Lipid Catabolism and its Disorders

Course Code: ZOOL 4008 (Biochemistry and Metabolism)

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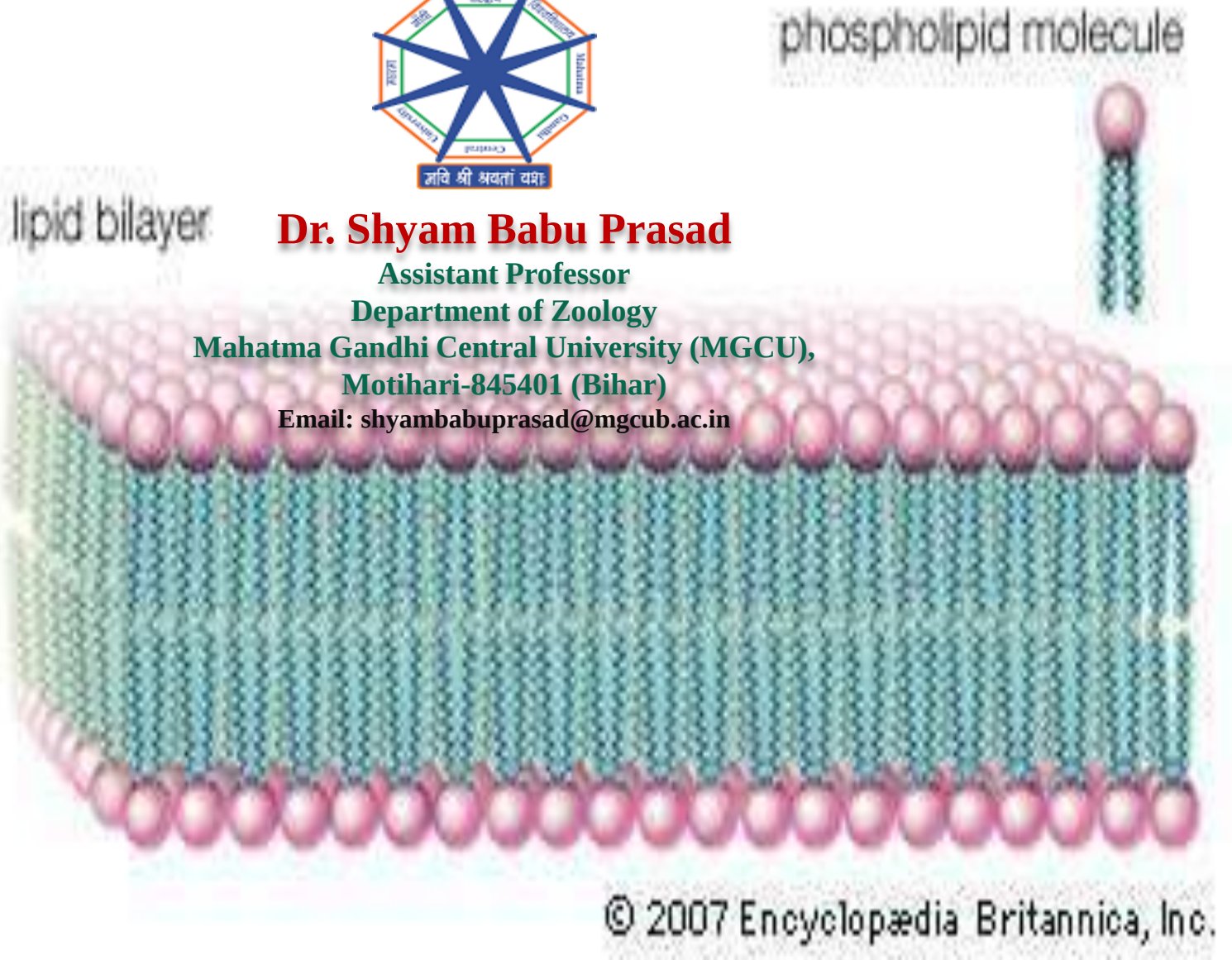


Lipid Catabolism

•**Catabolism:** refers to several metabolic reactions that produce energy after breakdown complex compound into simpler compound.

• Since lipids are important source of stored energy so produced Fatty acids will participate in fatty acid oxidation.

• The breakdown of lipid to produced Energy is called lipogenesis.

