5TH SEM MAJOR

OXIDATION AND BIOSYNTHESIS OF FATTY ACID

BY: DR. LUNA PHUKAN

OXIDATION OF FATTY ACID

- Fatty acid oxidation is the mitochondrial aerobic process of breaking down a fatty acid into acetyl-CoA units. ...The bond is broken between the second carbon/beta carbon and the third carbon/gamma carbon, hence the name beta oxidation. This process provides energy from fats.

In biochemistry and metabolism, beta-oxidation is the catabolic process by which fatty acid molecules are broken down in the cytosol in prokaryotes and in the mitochondria in eukaryotes to generate acetyl-CoA, which enters the citric acid cycle, and NADH and FADH2, which are co-enzymes used in the electron transport chain. It is named as such because the beta carbon of the fatty acid undergoes oxidation to a carbonyl group. Beta-oxidation is primarily facilitated by the mitochondrial trifunctional protein, an enzyme complex associated with the inner mitochondrial membrane, although very long chain fatty acids are oxidized in peroxisomes.

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$$C_n\text{-acyl-CoA} + FAD + NAD^+ + H_2O + CoA \rightarrow C_{n-2}\text{-acyl-CoA} + FADH_2 + NADH + H^+ + \text{acetyl-CoA}$$

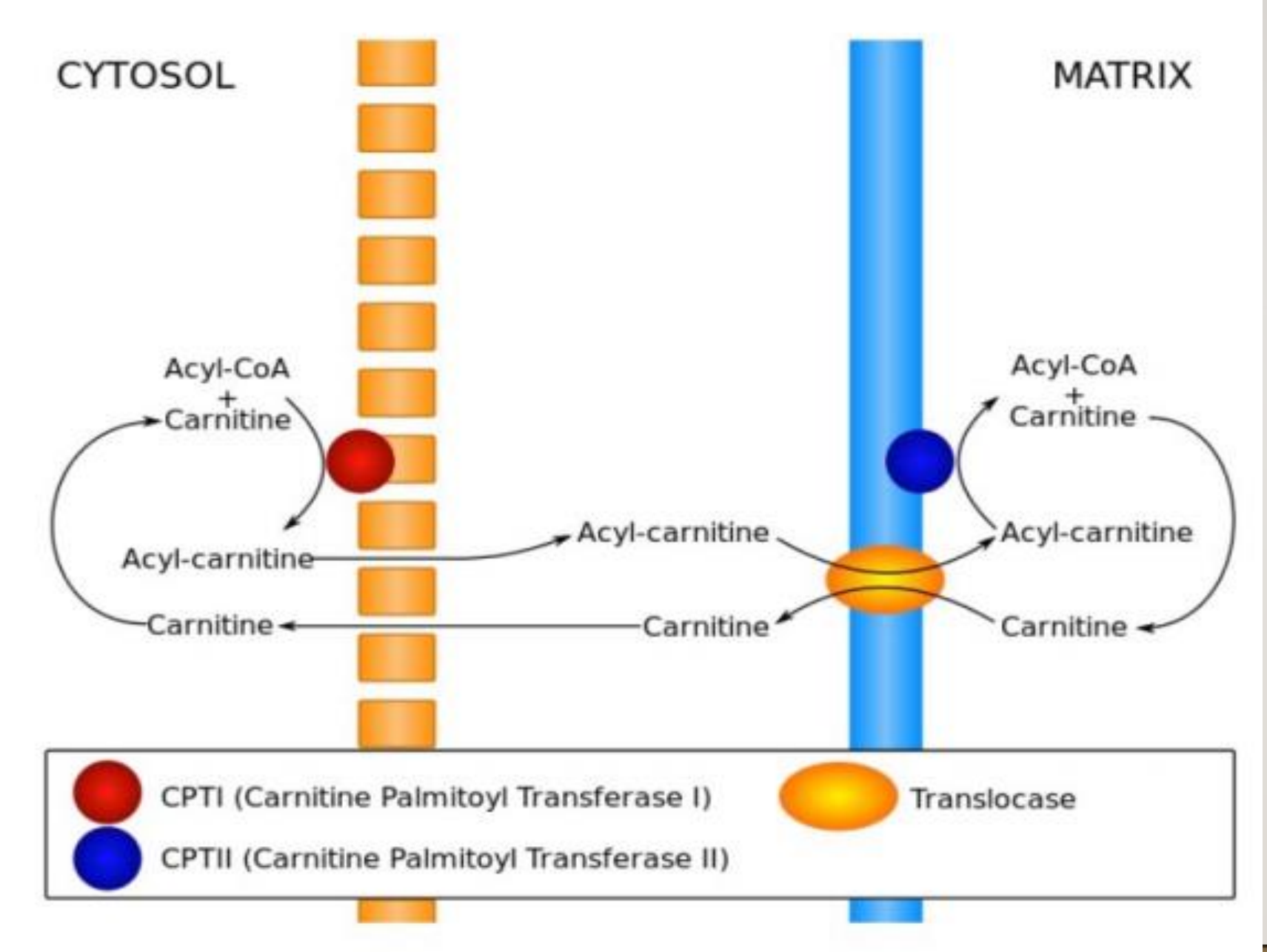


Figure : Movement of Acyl-CoAs into the Mitochondrial Matrix

The process of fatty acid oxidation, called beta oxidation, is fairly simple. The reactions all occur between carbons 2 and 3 (with #1 being the one linked to the CoA) and sequentially include the following:

1.dehydrogenation to create FADH2 and a fatty acyl group with a double bond in the trans configuration;

2,hydration across the double bond to put a hydroxyl group on carbon 3 in the L configuration;

3.oxidation of the hydroxyl group to make a ketone; and

4.thiolytic cleavage to release acetyl-CoA and a fatty acid two carbons shorter than the starting one.

