NATIONAL OPEN UNIVERSITY OF NIGERIA

NSC 207

Medical Biochemistry

Module 2

NSC 207 (Medical Biochemistry II)
Module 2

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Module 2 Fatty Acid Oxidation

Unit 1 Fatty Acid Oxidation

1.0 Introduction

Fatty acids serve as a more efficient source of energy than carbohydrates. This is because they are reduced and anhydrous. The energy yield from 1 g of fatty acids is approximately 9Kcal, compared to 4Kcal for CHOs. Since the hydrocarbon portion of FAs is hydrophobic, these molecules can be stored in a relatively anhydrous environment. CHOs are more highly hydrated. If the human body relied on CHOs to store energy, then a person will need to carry 31kg of hydrated glycogen to have the energy equivalent to 5kg of fat. Hibernating animals provide a good example for utilizing fat reserves as fuel e.g bears hibernate for about 7 months, during which it derives its energy from fat stores.

Utilization of fatty acids for energy production varies significantly from tissue to tissue and depends on the metabolic status of the tissue/ organ i.e fed or fasted, exercising or at rest. They are a major source of energy in cardiac and skeletal muscle, while the brain utilizes them poorly due to limited transport across the blood-brain barrier. Red blood cells cannot oxidize fa because they lack mitochondria. During prolonged fasting, the liver converts acetyl coA generated by FA oxidation and amino acid breakdown to ketone bodies which become a major fuel.

2.0 Objectives

At the end of this unit, you should be able to:

- describe the activation of fatty acids and the transport of fatty acyl coAs into the mitochondria, and list the steps of β-oxidation
- outline the steps involved in β-oxidation
- calculate the net ATP yield from Palmitate oxidation.

3.0 Main Content

3.1 Fatty Acid Activation

When hormones such as epinephrine or glucagon are secreted in response to olevels of glucose, it triggers an intracellular second messenger cascade that phosphorylates hormone – sensitive lipase to break triglycerides into glycerol and free fatty acids. The free fatty acids

move into the blood stream where they are bound by serum albumin and transported to the tissue in which fatty acid oxidation is to take place. They are then released by albumin and they move into the cytosol. Fatty acids that are to be oxidized for energy are first activated in the cytosol, then shuttled into the mitochondria for oxidation. In the mitochondria,FA are broken down to acetylcoA with the production of NADH & $FADH_2$. These 3 products are then used in the mitochondria matrix for energy production via the TCA cycle and oxidative phosphorylation

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$R - COOH + CoA + ATP \quad R - C - S - CoA + AMP + PP_i$

Note that the ATP is hydrolyzed to AMP and pyrophosphate. The pyrophosphate is subsequently hydrolyzed to 2 P_i. Therefore, the activation of a fatty acid consumes two high energy phosphate bonds.

The enzymes of fatty acid oxidation are located in the mitochondrial matrix. Therefore, fatty acyl CoAs generated in the cytosol must be transported into the mitochondrial matrix. The inner mitochondrial membrane is impermeable to CoA and its derivatives, so fatty acyl CoA enters the mitochondria via a special mechanism.

Entry of Fatty Acyl CoAs into Mitochondria

Fatty acyl groups enter the mitochondria by the *carnitine fatty acyl carrier system*

1. Carnitine acyl transferase I located on the outside of the inner mitochondrial membrane catalyzes the reaction:

   Acyl CoA + carnitine $\Longrightarrow$ Acyl carnitine + CoA-SH

2. Carninitine acyl translocase transports the acyl carnitine across the inner mitochondrial membrane into the matrix, and simultaneously transports free carnitine to the cytosol.
3. In the matrix, carnitine acyl transferase II resynthesizes the fatty acyl CoA and releases free carnitine.