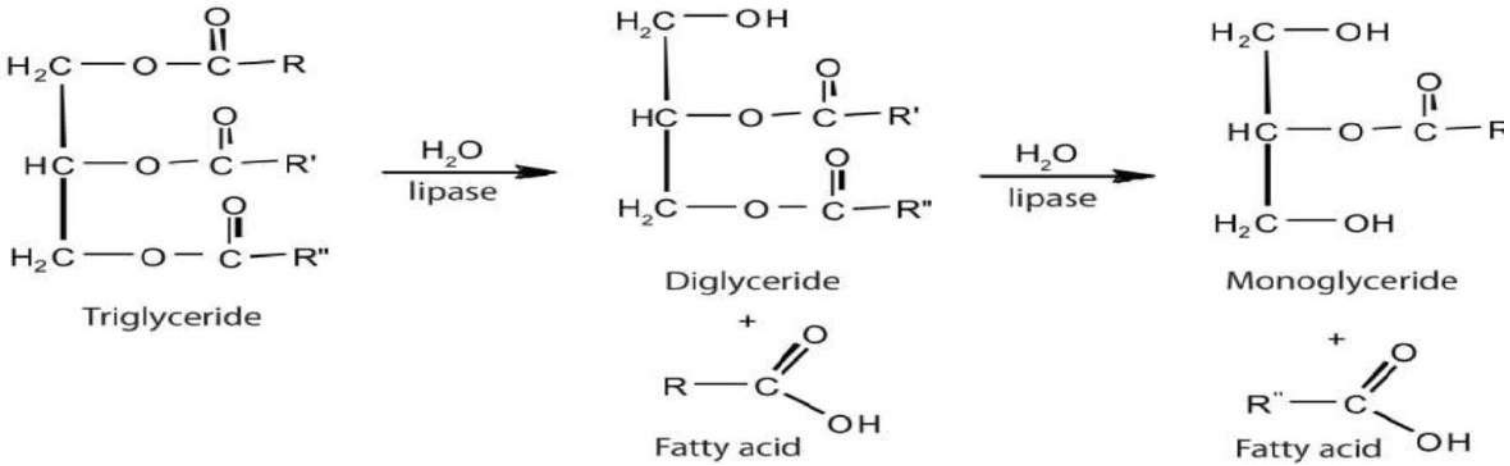
•Lipid Constitute 84% of stored energy
• Protein - 15%
• Carbohydrate (glucose or glycogen) - <1%

Steps for Lipogenesis

1. Lipolysis

- The breakdown of lipid is stimulated by cellular hormones: epinephrine, nor epinephrine and cortisol etc.
- **Triacylglycerols** (triglycerides) are the most abundant dietary lipids.
- **Lipases** hydrolyze triacylglycerols, releasing one fatty acid at a time,producing diacylglycerols, and eventually glycerol

- The end of the process 3 fatty acids and 1 glycerol will be releases.



Fate of Glycerol and Fatty acid releases after Lipolysis

•**Glycerol** arising from hydrolysis of triacylglycerols is converted to the Glycolysis intermediate:
Dihydroxyacetone phosphate.

• **Reactions is catalyzed two important enzyme:**

(1) Glycerol Kinase

(2) Glycerol Phosphate Dehydrogenase

•**Fatty acids** undergo β-Oxidation to release Acetyl- CoA.

