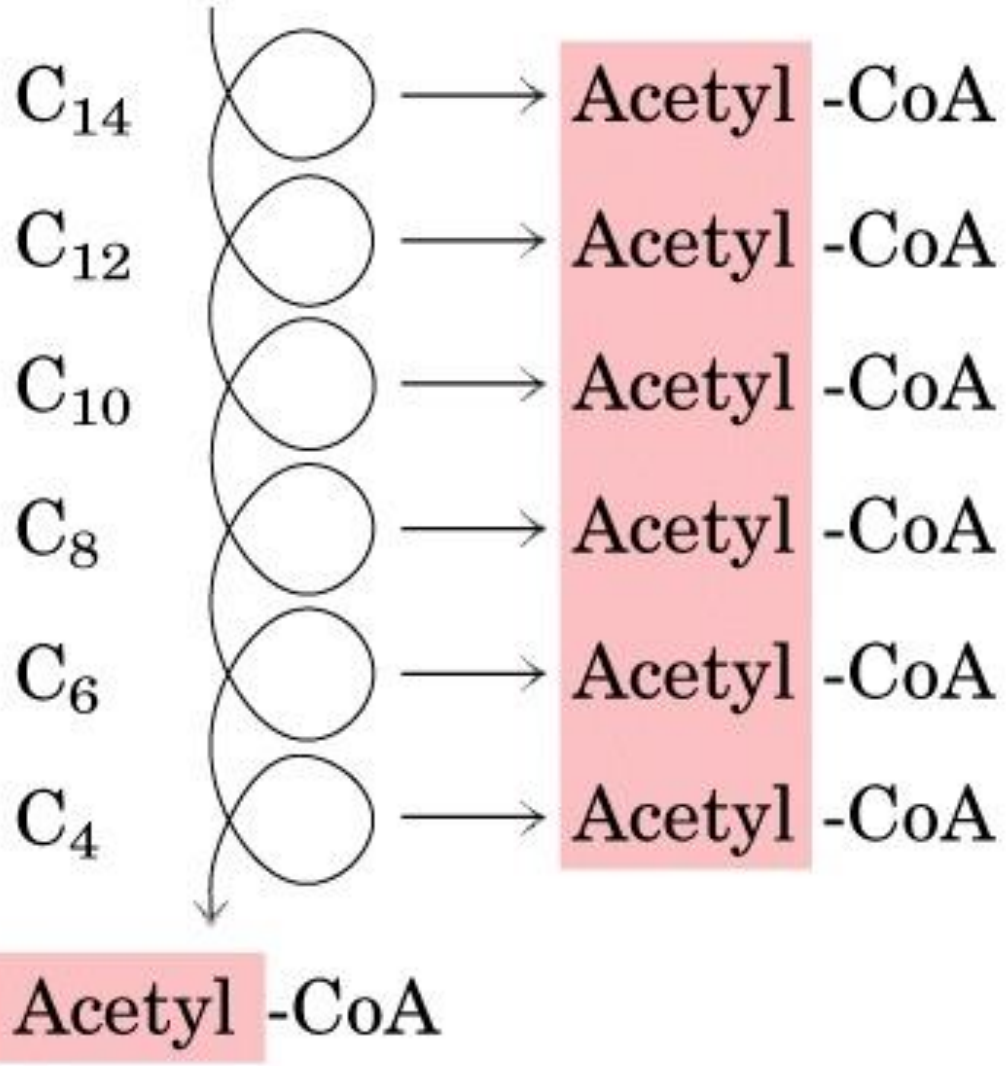
The four steps of β-oxidation are repeated to get FA completely converted to acetyl-CoA.

For example for a 16 carbon fatty acid, Palmityl-CoA, it will take 7 cycle of β-oxidation to generate 8 acetyl-CoA.

Thus there will be production of 7 $FADH_2$, 7 NADH molecules during the β-oxidation cycles.

From 8 acetyl-CoA there will be generation of;

8 GTPs, 8 $FADH_2$, 24 NADH and 16 CO_2



FA oxidation- Steps

table 17–1

Yield of ATP during Oxidation of One Molecule of Palmitoyl-CoA to CO_2 and H_2O

Enzyme catalyzing the oxidation step	Number of NADH or $FADH_2$ formed	Number of ATP ultimately formed*
Acyl-CoA dehydrogenase	7 $FADH_2$	10.5
β-Hydroxyacyl-CoA dehydrogenase	7 NADH	17.5
Isocitrate dehydrogenase	8 NADH	20
α-Ketoglutarate dehydrogenase	8 NADH	20
Succinyl-CoA synthetase		8†
Succinate dehydrogenase	8 $FADH_2$	12
Malate dehydrogenase	8 NADH	20
Total		108

*These calculations assume that mitochondrial oxidative phosphorylation produces 1.5 ATP per $FADH_2$ oxidized and 2.5 ATP per NADH oxidized.

