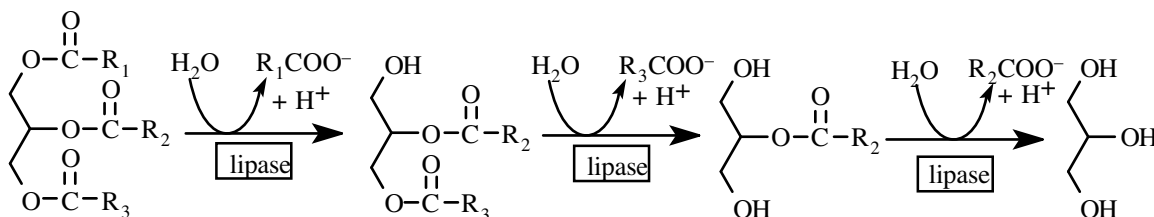


**Lipid Metabolism:** Now that we are aware of the types of lipids in our bodies, it is important to see how we make them or break them. We will start our discussion with **triacylglyceride degradation**, and move on to **fatty acid degradation**, which leads us back to the T.C.A. cycle. Then, we will talk about **lipid anabolism**.

**Triglyceride Degradation:** Since triglycerides are made of fatty acids and glycerol, the first step in metabolizing the lipid is to separate the fatty acid from the glycerol. The reaction (which when done using standard chemical techniques is called **saponification**) is an enzyme catalyzed hydrolysis which occurs in the adipose tissue, and is regulated by hormones.

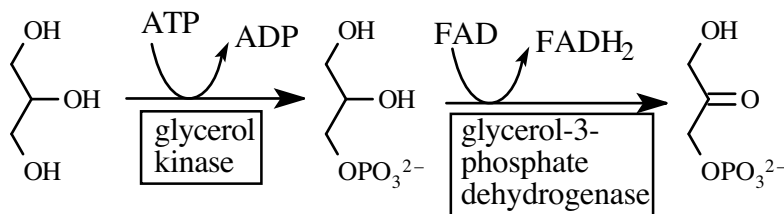
The enzyme that does the hydration is called **lipase**, and it is activated by phosphorylation. The process is a three step mechanism, where the "outer" fatty acids are removed first, then the center one:



The free fatty acids are released into the blood stream where they are picked up by the transport protein **albumin**.

Before we talk about the fatty acid degradation, it is interesting to look at the activation of the lipase. The normal, "inactive" form of the enzyme is called lipase b. The hormones (e.g. **adrenaline** or **glucagon**) activate a membrane protein (known as the **G<sub>s</sub>** complex) which in turn stimulates the production of a cofactor called **cAMP** (cyclic AMP, where the M stands for "mono"). This cAMP binds to another inactive enzyme, a protein kinase, which exists as a complex of two subunits - the enzyme and a regulatory subunit. The cAMP causes the regulatory unit to dissociate from the enzyme, leaving an active kinase. The kinase then phosphorylates lipase b to give the active lipase a.

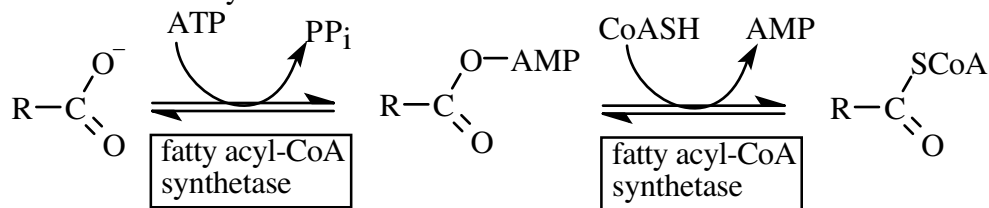
**Glycerine Metabolism:** Before we talk about the fatty acids, we should mention that the glycerol that is formed is two steps away from DHAP. The first step of the process is that the glycerol is phosphorylated; the glycerol-3-phosphate is further dehydrogenated to form DHAP:



This DHAP is metabolically no different from that produced in glycolysis. Therefore, it is converted to glyceraldehyde-3-P, and subsequently to acetyl CoA.

**Fatty Acid Catabolism:** Almost 100 years ago, the initial work on fatty acid metabolism was investigated by Franz Knoop (a German proto-bio-chemist). This work led to the  **$\beta$ -oxidation pathway**, which we will see below. However, it took about 50 years before the enzymatic description of this pathway was established. The short version of Knoop's work is that the second carbon from the acid group of the fatty acid (i.e. carbon 3, where carbon 1 is the carboxylic carbon) gets oxidized, and the fatty acid gets **cleaved** between the 2<sup>nd</sup> and 3<sup>rd</sup> carbons (the so-called  $\alpha$  and  $\beta$  carbons) to form a shorter fatty acid. The process continues until the whole fatty acid chain has been converted into units of two carbons. The fate of these 2-carbon units, as we will see, is that they enter the TCA cycle.