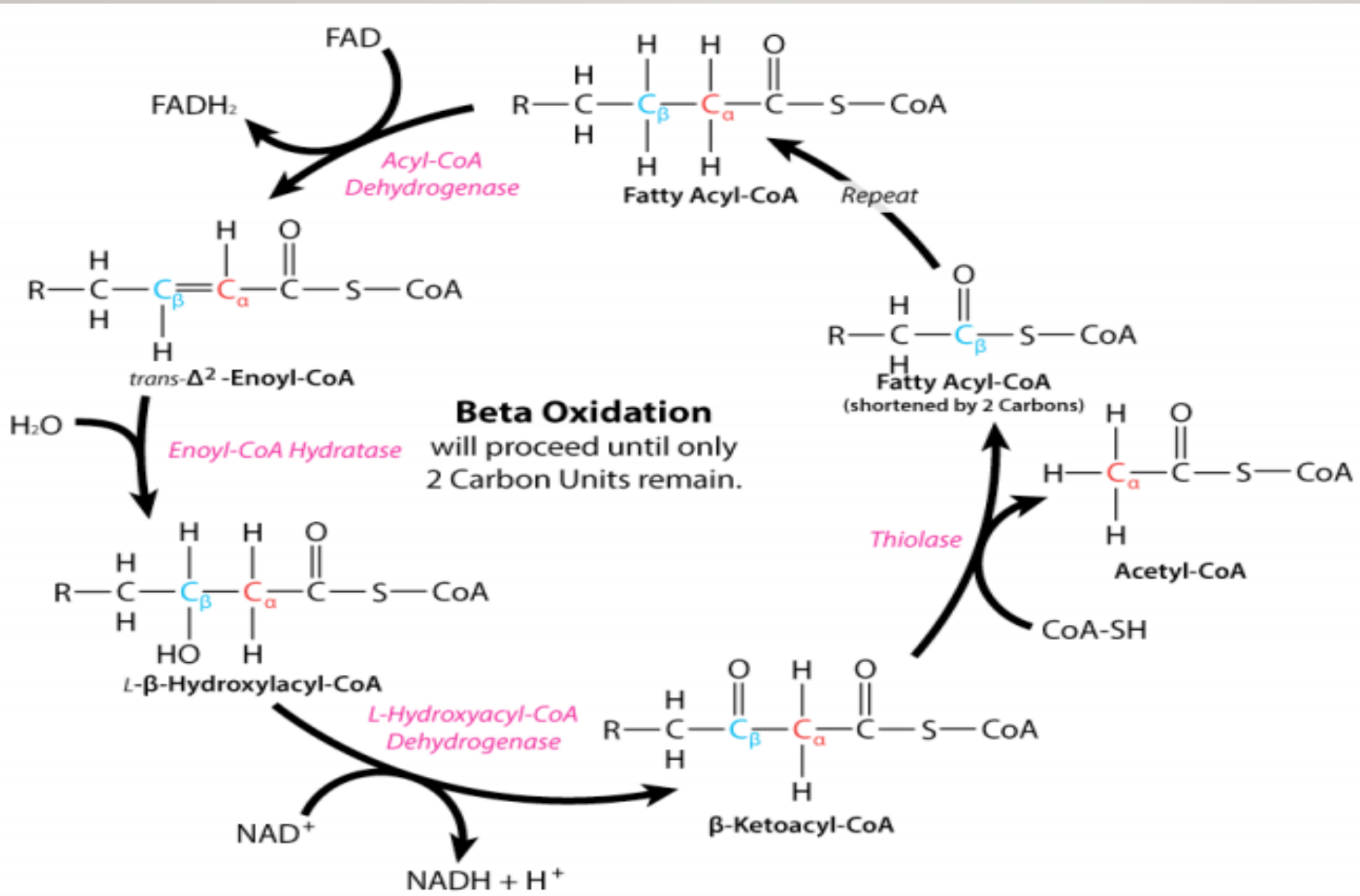


Figure : Beta Oxidation of Fatty Acids

Reactions two and three in beta oxidation are catalyzed by enoyl-CoA hydratase and 3-hydroxyacyl-CoA dehydrogenase, respectively. The latter reaction yields an NADH. The final enzyme of beta oxidation is thiolase and this enzyme is notable in not only catalyzing the formation of acetyl-CoAs in beta oxidation, but also catalyzing the joining of two acetyl-CoAs (essentially the reversal of the last step of beta oxidation) to form acetoacetyl-CoA– essential for the pathways of ketone body synthesis and cholesterol biosynthesis.

