Lipid breakdown and metabolism of ketone bodies

Content of subsection:

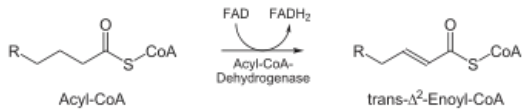
1. Introduction to lipid breakdown and ketone body metabolism.
2. Lipids as an energy source – TAG degradation in cells, β-oxidation of fatty acids.
3. Formation and use of ketone bodies.

Introduction to lipid breakdown and ketone body metabolism

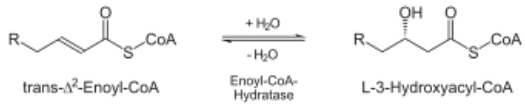
Triacylglycerols (TAGs) store large amounts of chemical energy. As an energy store, they are very advantageous because 1 g of anhydrous TAG stores six times more energy than 1 g of hydrated glycogen. The complete oxidation of 1 g of TAG yields approximately **38 kJ**, while only 17 kJ are obtained from 1 g of carbohydrates or proteins. A 70 kg man stores approximately **400,000 kJ** in his TAGs - the total weight of a TAG is around 10.5 kg. These supplies could allow us to survive several weeks of starvation. The main site of TAG accumulation is the cytoplasm of adipocytes.

Fatty acid oxidation

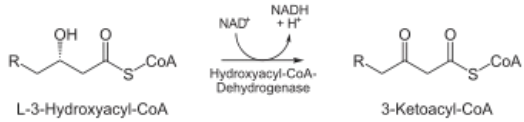
Individual types of fatty acid oxidation are indicated by Greek letters, which determine the carbon atom on which the reactions take place. **β-oxidation** taking place in the **mitochondrial matrix** is of major importance. Enzymes catalyzing the so-called **ω-** and **α-oxidation** occur on the membranes of the **endoplasmic reticulum**.



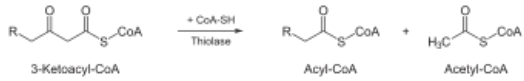
Beta oxidation of fatty acids - 1st step



Beta oxidation of fatty acids - 2nd step



Beta oxidation of fatty acids - 3rd step



Beta oxidation of fatty acids - 4th step

Conversion of fatty acids to glucose

Animals cannot convert fatty acids into glucose. Fatty acids represent a rich source of energy for gluconeogenesis, but glucose is not formed from their carbon atoms (with the exception of fatty acids with an odd number of C). **Acetyl-CoA cannot be converted** to either pyruvate or oxaloacetate - both carbons are split off as CO_2 during the Krebs cycle. The pyruvate dehydrogenase reaction is irreversible. Interestingly, plants also have two other enzymes that allow them to convert AcCoA to OAA, in the so-called **glyoxylate cycle**.

Links

Related articles

- Ketone bodies
- Glycogen
- Beta oxidation of fatty acids (FBLT)
- Citrate cycle

External links

- http://fblt.cz/en/skripta/ii-premena-latek-a-energie-v-bunce/11-odbouravani-lipidu-a-metabolismus-ketolatek/

Lipids as an energy source – TAG degradation in cells, β-oxidation of fatty acids

The utilization of lipids for energy production takes place in three basic phases:

1. **Lipid mobilization** - hydrolysis of TAG to MK and glycerol and their transport blood.
2. **Activation of MK** in the cytosol and **their transport** into the matrix mitochondria.
3. **β-oxidation** - breaking down MK into acetyl~CoA, which enters the Krebs cycle, or ketone bodies are formed from it.

Lipid mobilization – lipolysis

The mobilization of stored lipids is enzymatically ensured by **hormone-sensitive lipase'** (*HSL*). It catalyzes the reaction:

TAG → 3 MK + glycerol

The released fatty acids bind to *serum albumin*, which transports them to their destination (e.g. the liver). Glycerol is transported freely dissolved in plasma.

Regulation of lipolysis

As the name suggests, the enzyme is under strict hormonal control. Its activity is stimulated by the ``phosphorylation *of its molecule. Insulin as an anabolic hormone causes its **inhibition**, counterregulatory hormones (glucagon, catecholamines) or thyroid hormones on the contrary **activate** it.*

Reference

- ws:Lipidy jako zdroj energie

Utilization of glycerol

Glycerol utilization

Penetration of fatty acids into cells

The way of passing through the cell membrane **depends on the length of the chain**. Short chain fatty acids (↓12C) can penetrate **by simple diffusion**. Those with a longer chain use different **transport systems** in the membrane enabling their facilitated diffusion - for example **FATP** (fatty acid transport protein) or **FAT/CD36** (fatty acid translocase).

