BIOCHEMISTRY

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METABOLISM OF LIPIDS

II. Lipolysis (Breakdown of TG)

TG in adipose tissue undergoes hydrolysis by a **hormone-sensitive TG lipase enzyme** to form free fatty acids and glycerol.

Adipolytic lipases are three:

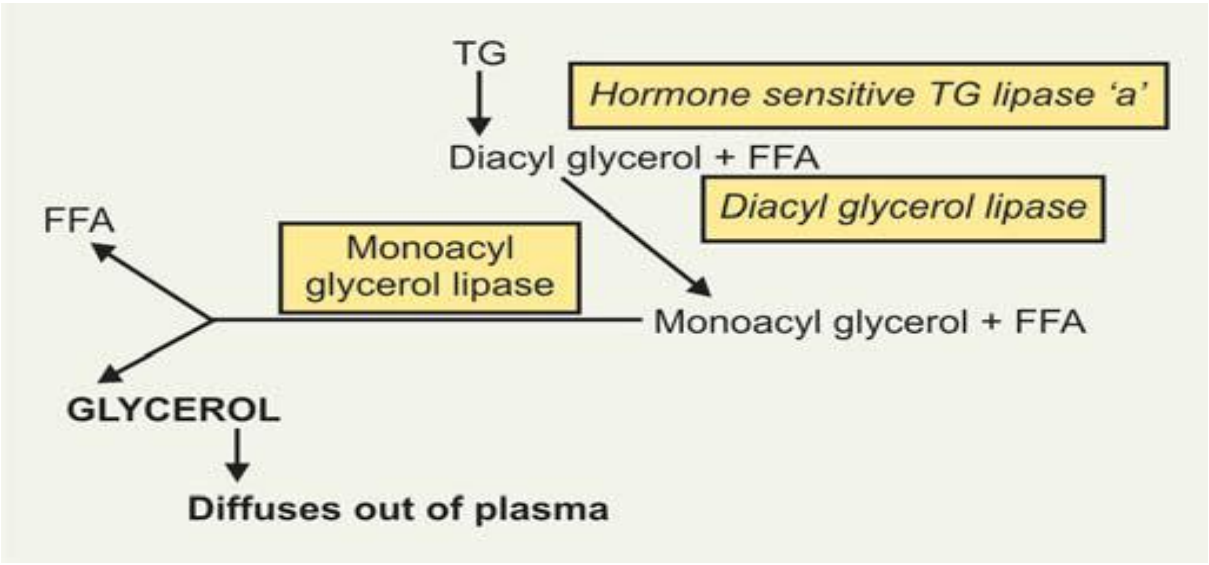
1. Hormone sensitive triacyl glycerol lipase: Key regulating enzyme.

2. Two others are not hormone-sensitive:

- **Diacyl glycerol lipase**
- **Monoacyl glycerol lipase.**

These lipases are distinct from lipoprotein lipase that catalyses lipoprotein TG (Present in chylomicrons and VLDL) hydrolysis before it is taken up by extrahepatic tissues.

The free fatty acids formed by lipolysis can be reconverted in the tissue to acyl-CoA by Acyl-CoA synthase and re-esterified with α-Glycero-P to form TG. Thus, there is a continuous cycle of lipolysis and reesterification within the tissue.



Note

When the rate of re-esterification is less than rate of lipolysis, FFA accumulates and diffuses into the plasma where it raises the level of FFA ↑ in plasma.

Adipose tissue metabolism in diabetes mellitus and in starvation:

In diabetes mellitus and in starvation, availability of glucose in adipose tissue is grossly reduced, resulting to lack of α-Glycero-P. Thus, rate of re-esterification is decreased↓. Lipolysis is greater than re-esterification, resulting to accumulation of FFA and increase in plasma FFA level.

INFLUENCE OF HORMONES ON ADIPOSE TISSUE

Rate of release of FFA from adipose tissue, is affected by many hormones which influence either the (a) rate of esterification or (b) the rate of lipolysis.

I. List of hormones that increase the rate of esterification:

1. **Insulin** is the principal hormone: Net result of insulin on adipose tissue is to inhibit the release of free FA from adipose tissue, which **results in fall of circulating plasma FFA↓**.
2. **Prolactin** effective in large doses: Effect of prolactin is similar to insulin, provided it is given in larger doses.