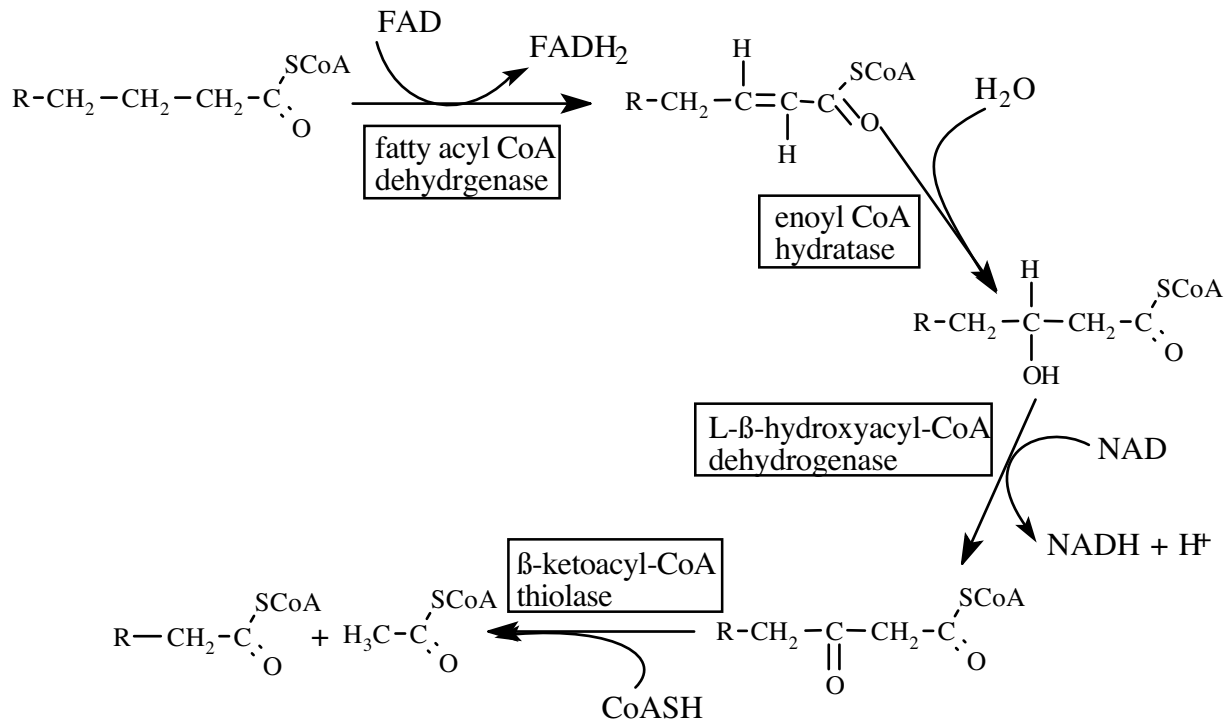
The actual process was discovered by the work of many people, most notably Albert Lehninger, a pioneer in the field of biochemistry (who either discovered the mitochondrion, or figured out what it was used for). The process involves making "fatty acyl CoA" from the fatty acid:



The side product  $\text{PP}_i$  is called **pyrophosphate**, and consists of two phosphates bound together. It is called "pyro" because it is a fairly reactive species.

The fatty acyl CoA is transported into the mitochondrion in a two step process, where it is then subject to the degradation process we are about to discuss. It is interesting to note that shorter fatty acids do not enter via the same route as the longer chain ones. Also, there are several diseases associated with the inability (or difficulty) to transfer longer chain fatty acids into the mitochondria. The symptoms are usually muscle cramps and weakness.