- Acyl carnitine + CoA $\Longrightarrow$ Acyl CoA + carnitine

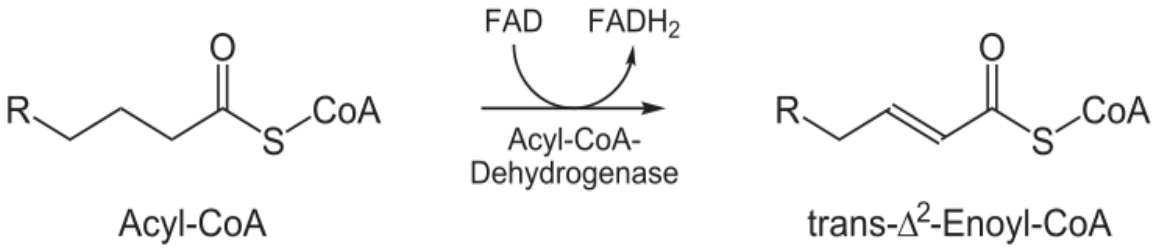
Thus, the carnitine fatty acyl carrier system depends on the presence of CoA on both sides of the inner mitochondrial membrane.

3.2 β-Oxidation of Fatty Acids

In the mitochondrial matrix, fatty acyl CoAs are oxidized to acetyl CoA by a recurring 4 step reaction sequence that cleaves successive two-carbon units off of the fatty acid chain. This process is known as β-oxidation. The reactions of β-oxidation are as follows:

1. Oxidation

The fatty acyl CoA is oxidized by the appropriate acyl CoA dehydrogenase. FAD is reduced in the process:



Acyl-CoA trans-Δ^2-Enoyl-CoA

The mitochondrion contains at least 4 dehydrogenases specific for fatty acyl CoAs of different chain lengths. They are very long chain, long chain, medium chain and short chain acyl-CoA dehydrogenases (VLCAD, LCAD, MCAD and SCAD).

VL CAD – oxidizes straight chain acyl-CoA from C 12 – C 24.

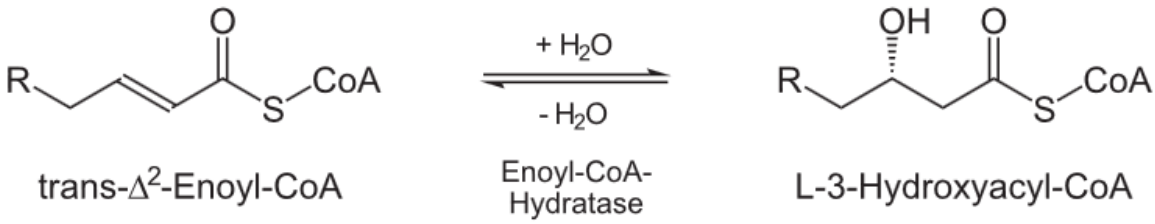
M CAD has broad chain length specificity but is most active with C6 and C8 substrates.

S CAD order of preferred C4 > C6 > C8

LCAD is involved in initiating the oxidation of branched chain FA.

2. Hydration

The unsaturated fatty acyl CoA is hydrated by an enoyl CoA hydratase to yield the β-hydroxyacyl derivative:

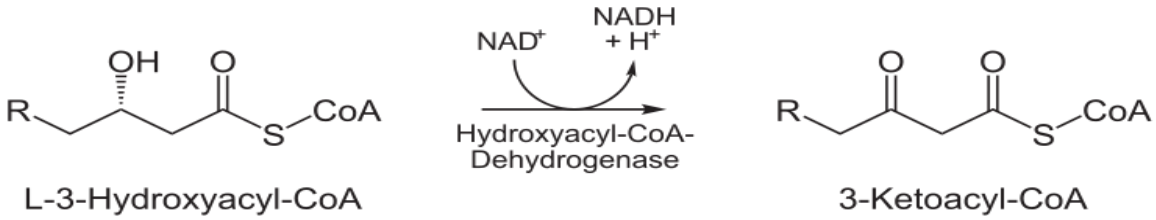


trans-Δ^2-Enoyl-CoA Enoyl-CoA-Hydratase L-3-Hydroxyacyl-CoA

The hydratases also show chain length specificity.

