

# **METABOLISM OF LIPIDS**

# METABOLISM OF FAT

- The lipids of metabolic significance include synthesis and degradation of
  - triglycerides
  - phospholipids
  - steroids together with long chain fatty acids
  - glycerol and
  - ketone bodies
- Oxidation of triglycerides takes place in the adipose tissue.
- The complete degradation of fatty acid in the body leads to the oxidation to  $\text{CO}_2$  and water

## **b) Metabolism of fatty acids**

The fatty acids components of the lipids entering the liver also have several different pathways

1. Oxidation to CO<sub>2</sub> with ATP production
2. Biosynthesis of cholesterol
3. Biosynthesis of lipids of plasma lipoproteins  
(Triglyceride and phospholipids)
4. Formation of free fatty acids
5. Formation of ketone bodies

## **a) Metabolism of Triglycerides**

- Triglycerides are first converted to fatty acids and glycerol mostly in adipose tissue.
- The fatty acids are released into the plasma where they combine with serum albumin.
- Long chain fatty acids are oxidized in liver, heart, kidney, muscle, lung, brain and adipose tissue.
- Glycerol is utilized by liver, kidney, intestine and lactating mammary gland where the activating enzyme glycerokinase is present.

# 1. Oxidation of fatty acids to CO<sub>2</sub> with ATP production

- Fatty acids are oxidized by  $\beta$ ,  $\alpha$ , and  $\omega$  oxidation.  $\beta$ -Oxidation is the most important pathway for the production of energy.
- The term  $\beta$  -oxidation means the oxidation takes place in the  $\beta$  -carbon in the fatty acid with the removal of 2 carbon atoms at a time from the carboxyl end of the molecule.
- The saturated fatty acids containing even number and odd number of carbon atoms and the unsaturated fatty acids are oxidized by  $\beta$  -oxidation.

## (a) $\beta$ -Oxidation of saturated fatty acids

- Saturated fatty acids are oxidized to acetyl-CoA by  $\beta$  oxidation.
- It takes place in mitochondria.
- Five steps are involved and each step involves acyl-CoA derivatives catalyzed by separate enzymes, utilizes NAD<sup>+</sup> and FAD as coenzymes, and generates ATP.
- Fatty acid oxidation is an aerobic process, requiring the presence of oxygen.

# Step 1 Activation of Fatty Acids

- Long chain fatty acids are first converted to an 'active fatty acid' or acyl CoA in the cytosol
- But activation of lower fatty acids occurs within the mitochondria.
- Thiokinase is found both inside and outside the mitochondria.

## • Thiokinase



- The presence of inorganic pyrophosphatase ensures that activation goes to completion by facilitating the loss of the additional high-energy phosphate associated with pyrophosphate.
- Two high energy phosphates are expended during the activation of each fatty acid molecule.

- **(i) Transport of smaller fatty acids**

- Small fatty acids are able to penetrate the inner membrane of mitochondria and become oxidized within the mitochondria.

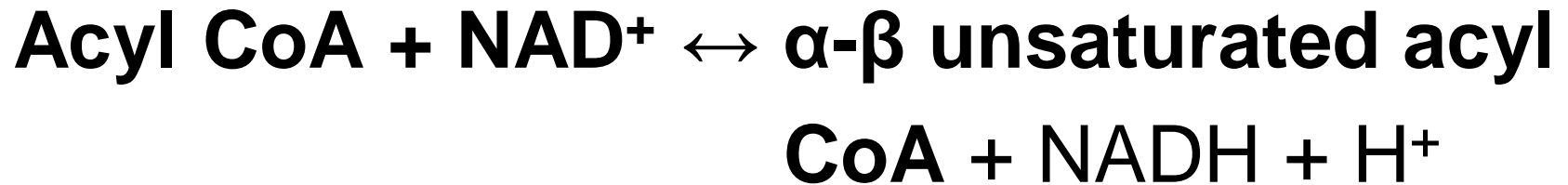
- **(ii) Transport of long-chain fatty acids**

- Long-chain fatty acids penetrate the inner mitochondrial membrane only as carnitine derivatives.
- **Carnitine acyl transferase I**, -in outer mitochondrial membrane, converts long-chain acyl CoA to acyl carnitine, -penetrates the inner membrane of mitochondria
- **Carnitine-acyl carnitine translocase** -in mitochondria, catalyses the transfer of acylcarnitine into the inner membrane.
- **Carnitine acyl transferase II**- in the inner mitochondrial membrane, converts acyl carnitine to long-chain acyl CoA and carnitine.
- Acyl CoA then undergoes further reactions of  $\beta$ -oxidation



# Step 2 Dehydrogenation of Acetyl CoA

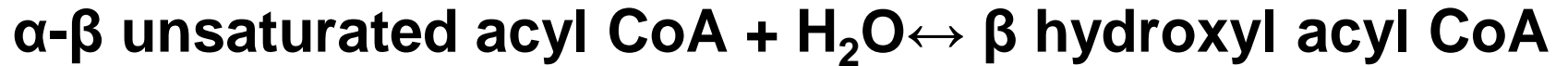
## Acetyl CoA dehydrogenase



NADH + H<sup>+</sup> is reoxidised via electron transport chain.

# Step 3 Conversion of $\alpha$ - $\beta$ unsaturated acyl CoA to $\beta$ hydroxyl acyl CoA

**Enoyl-CoA hydratase.**



# Step4 Dehydrogenation at the $\beta$ -carbon of $\beta$ -hydroxyacyl CoA

$\beta$ -hydroxyacyl-CoA dehydrogenase



The  $\text{NADH} + \text{H}^+$  formed is reoxidised via electron transport chain.