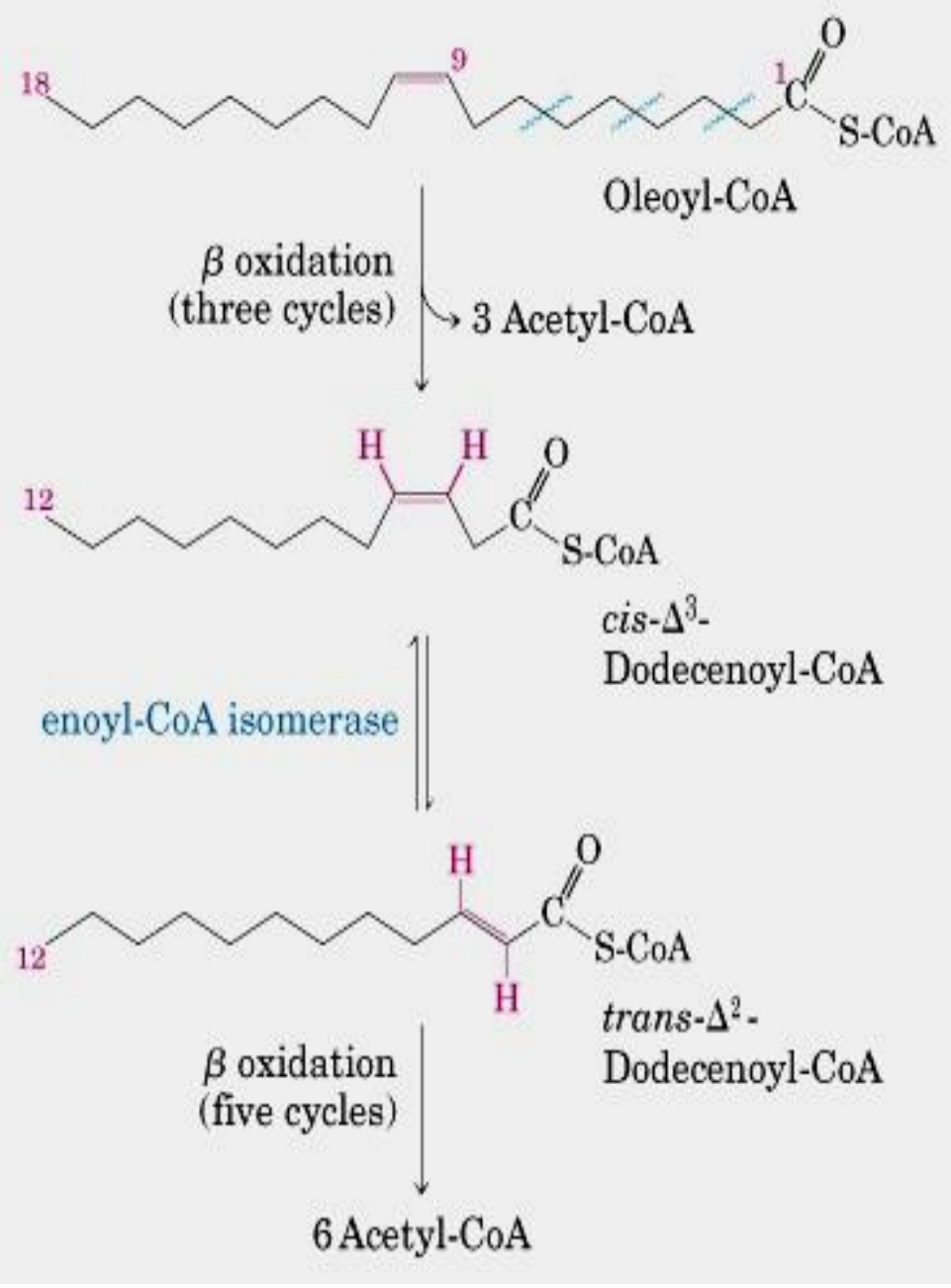
†GTP produced directly in this step yields ATP in the reaction catalyzed by nucleoside diphosphate kinase (p. 578).

FA oxidation (unsaturated)- Steps

Oxidation of unsaturated fatty acids

All the steps are same except, and additional enzyme called enoyl-CoA isomerase is required to convert the cis-double bond to trans double bond that can be recognized by enoyl-CoA hydratase.

Now the rest of the chain can be oxidized as described before.

