

Fatty Acid Metabolism III—updated 12 Oct. 2004

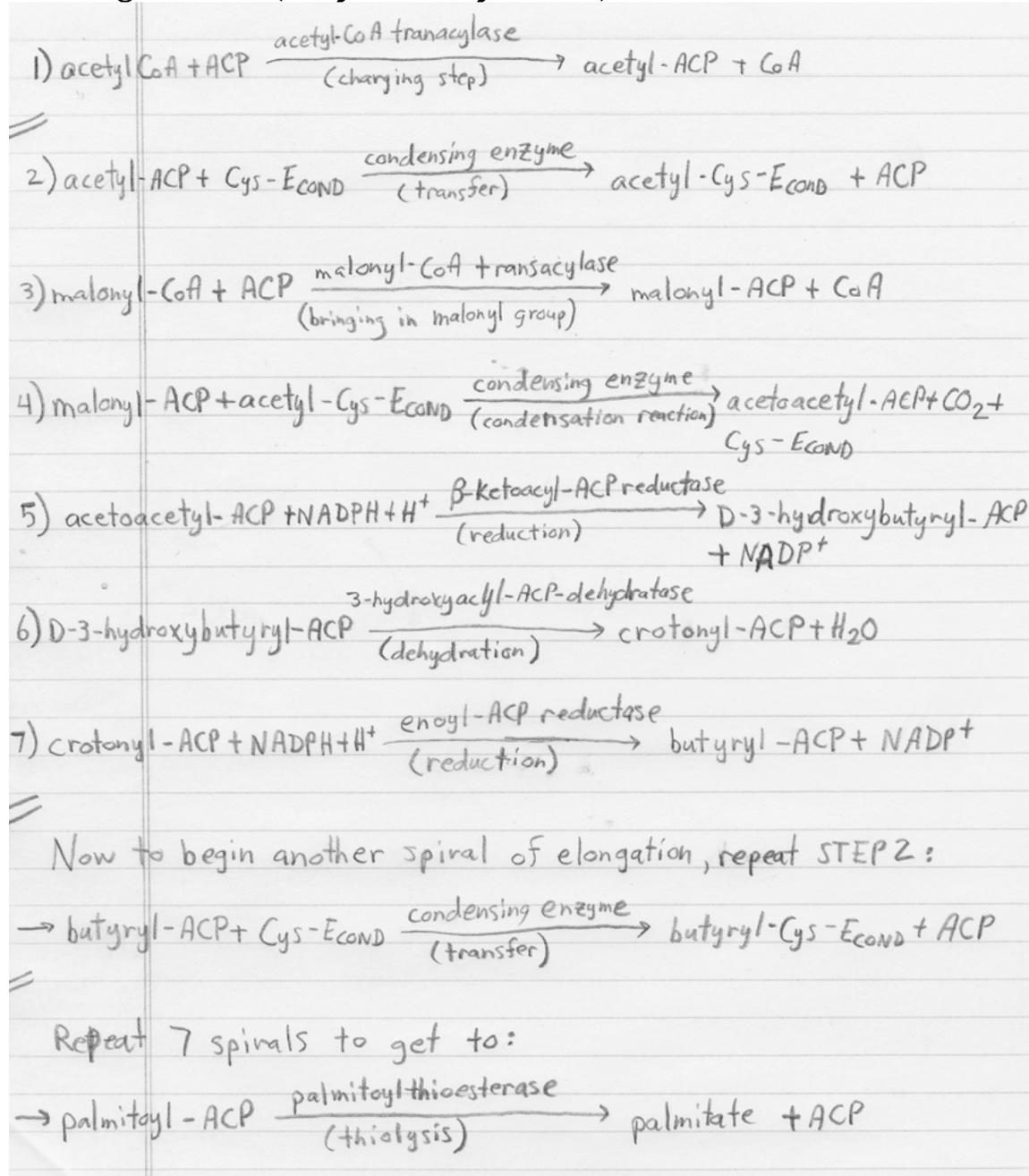
1) What is the committed step in FA synthesis?