II. List of hormones that increases the rate of lipolysis:

Catecholamines (epinephrine and norepinephrine) are the principal hormones. Other lipolytic hormones are:

- **Glucagon,**
- **Growth hormone,**
- **Glucocorticoids**
- **ACTH,** α **and** β **MSH, TSH** and **Vasopressin.**

These hormones accelerate the release of FFA from adipose tissue and **raise the plasma FFA ↑** level by increasing the rate of lipolysis of TG stores.

BROWN ADIPOSE TISSUE

Types of storage fats: There are **two types** of storage fats: • **Storage "white" fat** present in depot fats—predominant
• In addition to usual white storage fat, another type of **"pigmented" brown fat** is stored in some species including humans.

Role in Thermogenesis

1. Brown adipose tissue is involved in metabolism particularly at times when a heat generation is necessary.
Thus, **the tissue is extremely active**
• In arousal from hibernation,
• In animals exposed to cold, and
• In heat production in newborn animals.
2. Though not a prominent tissue in humans, recently it has been shown to be active in normal individuals, where it appears to be responsible for **diet-induced** Thermogenesis, which may account for how some persons can eat and do not get fat.

Characteristics of Brown Adipose Tissue: It is characterized by:

1. **A high content of mitochondria,**
2. **A high content of cytochromes,**
3. **A well-developed blood supply,**
4. Also relatively **rich in carnitine**, which is significant for

FA oxidation,

5. Unlike white adipose tissue, it **has the enzyme glycerokinase.**

OXIDATION OF FATTY ACIDS

Sources of Plasma FFA

Plasma free fatty acids are derived:
1. Mainly from lipolysis in adipose tissue **(Pool-1)**.
2. Portion of FFA is derived from degradation of circulating chylomicrons and VLDL by the action of the enzyme lipoprotein lipase **(Pool-2)**.
3. A small portion of plasma FFA is derived from absorption of dietary source specially small chain and medium chain fatty acids.

4. Also FFA is obtained from synthesis from acetyl-CoA in liver cells, which are incorporated in TG.

Methods by which fatty acids are oxidized in the body are as follows:

• β-**oxidation:** Principal method of oxidation of FA.
Other ancillary and specialized methods are:
• α-**oxidation,**
• ω-**oxidation,** and
• **Peroxisomal FA oxidation.**

A. β-OXIDATION

Principal method by which FA is oxidized is called β-oxidation. Several theories have been proposed to explain the mechanism of the oxidation of FA chains.

Tissues in which β-Oxidation is carried out:

The circulating FA are taken up by various tissues and oxidized. Tissues like **liver, heart, kidney, muscle, brain, lungs, testes and adipose tissue** have the ability to oxidize long chain FA. In cardiac muscle, fatty acids are an important fuel of respiration (80% of energy derived from FA oxidation).