3. Oxidation

The β-hydroxy derivative is oxidized by β-hydroxyacyl CoA dehydrogenase to the corresponding β-ketoacyl CoA, with the reduction of an NAD^+:



L-3-Hydroxyacyl-CoA

3-Ketoacyl-CoA

4. Thiolysis

The final reaction is the thiolytic cleavage of the bond in the β-ketoderivative by an incoming CoA to yield acetyl CoA and the shortened fatty acyl CoA. This reaction is catalyzed by thiolase:

3-Ketoacyl-CoA Acyl-CoA Acetyl-CoA

The shortened fatty acid chain is now ready for the next cycle of β-oxidation.

A feature unique to the oxidation of a long chain FA is that the enoyl CoA hydratase, 3-hydroxyacyl. CoA DH and β-ketothiolase steps are all cat by a membrane bond complex of the 3 enzymes called a trifunctional protein. This complex is different from the enzyme that catalyzes oxidation of medium and short chain acyl CoAs, all of which are soluble proteins in the mitochondria matrix.

3.3 Net ATP Yield from Palmitate Oxidation

Each cycle of β-oxidation produces one **$FADH_2$**, one **NADH**, and one acetyl CoA. During the last β-oxidation cycle, two acetyl CoAs are formed. Thus, the products of complete β-oxidation of palmitate are 8 acetyl CoA,7 $FADH_2$ and 7 NADH.

Oxidation of $FADH_2$, and NADH by electron transport and oxidative phosphorylation yield respectively 1.5 and 2.5 ATPs, while oxidation of acetyl CoA by the TCA cycle coupled to electron transport and oxidative phosphorylation yields 10 ATPs. Therefore, the total yield of oxidation of palmitate to CO_2 and H_2O is 108 ATPs. However, two high-energy phosphate bonds (the equivalent of two ATPs) are consumed in the activation of palmitate. Thus, the net yield of palmitate oxidation is 106 ATPs.

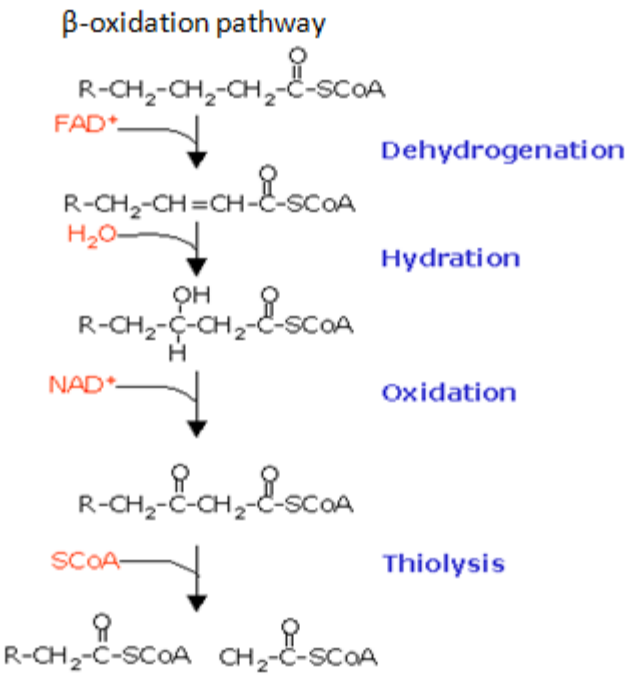


Fig 1.1: β-Oxidation Pathway

4.0 Conclusion

5.0 Summary

In this unit, you have learnt about the following:

- The process of Fatty Acid Activation
- β-Oxidation of Fatty Acids
- Net ATP Yield from Palmitate Oxidation

Activity

Your course facilitator would inform about a practical assignment you are expected to carry out.

6.0 Self Assessment Exercise

1. Explain why fatty acids are more efficient than carbohydrates as fuel molecules
2. Write balanced equations for the first β-oxidation cycle of palmitate.

7.0 References/Further Reading

Katherine, M. A. Rogers & William N. Scott (2011). *Nurses!* Test yourself in anatomy and physiology

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Unit 2 Fatty Acid Oxidation 2

1.0 Introduction

Although β-oxidation is the major pathway of fatty acid oxidation, it is limited to the oxidation of even numbered saturated fatty acids. Other fatty acids (Unsaturated FA, those with odd no of carbon atoms) require modification of the Beta oxidation pathway.