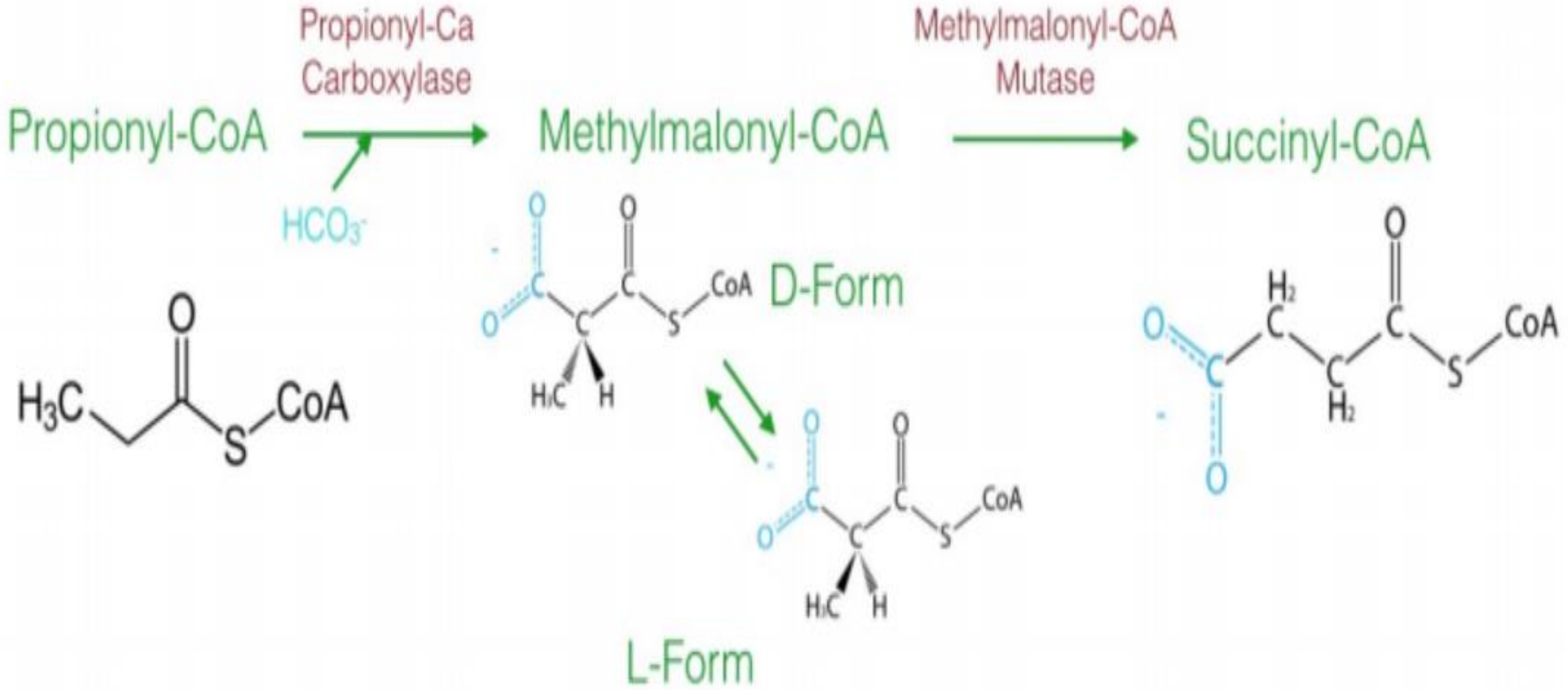
Oxidation of Odd-Chain Fatty Acids

Though most fatty acids of biological origin have even numbers of carbons, not all of them do. Oxidation of fatty acids with odd numbers of carbons ultimately produces an intermediate with three carbons called propionyl-CoA, which cannot be oxidized further in the beta-oxidation pathway. Metabolism of this intermediate is odd. Sequentially, the following steps occur:

carboxylation to make D-methylmalonyl-CoA;

isomerization to L-methylmalonyl-CoA;

rearrangement to form succinyl-CoA. The last step of the process utilizes the enzyme methylmalonyl-CoA mutase, which uses the B12 coenzyme in its catalytic cycle. Succinyl-CoA can then be metabolized in the citric acid cycle.



UNSASURATED FATTY ACID OXIDATION

On the other hand, if beta oxidation produces an intermediate with a cis double bond between carbons four and five, the first step of beta oxidation (dehydrogenation between carbons two and three) occurs to produce an intermediate with a trans double bond between carbons two and three and a cis double bond between carbons four and five. The enzyme 2,4 dienoyl CoA reductase reduces this intermediate (using NADPH) to one with a single cis bond between carbons three and four. This intermediate is then identical to the one acted on by cis- Δ 3-Enoyl-CoA Isomerase above, which converts it into a regular beta oxidation intermediate, as noted above.

Alpha Oxidation

Yet another consideration for oxidation of fatty acids is alpha oxidation. This pathway is necessary for catabolism of fatty acids that have branches in their chains. For example, breakdown of chlorophyll's phytol group yields phytanic acid, which undergoes hydroxylation and oxidation on carbon number two (in contrast to carbon three of beta oxidation), followed by decarboxylation and production of a branched intermediate that can be further oxidized by the beta oxidation pathway. Though alpha oxidation is a relatively minor metabolic pathway, the inability to perform the reactions of the pathway leads to Refsum's disease where accumulation of phytanic acid leads to neurological damage.

