BIOCHEMISTRY

Lec:4 : 2nd stage Dr.Shaimaa S.Mutlak

METABOLISM OF LIPIDS

ROLE OF PEROXISOMES IN OXIDATION OF FATTY ACIDS

1. ***Oxidation of very long chain fatty acids:***

Peroxisomes facilitate the oxidation of very long chain fatty acids like C20, C22,. The enzymes in peroxisomes do not attack shorter chain fatty acids.

A modified form of β-oxidation is found in peroxisomes and leads to the formation of **acetyl-CoA** and **H2O2**—from the Fp linked dehydrogenase step. H2O2 formed in the process is broken down by the enzyme **Catalase**.

2. Another role of peroxisomal β-oxidation is to shorten the side chain of cholesterol in bile acid formation.

• Peroxisomes also take part in the synthesis of:

– ***Glycolipids*** – ***Cholesterol*** – ***Dolichol.***

Inherited Disorders

1. **Zellweger's syndrome** (Hepato-renal syndrome): Rare inherited disorder. There is **inherited absence of peroxisomes** in all tissues. Due to the absence of peroxisomes and its enzymes, fail to oxidize long-chain FA in peroxisomes. As a result there is accumulation of FA C26-C38 chain-length in brain tissue and other tissues like liver/kidney.
2. **Brown–Schilder's Disease: Also called Adreno leukodystrophy (ALD).**

   Inheritance: Autosomal recessive.

   Defect: Main defect is insufficient oxidation of very long chain fatty acids by peroxisomes due to deficiency of peroxisomal matrix proteins. **VLCFAS are accumulated and myelin sheaths are destroyed.**

   <u>Clinical Feature</u>

   Characterised by progressive degeneration of liver, kidney and brain.

3. **Carnitine deficiency:** Deficiency of carnitine can occur:

(a) In newborns: especially premature infants, owing to inadequate synthesis or renal leakage.

(b) In adults:

• Losses can occur in hemodialysis

• In patients with organic acidurias, carnitine is lost in urine being conjugated with organic acid.

Clinical Features

• **Hypoglycaemia:** Episodic periods of hypoglycaemia owing to reduced gluconeogenesis resulting from impaired FA oxidation

• Impaired ketogenesis in the presence of raised plasma FFA

• Accumulation of lipids

• Muscular weakness.

Treatment: Oral therapy with carnitine.

4. Carnitine-Palmitoyl Transferase Deficiency

(a) Hepatic deficiency of the enzyme results in hypoglycaemia and low plasma ketone bodies.

(b) Muscular carnitine-palmitoyl transferase deficiency:

Produces impaired FA oxidation which results in recurrent muscle weakness and myoglobinuria.

Note: Hypoglycaemic sulphonyl ureas like glyburide and tolbutamide used in diabetes mellitus treatment have been reported to inhibit FA oxidation by inhibiting the enzyme carnitine-palmitoyl transferase.

FATTY ACID SYNTHESIS

Earlier it was believed that fatty acid synthesis was reversal of fatty acid oxidation. But now it is clear that there are **three systems** for fatty acid synthesis.

A. Extramitochondrial system: This is a radically different and highly active system responsible for ***de novo*** synthesis of palmitic acid from 2-carbon unit acetyl-CoA.

B. Chain Elongation System

1. Microsomal system: A system present in microsomes which can lengthen existing fatty acid chains. The palmitic acid formed in cytosol is lengthened to stearic acid and arachidonic acids.

2. Mitochondrial system: This system is mostly restricted to lengthening of an existing fatty acid of moderate chain-length. It operates under ***anaerobiosis*** and is favored by a high NADH/NAD+ ratio.

A. Extramitochondrial (Cytoplasmic) Synthesis of Fatty Acids: (De Novo Synthesis) The synthesis takes place in cytosol. Starting material is acetyl-CoA and synthesis always ends in formation of palmitic acid.

Materials Required for the Synthesis

1.Enzymes: – Fatty acid synthase, a multienzyme complex
– Acetyl-CoA carboxylase, also a multienzyme complex

2.Coenzymes and cofactors: Biotin, NADPH, Mn++

3.CO2: Source of CO2 is bicarbonate and

4.ATP: For energy.