Also, Animal tissues contain minor pathways that involve oxidation of fatty acids at the α- and ω- carbons. The products of α and ω oxidation can enter β-oxidation. Ketone bodies serve as alternate sources of fuel during periods of fasting or starvation and in conditions when the body is unable to utilize glucose, as occurs in Diabetes mellitus. Disorders of fatty acid oxidation include carnitine deficiency, Refsum's disease, Jamaican vomiting sickness, Zellwegers disease and ketoacidosis.

Other Mechanisms of Fatty Acid Oxidation

Most fatty acids (especially saturated fatty acids) can be oxidized by the β- oxidation pathway described in the previous study. However, fatty acids that contain an odd number of carbon atoms, certain unsaturated fatty acids, and methylated fatty acids require modifications of the β-oxidation sequence.

2.0 Objectives

At the end of this unit, you should be able to:

- describe pathways for oxidation of unsaturated fatty acids and fatty acids with an odd number of carbon atoms
- describe α and ω oxidation of fatty acids
- outline the process by which fatty acid oxidation is regulated
- explain how ketone bodies are utilized for energy production
- describe some disorders of fatty acid oxidation.

3.0 Main Content

3.1 Oxidation of Unsaturated Fatty Acids

While the double bond that is generated between the α and β carbons in the first step of β-oxidation is in the trans configuration,the double bond in most unsaturated fatty acids are cis, and yield the D-isomer when hydrated by the hydratase. These D isomers are converted to the L-isomers by a racemase. β- oxidation then proceeds normally. If a double bond in an unsaturated fatty acid is located between the β and γ carbon atoms instead of between the α and β carbons, the fatty acid cannot directly enter β-oxidation.

Instead, an *isomerase* moves the double bond to the correct position, and β-oxidation proceeds. If a double bond in an unsaturated fatty acid is located between the β and γ carbon atoms instead of between the α and β carbons, the fatty acid cannot directly enter β-oxidation. Instead, an *isomerase* moves the double bond to the correct position, and β-oxidation proceeds.

3.2 Oxidation of Fatty Acids Containing an Odd Number of Carbons

Fatty acids that contain and odd number of carbons are oxidized by β-oxidation, with the successive removal of two-carbon units, until a final three-carbon propionyl CoA is obtained. Propionyl CoA is utilized as shown in Figure 2.3. First, propionyl CoA is carboxylated to D-methylmalonyl CoA by propionyl CoA carboxylase. Methylmalonyl CoA. racemase then converts D-methylmalonyl CoA to L-methylmalonyl CoA. Finally, L-methyl CoA undergoes rearrangement by methlmalonyl CoA mutase to yield succinyl CoA. As a result of entering the TCA cycle, succinyl CoA may be oxidized to CO_2 and H_2O or used as a precursor for gluconeogenesis.

