

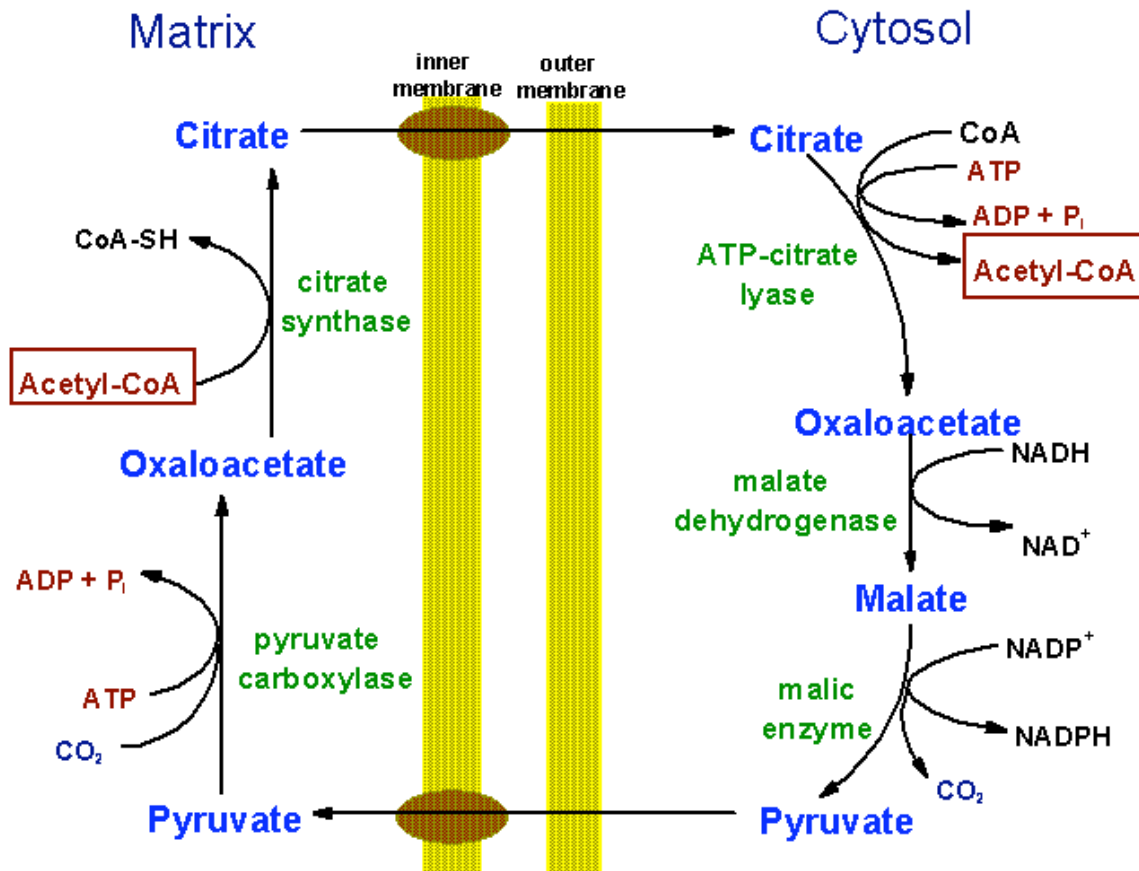
## Lecture: 27

### Fatty acid and triacyl glycerol biosynthesis

#### Biosynthesis of fatty acids

- ❖ It was thought that fatty acid biosynthesis occurred by **reversal of the  $\beta$ -oxidation pathway**.
- ❖ On the contrary, it occurs by a separate pathway that differs from  $\beta$ -oxidation in several ways.
  - i. Synthesis takes place in the **cytosol**, in contrast with degradation or oxidation, which occurs in the **mitochondrial matrix**.
  - ii. Intermediates in fatty acid synthesis are covalently linked to the sulfhydryl group of an **acyl carrier protein (ACP)** whereas intermediates in fatty acid breakdown are bonded to coenzyme A.
  - iii. The enzymes of fatty acid synthesis in animals are **joined in a single polypeptide chain called fatty acid synthase**. In contrast, the degradative enzymes do not seem to be associated. Plants employ separate enzymes to carry out the biosynthetic reactions.
  - iv. The reductant in fatty acid synthesis is **NADPH**, whereas the oxidants in fatty acid oxidation are  $\text{NAD}^+$  and FAD.