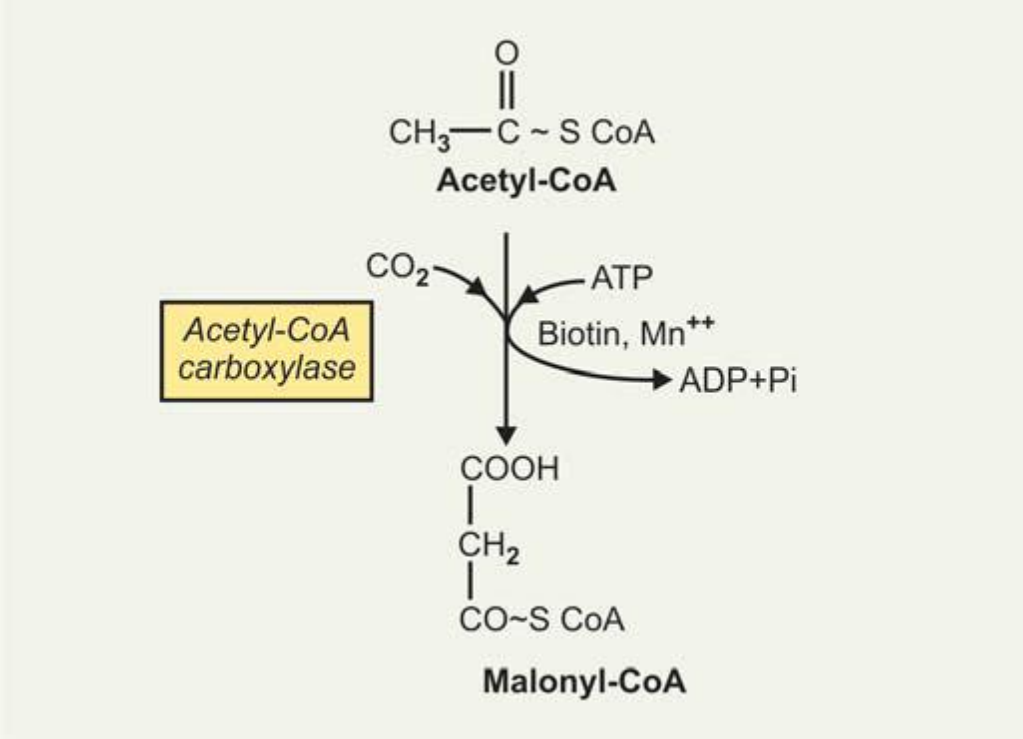
Protein ACP(acyl carrier protein) which binds the acyl radicals. ACP is a single polypeptide chain of 77 amino acids, a serine moiety of this peptide chain is in combination with phosphopantothene. The –SH group of pantothene moiety takes active part in synthesis of fatty acid.

• **Acetyl-CoA carboxylase*:*** Also a multienzyme complex containing:Biotin– Biotin carboxylase – Biotin carboxyl carrier protein – Transcarboxylase and– A regulatory allosteric site.

Steps of FA Synthesis

• **The starting material for the synthesis is acetyl-CoA**.
Acetyl-CoA is formed in mitochondrion but synthesis occurs in cytosol. **Acetyl-CoA is impermeable to mitochondrial membrane.**

1. **Formation of malonyl CoA from acetyl-CoA:** In presence of the enzyme **"acetyl-CoA carboxylase",** the acetyl-CoA is converted to malonyl-CoA by **"CO2-fixation reaction".** Mn++ is required as a cofactor and ATP provides the energy.



Characteristics

• The reaction is **irreversible.**
• CO2 is provided by HCO^{-}_{3}.
• One high energy bond of ATP is utilized.

• **Acetyl-CoA carboxylase is a rate-limiting enzyme.**

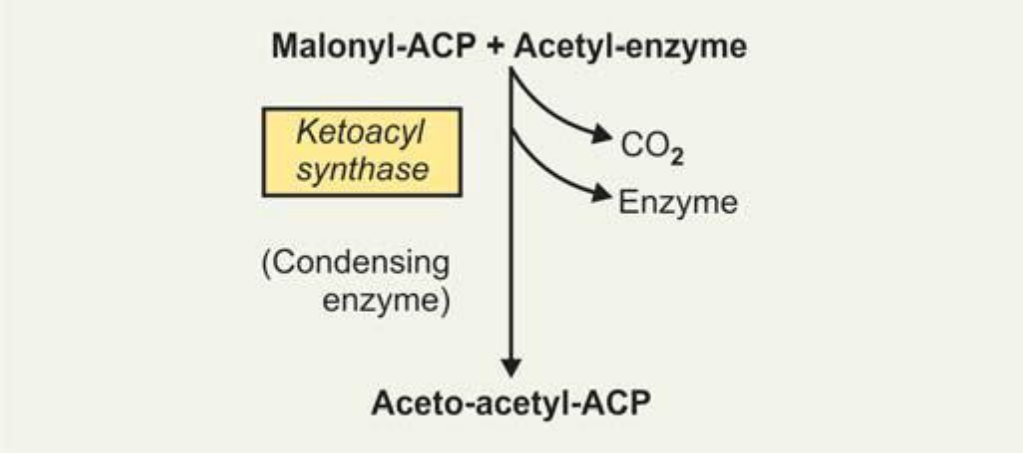
2.