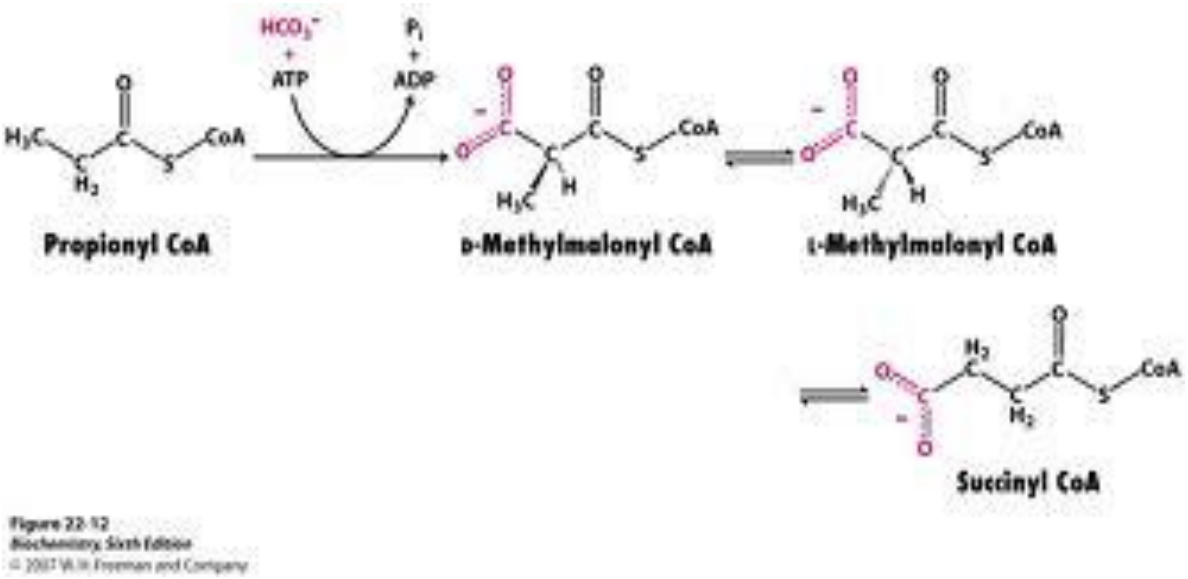

Figure 22-12
Biochemistry, Sixth Edition
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Fig 2.1: Metabolism of Propionyl coA

3.3 α- and ω-Oxidation of Fatty Acids

Animal tissues contain minor pathways that involve oxidation of fatty acids at the α- and ω-carbons. The products of α and ω oxidation can enter β-oxidation.

α-Oxidation

During their metabolism, some fatty acids are hydroxylated on C-2 (the α carbon). The resulting α-hydroxy derivatives may be further oxidized to yield CO_2 and fatty acids consisting of one less carbon atom, which may then be metabolized by β-oxidation. α -

Oxidation, which occurs in the endoplasmic reticulum, is especially important in the oxidation of methylated fatty acids. It is a method of generating odd-chain fatty acids.

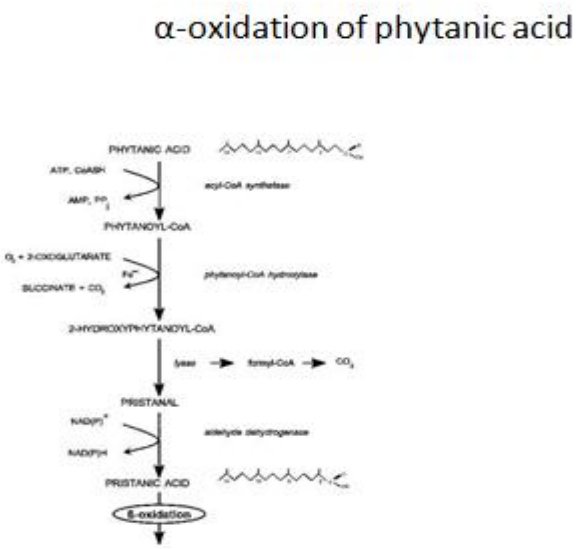

Fig 2.2: α-oxidation of phytanic acid

ω-Oxidation

Fatty acids that are hydroxylated on the terminal carbon can undergo ω-oxidation. The ω-hydroxy group is converted to an ω-carboxy group, yielding an α, ω-dicarboxylic fatty acid. If this dicarboxylic fatty acid enters β-oxidation, it can be oxidized from both ends. ω-Oxidation of fatty acids has been detected on the endoplasmic reticulum of liver cells.