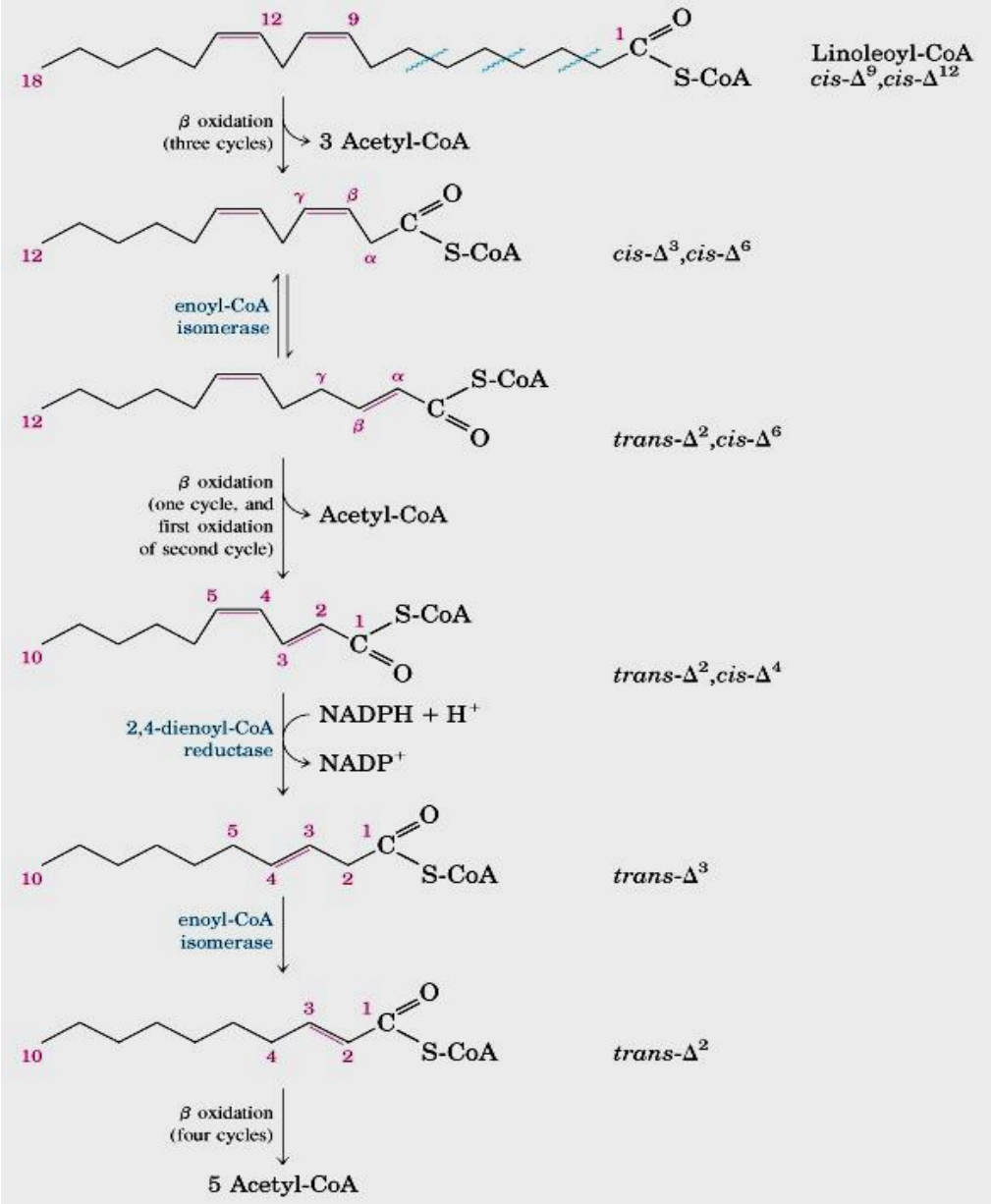


FA oxidation- Steps

When more than one bonds are unsaturated, then one more additional enzyme is used to saturate the second double bond using NADPH.

This enzyme is called 2,4 dienoyl reductase.

This is followed by isomerization reaction and β-oxidation.