3. **Subsequent steps:** Once malonyl-CoA is synthesised, rest of fatty acid synthesis reactions take place with FA synthase complex. **"Cys-SH" and "Pan-SH" may be considered as two arms of the enzyme complex. "Cys-SH" is the acceptor of Acetyl-CoA whereas "Pan-SH" takes up malonyl-CoA.**

   Initially, a molecule of acetyl-CoA combines with the "Cys-SH" of "keto acyl-synthase" of one monomeric unit **(monomer I)**. The coenzyme A is removed, the reaction is catalysed by the enzyme "transacylase",

   • In a similar manner, a molecule of malonyl-CoA (formed as above) combines with the adjacent "Pan-SH" of ACP of opposite monomeric unit **(Monomer II)**, to form "Malonyl-ACP-enzyme". The coenzyme A of Malonyl-CoA is also removed in this step and the reaction is catalysed by the same "transacylase" enzyme.

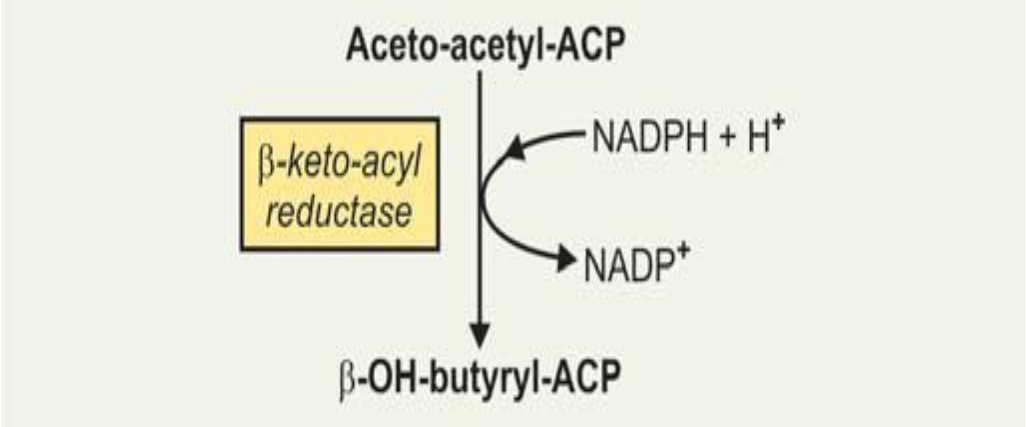
4. **Condensation reaction:** Now, the acetate attacks malonate to form "aceto-acetyl-ACP". The reaction is catalysed by the enzyme "Keto-acyl synthase" (condensing enzyme) and **there is loss of one molecule of CO2** (decarboxylation).



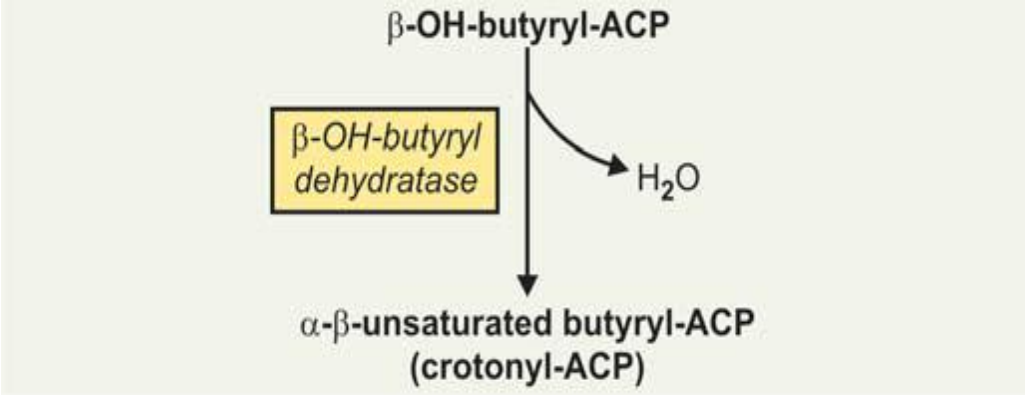
The aceto-acetate remains attached to Pan-SH of monomer II, **the cys-SH of monomer I becomes free.**

• While aceto-acetate remains attached to "Pan-SH", **three reactions** take place, **reduction, dehydration,** followed by another **reduction**.