FATTY ACID SYNTHESIS

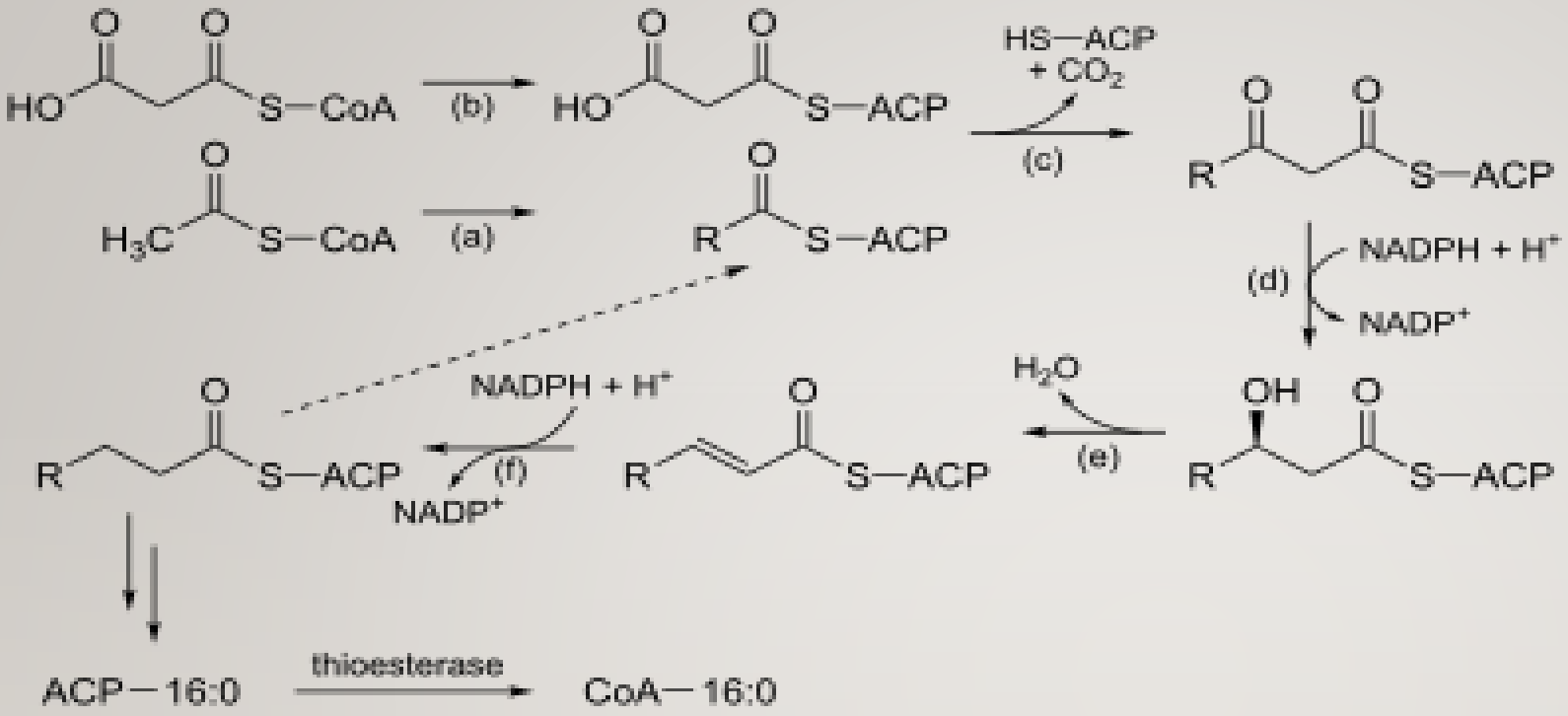
Fatty acid synthesis is the creation of fatty acids from acetyl-CoA and NADPH through the action of enzymes called fatty acid synthases. This process takes place in the cytoplasm of the cell. Most of the acetyl-CoA which is converted into fatty acids is derived from carbohydrates via the glycolytic pathway. The glycolytic pathway also provides the glycerol with which three fatty acids can combine (by means of ester bonds) to form triglycerides (also known as "triacylglycerols" – to distinguish them from fatty "acids" – or simply as "fat"), the final product of the lipogenic process. When only two fatty acids combine with glycerol and the third alcohol group is phosphorylated with a group such as phosphatidylcholine, a phospholipid is formed. Phospholipids form the bulk of the lipid bilayers that make up cell membranes and surround the organelles within the cells (e.g. the cell nucleus, mitochondria, endoplasmic reticulum, Golgi apparatus etc.)