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Mechanism

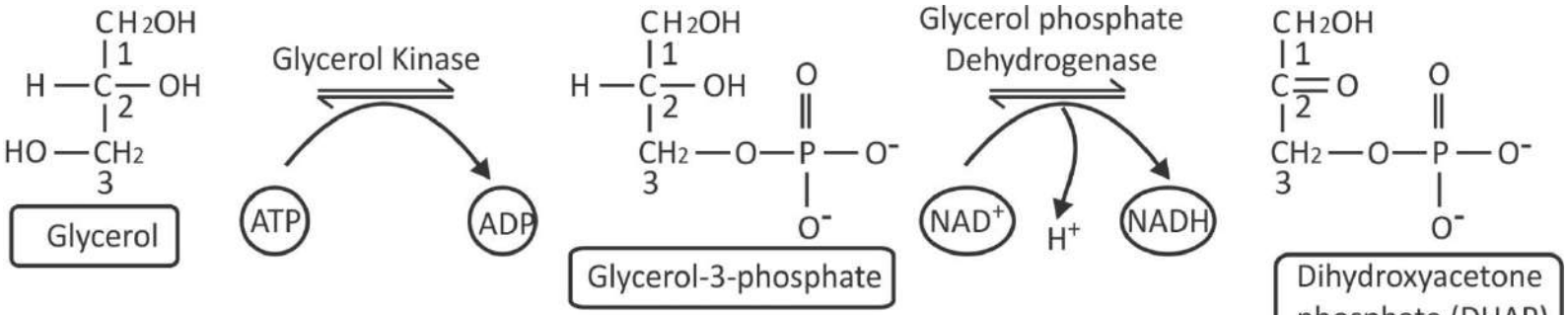


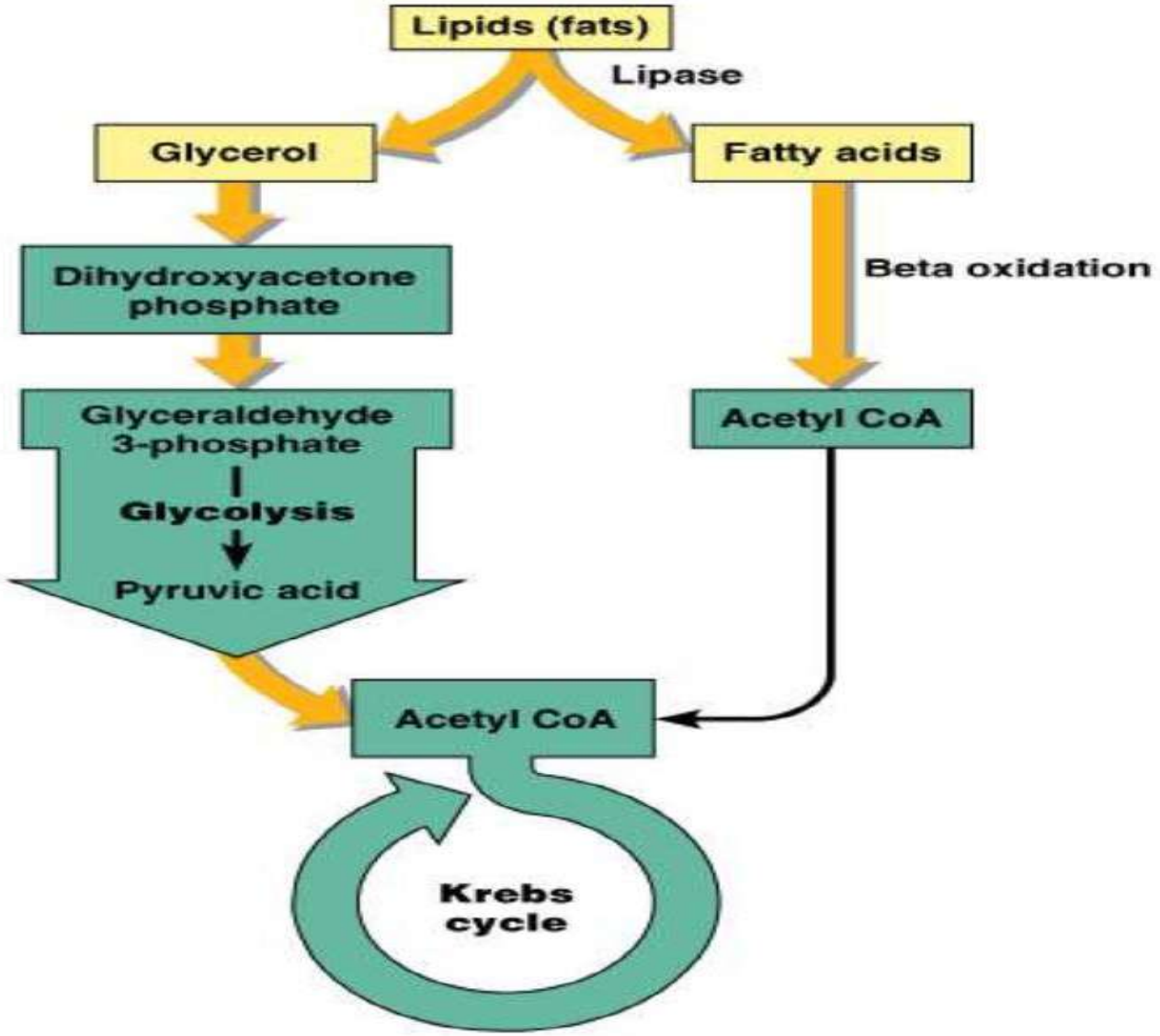
Fig. : Formation of DHAP from glycerol

Phosphotriose Isomerase

Glycerol ⇌ Glyceraldehyde 3-Phosphate

Direct

Phosphorylation



Beta Oxidation of Fatty Acid

•**β-oxidation of fatty acid:** The break down of a fatty acid to acetyl-CoA that occurs in Mitochondria.

