Topic - Biosynthesis of Palmitic acid

- ✓ Lipid which is considered as a principal form of stored energy, is the major component of phospholipid bilayer Plasma Membrane.
- ✓ Liver, Kidney, adipose tissue and lactating mammary glands are the organs where de novo synthesis of fatty acid occurs.
- ✓ Site for Fatty acid biosynthesis is cytosol.
- ✓ **Prerequisite for Fatty acid biosynthesis include following things**
- ✓ 1. Acetyl CoA
- ✓ 2. NADPH.
- ✓ 3. ATP
- ✓ **Fatty acid biosynthesis can be understand in 3 stages:-**

- ✓ **1. Production of Acetyl CoA and NADPH.**
- ✓ **2. Conversion of Acetyl CoA to malonyl CoA**
- ✓ **3. Reactions which are catalyzed by Fatty Acid Synthase complex.**
- ✓

What is Fatty acid synthase enzyme?

- ✓ **Fatty Acid Synthase complex is a multifunctional enzyme which is made up of dimer with two identical subunits including ACP (Acyl Carrier Protein). ACP is responsible for transfer of acyl group from acetyl CoA and 2 carbon fragment from malonyl CoA for the elongation of carbon chain required for fatty acid biosynthesis like 16 Carbon compounds called palmitate.**

Fatty acid synthase complex is made up of

- ✓ **1. Acetyl transacylase**
- ✓ **2. Malonyl transacylase**

- ✓ **3. Ketoacyl synthase**
- ✓ **4. Ketoacyl reductase**
- ✓ **5. Dehydratase**
- ✓ **6. Enoyl reductase.**
- ✓ **7. Thioesterase.**

Production of Acetyl CoA and NADPH

Acetyl CoA is produced in mitochondria by oxidation of pyruvate (PDH complex) and oxidation of fatty acid.

Oxidation of fatty acid gives 8 molecules of acetyl CoA.

But the problem is that acetyl CoA cannot permeable to mitochondria as it has to go cytosol for FAB.

So, in mitochondria, acetyl CoA condense with OAA to form citrate.

Citrate can pass through mitochondrial membrane and comes to cytosol where an enzyme called citrate lyase cleaved citrate into OAA and Acetyl CoA.

OAA is converted into malate in cytosol and malate into pyruvate by malic enzyme with NADPH formation which is a reducing equivalent and required for fatty acid biosynthesis.

Formation of malonyl CoA

It is formed by carboxylation of acetyl CoA by an enzyme called acetyl CoA carboxylase.

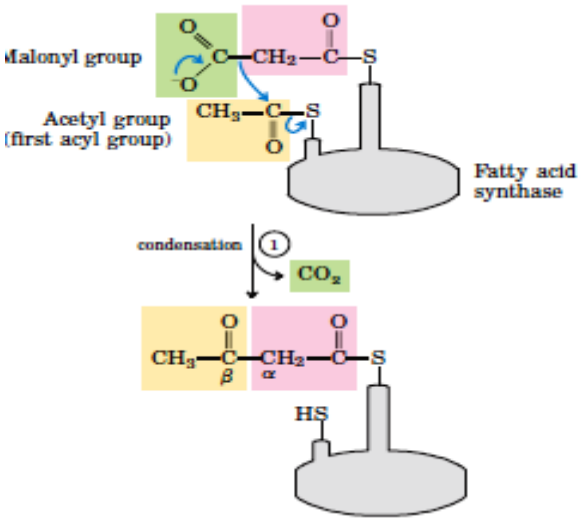
This enzyme is a ATP dependent and requires biotin as a cofactor.

Reactions which are catalyzed by Fatty Acid Synthase complex to form long chain fatty acid called Palmitic acid/Palmitate.

Acyl group from acetyl CoA and malonyl group from malonyl CoA is transferred to fatty acid synthase complex by Acetyl CoA-ACP transacylase and Malonyl CoA-ACP transacylase.

Step 1 . CONDENSATION RACTION

Acyl (from acetyl CoA) which is the first acyl group and 2 carbon derived from malonyl extends the acyl chain by 2 carbons so this condensation of both molecules is associated with decarboxylation and product form is **Beta ketobutyryl-ACP. Enzyme is Beta ketoacyl-ACP synthase.**