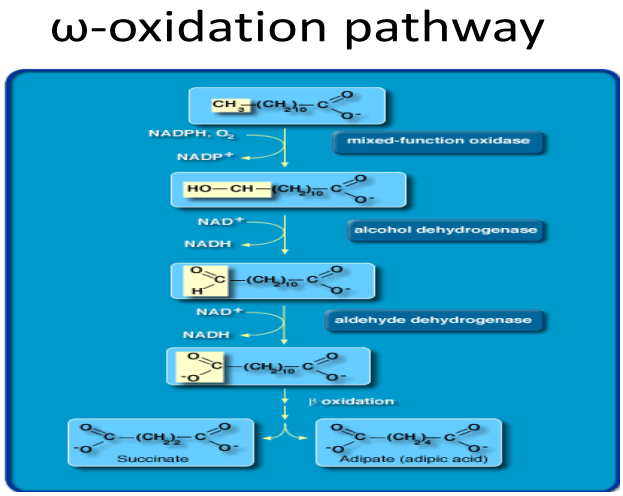

Fig 2.3: ω-Oxidation pathway

3.4 Regulation of Fatty Acid Oxidation

The rate of fatty acid oxidation in Mitochondria is controlled by regulating the entry of substrate into this organelle. The key enzyme is CPT1. In the fed state, malonyl coA, whose formation is the commitment step of FA synthesis) inhibits CPT1, while the enzyme is made very active in the fasted state. Fa oxidation in muscle is also regulated by malonyl coA, even though this tissue does not synthesize Fas. Muscle contains an isozyme os acetyl coA carboxylase, which produces malonyl coA solely for the purpose of regulation of CPT1. The enzyme is activated by citrate and inhibited by phosphorylation. It is phosphorylated by both protein kinase A and AMP-dependent kinase. Phosphorylation by the former enzyme allows fatty acid oxidation to be regulated by dietary status.

In the fed state, high concentrations of insulin results in low levels of phosphorylation. The enzyme produces malonyl coA , which inhibits CPT1 and blocks fatty acid oxidation. The second kinase, which is regulated by AMP, limks the rate of fatty acid oxidation to the energy status of the muscle. In resting muscle, AMP levels are low. As a result, the AMP-dependent kinase is inactive, acetyl –coA carboxylase is active, and the malonyl coA that is generated inhibits CPT1 kinase. The resulting inhibition of acetyl coA carboxylase results in low levels of malonyl coA and the activation of both CPT1 and fatty acid oxidation.

3.5 Ketone Bodies

Ketone bodies are water-soluble products of lipid oxidation that are formed in liver and kidney mitochondria during prolonged fasting. The ketone bodies, acetoactic acid and its reduction product- hydroxybutyric acid, are made from acetyl coA that is produced by fatty acid and amino acid catabolism. Ketone body synthesis occurs in the mitochondrial matrix and begins with condensation of two acetyl coA molecules to form acetoacetyl coA, in a reaction that is the reverse of the final step of β - oxidation.

The enzyme involved, β-ketothiolase is an isozyme of the enzyme that functions in β-oxidation. HMG-coA synthase catalyzes the condensation of acetoacetyl coA with another molecule of acetyl coA to form β-hydroxy- β-methyl glutayl coenzyme A(HMG-coA). HMGcoA lyase then cleaves HMGCoA to yield acetoacetic acid and acetyl coA. Some of the acetoacetate is reduced to D- β-hydroxybutyrate in lever mitochondria by β-hydroxybutyrate dehydrogenase. The extent of this reaction depends on the intramitochondrial [NADH]/[NAD+] ratio. During fasting, the oxidation of fatty acids generates NADH. Part of this is used in the reduction of acetoacetate. The β-hydroxybutyrate and acetoacetate are released from liver and kidney for use by other tissues.

Some aceto-acetate continually undergoes slow, spontaneous nonenzymatic decarboxylation to acetone. Acetone formation is negligible under normal conditions, but at high cobn centrations of acetoacetate, which can occur in severe diabetic ketoacidosis, acetone can reach levels high enough to be detectable in the breath. HMG CoA is also an intermediate in cholesterol synthesis. However, the HMG-coA used for ketone body and cholesterol synthesis are present in different metabolic pools. While the HMG-CoA used for ketogenesis is synthesized in hepatic mitochondria by an isozyme of HMG-CoA synthase that is expressed at high levels during prolonged fasting.

Moreover, HMG-CoA lyase, which converts HMG CoA to acetoacetate and acetyl CoA is expressed only in hepatic mitochondria. In contrast, HMG-CoA for cholesterol synthesis is made at low levels in the cytosol of many tissues by a cytosolic isozyme of HMG-CoA synthase.