The committed step is the formation of malonyl CoA from acetyl CoA and bicarbonate in a reaction catalyzed by acetyl CoA carboxylase (ACC).

How is ACC regulated?

malonyl CoA and palmitoyl CoA are allosteric inhibitors of ACC and citrate is an allosteric activator of ACC. ACC is also regulated by phosphorylation. AMP-activated protein kinase phosphorylates ACC and inactivates it and this occurs when the level of AMP in the cell only slightly rises. Its not clear if AMP-activated kinase is important in vivo. It is also regulated hormonally. Epinephrine and glucagon can activate cAMP-dependent protein kinase (a.k.a. protein kinase A) that phosphorylates ACC and turns it off and insulin activates a protein phosphatase that dephosphorylates ACC and turns it on.

2) Draw one round of fatty acid synthesis starting with an uncharged FAS (fatty acid synthase).



There are two steps that occur one time each in the synthesis of palmitate. What are they?

The addition of the acetyl group from acetyl CoA to ACP to begin the cycle (all other additions come from malonyl CoA) and thiolysis to cleave palmitate from the ACP.

3) Where does FA elongation occur?

The enzymes are found on the cytoplasmic surface of the ER membrane.

Note that fatty acid synthesis occurs in the cytoplasm.

What are the similarities in the biosynthetic pathways of FA elongation on the RER and FA synthesis by FAS?

a. Condensation of malonyl CoA with fatty acyl CoA by acyl-malonyl CoA condensing enzyme to form a α -ketoacyl CoA. This is very similar to the condensation reaction of FAS except that the acyl group and the malonyl group are attached to CoA and not to ACP and the reactive cysteine of the FAS condensing enzyme.

b. Reduction of the C3 keto group that consumes a molecule of NADPH--just like in FAS but with a different enzyme.

c. Dehydration to form a C2=C3 double bond--just like in FAS but with a different enzyme.

d. Reduction of the C2=C3 double bond again with the consumption of another molecule of NADPH--just like in FAS but with a different enzyme.

Why can't a double bond be inserted after position C9 of a fatty acid?

The desaturase enzymes cannot use fatty acids shorter than 16 carbon atoms long and cannot place them closer than 6 carbon atoms from the omega end. For palmitate (16:0) that means that you could not insert the double bond between atoms C10 and C11 (C11 is less than 6 carbon atoms from the omega end), but could insert one between C9 and C10.

A typical question is to give you a list of fatty acids of different lengths and with various degrees of unsaturation and ask you to pick which one can be made from glucose.

To solve that kind of problem, look at the closest double bond to the omega end. If it is less than 6 carbon atoms away it cannot be made in man.

Also, look at the double bond positions. They cannot be closer than 3 carbon atoms apart.

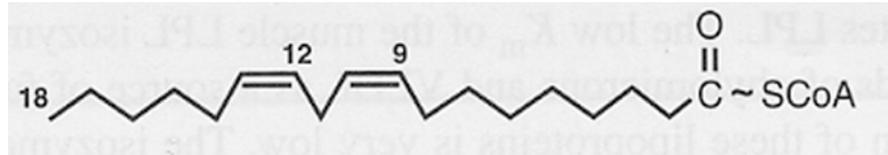
Next, look at the locations of the C=C. There are 3 desaturases that we discussed in class as being present in man: delta-5, delta-6 and delta-9. There is actually a fourth one present in man delta-4, but it is used only in desaturating very long chain fatty acids (C22 and longer) present in sphingolipids. This last one was not discussed in lecture i.e. its not testable.

Finally, look at the chain length. Generally, they should be C14 or longer (Myristate is not an essential FA. Therefore, the tiny amount needed for myristylation of proteins must be able to be obtained by removing 2 carbon atoms from the carboxyl terminal end of C16 OR lack of myristylation doesn't cause human disease), but if they are C12 or shorter it would be difficult to synthesize them from glucose to any significant extent.