**Pathway for the movement of acetyl-CoA units from within the mitochondrion to the cytoplasm for use in lipid and cholesterol biosynthesis.**

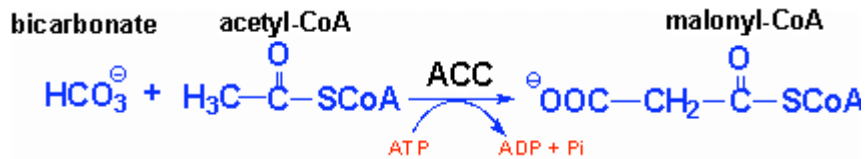


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The following seven steps are involved in fatty acid biosynthesis.

### Formation of malonyl CoA

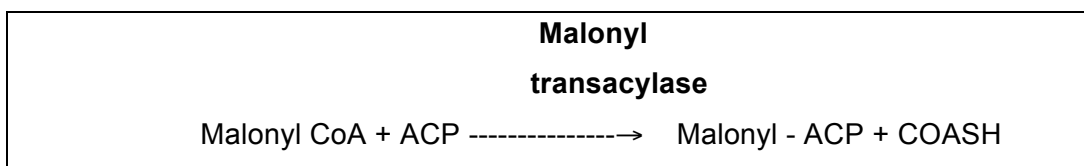
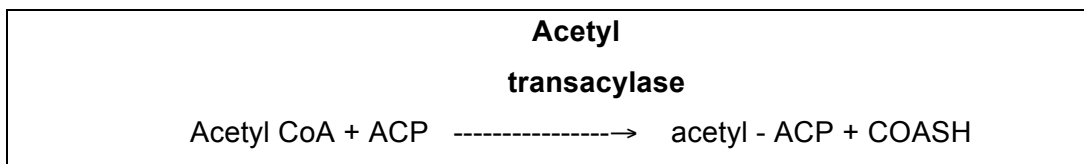
The synthesis of malonyl CoA from acetyl CoA is catalyzed by acetyl CoA carboxylase having biotin as prosthetic group. The production of malonyl CoA is the initial and controlling step in fatty acid synthesis. In this reaction, bicarbonate serves as a source of CO<sub>2</sub>. The reaction takes place in two steps, namely carboxylation of biotin involving ATP and transfer of the carboxyl group to acetyl CoA resulting in malonyl CoA.



- **Acetyl CoA carboxylase** plays a key role in regulating fatty acid metabolism and the same is inactivated by phosphorylation.

## ii) Formation acetyl and malonyl ACP

Acetyl transacylase and malonyl transacylase catalyze the formation of acetyl ACP and malonyl ACP respectively. Acetyl transacylase can transfer acetyl as well acyl groups whereas malonyl transacylase is highly specific.



## iii) Formation of acetoacetyl - ACP ( $\beta$ -ketoacyl ACP)

- ❖ Acetyl ACP condenses with malonyl ACP to form acetoacetyl ACP.
- ❖ Carbondioxide is eliminated from malonyl ACP.

## iv) Reduction of $\beta$ -ketoacyl ACP to $\beta$ -hydroxyl acyl ACP.

- ❖ The  $\beta$ - keto group in acetoacetyl ACP is reduced by **NADPH- dependent  $\beta$ -ketoacyl reductase**.

## v) Formation of unsaturated acyl ACP.

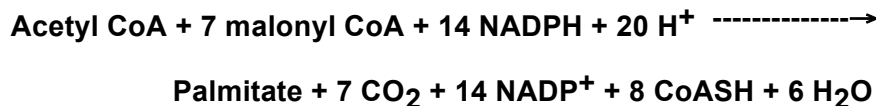
The  $\beta$ -hydroxyl group combines with the hydrogen atom attached to the  $\gamma$ -carbon and a water molecule is removed to form  $\alpha, \beta$ -unsaturated acyl ACP.

## vi) Formation of Acyl ACP

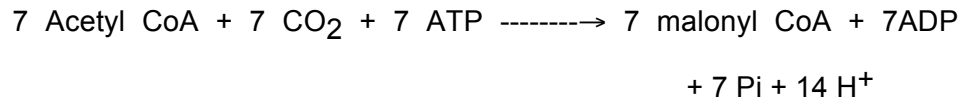
- ❖ The unsaturated acyl ACP is converted in the next step to a saturated acyl ACP by the enzyme  **$\alpha, \beta$ -unsaturated acyl ACP reductase** using NADPH as the coenzyme.
- ❖ The resultant product contains two carbon atoms more than the starting material.
- ❖ Addition of subsequent acetyl units through malonyl ACP leads to the formation of 16-carbon palmitate.