Straight-chain fatty acids

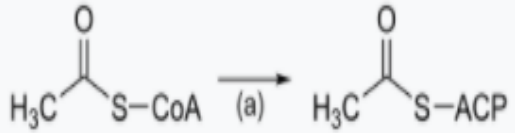
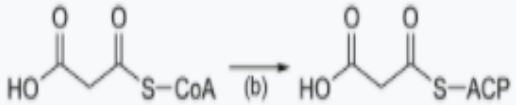
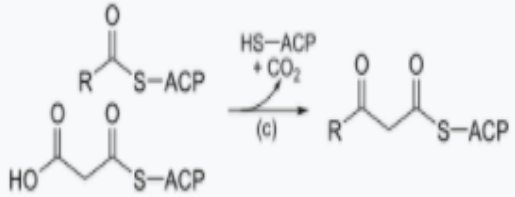
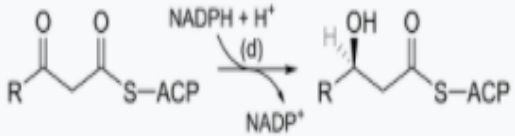
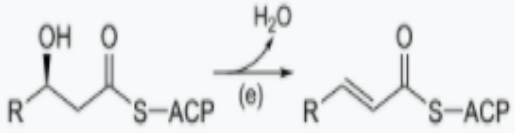
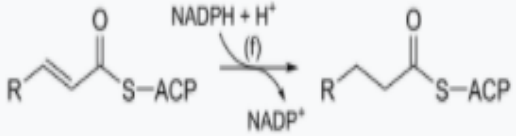
Much like β-oxidation, straight-chain fatty acid synthesis occurs via the six recurring reactions shown below, until the 16-carbon palmitic acid is produced.

The diagrams presented show how fatty acids are synthesized in microorganisms and list the enzymes found in Escherichia coli. These reactions are performed by fatty acid synthase II (FASII), which in general contain multiple enzymes that act as one complex. FASII is present in prokaryotes, plants, fungi, and parasites, as well as in mitochondria.

In animals, as well as some fungi such as yeast, these same reactions occur on fatty acid synthase I (FASI), a large dimeric protein that has all of the enzymatic activities required to create a fatty acid. FASI is less efficient than FASII; however, it allows for the formation of more molecules, including "medium-chain" fatty acids via early chain termination.



Once a 16:0 carbon fatty acid has been formed, it can undergo a number of modifications, resulting in desaturation and/or elongation. Elongation, starting with stearate (18:0), is performed mainly in the ER by several membrane-bound enzymes. The enzymatic steps involved in the elongation process are principally the same as those carried out by FAS, but the four principal

Step	Enzyme	Reaction	Description
(a)	Acetyl CoA:ACP transacylase		Activates acetyl CoA for reaction with malonyl-ACP
(b)	Malonyl CoA:ACP transacylase		Activates malonyl CoA for reaction with acetyl-ACP
(c)	3-ketoacyl-ACP synthase		Reacts ACP-bound acyl chain with chain-extending malonyl-ACP
(d)	3-ketoacyl-ACP reductase		Reduces the carbon 3 ketone to a hydroxyl group
(e)	3-Hydroxyacyl ACP dehydrase		Eliminates water
(f)	Enoyl-ACP reductase		Reduces the C2-C3 double bond.