Palmitate, C16 is the end product of FAS. To get down to a C12, you have to partially α -oxidizing the FA and then stop (either in the mitochondria or the peroxisome). This is unlikely to occur to any significant extent physiologically unless there is a defect in the normal beta-oxidation of fatty acids. LCAD deficiency is one instance where oxidation of long chain fatty acids to C12 and shorter may occur in the peroxisome. Some of these shorter chain fatty acids can escape the peroxisome under these conditions.

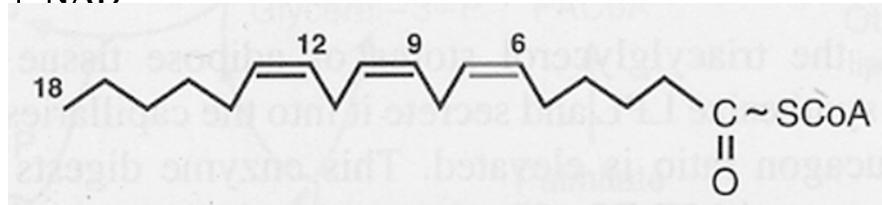
4. Draw the biosynthetic pathway from linoleate to arachidonate.

STEP 1) Acyl CoA Synthetase
Linoleate (from the diet) + ATP -----> AMP + PPI + Linoleoyl CoA



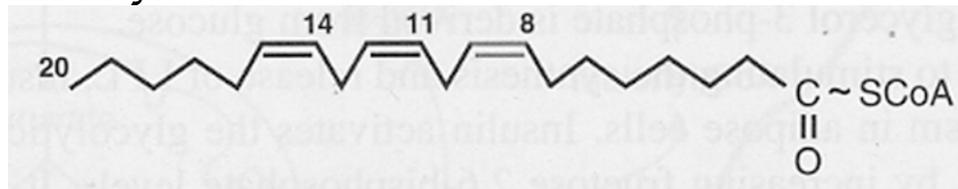
Structure of Linoleoyl CoA is above

STEP 2) Delta6 Desaturase
Linoleoyl CoA + O₂ + NADH + H⁺ -----> Δ Linoleoyl CoA + 2H₂O + NAD⁺



Structure of Δ Linoleoyl CoA is above

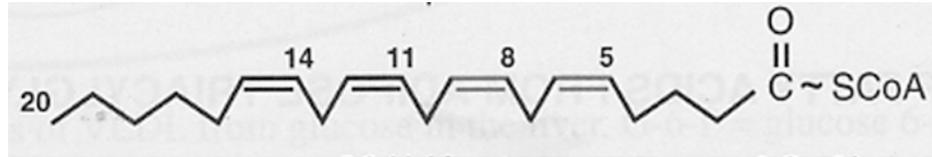
STEP 3) Elongase
 Δ Linoleoyl CoA + malonyl CoA -----> CO₂ + CoA + dihomo- Δ Linoleoyl CoA



Structure of dihomo- Δ Linoleoyl CoA is above

STEP 4)

dihomo- ω -Linoleoyl CoA + O₂ + NADH + H⁺ $\xrightarrow{\text{Delta5 Desaturase}}$ arachidonyl CoA



Structure of arachidonyl CoA is above

To generate a free molecule of arachidonate, thioesterase can cleave off the CoA and liberate arachidonate. Usually the arachidonyl CoA would be used as a substrate to donate the arachidonate to the second position of a glycerophospholipid or triacylglycerol.

This pathway is a common pathway tested on medical board style exams. You will want to memorize this before the shelf exam.

5) What is essential fatty acid deficiency and what are its symptoms? Essential fatty acid deficiency results from a lack of linoleate and/or linolenate in the diet. It is exceedingly uncommon in any western nation but can occur in infants that are not breast fed but fed rice water which is lacking in essential amino acids. Affected individuals present initially with dry, scaly skin that later begins peeling and puslike fluid seeps from areas around skinfolds. Long-term deprivation can result in neurologic conditions including numbness, blurred vision, leg pain and the inability to walk