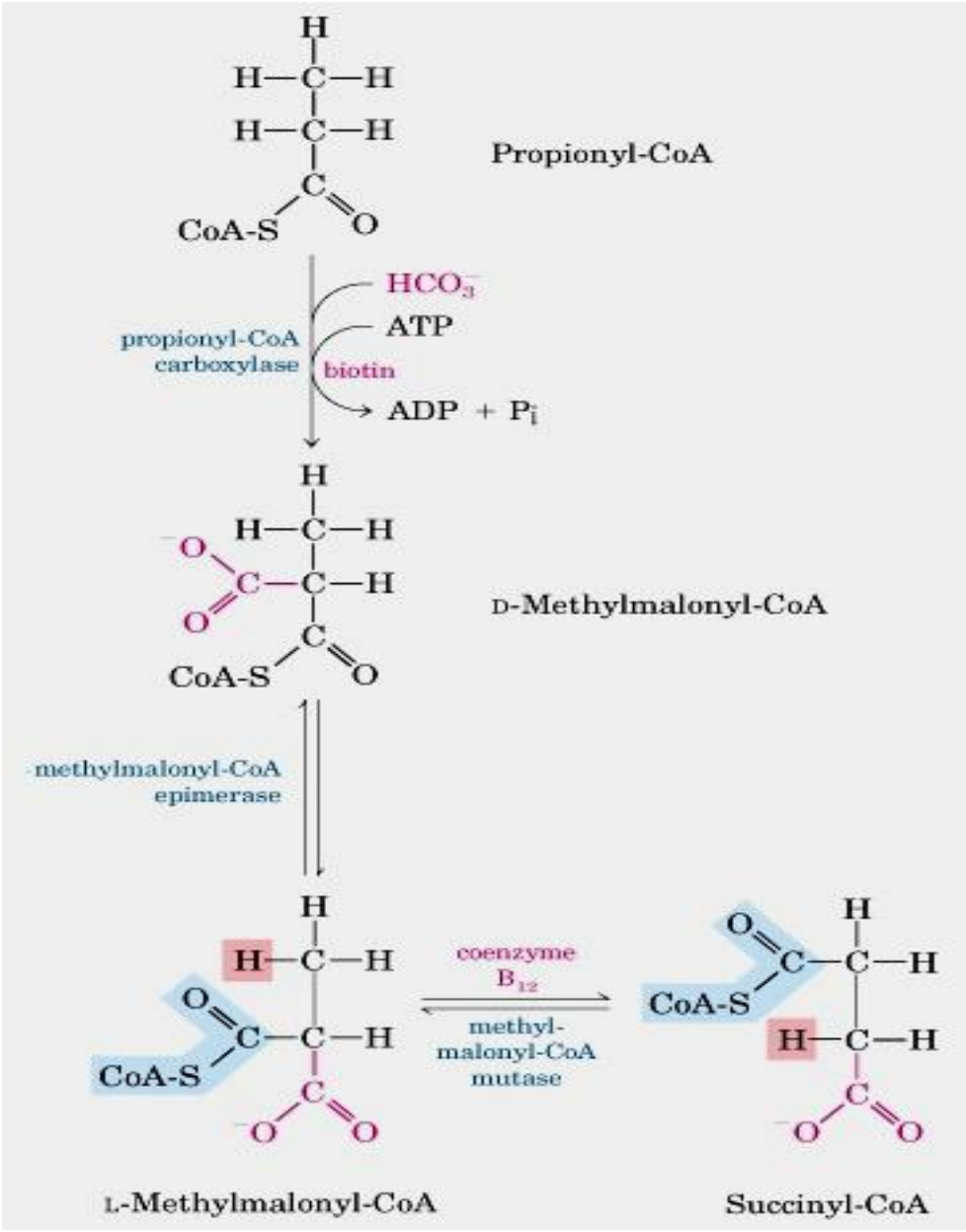
FA oxidation- Odd Chain FA

What about odd-chain fatty acids;

In case of odd-chain fatty acyl-CoA, a three carbon unit , the propionyl-CoA is left at the last cycle of boxidation.

The three carbon chain propionyl-CoA is converted to four carbon methyl-malony-CoA by propionyl-CoA carboxilase and methyl-malony-CoA epimerase.

The methyl-malony-CoA is converted to succinyl-CoA by methyl-malony-CoA mutase which uses vitamin B12 as cofactor.



Peroxisomal FA oxidation

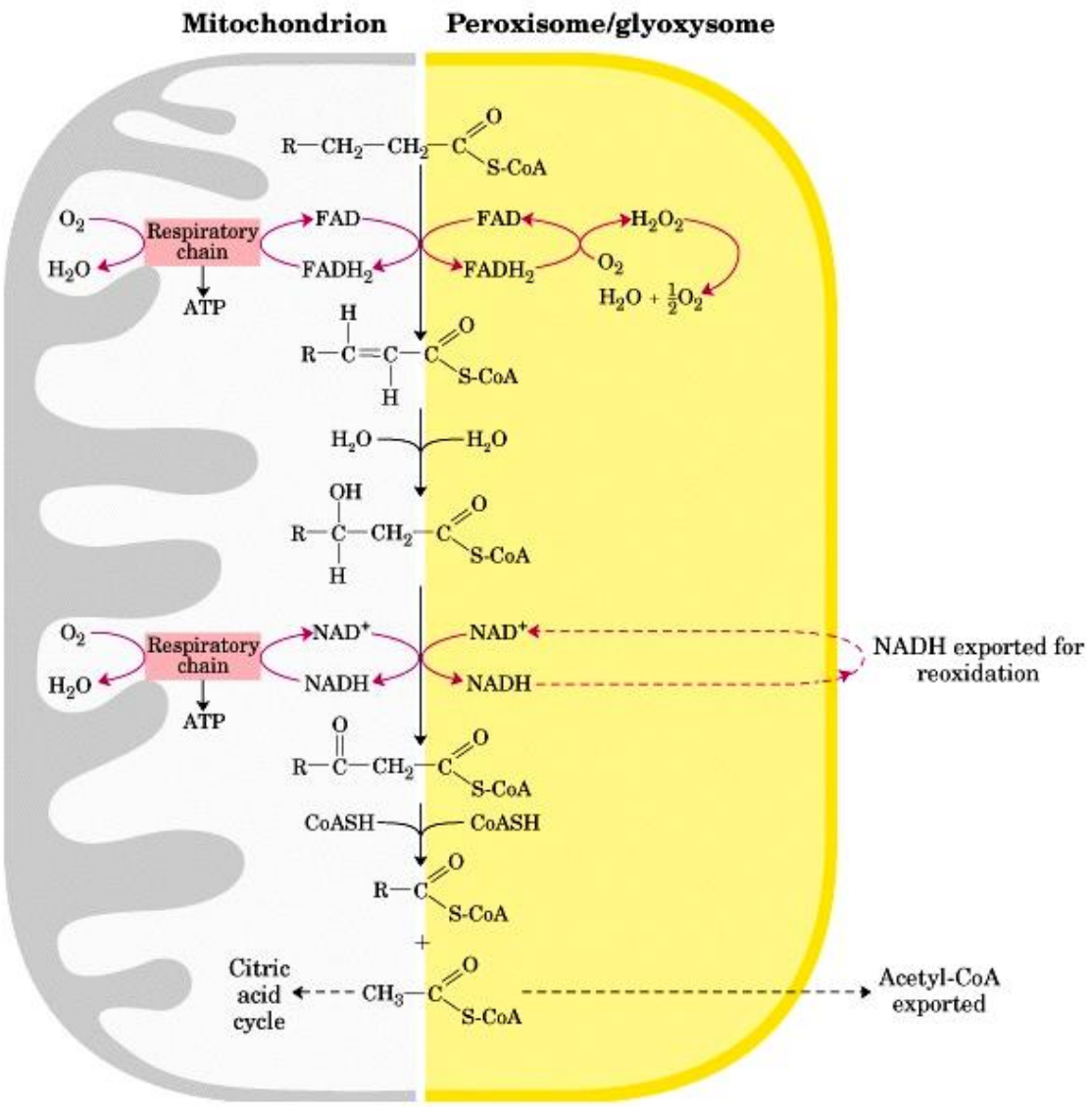
Peroxisomal oxidation of fatty acids:

Most of the steps are same as b-oxidation in mitochondria except that the first dehydrogenase is not linked to ETC in proxisomes.

Electrons from the first reaction are transferred directly to O2 producing p hydrogen peroxide.