Acetoacetate and β- hydroxybutyrate are excellent fuels for many non hepatic tissues including cardiac muscle, skeletal muscle and brain, particularly when glucose is in short supply or inefficiently used. The brain begins to utilize ketone bodies after 2-3 days of fasting. This reduces the requirement for glucose production by gluconeogeesis during a prolonged fast, thus sparing muscle proteins. They also serve as precursors for cerebra lipid synthesis during the neonatal period. They are metabolized in the mitochondria of non hepatic tissues. B-hydroxybutyrate dehydrogenase converts β-hydroxybutyrate to acetoacetate by an NAD-linked oxidation. Acetoacetate is the converted to its CoA derivative by acetoacetate:succinyl-CoA transferase, which is present in tissue that use ketone bodies but is not present in liver. Succinyl CoA serves as the source of the CoA. B-ketothilase converts tha acetoacetyl CoA into 2 acetyl CoAs, which enter the TCA cycle for energy production.

Thus, the key enzymes of ketone body synthesis, HMG-CoA synthase and HMG-CoA lyase are present in liver (and kidney cortex) but not in other tissues. The key enzymes of ketone body utilization, acetoacetate: succinyl-CoA transferase is found in many tissues, but not in liver. These differences ensure that ketone bodies are made in the liver and utilized in other tissues.