•It is completely aerobic Process.

•After Acetyl-CoA production, its directly involves in to **Krebs Cycle** for energy production.

•It occurs in many tissues including liver, kidney and heart except Brain.

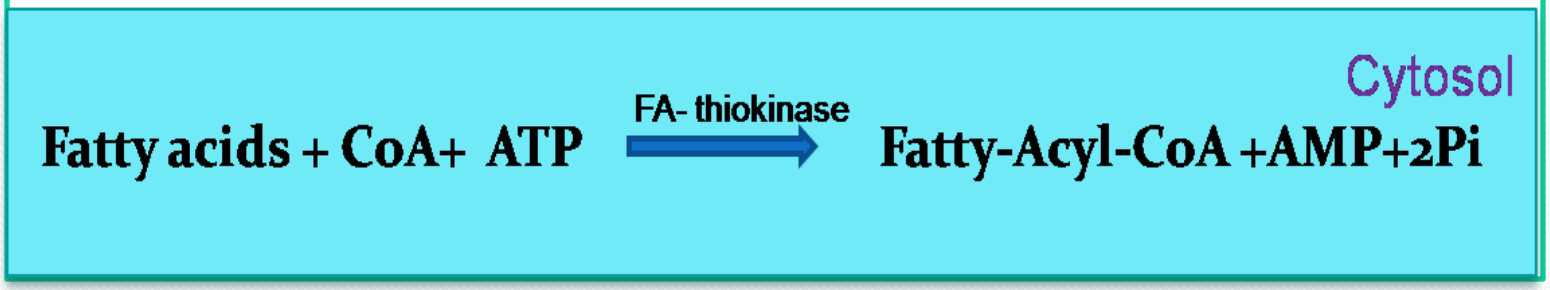
There are following steps:

1. **Activation of fatty acids in the cytosol.**
2. **Transport of activated fatty acids into mitochondria by carnitine shuttle.**
3. **Beta oxidation occurs proper in the mitochondrial matrix.**

1. Activation of fatty acids in the cytosol

•The enzyme FA thiokinase (acyl CoA synthetase) present in cytosol and its requires ATP, CoA SH, Mg++ for the conversion of Fatty acid to FA acyl COA and water.

•Acyl CoA synthetase is a family of isoenzyme and it is specific for short, medium and long chain FA that catalyzed the production of fatty-acyl-CoA in the cytosol.



