Ketone Body Synthesis

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Ketone bodies are an important energy source for our bodies during periods of fasting. They provide the brain, myocardial muscles, and skeletal muscles with energy so that our body can live off its reserves if needed. This article examines the synthesis and degradation of ketone bodies, their impact on the blood's pH levels, and their clinical relevance for patients with diabetes.

Types of Ketone Bodies and Their Function

Our bodies comprise three kinds of ketone bodies:

- **Acetoacetate** is a metabolic product of the liver. It can be converted into acetone and beta-hydroxybutyrate.
- **Acetone** is a product of spontaneous decarboxylation of acetoacetate or the action of acetoacetate decarboxylase. It is disposed of through breath or in the urine. Acetone does not play any role in regulating our metabolism.
- **Beta-hydroxybutyrate** is not, strictly speaking a ketone body: it is derived from acetoacetate via the action of D-beta hydroxybutyrate dehydrogenase. It is the most abundant ketone body.

Acetoacetate and beta-hydroxybutyrate are synthesized in the mitochondrial matrix of hepatocytes. Because they traverse membranes easily, the brain, myocardial muscles, and skeletal muscles all rely on the re-conversion of these substances when glucose levels are low.Since the **brain** cannot use fatty acids for energy generation because the blood-brain barrier is not permeable to fatty acids, it **is dependent on ketone bodies**

as its sole energy resource during periods of fasting. Using ketone bodies, the brain can reduce its glucose demand from an average of approximately 150g/day to 50g/day. Ketone bodies are transported to the brain via monocarboxylate transporters 1 and 2.

Activation of Ketone Body Synthesis

From a biochemical perspective, ketone body synthesis will be reinforced whenever there is an increased presence of **acetyl-CoA** (the starting substance of ketone body synthesis), as occurs during long periods of fasting or starvation.

Diabetes mellitus also causes an accumulation of acetyl-CoA: lowered insulin production or higher insulin resistance leads to an increase in the degradation of fatty acids which, in turn, leads to more acetyl-CoA being produced. Acetyl-CoA can only enter the citric acid cycle if there is enough **oxaloacetate** available for the first reaction in that cycle; however, in diabetes mellitus, the absorption of glucose from the blood into the cell is inhibited, leading to reduced activity of glycolysis and thus reduced production of pyruvate and oxaloacetate.

This means that patients with diabetes have increased amounts of acetyl-CoA and a simultaneous deficiency of oxaloacetate, resulting in an intensified synthesis of ketone bodies via the acetyl coA and HMG coA pathways. As well, there is an attempt to increase the amount of oxaloacetate for the Krebs cycle via deaminated amino acids that are ketogenic, such as leucine. The synthesis of ketone bodies takes place mainly in the hepatocytic mitochondria.

Supply of Acetyl-CoA

Acetyl-CoA is the product of various metabolic pathways:

- The degradation of fatty acids yields 1 acetyl-CoA with every cycle of beta-oxidation.
- The primary product of glycolysis is pyruvate, which is decomposed into acetyl-CoA via pyruvate dehydrogenase or into oxaloacetate via pyruvate carboxylase, eventually entering the citric acid cycle.
- Acetyl-CoA is also produced during the degradation of certain amino acids, appropriately called ketogenic amino acids.

Ketogenesis

Step 1

Initially, **2 acetyl-CoA** are condensed to form **acetoacetyl-CoA**, catalyzed by the enzyme **thiolase**. In this step, **one CoA is cleaved**, thereby providing enough energy for the synthesis of the product.

Step 2

The next step, which is catalyzed by **β-hydroxy-β-methylglutaryl-CoA synthase** (HMG-CoA synthase), uses water to add another molecule of **acetyl-CoA** to the beta carbon of the acetoacetyl-CoA.

This step produces **β-hydroxy-β-methylglutaryl-coenzyme A** (HMG-CoA), which is a branched 6-carbon compound and an intermediate in the synthesis of cholesterol in the cytosol.

Step 3

One acetyl-CoA is cleaved by HMG-CoA lyase, producing acetoacetate.

Step 4

Acetoacetate can now either be reduced to **D-β-hydroxybutyrate** by **D-β-hydroxybutyrate dehydrogenase** in a NADH+H+-dependent reaction, or undergo spontaneous decarboxylation to form acetone.

Beta-hydroxybutyrate is the ketone body with the highest blood concentration during periods of fasting or starvation. Figure 1 summarizes ketogenesis reactions.