Stoichiometry of fatty acid synthesis

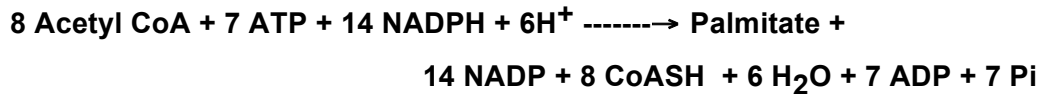
The stoichiometry of the synthesis of palmitate is given below:



The equation for the synthesis of the malonyl CoA used in the above reaction is



The overall stoichiometry for the synthesis of palmitate is



Fatty acid synthesis and degradation are reciprocally regulated so that both are not simultaneously active.

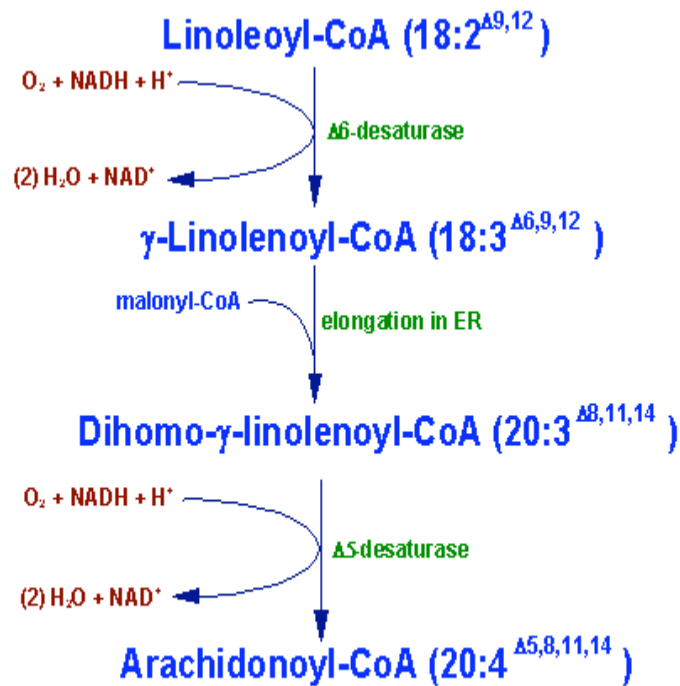
### **Elongation of fatty acids or synthesis of long chain fatty acids**

- ❖ Elongation by the **fatty acid synthase complex** stops upon formation of palmitate (16 C).
- ❖ Further elongation and the formation of double bonds are carried out by other enzyme systems.
- ❖ The major product of fatty acid biosynthesis is the 16-carbon fatty acid, palmitate.
- ❖ Additional enzymes are required to synthesise longer chain fatty acids.
- ❖ Chain elongation reactions occur both in **mitochondria** and in **microsomes**. Microsomes are small membrane-enclosed vesicles derived from the endoplasmic reticulum of cells.
- ❖ Mitochondria and microsomes carry out chain elongation by adding two-carbon units to fatty acids.
- ❖ The microsomal system has great physiological significance in that it provides the long chain fatty acids (18-24C) required for the **myelination of nerve cells in animal system**.
- ❖ Chain elongation occurs by a cycle of **condensation, reduction, dehydration followed by another reduction** that parallels cytosolic fatty acid biosynthesis.
- ❖ The more active elongation system adds **two carbons to palmitoyl-CoA to make it steroyl CoA**.
- ❖ The mechanism of elongation is identical with that known in the synthesis of palmitate except the enzyme systems and the acyl carrier protein.

### **Biosynthesis of unsaturated fatty acids**

- ❖ Palmitate and stearate serve as precursors of the two most common monounsaturated fatty acids, **palmitoleate, 16:1, ( $\Delta^9$ )** and **oleate, 18:1 ( $\Delta^9$ )** respectively.