Activation of fatty acids

Fatty acid activation occurs in the **cytosol, on the outer mitochondrial membrane** immediately after their entry into the cell. Without the activation, it is impossible to consider the involvement of their molecules in metabolism. Activation then simultaneously maintains their **steady concentration gradient** (analogous to glucose phosphorylation - see glycolysis). The principle of fatty acid activation is the ester linkage of a fatty acid binding molecule to the **SH-group of coenzyme A** via **acyl-Coenzyme A synthetase** (fatty acid thiokinase):

MK + ATP + HS−CoA → acyl−CoA + AMP + 2 P_i

The activation of the fatty acid actually passes off in two stages. First, **acyl adenylate** (acyl-AMP) is formed and in the second phase AMP is exchanged for **coenzyme A**.

Entry of fatty acids into the mitochondria matrix

Entry of fatty acids into matrix mitochondria

Beta oxidation of fatty acids

β-oxidation takes place only under **aerobic conditions** - it is closely related to the respiratory chain. The individual reactions of β-oxidation of fatty acids are catalyzed by four enzymes :

1. **Acyl~CoA−dehydrogenase** – the prosthetic group is FAD;
2. **Enoyl~CoA−hydratase** ;
3. **L-3-hydroxyacyl~CoA-dehydrogenase** – the coenzyme is NAD + ;
4. **β-ketothiolase**

The reactions can be summarized in the sequence of dehydrogenation – hydration – dehydrogenation – thiolytic cleavage . The first three reactions are analogous to those occurring in the Krebs cycle starting with succinate (see Krebs cycle):

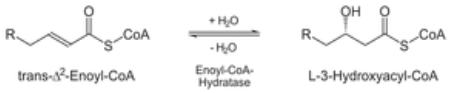
Oxidation of **succinate** to fumarate using succinate dehydrogenase - FAD is the cofactor.

1. Oxidation of succinate to fumarate using **succinate dehydrogenase** - FAD is the cofactor.
2. **Addition of water** to the double bond in fumarate results in malate catalyzed by fumarate hydratase.
3. **Oxidation of malate** to oxaloacetate using the enzyme **malate dehydrogenase** – the cofactor is NAD + .

1. Acyl~CoA-dehydrogenase - first oxidation

This enzyme catalyzes the formation of a double bond between the 2nd (α) and 3rd (β) carbons of the fatty acid chain. This is a ***stereospecific reaction*** that produces trans-enoyl-CoA. The electron acceptor is **FAD** . There are different types of dehydrogenases in cells, which differ in the length of the MK chain that they oxidize:

- short MK (4–6 C),
- medium MK (6–10 C),
- long MK (12–18 C).

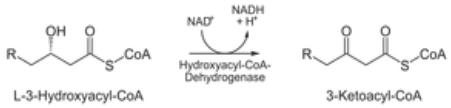


2. Enoyl-CoA-hydratase

This enzyme catalyzes the **hydration of the trans double bond** formed in the first step. A **hydroxyl group** is formed – L-3-hydroxyacyl-CoA.

3. Hydroxyacyl-CoA-dehydrogenase

This enzyme catalyzes the **oxidation** of the hydroxyl group at the third (β) carbon to a keto group. Electrons are accepted by the coenzyme NAD + .



4. β-ketothiolase

The final step of one turn of β-oxidation is **thiolytic cleavage** catalyzed by β-ketothiolase. It involves an attack of the SH− group of the coenzyme on the β-keto carbon of the fatty acid chain. The reaction leads to the formation of AcCoA and acyl-CoA, which is two carbons shorter.

One turn of β-oxidation

β-oxidation is a cyclic process, one turn of which can be written as:

Acyl−CoA + FAD + NAD^+ + HS−CoA → acyl−CoA (2 C shorter) + $FADH_2$ + NADH+H^+ + AcCoA

The intermediate product (acyl−CoA 2 C shorter) enters the next round of β-oxidation. Most fatty acids have an even number of Cs, so the last turn converts butyryl-CoA into two molecules of AcCoA.

Yield of complete oxidation of palmitate

To give an idea of the overall yield of fatty acid oxidation, here is the equation and energy balance of the complete oxidation of palmitate:

Palmitoyl~CoA + 7 FAD + 7 NAD^+ + 7 HSCoA + 7 H_2O → 8 AcCoA + 7 $FADH_2$ + 7 NADH+H^+

As you can read in the article on the respiratory and ATP production, article on the respiratory chain and ATP production , we cannot determine the exact amount of ATP produced in the respiratory chain during the oxidation of nutrients. Therefore, please consider the following numbers only as approximate and generally correct quantities. We present them here so that you can compare them with the oxidation of other nutrients, eg glucose. In the respiratory chain, 2.5 (3) ATP is obtained from one NADH and 1.5 (2) ATP from one FADH 2 , which in total represents:

- 7 × $FADH_2$ = 10, 5 (14) ATP,
- 7 × NADH = 17, 5 (21) ATP
- Oxidation of 8 AcCoA in the Krebs cycle = 80 (96) ATP.