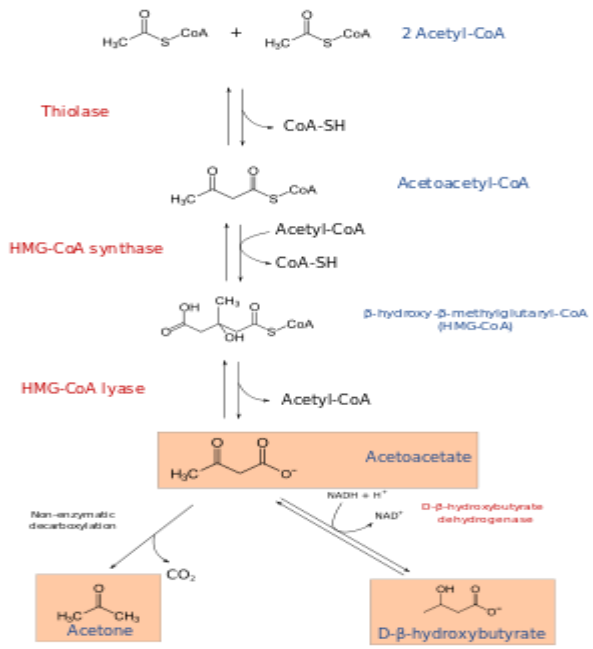

Fig 2.4: Ketogenesis

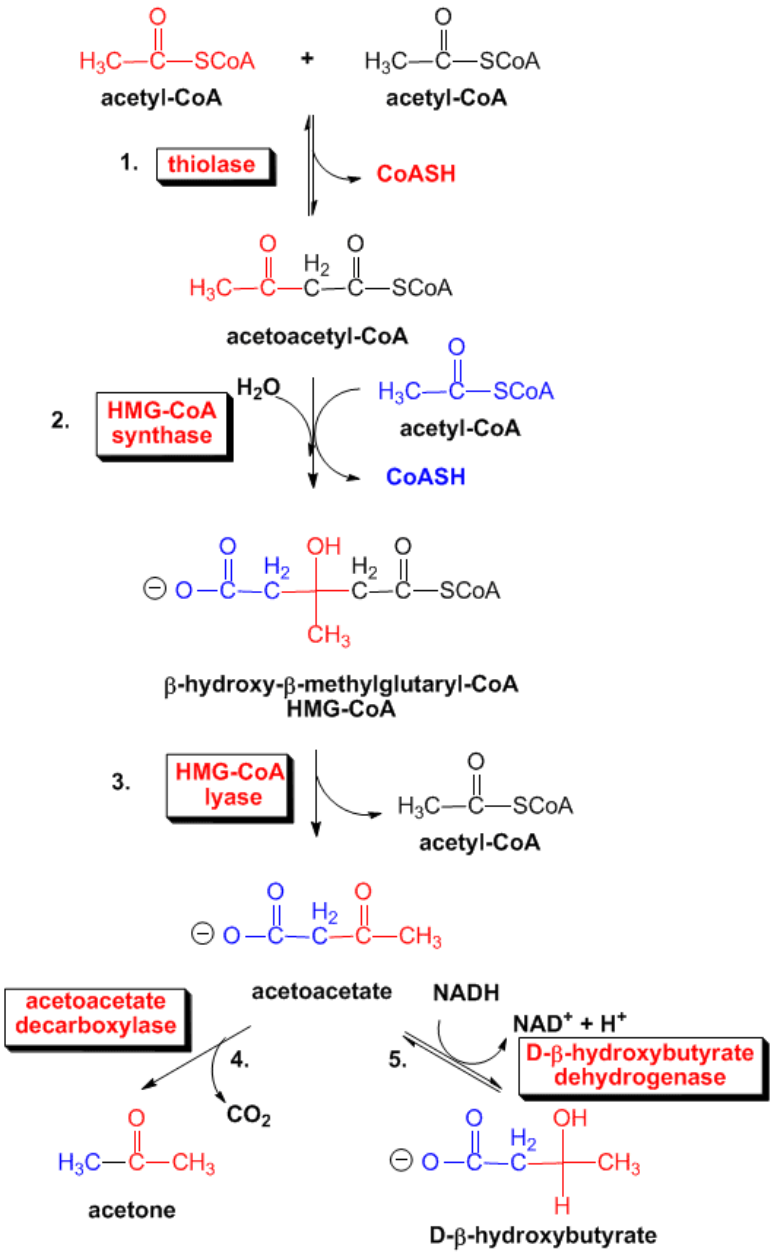

Fig 2.4b: Utilization of ketone bodies for energy production

3.6 Clinical Aspects

Carnitine deficiency

Occurs particularly in the new-born and preterm infants due to inadequate biosynthesis or renal leakage. Symptoms include hypoglycemia, lipid accumulation and muscular weakness. Treatment is by oral supplementation with carnitine.

Refsum's disease

An autosomal recessive neurologic disorder of lipid metabolism which occurs due to a metabolic defect that results in accumulation of phytanic acid and phytol (dietary lipids derived from chlorophyll.) Affected individuals may display retinitis pigmentosa, diminished deep tendon reflexes and incoordination.

Zellweger's syndrome
Occurs in individuals with a rare inherited absence of peroxisomes in all tissues. They accumulate C26-C38 polyenoic acids in brain tissue and also exhibit a generalized loss of peroxisomal functions. The disease causes severe neurological symptoms, and most patients die in the first year of life.

Jamaican Vomiting Sickness
Caused by eating the unripe fruit of the akee tree which contains the toxin hypoglycin. This inactivates medium and short chain acyl-CoA dehydrogenase, inhibiting β- oxidation and causing hypoglycemia and is caused by a lack of mitochondrial medium chain acyl CoA dehydrogenase.

Ketoacidosis
Higher than normal quantities of ketone bodies present in blood or urine constitute ketonemia and ketonuria respectively. The overall condition is called ketosis. It is pathologic in Diabetes Mellitus. Non pathologic forms of ketosis are found under conditions of high fat feeding and after severe exercise in the post absorptive phase.

4.1 Conclusion

5.0 Summary

In this unit, you have learnt about the following:

- Oxidation of Unsaturated Fatty Acids
- Oxidation of Fatty Acids Containing an Odd Number of Carbons
- α- and ω-Oxidation of Fatty Acids
- Regulation of fatty acid oxidation
- Ketone Bodies
- Clinical Aspects.

6.0 Self Assessment Exercise

1. Describe pathways for oxidation of unsaturated fatty acids and fatty acids with an odd number of carbon atoms
2. Describe α and ω oxidation of fatty acids
3. Outline the process by which fatty acid oxidation is regulated
4. Explain how ketone bodies are utilized for energy production
5. Describe some disorders of Fatty acid oxidation

Activity: Your course facilitator would inform you about a practical assignment you expected to carry out

7.0 References/Further Reading

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