Peroxisomal enzymes are up-regulated when fat rich diets are consumed.

Generally very long chain fatty acids diffuse into peroxisomes, get acivated by long chain fatty acyl-CoA synthase and then they are oxidized to short chain FA.

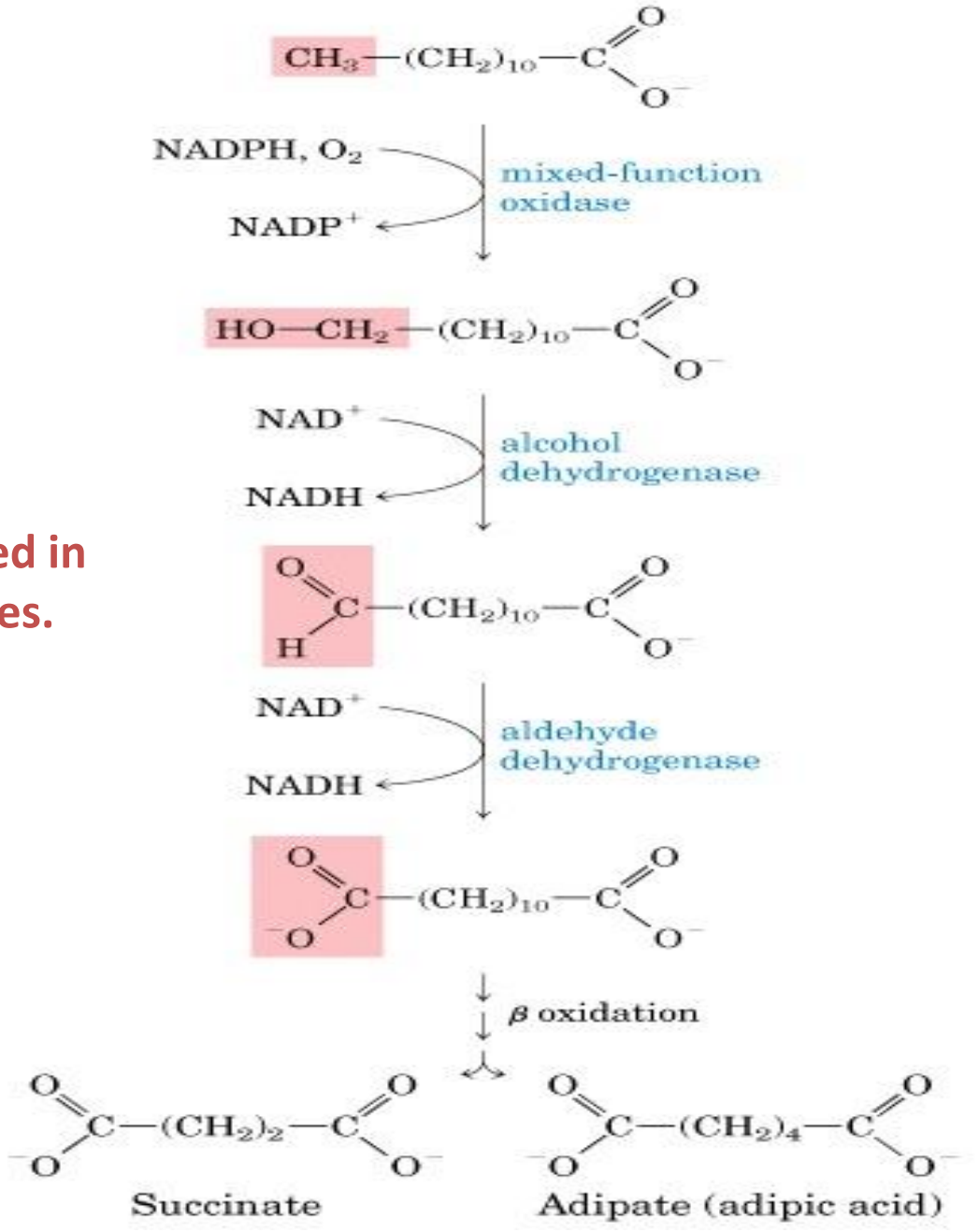


Omega FA oxidation

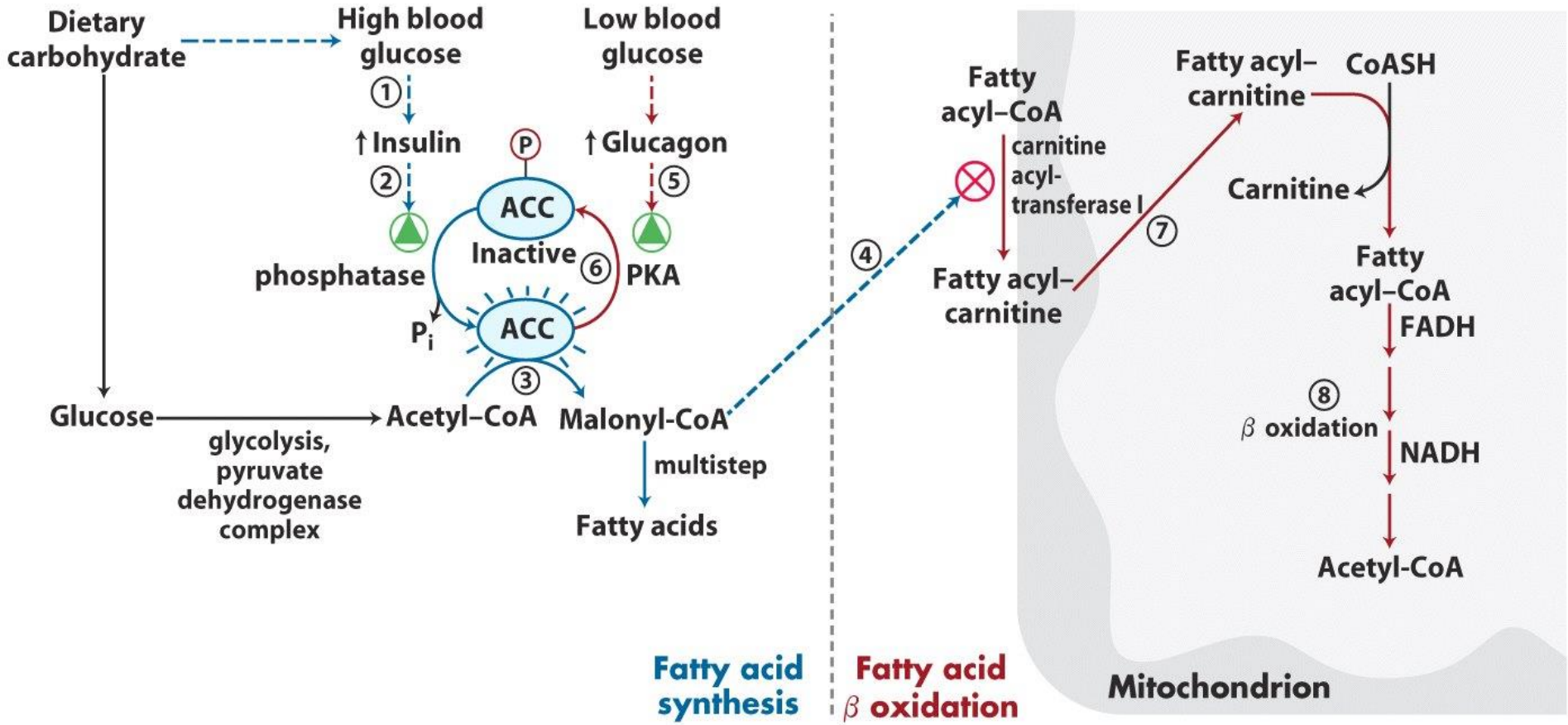
Omega-oxidation:

This is a rare pathway of fatty acid oxidation where FA oxidation starts from the farther most carbon (ω-carbon).

Enzymes for this pathway are located in endoplasmic reticulum of vertebrates.



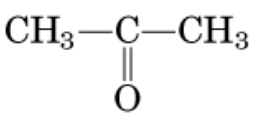
Hormonal control of Fatty acid synthesis and catabolism



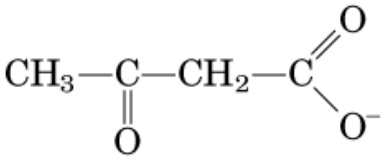
Ketone Bodies

Ketone Bodies: Acetyl-CoA produced in liver as a result of b oxidation, can go to CAC or it can be converted to ketone bodies and exported to other tissues for energy generation.

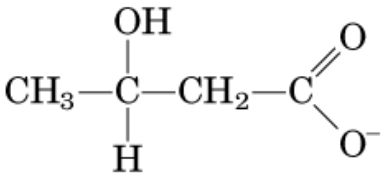
Ketone bodies are produced when glucose is not available as fuel source,