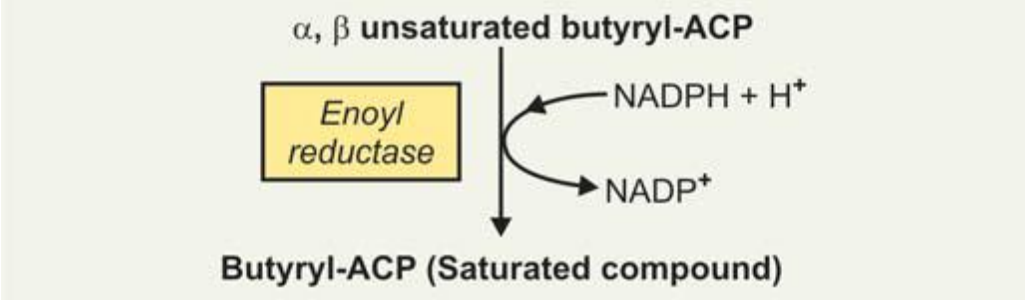
• **First reaction (reduction):** The keto-acyl group is reduced to hydroxy group (–OH) to form "β-OH butyryl-ACP" catalysed by the enzyme "keto-acyl reductase".



• **Second reaction (dehydration):** A molecule of H2O is removed from "β-OH-butyryl-ACP" to form "α, β-unsaturated butyryl-ACP" (also called crotonyl-ACP), catalysed by the enzyme "β-OH-acyl dehydratase".



• **Third reaction (reduction):** The third and final reduction is catalysed by "enoyl-reductase"using NADPH +H+, as a result the double bond is saturated to form "butyryl-ACP" **(4 carbon).**

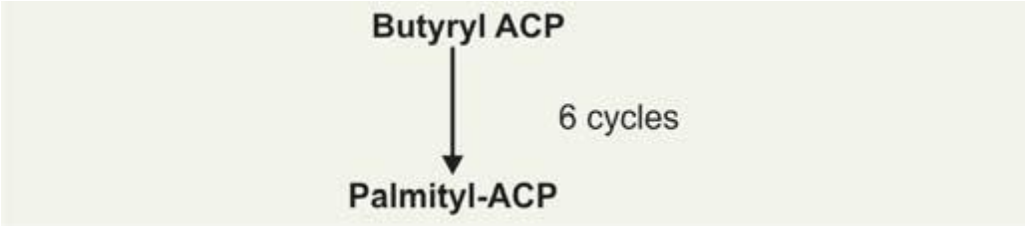


All the above three reactions occur on "Pan-SH" of monomer II. Once saturated butyric acid is formed; it is now transferred to the "Cys-SH" of monomer I which is free to accommodate.

5. Continuation reaction: Now a fresh molecule of Malonyl-CoA is taken up on to the free "
6. Pan-SH" group of monomer II and the sequence of events is repeated to form a saturated six carbon fatty acid.

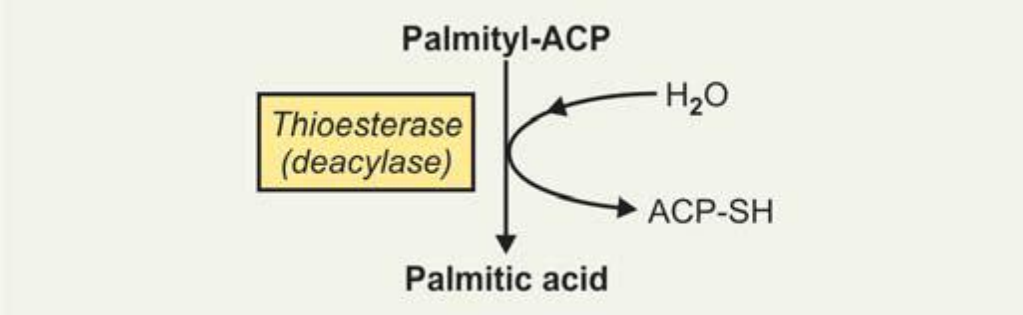
Once formed this is again transferred to "Cys-SH" of monomer I.