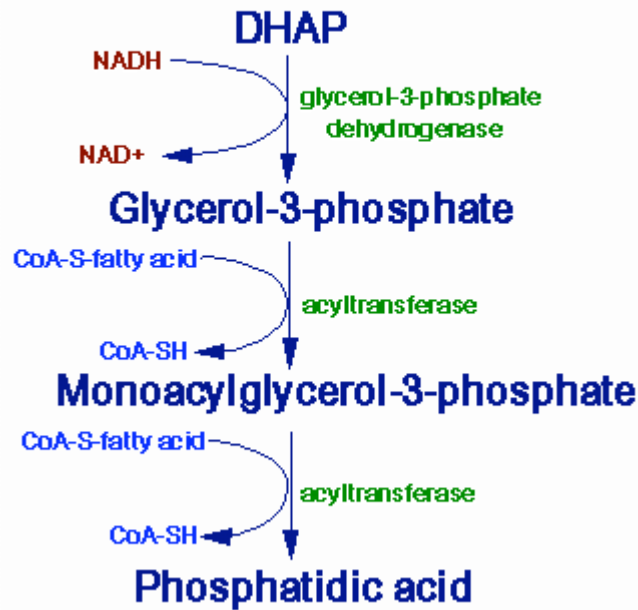
- ❖ Each of these fatty acids has a single double bond between C-9 and C-10.
- ❖ The **double bond is introduced into the fatty acid chain** by an oxidative reaction catalysed by **fatty acyl-CoA desaturase**, which is **NADPH-dependent enzyme**.
- ❖ The unsaturated fatty acids, linoleate, 18:2 ( $\Delta^{9,12}$ ) and  $\alpha$ -linolenate, 18:3 ( $\Delta^{9,12,15}$ ) cannot be synthesised by mammals; but plants can synthesise both.
- ❖ The **desaturases** responsible for synthesis of both the above fatty acids are present in **endoplasmic reticulum of plants**.
- ❖ The plant **desaturases** oxidise phosphatidylcholine-bound oleate and produce polyunsaturated fatty acids and do not directly add double bonds to the fatty acids.
- ❖ Once ingested, the linoleate are readily converted to other **polyunsaturated fatty acids** like  $\gamma$ -linolenate, **arachidonic acid** etc. in animals and human beings.



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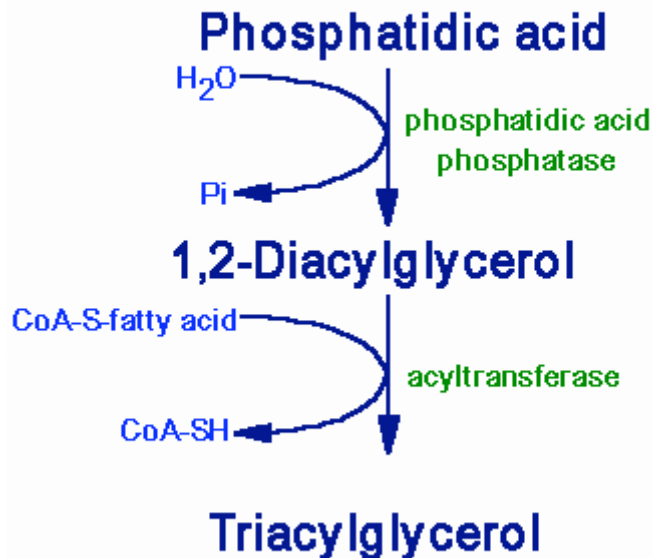
### Biosynthesis of triacylglycerols

## Phosphatidic Acid Synthesis



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## Triacylglycerol Synthesis



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- Triacylglycerols are not synthesised by reversal of lipolysis.
- They are synthesised by a different mechanism in which both glycerol and fatty acids are activated by ATP before they are incorporated into acylglycerols.

#### **i) Activation of glycerol**

- *Glycerol kinase* catalyses the activation of glycerol to glycerol 3-phosphate.
- If glycerol kinase is found in low quantity or absent, glycerol 3-phosphate will be formed from dihydroxyacetone phosphate obtained from glycolysis and this reaction is catalysed by the enzyme ***glycerol 3-phosphate dehydrogenase***.

#### **ii) Activation of fatty acids**

- Fatty acids are activated to acyl CoA by the enzyme **acyl CoA synthetase**, utilizing ATP and CoASH.
- Two molecules of acyl CoA combine with glycerol 3-phosphate to form 1,2-diacylglycerol phosphate.
- Formation of 1,2-diacyl glycerol phosphate takes place in two stages, catalysed by **glycerol 3-phosphate acyl transferase** and then by **1-acyl glycerol 3-phosphate acyl transferase**.
- The phosphate group is removed from 1,2-diacyl glycerol phosphate by **phosphatidate phosphatase** to form 1,2-diacyl glycerol.
- Triacylglycerols are finally formed by esterification of one or more molecule of acyl CoA with the diacylglycerol.

#### **Alternative pathway for triacylglycerol biosynthesis**

- In this pathway, dihydroxyacetone phosphate from glycolysis is reduced by NADPH, acylated and converted to lysophosphatidate.

This pathway accounts for less than 10% of total triacylglycerol synthesis.