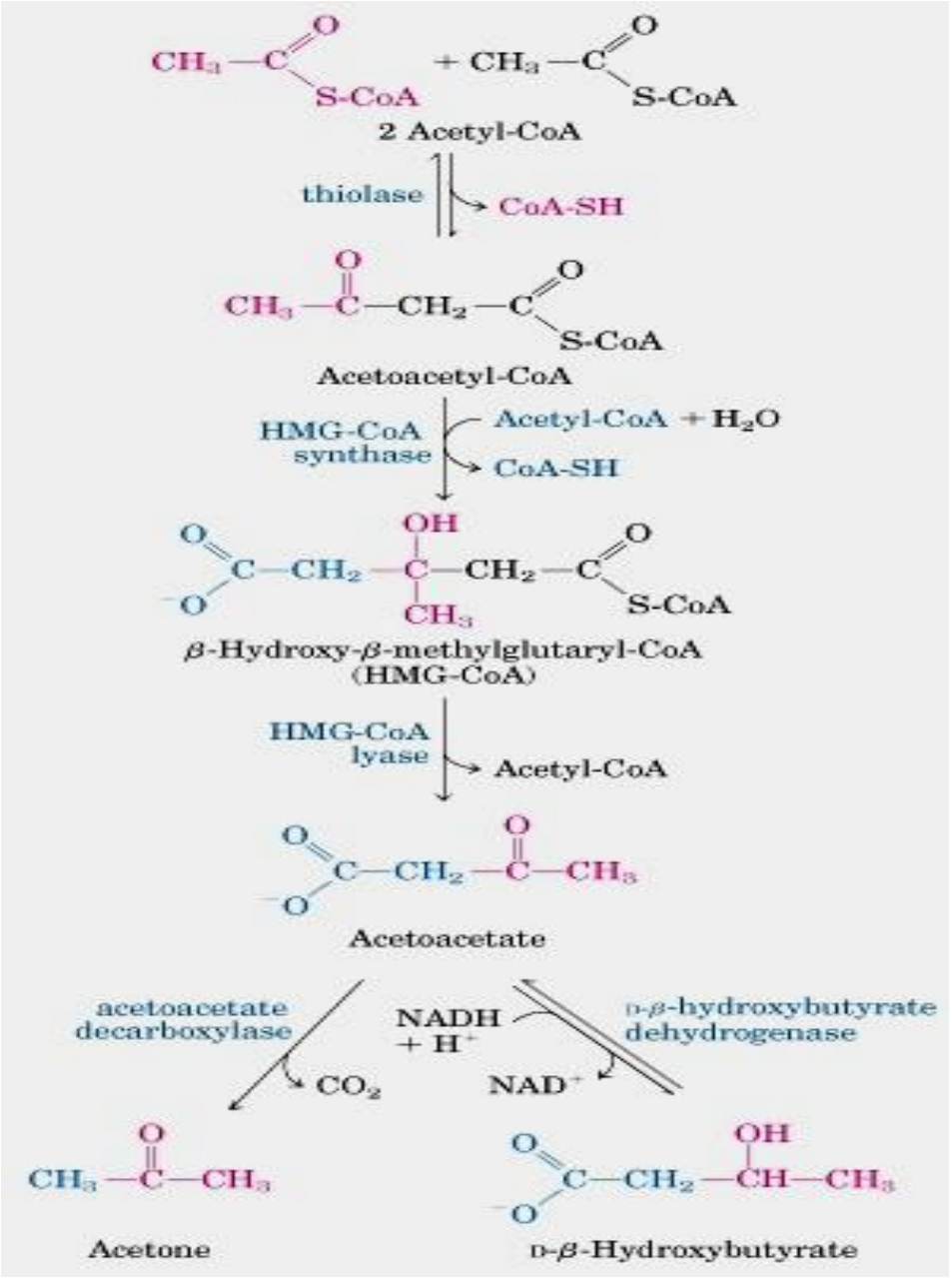
Acetone



Acetoacetate



D-β-Hydroxybutyrate



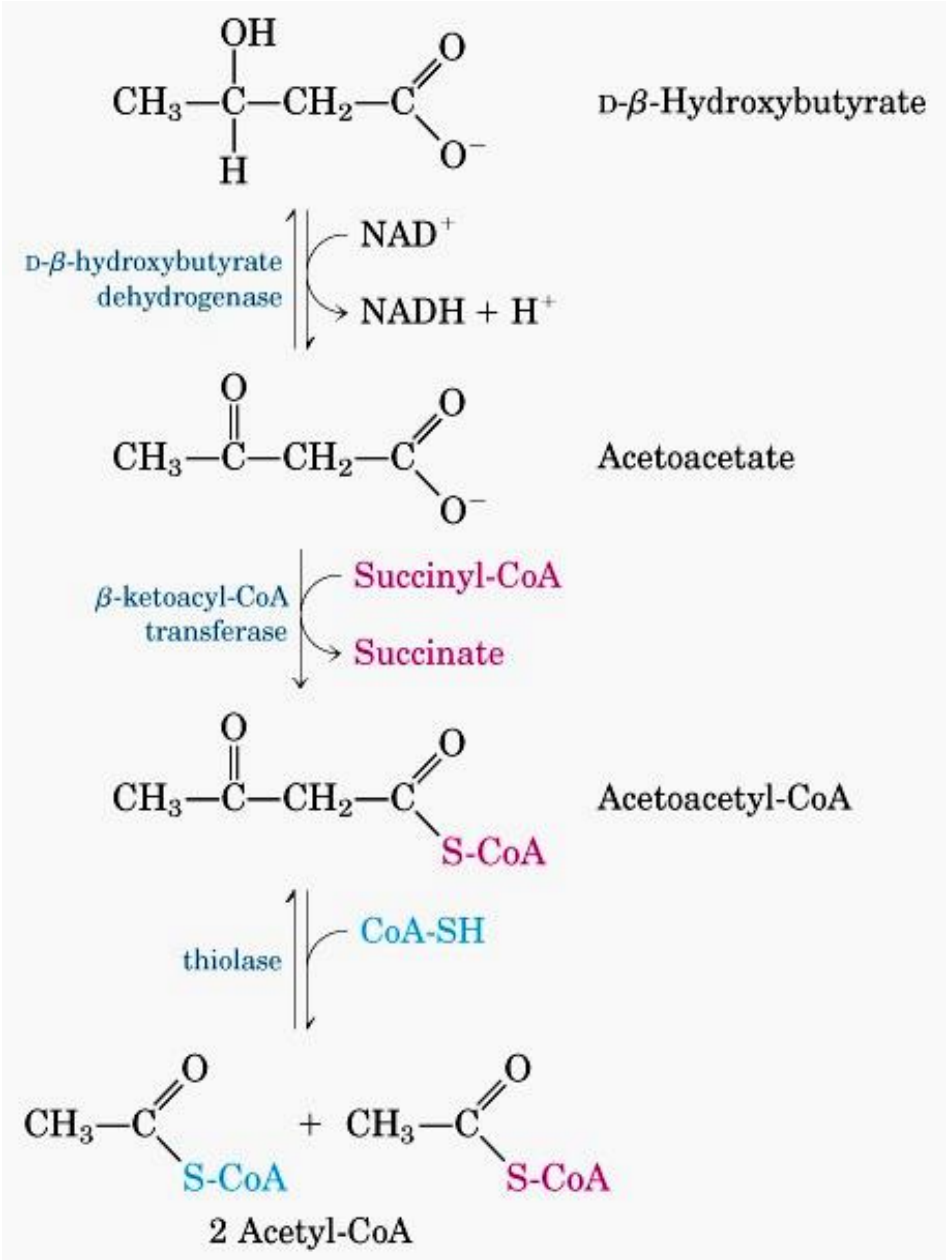
Ketone Bodies

In cases of extreme starvation of untreated diabetes (in both cases glucose availability to tissues are very low), liver starts gluconeogenesis (synthesis of glucose). This process uses CAC intermediates such as oxaloacetate, and thus the consumption of Acetyl-CoA in CAC is slowed down.