The set of reactions on each of the monomer is repeated till a 16 carbon palmityl-ACP is formed on "Pan-SH" of monomer II.



Note: The lengthening of the acyl group by each two carbon units at a time is brought about by one ATP molecule which is used for formation of malonyl-CoA from acetyl-CoA.

5.Termination reaction: Palmityl-ACP is released as palmitic acid from the enzyme complex by the enzyme "thioesterase" (deacylase).


Palmityl-ACP
Thioesterase
(deacylase)
H2O
ACP-SH
Palmitic acid

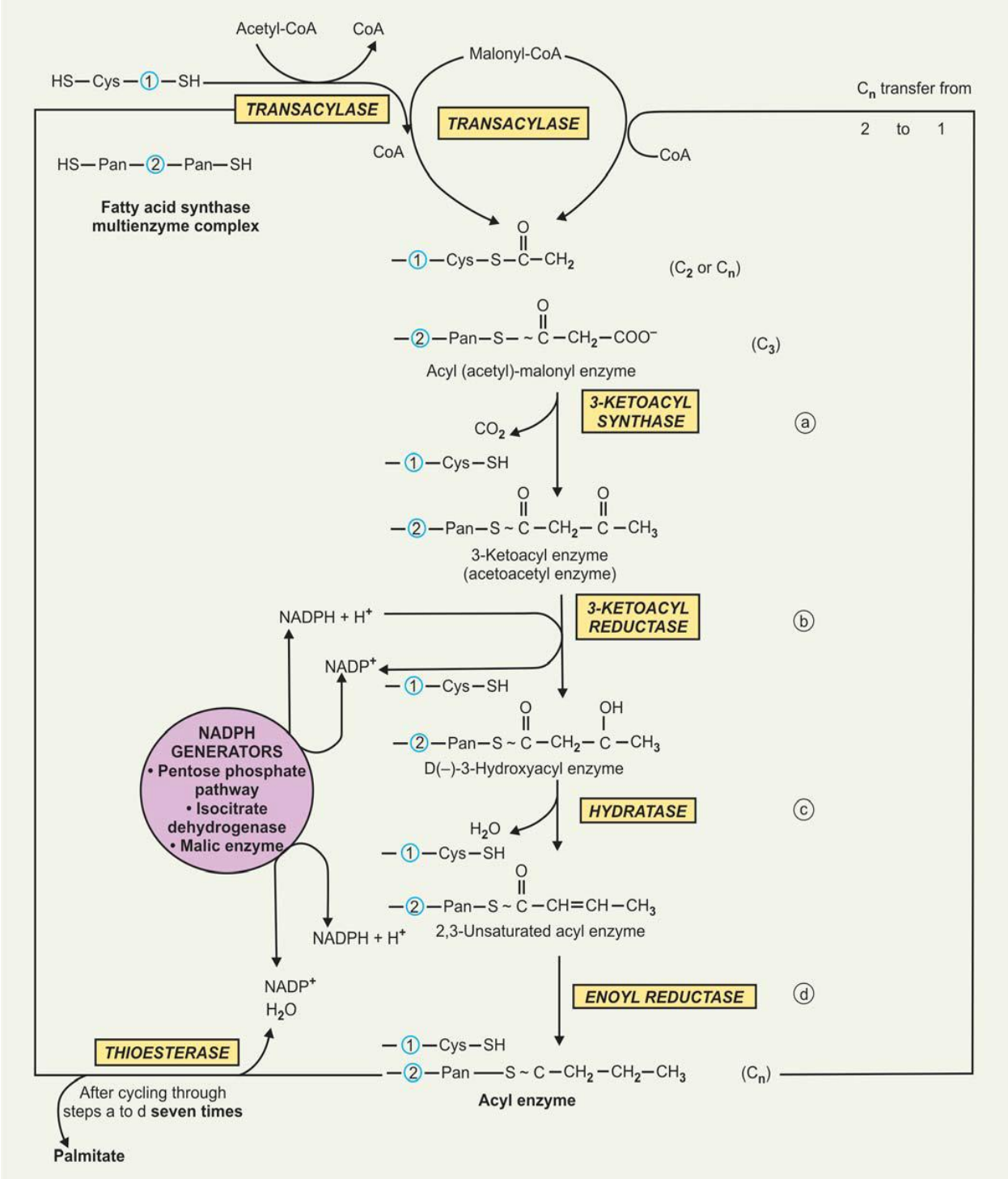


Fig.: Biosynthesis of long-chain fatty acids—extramitochondrial de novo synthesis