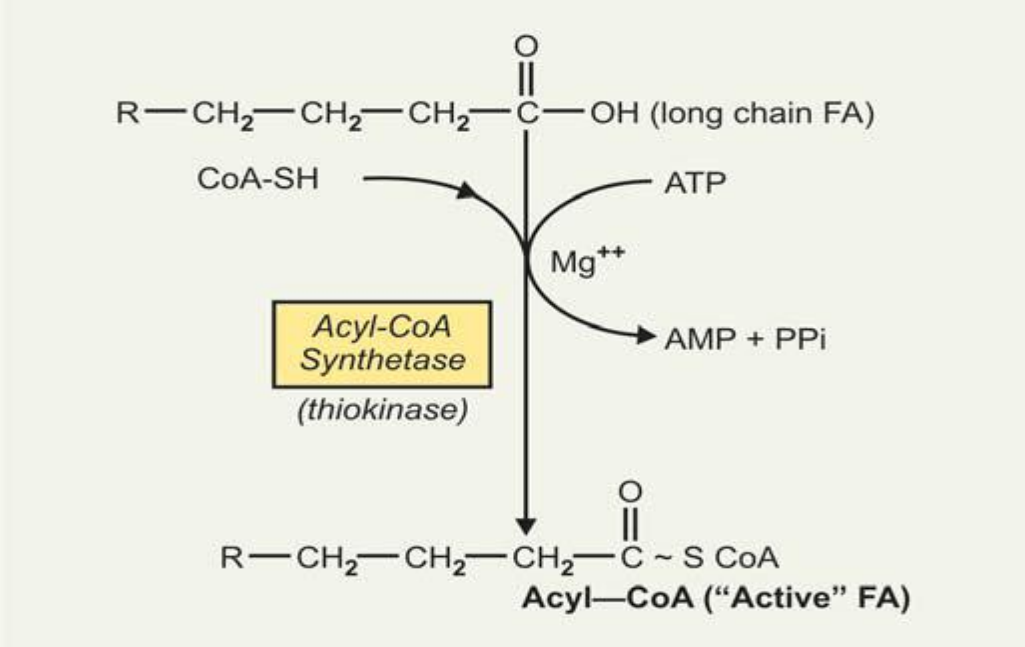
Enzymes Involved in β-Oxidation

β-**oxidation takes place in mitochondrion.** Several enzymes known collectively as **FA-oxidase system** are found in the mitochondrial matrix, adjacent to the respiratory chain, which is found in the inner membrane. These enzymes catalyse the oxidation of FA to acetyl-CoA.

Activation of FA:

Fatty acids are in cytosol of the cell **(extramitochondrial).** Fatty acids must be first activated so that they participate in metabolic pathway. The activation requires energy which is provided by ATP. In presence of ATP, and coenzyme A, the enzyme **acyl-CoA synthetase** (previously called as thiokinases) catalyses the conversion of a free fatty acid to an 'active' FA (acyl-CoA).
The presence of inorganic pyrophosphatase ensures that activation goes to completion by facilitating the loss of additional high energy ~ P bond of PPi.

Thus, in effect 2 ~ P bonds are expended during activation of each FA molecule. Not only saturated FA but unsaturated FA and –OH fatty acids are also activated by these acyl-CoA synthetases.



Location and types of Acyl-CoA synthetases:

The enzymes are found in the endoplasmic reticulum and inside (for short-chain FA) and outside (for long-chain FA) of the mitochondria. Several varieties of the enzyme have been described, each specific for FA of different chain lengths.

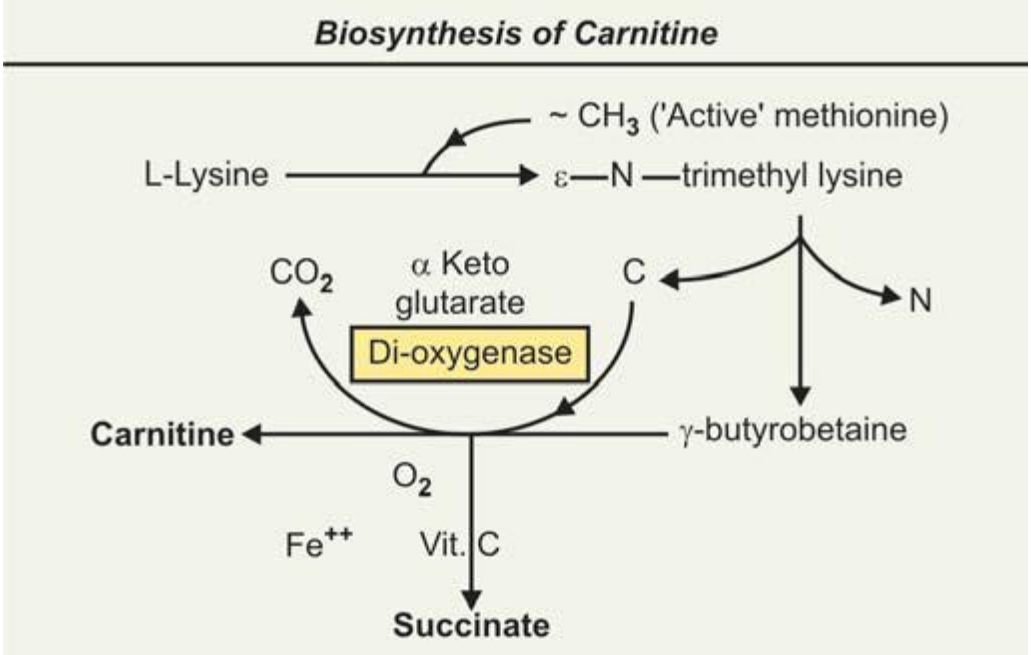
- Acetyl-CoA synthetase → acts on acetic acid and butyric acid
- Second medium chain synthetase → acts on FA with chain length C4 to C12
- Long chain acyl-CoA synthetase → Acts on FA with chain length C8 to C22
- Recently, a GTP-specific mitochondrial acyl-CoA synthetase described which forms GDP + Pi.

CARNITINE AND ITS ROLE IN FA METABOLISM

"Active" FA (acyl-CoA) is formed in cytosol, whereas β-oxidation of FA occurs in mitochondrial matrix. **Acyl-CoA is impermeable to mitochondrial membrane**. Long chain activated FA penetrate the inner mitochondrial membrane only in combination with carnitine.