Abbreviations: ACP – Acyl carrier protein, CoA – Coenzyme A, NADP – Nicotinamide adenine dinucleotide phosphate.

during fatty synthesis the reducing agent is NADPH, whereas NAD is the oxidizing agent in beta-oxidation (the breakdown of fatty acids to acetyl-CoA). This difference exemplifies a general principle that NADPH is consumed during biosynthetic reactions, whereas NADH is generated in energy-yielding reactions.[6] (Thus NADPH is also required for the synthesis of cholesterol from acetyl-CoA; while NADH is generated during glycolysis.) The source of the NADPH is two-fold. When malate is oxidatively decarboxylated by "NADP+-linked malic enzyme" to form pyruvate, CO2 and NADPH are formed. NADPH is also formed by the pentose phosphate pathway which converts glucose into ribose, which can be used in synthesis of nucleotides and nucleic acids, or it can be catabolized to pyruvate

Conversion of carbohydrates into fatty acids

De novo synthesis § Fatty-acid

In humans, fatty acids are formed from carbohydrates predominantly in the liver and adipose tissue, as well as in the mammary glands during lactation.

The pyruvate produced by glycolysis is an important intermediary in the conversion of carbohydrates into fatty acids and cholesterol.

This occurs via the conversion of pyruvate into acetyl-CoA in the mitochondrion. However, this acetyl CoA needs to be transported into cytosol where the synthesis of fatty acids and cholesterol occurs. This cannot occur directly. To obtain cytosolic acetyl-CoA, citrate (produced by the condensation of acetyl CoA with oxaloacetate) is removed from the citric acid cycle and carried across the inner mitochondrial membrane into the cytosol.

There it is cleaved by ATP citrate lyase into acetyl-CoA and oxaloacetate. The oxaloacetate can be used for gluconeogenesis (in the liver), or it can be returned into mitochondrion as malate.

The cytosolic acetyl-CoA is carboxylated by acetyl CoA carboxylase into malonyl CoA, the first committed step in the synthesis of fatty acids.

Unsaturated straight chain fatty acids

Anaerobic desaturation

Many bacteria use the anaerobic pathway for synthesizing unsaturated fatty acids. This pathway does not utilize oxygen and is dependent on enzymes to insert the double bond before elongation utilizing the normal fatty acid synthesis machinery. In Escherichia coli, this pathway is well understood.

FabA is a β-hydroxydecanoyl-ACP dehydrase – it is specific for the 10-carbon saturated fatty acid synthesis intermediate (β-hydroxydecanoyl-ACP).

FabA catalyzes the dehydration of β-hydroxydecanoyl-ACP, causing the release of water and insertion of the double bond between C7 and C8 counting from the methyl end. This creates the trans-2-decenoyl intermediate.