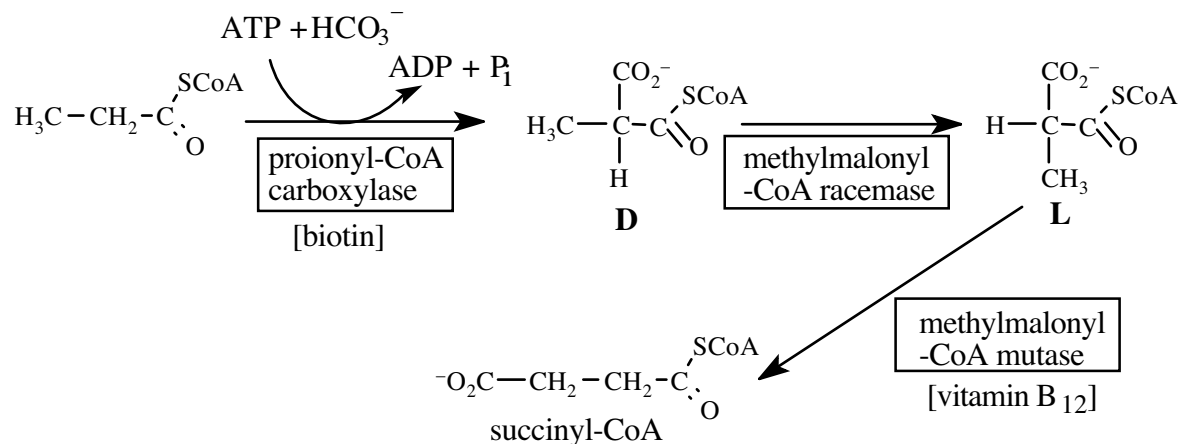
Once in the mitochondrial matrix, the  $\beta$ -oxidation pathway can start. The process can be summarized by the following list of steps: dehydrogenation, hydration, oxidation, and thio-acyl cleavage (i.e. breaking the molecule by making a thio ester bond). There is a slight difference, as we will see, between saturated and unsaturated fatty acids:



This pathway is very similar to the first few steps of the Krebs cycle.

For unsaturated fatty acids, the position and type of double bond makes a difference. In the pathway above, the first dehydrogenase produces a trans double bond. If the unsaturated fatty acid has a cis double bond, the enzyme **enoyl-CoA isomerase** is used to make it trans. Similarly, if there are two adjacent double bonds (either naturally or due to the dehydrogenation process), the one further from the CoA must be hydrogenated to allow for the next step. Thus, the enzyme **2,4,dienoyl-CoA reductase** is used (with  $NADPH$  and  $H^+$ ) to give the hydrogenated product (and  $NADP$ ).

Odd chain fatty acids also add a little "wrinkle" into the mix. The last molecule remaining after the fatty acid is transformed into molecules of acetyl CoA has three carbons (**propanoyl CoA**). This molecule cannot enter the Krebs cycle as acetyl CoA. Instead, it undergoes the following series of steps:

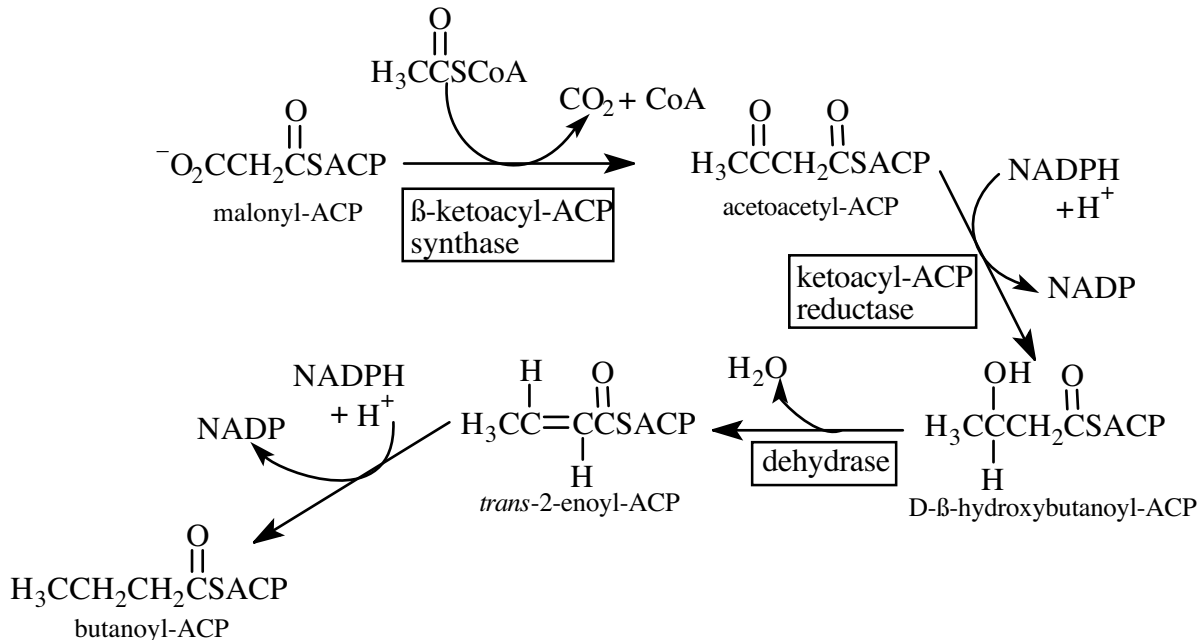


The cofactors are written in brackets below the enzymes.