The total profit stopped at a total of 108 (131) ATP. But we used 2 ATP to activate the fatty acid , so the net gain is 106 (129) ATP .

References:

Fontana J., Trnka J., Maďa P., Ivák P. et al.: Transformation of substances and energy in the cell. In: Functions of cells and the human body : Multimedia scripts.

Regulation of beta-oxidation of fatty acids

Kategorie:Vložené články

Regulation of β-oxidation takes place at the level **of entry of fatty acids into mitochondria** – more precisely at the level of the carnitine transporter **carnitine acyltransferase I** (CAT I). This enzyme is **inhibited by** the intermediate product of fatty acid formation - **malonyl~CoA**. We are talking about the so-called **cross regulation**. The principle is that fatty acid synthesis takes place in the cytosol, just like the reaction catalyzed by CAT I. Malonyl~CoA is formed as a product of the first reaction of fatty acid formation. Cross-regulation prevents simultaneous synthesis and degradation of MK. Inzulin inhibits β-oxidation, while counterregulatory hormones activate it.Kategorie:Biochemie Kategorie:FBLT

Fatty acids with an odd number of C

Oxidation of odd-numbered fatty acids

Breakdown of unsaturated fatty acids

Most of the unsaturated fatty acids in the human body and in food have **a cis configuration** of double bonds. Their degradation in β-oxidation proceeds by the process described above until their double bond comes into contact with enoyl-CoA hydratase. This requires only **trans isomers** – it is therefore necessary to convert the cis isomer to trans using **an isomerase**.

Breakdown of very long chain fatty acids

Oxidation of very long chain **fatty acids** (more than 18 carbons) takes place in **peroxisomes**. The first step is catalyzed by **flavoprotein dehydrogenase**, which transfers electrons to O_2 – H_2O_2 is formed :

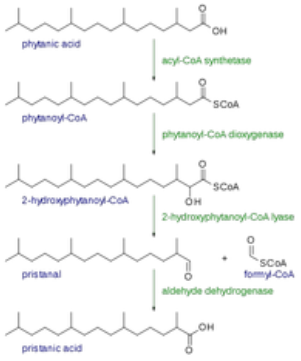
1. $FADH_2$ from the first step is reoxidized not in the respiratory chain, but by reaction with O_2: **$FADH_2 + O_2 \rightarrow FAD + H_2O_2$**
2. Peroxisomal catalase decomposes H_2O_2: **$2\ H_2O_2 \rightarrow 2\ H_2O + O_2$**

Oxidation ends with octanoyl-CoA, which is transported from peroxisomes bound to carnitine and goes to **β-oxidation**. The reactions described above **do not lead to the formation ATP**.

α-oxidation and ω-oxidation

Those are **minor fatty acid oxidation pathways**. In ω-oxidation, reactions happen on the terminal carbon of the chain. In α-oxidation, oxidation is on the α-carbon.

Omega oxidation occurs in the enoplasmic reticulum. The terminal methyl group is hydroxylated, which is further oxidized to a carboxyl group. A dicarboxylic acid is formed, which can be degraded to dicarboxylic acid with 6-10C, which is already sufficiently soluble in water.



Alpha oxidation

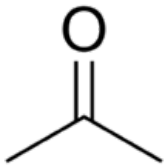
Formation and utilization of ketone bodies

Formation and function of ketone bodies

Ketone (*bodies*) include **acetoacetate**, **β-hydroxybutyrate** and **acetone**. The main site of their formation is the **mitochondria of hepatocytes**. Ketones represent a water-soluble transport form of acetyls. It is formed when there is an **excess of acetyl~CoA** produced by liver

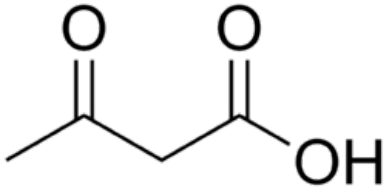
beta-oxidation – the liver „pre-chews“ fatty acids and provides the body with ketone bodies as **an alternative source of energy**.