2. Transport of activated fatty acids into mitochondria by carnitine shuttle

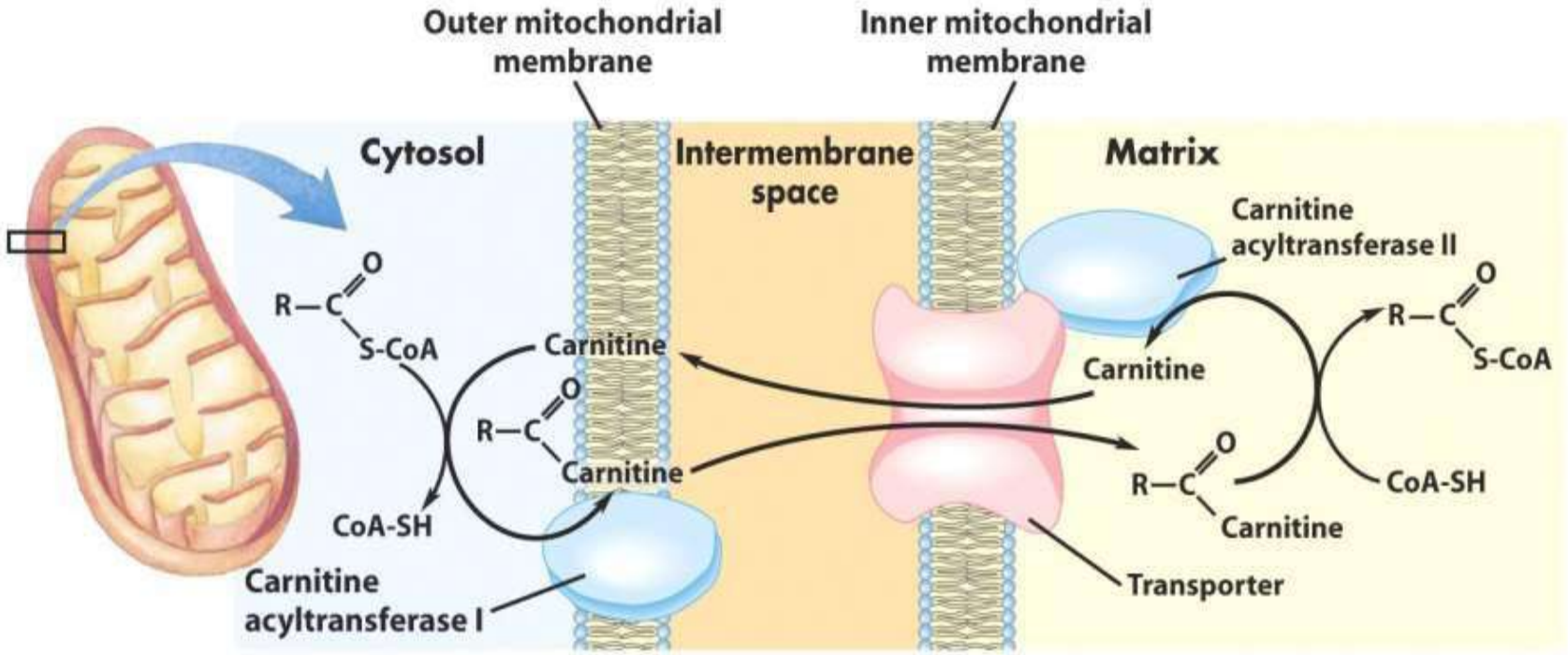
•**Long chain** acyl-CoA cross the inner mitochondria membrane with the help of special transport mechanism called **Carnitine shuttle.**

• First the Acyl groups from acyl-CoA is transferred to carnitine to form acyl carnitine catalyzed by enzyme **carnitine acyltransferase I**, in the outer mitochondrial membrane.

•Acyl-carnitine is then shuttled across the inner mitochondrial membrane by **a translocase** enzyme.

•The acyl group is transferred back to CoA in matrix by **carnitine acyl transferase II**.

Mechanism of Activated FA transport in to the Mitochondria



3. Beta oxidation of FA in the mitochondrial matrix.

• First Long chain FA-acyl-CoA transported in to Mitochondrial matrix.

• Then the Beta oxidation of Fatty acids **(Saturated and Unsaturated)** get start in the matrix of the Mitochondria.

•There are **four** important steps take place with help of different enzyme:

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Enzymes Involved

Step-1 Acyl CoA Dehydrogenase + FAD^+ → Oxidation of FA-acyl-CoA → $FADH_2$

Step-2 Enoyl CoA Hydratase → Hydration

Step-3 Hydroxyacyl CoA dehydrogenase+ NAD^+ → Oxidation → NADH

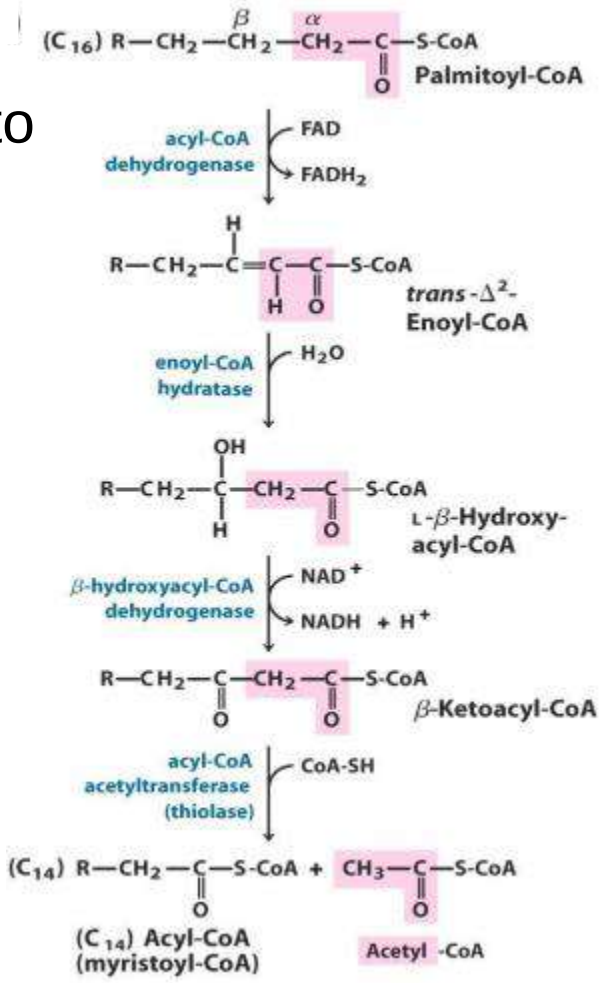
Step-4 β-Ketothiolase → Thiolysis

Note# Thus the breakdown of Fatty acids occurs as a repeating sequence of the above four reaction