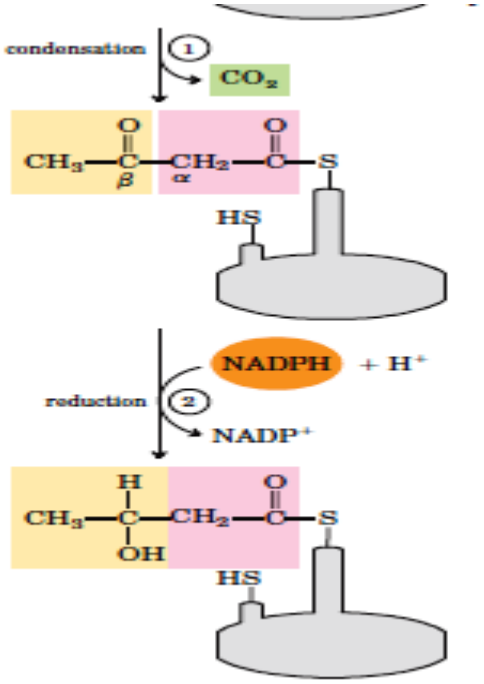


(Adapted from Lehninger)

Step 2 . Reduction Reaction

Beta ketobutyryl-ACP is then undergo reduction and ketoacyl group is turned into hydroxyl group. Electron donar is NADPH. Enzyme is beta ketoacyl-ACP reductase.

Final product is Beta hydroxybutyryl-ACP



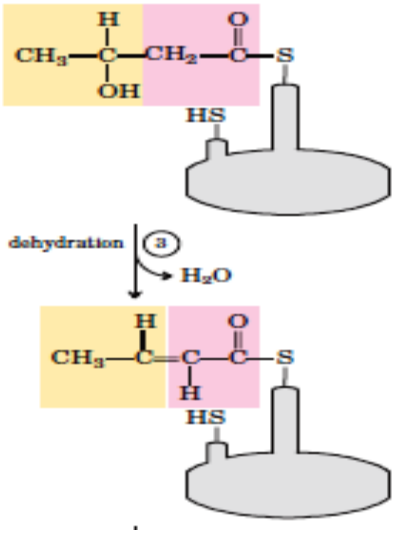
(Adapted from Lehninger)

Step 3 . Dehydration reaction

Beta hydroxybutyryl ACP undergoes dehydration and forms enoyl ACP. Enzyme is Beta hydroxyacyl-ACP dehydratase.

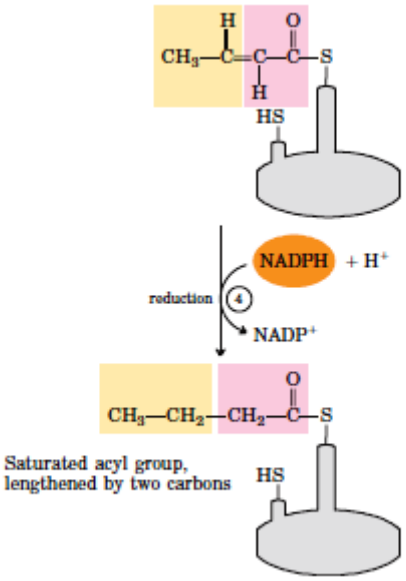
Elimination of water takes place during dehydration reaction.

Product formed will be butenoyl-ACP.



Step 4. Reduction reaction

Enoyl ACP reductase catalyses this reaction using NADPH as a reducing equivalent and forms Acyl ACP.



The 4 carbon unit attached to ACP is butyryl. ACP is the carrier molecule which has to transfer carbon chain to cysteine part of Fatty acid synthase enzyme complex and in this way the above mentioned reactions repeated 6 more times.

Note- total 7 times reactions repeated to form 16 Carbon palmitate molecule. In EACH time, chain is elongated by 2 carbon unit. Then finally, palmitoyl thioesterase separates palmitate from ACP. In this way a fully saturated 16 carbon compound is formed which is called Palmitate.