Distribution*:* Carnitine is widely distributed in yeast, milk, liver and particularly large quantities in muscles and in meat extracts.

Biosynthesis of carnitine: It is synthesised from lysine and methionine in liver principally, also in kidneys. Synthesis of carnitine is shown below in the box.



Functions*:* Carnitine is considered as a "carrier molecule";

It acts like a ferry-boat. It transports long-chain acyl-CoA across mitochondrial membrane which is impermeable to acyl-CoA.

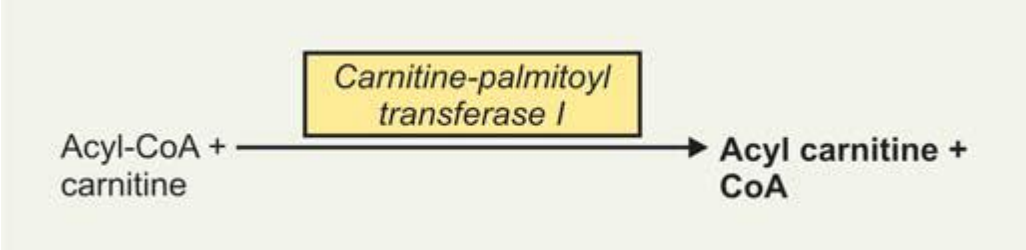
• Facilitates transport of long-chain acyl-CoA for oxidation in mitochondria.

• Facilitates exit of acetyl-CoA and acetoacetyl-CoA from within mitochondria to cytosol, where FA synthesis takes place.

Mechanism of transport of long-chain acyl-CoA:

Activation of lower FA and their oxidation may occur within the mitochondria, independently, of carnitine; but long chain acyl-CoA (or FFA) will not Penetrate mitochondria and become oxidized unless they form **acyl carnitines.**

• An enzyme **carnitine-palmitoyl transferase I**, present on the inner side of the outer mitochondrial membrane, converts long-chain acyl-CoA to **acyl-carnitines;** which is able to penetrate mitochondria and gain access to the β-oxidation systems of the enzymes.



• Another enzyme **carnitine-acyl-carnitine translocase** acts as a membrane-carnitine exchange transporter. Acyl-carnitine is transported in, coupled with the transport out of one molecule of carnitine.

• The acyl-carnitine then reacts with CoA-SH, catalysed by **carnitine-palmitoyl transferase II,** attached to the inside of the inner membrane. Acyl-CoA is reformed in the mitochondrial matrix and carnitine is liberated.

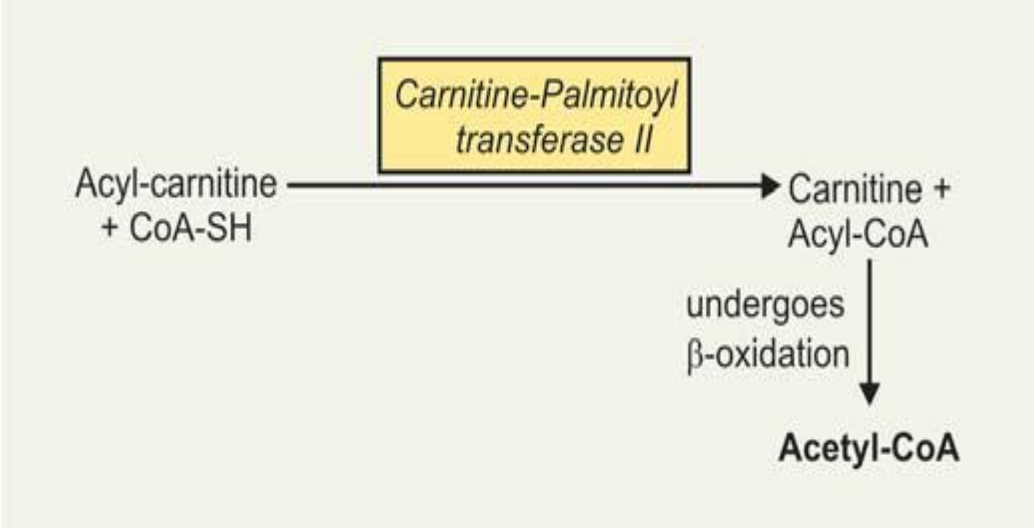


Figure: shows the mechanism of action of carnitine.