**Fatty Acid Synthesis:** Since we have discussed how to catabolize fatty acids, we will switch our attention briefly to the anabolism of fats. As we know, energy is stored in the body as fat, regardless of what we eat. That is not to say that fat is fuel, like ATP. Rather, fat catabolism produces many ATP. But if the ATP is not being used, they cannot be stored. Instead, the body produces fat, which can be catabolized when needed.

The starting point of fatty acid synthesis is, not surprisingly, acetyl CoA. However, the synthesis is not simply the reverse of the degradation. Instead, the acetyl CoA is carboxylated (i.e. another  $\text{-COO}^-$  is added to form **malonyl-CoA**) via a two step enzymatic process. The enzyme (**acetyl-CoA carboxylase**) has a biotin molecule bound to a lysine **residue**. The biotin is carboxylated by adding **bicarbonate**,  $\text{HCO}_3^-$ , in a process that requires 1 ATP. The carboxylated enzyme transfers the carboxylic group to acetyl CoA. The next step involves swapping the CoA for a protein called an **acyl carrier protein**, or **ACP** for short, which is the "active form" of the malonate molecule, i.e. malonyl-ACP.

The subsequent steps involve a **condensation**, **reduction**, **dehydration**, and another **reduction**. The resulting molecule can then continue the process. These steps are illustrated below. It should be pointed out that acetyl-CoA or acetyl-ACP can be used in the synthesis, but only the CoA is shown in my diagram.

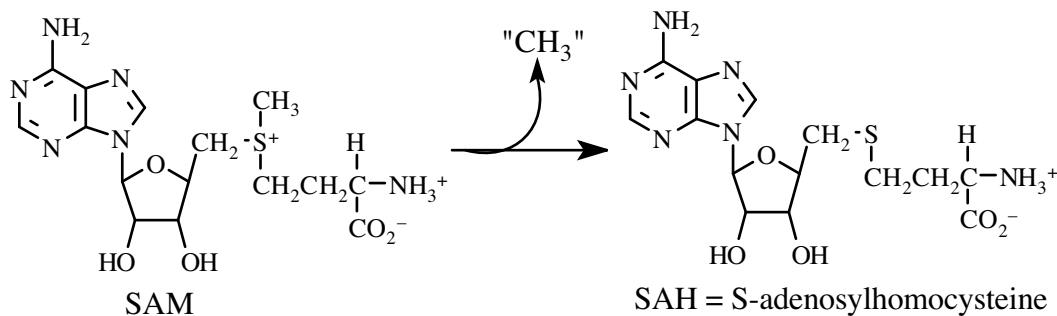


The butanoyl-ACP takes the place of the acetyl-CoA in the next step of the synthesis. The enzymes listed in the pathway above are actually those found in bacteria. In higher animals, the enzymes have complexed together to form one unit known collectively as **fatty acid synthase**. Once the long chain saturated fatty acid is synthesized, double

bonds can be introduced by **oxidative desaturation**, where  $O_2$ ,  $NADH/H^+$ , and two Hs from the fatty acid react to produce  $2 H_2O$ ,  $NAD$ , and the mono-unsaturated fatty acid.

**Triglyceride Synthesis:** To produce the fat that is actually stored, the fatty acids must combine with glycerol. The active form of glycerol is the glycerol-3-phosphate, and the active fatty acid is a acyl-CoA. Once two esters are formed, the molecule dephosphorylates, and subsequently picks up another fatty acid. Thus, phospho-lipids are intermediates to triacyl glycerides.

**S-Adenosyl Methionine (SAM)** - This molecule is formed by combining ATP with methionine, and it serves as a **methyl group donor**. This property is due to the "activated" nature of the thio-ether containing the methyl group:



The methylation generally occurs in conjunction with phospholipid and neurotransmitter synthesis. One common use of the methyl group is forming phosphatidyl choline from phosphatidyl ethanolamine. (Similarly, the reverse is possible, i.e. choline donates its methyl group to SAH to produce SAM, which is a source of methionine.) In mammals, this is the sole manner in which choline is formed. SAM also is used in converting Norepinephrine to Epinephrine (adrenaline).

Homework:

Chapter 25 3<sup>rd</sup> ed.: 21, 32, 34, 37, 39, 41