The entry of AcCoA into the Krebs cycle depends on the availability of oxaloacetate. It is produced by the carboxylation of pyruvate. During starvation or diabetes mellitus OAA is consumed in the process of gluconeogenesis. The lack carbohydrates leads to a decrease in the amount of OAA and thus to a slowing down of the Krebs cycle. It could be said that "fats burn in the fire of carbohydrates"..



The environment of the organism

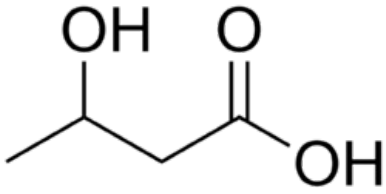
Before we get to the specific reactions of the formation of ketone bodies – **ketogenesis**, we will describe the situation in the organism under which it takes place. At the beginning is the **activation of lipolysis** through **hormone-sensitive lipase** (HSL). After the activation of lipolysis, plasma concentrations of fatty acids increase, which enter the liver cells to an increased extent. In them, they undergo **β-oxidation**, which produces **an excess of AcCoA**. It cannot be used sufficiently in other pathways and therefore enters ketogenesis. Therefore, the source of carbon atoms in ketogenesis is only **acetyl~CoA**.



The course of the formation of ketone bodies

The course of the formation of ketone bodies can be described by the following reactions:

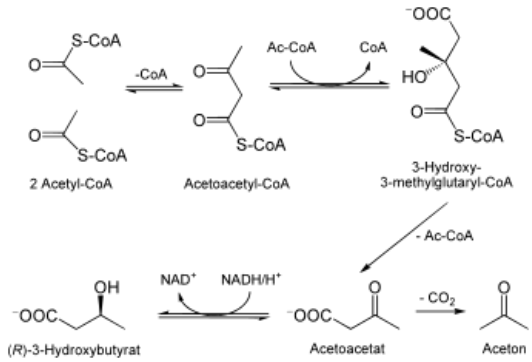
1. **Condensation of two molecules of AcCoA → acetoacetyl~CoA** .
2. **Reaction with another AcCoA → 3-hydroxy-3-methylglutaryl~CoA** (HMG~CoA).
3. **Cleavage of HMG~CoA → AcCoA and acetoacetate**.
4. **Reversible conversion of acetoacetate and β-hydroxybutyrate**.
5. **Decarboxylation of acetoacetate**.



Chemical structures of various ketone bodies – acetone, acetoacetate, β-hydroxybutyrate

β-Ketothiolase

β-Ketothiolase catalyzes the last step of β-oxidation of fatty acids – **thiolytic cleavage**. During the formation of ketone bodies, the **reaction is reversed** and one molecule of acetoacetyl~CoA is formed from two molecules of AcCoA. The reaction takes place in the **matrix of mitochondria**.



Ketogenesis

3-hydroxy-3-methylglutaryl-CoA synthase

This enzyme catalyzes **the condensation of acetyl-CoA with acetoacetyl-CoA**. Condensation takes place on the third carbon of acetoacetyl~CoA to form **3-hydroxy-3-methylglutaryl-CoA**. This important intermediate occurs not only in the metabolism of ketone bodies, but also occurs during the **synthesis of cholesterol**.

3-hydroxy-3-methylglutaryl-CoA lyase

This enzyme catalyzes the **cleavage of HMG-CoA** into acetoacetate and AcCoA. This **creates the first ketone body**.

β-hydroxybutyrate dehydrogenase

This enzyme catalyzes the mutua **reversible conversion of** two ketone bodies – acetoacetate and β-hydroxybutyrate. The cofactor is NAD^+. During the massive formation of ketone bodies **β-hydroxybutyrate** is quantitatively the most important ketone body in the blood, i.e. most of the acetoacetate is converted to it.

Decarboxylation of acetoacetate

Part of the acetoacetate molecules **spontaneously** i.e. **non-enzymatically decarboxylates into acetone**, which has no use in the human body and is **excreted by** breathing or urine.

Activation and utilization of ketone bodies

Usage of ketone bodies

Regulation of ketogenesis

Regulation of ketogenesis takes place at **four levels**:

1. **Hormone-sensitive lipase** – lipolysis in adipose tissue.
2. **Carnitine acyltransferase I** – entry of fatty acids into mitochondria, where their β-oxidation takes place.
3. **Routing of acetyl-CoA from β-oxidation to ketogenesis and not to the Krebs cycle** .
4. **Mitochondrial HMG-CoA synthase**.

A high level of ketone bodies in the blood signals the presence of a large amount of acetyl-CoA. Its consequence is the inhibition of lipolysis.

Concentration of ketone bodies in plasma and ketoacidosis

Concentration of ketone bodies in plasma

Ketoacidosis

Ketoacidosis