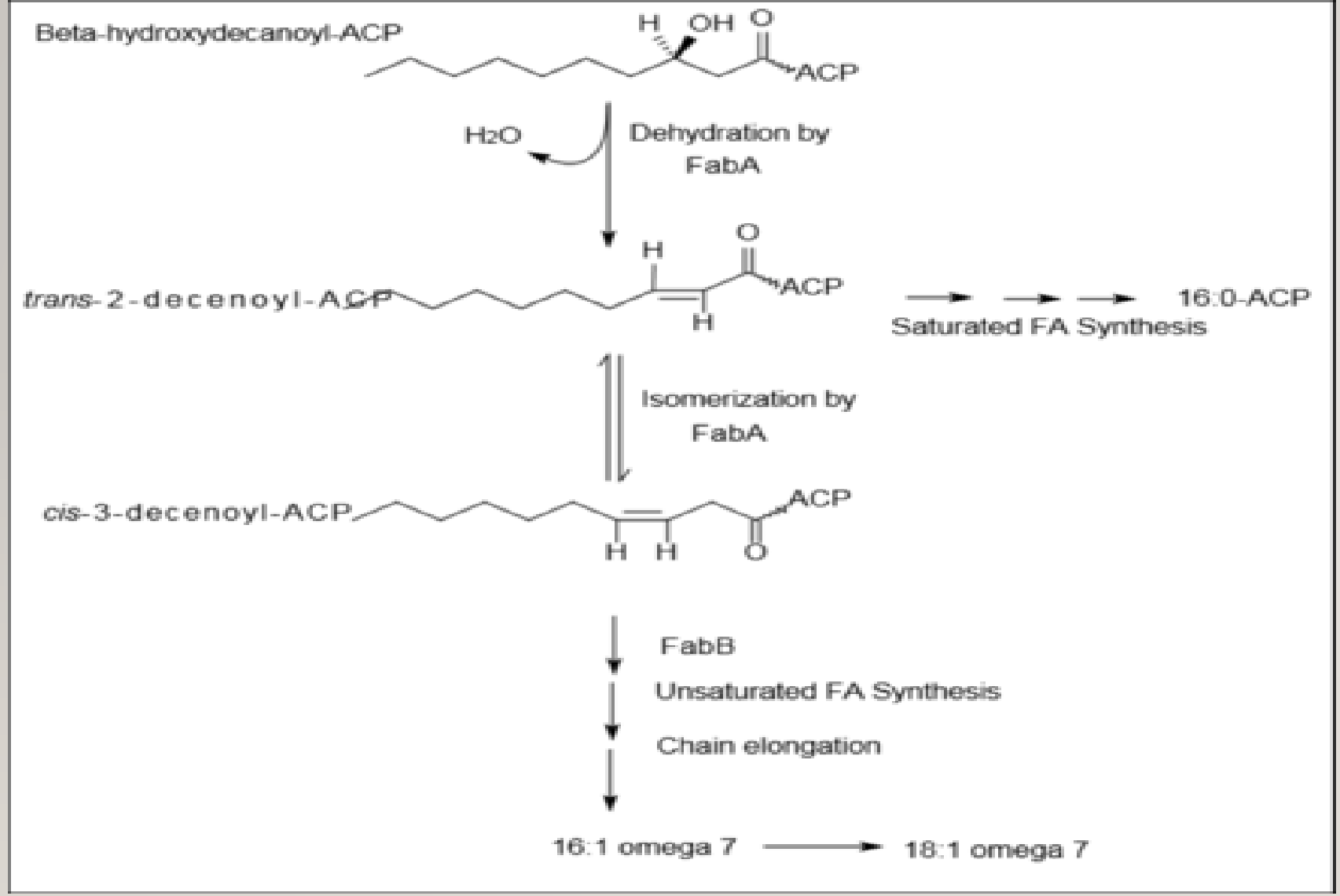
Either the trans-2-decenoyl intermediate can be shunted to the normal saturated fatty acid synthesis pathway by FabB,

where the double bond will be hydrolyzed and the final product will be a saturated fatty acid, or FabA will catalyze the isomerization into the cis-3-decenoyl intermediate.

FabB is a β-ketoacyl-ACP synthase that elongates and channels intermediates into the mainstream fatty acid synthesis pathway. When FabB reacts with the cis-decenoyl intermediate, the final product after elongation will be an unsaturated fatty acid.

The two main unsaturated fatty acids made are Palmitoleoyl-ACP (16:1ω7) and cis-vaccenoyl-ACP (18:1ω7)

Most bacteria that undergo anaerobic desaturation contain homologues of FabA and FabB. Clostridia are the main exception; they have a novel enzyme, yet to be identified, that catalyzes the formation of the cis double bond.



Synthesis of unsaturated fatty acids via anaerobic desaturation

Omega-alicyclic fatty acids

Omega-alicyclic fatty acids typically contain an omega-terminal propyl or butyryl cyclic group and are some of the major membrane fatty acids found in several species of bacteria. The fatty acid synthetase used to produce omega-alicyclic fatty acids is also used to produce membrane branched-chain fatty acids. In bacteria with membranes composed mainly of omega-alicyclic fatty acids, the supply of cyclic carboxylic acid-CoA esters is much greater than that of branched-chain primers.

The synthesis of cyclic primers is not well understood but it has been suggested that mechanism involves the conversion of sugars to shikimic acid which is then converted to cyclohexylcarboxylic acid-CoA esters that serve as primers for omega-alicyclic fatty acid synthesis

THANK YOU