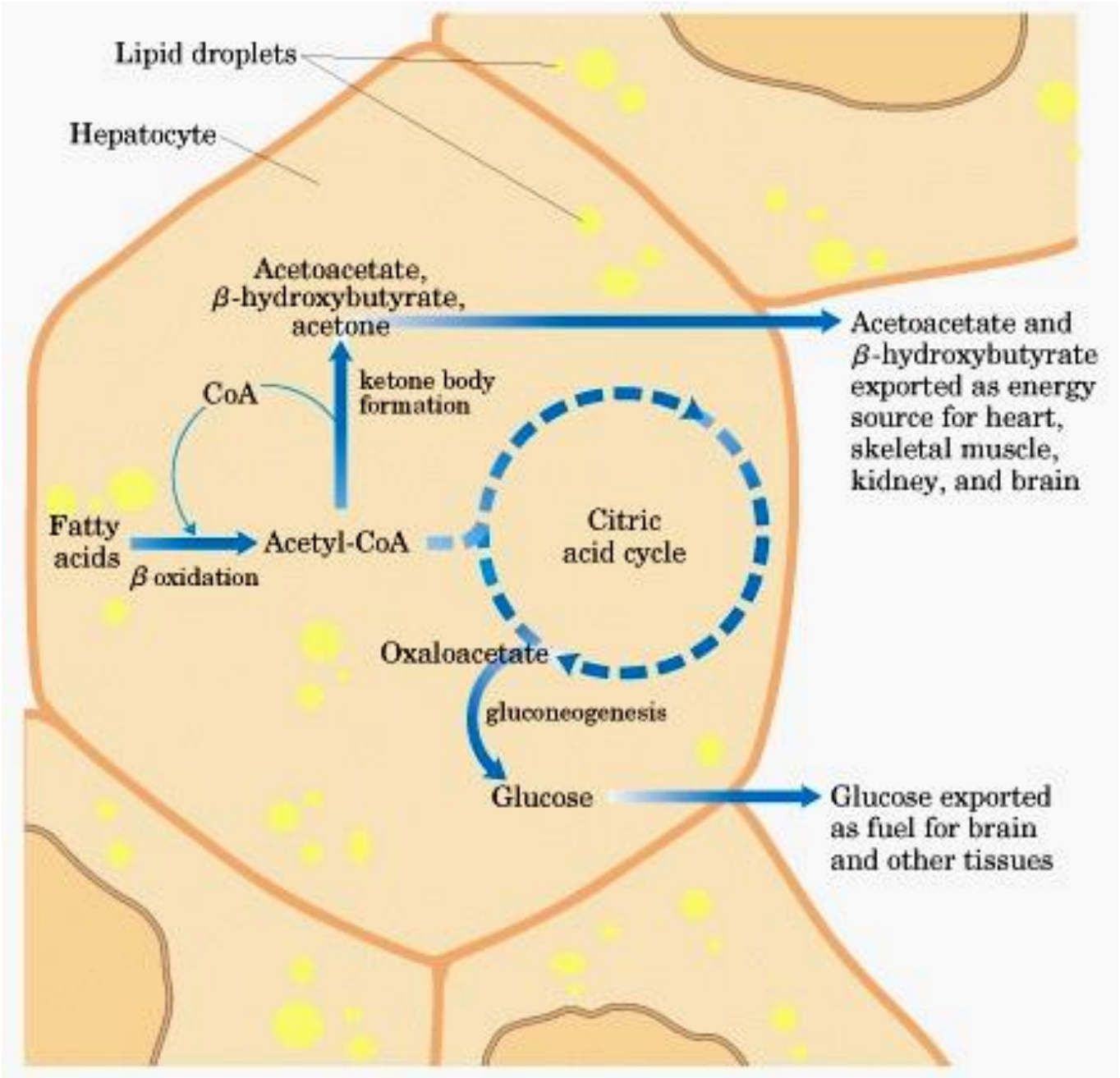
These leads to excess of acetyl-CoA in liver.

In order to meet the energy demand by other tissues, liver catabolizes fatty acids, produces excess of acetyl-CoA and then produces ketone bodies which are transported by blood to muscle and brain.

Ketone body formation regenerates free CoA which are required for b-oxidation.



Fatty acid oxidation



Fatty acid oxidation

In untreated diabetes, the concentration of ketone bodies (two of which are acids) in blood increases so much that it decreases the pH of blood. This condition is called "acidosis" which can lead to com or death.

High concentration of ketone bodies in blood and urine is referred as "ketosis". Due to high concentration of acetoacetate, which is converted to acetone, the breath and urine of the untreated diabetic patients smells like acetone.

table 17–2

Ketone Body Accumulation in Diabetic Ketosis

	Urinary excretion (mg/24 h)	Blood concentration (mg/100 mL)
Normal	≤125	<3
Extreme ketosis (untreated diabetes)	5,000	90