Mechanism of β-Oxidation of Palmitoyl-CoA (C16)

•The C16 Saturated acyl CoA such as Palmitoyl CoA, completely degraded in to **8 molecules of acetyl CoA by seven** round of degradation.

•The release of **acetyl CoA** leaves an acyl CoA molecule shortened by 2 carbons.



Over all reaction:

Palmitoyl CoA+7FAD+7NAD+CoA+7H_2O ⟶

8Acetyl CoA +7$FADH_2$+7NADH+H^+

Note# Animal can not produce fatty acid in to Glucose. However plant have two additional enzyme **Isocitrate Lyase** and **Malate Synthase** that convert acetyl-CoA into Oxaloacetate (by Glyoxylate Cycle).

Energetic of FA oxidation e.g. Palmitic (16C):

1.β-oxidation of palmitic acid will be repeated 7 cycles producing 8 molecules of acetyl COA.

2.In each cycle FADH2 and NADH+ H^+ is produced and it will be transported to the respiratory chain where they produced ATP.

- FADH X2= 2ATP
- NADH + H+= 3 ATP

Total ATP per cycle = 5

- So 7 cycles 5x7 = 35 ATP

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3. Each acetyl COA which is oxidized in citric cycle gives 12 ATP (8 x 12 = 96 ATP).

4. 2 ATP are utilized in the activation of fatty acid (It occurs once).

Total Energy gain = Energy produced - Energy utilized

= 35 ATP + 96 ATP - 2 ATP = **129 ATP**

Fatty Acid Metabolism Disorders

- Fatty acid oxidation disorders (FAODs) are a group of rare inherited disorders.

- They are caused by enzymes that do not work properly.

- As oxidation of Fatty acids takes various steps and also many enzymes are involved .

- Problems with any of these enzymes can cause a fatty acid oxidation disorder.

1. CTD stands for “carnitine transporter deficiency: People with CTD have problems using fat as a source of energy for the body.

- CTD begins in infancy, and in childhood. CTD is inherited in an autosomal recessive manner.
- It affects both boys and girls equally.

Symptoms of Childs includes:

✓ extreme sleepiness
✓ behavior changes
✓ irritable mood
✓ poor appetite, and some time fever, vomiting also reported.

2. Hyperlipidemia causes abnormal renal diseases including nephrotic syndrome and chronic renal failure. In this pateints having too much LDL **cholesterol** in blood and not enough HDL **cholesterol** to clear it up.

3. Gaucher disease: It is the result of a buildup of certain fatty substances in certain organs, particularly your spleen and liver.

Gaucher disease is a rare genetic disorder characterized by the deposition of **glucocerebroside** in cells of the macrophage-monocyte system. Which is cause by deficiency of the enzyme **glucocerebrosidase**.

4. Tay-Sachs disease is a rare, neurodegenerative disorder in which excessive accumulation of certain fats (lipids) known as gangliosides in the brain. Which is cause by deficiency of an enzyme hexosaminidase A.

5. **Genetic defects in ketone body synthesis:**

•**Ketone bodies** are acetone, acetoacetate, and beta-hydroxybutyrate toxic acidic chemicals.

• The Synthesis of **Ketone bodies** becomes very high, when not enough insulin produced in the blood and break down of **fat** instead of the glucose for energy in the body occurs.

•In diabetes acetoacetone form faster than normal metabolism. Hence untreated diabetes have high level of **ketone bodies** in the blood and smell of ketone is also observed in breath of diabetic patients.

•The formation of ketone bodies also get affected due to genetic defects in **3-hydroxy3-methylglutaryl-CoA synthase,** and **3-hydroxy-3-methylglutaryl-CoA lyase** enzymes.

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• Lehninger principles of biochemistry (4th ed.): Nelson, D., and Cox, M, W.H. Freeman and Company, New York, 2005 .

Thank You