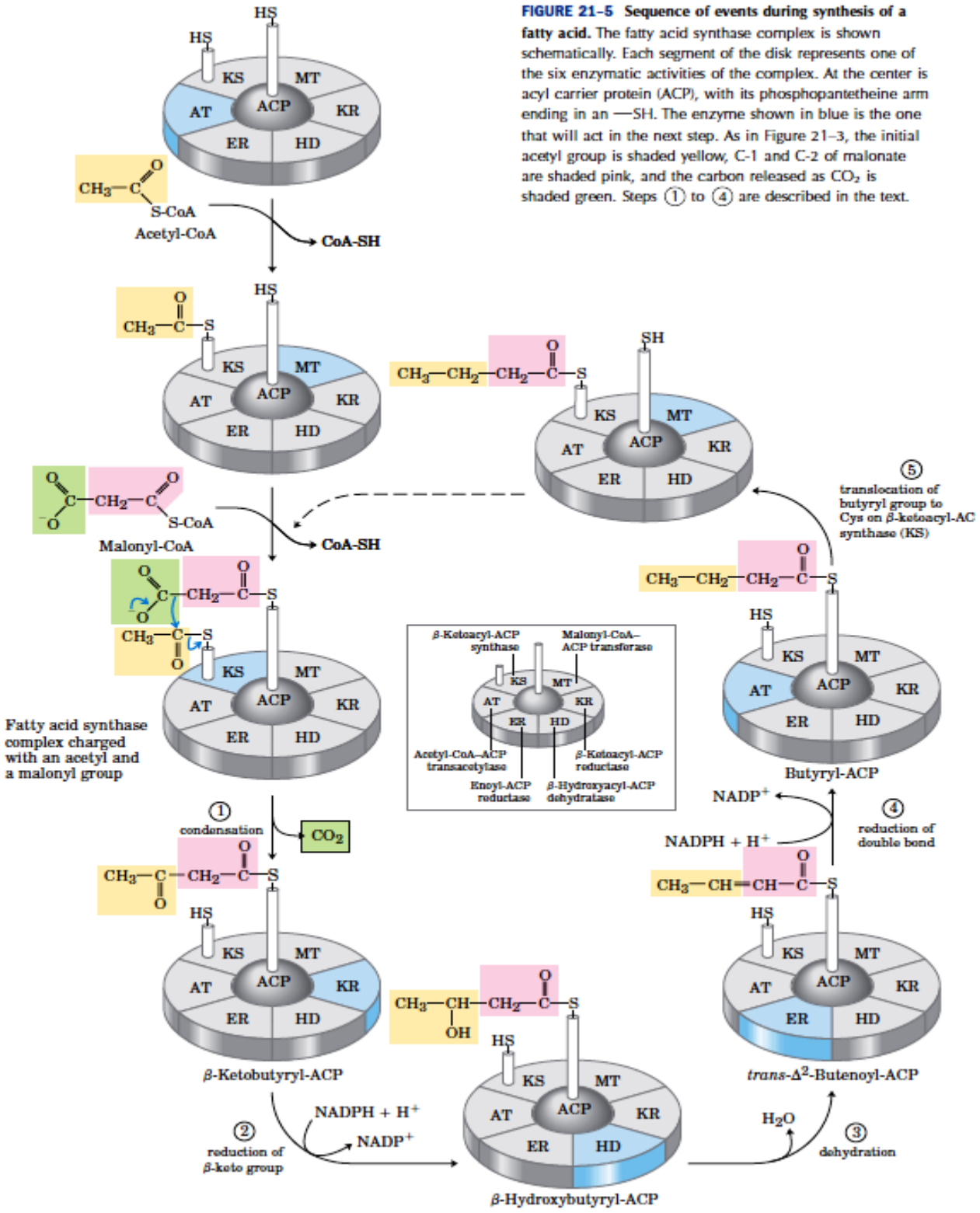


FIGURE 21–5 Sequence of events during synthesis of a fatty acid. The fatty acid synthase complex is shown schematically. Each segment of the disk represents one of the six enzymatic activities of the complex. At the center is acyl carrier protein (ACP), with its phosphopantetheine arm ending in an —SH. The enzyme shown in blue is the one that will act in the next step. As in Figure 21–3, the initial acetyl group is shaded yellow, C-1 and C-2 of malonate are shaded pink, and the carbon released as CO_2 is shaded green. Steps ① to ④ are described in the text.

(Taken from Lehninger)

Overall reaction will be :-

Firstpart

$$7\ \text{Acetyl-CoA} + 7CO_2 + 7ATP \rightarrow 7\ \text{malonyl-CoA} + 7ADP + 7P_i$$

Second part (7 cycles of condensation and reduction)

$$\text{Acetyl-CoA} + 7\ \text{malonyl-CoA} + 14NADPH + 14H^+ \rightarrow \text{palmitate} + 7CO_2 + 8\ \text{CoA} + 14NADP^+ + 6H_2O$$

Regulation of Fatty acid synthesis:-

1. **Controlled by hormones, enzyme and metabolites and end products.**
2. **Acetyl CoA carboxylase:- This enzyme is active in polymeric form and inactive when exist in monomeric form.**
   Citrate promotes polymeric form whereas palmitoyl CoA and malonyl CoA promotes its inactivation.
3. **Hormonal control – it includes cAMP dependent phosphorylation for inactivation and vice versa for activation. Insulin promotes fatty acid synthesis and glucagon inhibits.**
4. **Availability of NADPH – It is provided by citrate (Acetyl CoA) or PPP/HMS (Hexose monophosphate shunt pathway) which significantly influences Fatty acid synthesis**