## Step5. Cleavage by thiolase

- **Thiolase**
- **$\beta$ -ketoacyl-CoA  $\leftrightarrow$  Acetyl-CoA + acyl-CoA**
- The products of this reaction are acetyl-CoA and an acyl-CoA derivative containing two carbons less than the original acyl-CoA molecule that underwent this oxidation.
- The acyl-CoA formed in the cleavage reaction reenters the oxidative pathway at reaction 1.

A long chain fatty acid may be degraded completely to acetyl-CoA (C2 units).

In the case of palmitic acid the reactions are repeated 7 times and 8 molecules of acetyl CoA are formed.

Since acetyl-CoA can be oxidized to  $\text{CO}_2$  and water via the citric acid cycle, the complete oxidation of fatty acids is achieved

# Production of ATP

Synthesis of high energy phosphates (ATP) for Electron transport chain reoxidation of FADH<sub>2</sub> and NADH of formation of 7 acetyl-CoA molecules for β-oxidation of palmitate : **five**.

No. of ATP derived from β-Oxidation Since 8 molecules of acetyl CoA are formed : **7x5 = 35**

No. of ATP formed on oxidation of 8 acetyl-CoA molecules (via citric acid cycle) : **8x12 = 96**

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	<b>Total</b>	<b>: 131</b>
ATP utilized for initial activation of the <u>fatty acid</u> :		<b>-2</b>
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	<b>Net total yield</b>	<b>: 129</b>

## Calorific value per mole of palmitic acid:

- The calorific value is  $129 \times 7.6 = 980$  K.cal/mole.
- The calorific value per mole of combustion of palmitic acid is 2340 K.cal/mole.
- The process captures as high-energy phosphate in the order of 41% of the total energy of combustion of the fatty acid.

## ( $\beta$ )Oxidation of a fatty acid with an odd number of carbon atoms

Fatty acids with an odd number of carbon atoms are oxidized by the pathway of  $\beta$  - oxidation, producing acetyl-CoA until a three- carbon (propionyl-CoA) residue remains.

This compound is converted to succinyl-CoA, a constituent of the citric acid cycle and metabolized.

### **Propionyl-CoA carboxylase**





D-Methylmalonyl-CoA is converted to its stereoisomer, L-methylmalonyl-CoA, by methylmalonyl-coA racemase before its final isomerization to succinyl-CoA by the enzyme methylmalonyl-CoA isomerase.

### **Methylmalonyl-CoA racemase**

**D-Methylmalonyl-CoA  $\leftrightarrow$  L- methylmalonyl-CoA**

### **Methylmalonyl-CoA isomerase**

**L- methylmalonyl-CoA  $\leftrightarrow$  Succinyl-CoA**

Thus the propionyl fatty acid I residue from an odd-chain fatty acid is the only part of a

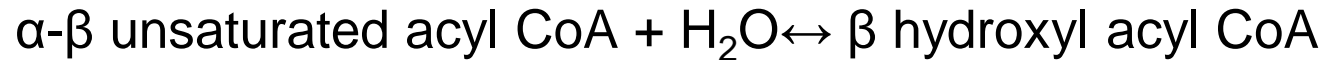
## c) Oxidation of unsaturated fatty acids

- Oxidation of unsaturated fatty acids occurs by a modified beta-oxidation pathway.
- **1. Initial reaction**
- The CoA ester of these acids are degraded by the enzymes normally responsible for  $\beta$  - oxidation until either a  $\Delta^3$ -*cis*- acyl-CoA compound or  $\Delta^4$ -*Cis*-acyl-CoA compound is formed, depending upon the position of the double bonds.
- **2. Reaction of Isomerase**
- The former compound is isomerized ( $\Delta^3$  ***cis*- $\Delta^2$  Acyl CoA isomerase**) to the corresponding  $\Delta^2$  -*trans*-CoA stage of  $\beta$  - oxidation for subsequent hydration and oxidation.

## (One cycle of Beta Oxidation)

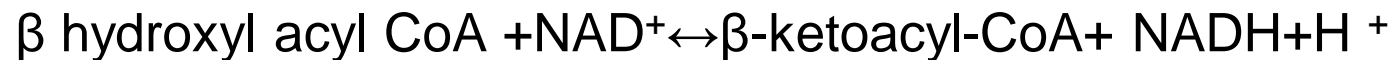
### 3. Conversion of $\alpha$ - $\beta$ unsaturated acyl CoA to $\beta$ hydroxyl acyl CoA

Enoyl-CoA hydratase.



### 4. Dehydrogenation at the $\beta$ -carbon of $\beta$ -hydroxyacyl CoA

$\beta$ -hydroxyacyl-CoA dehydrogenase



### 5. Action of thiolase

## 6. Conversion of $\Delta^4$ -*cis*-acyl-CoA to $\Delta^2$ -*trans* enoyl-CoA

Any  $\Delta^4$  -*cis*-acyl-CoA remaining, as in the case of linoleic acid, is converted to  $\Delta^2$  -*trans* enoyl-CoA by an NADP dependent enzyme,  $\Delta^2$  - *trans* -  $\Delta^3$ -*cis* dienoyl-CoA reductase.

## 7. Action of Acyl-CoA dehydrogenase

$\Delta$ -*cis* (or *trans*)  $\Delta^2$  enoyl-CoA isomerase will attack the *trans* double bond to produce  $\Delta^2$  - *trans* enoyl-CoA, This compound is further metabolised via  $\beta$  - oxidation