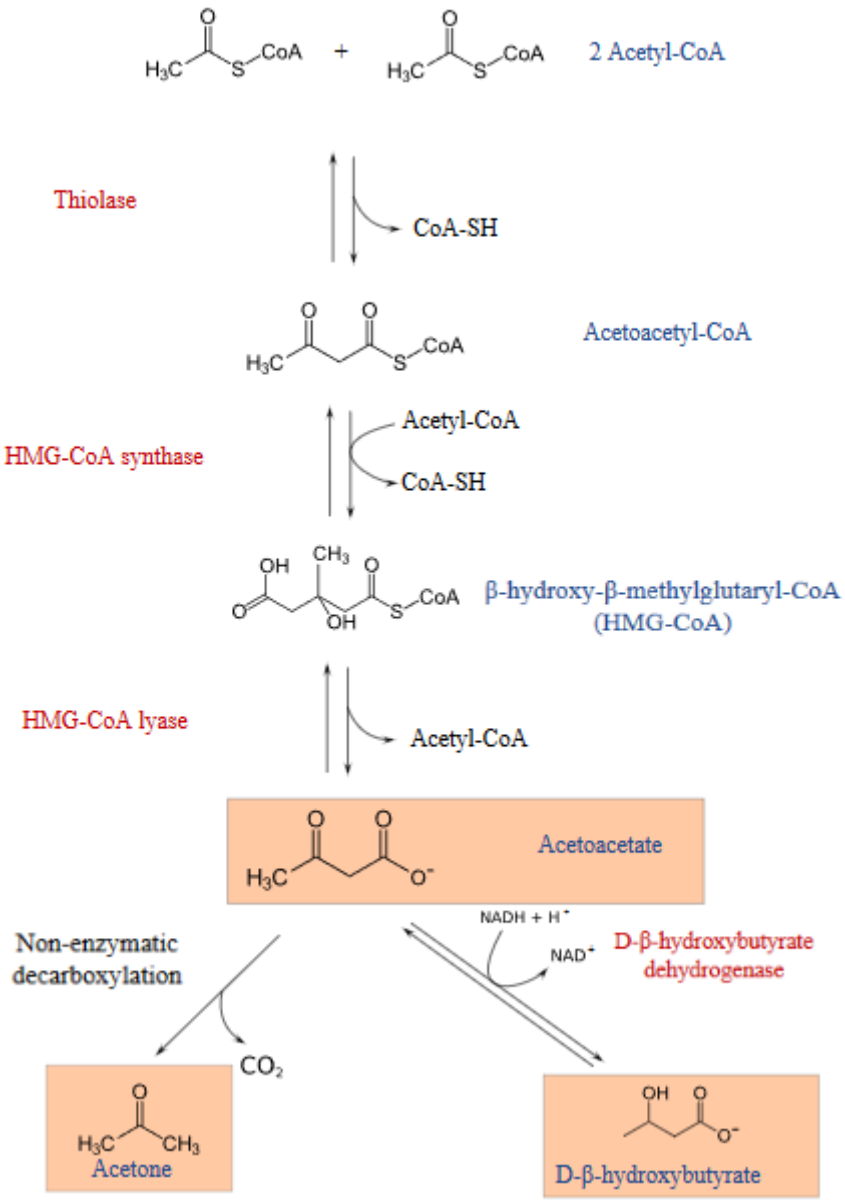

Image: "Ketogenesis pathway. The three ketone bodies (acetoacetate, acetone and beta-hydroxybutyrate) are marked within an orange box" by Sav vas. License: CC0 1.0

Ketone Body Uptake

The ketone bodies that have now been formed travel through the bloodstream toward their target tissue. The brain utilizes ketone bodies with the assistance of monocarboxylate transporters (MCTs).

These transporters are located, for example, in the plasma membrane of endothelial cells of astrocytes and neurons; they also organize the transport of lactate, which can be reduced to pyruvate. Uptake occurs through proton symport.

Ketone Body Utilization

Ketone bodies can be utilized **in the entire body** (especially the brain) **except for the liver**, since the this organ functions exclusively as a site of synthesis.

Step 1 and 2

In the first step of utilization (unless this has already occurred), beta-hydroxybutyrate is oxidized to acetoacetate, the second-most common ketone body in the blood. This is an NAD+-dependent reaction and is catalyzed by beta-hydroxybutyrate dehydrogenase.

In step 2, **acetoacetate is then activated to acetoacetyl-COA through one of 2 mechanisms**:

- **3-ketoacyl-CoA transferase** transfers the CoA-group of the succinyl-CoA (a by-product of the citric acid cycle) to the carboxyl group of the acetoacetate, yielding **acetoacetyl-CoA** as well as succinate.
- Catalyzed by acetoacetyl-CoA synthetase, CoA undergoes an ATP-dependent reaction with the carboxyl group of acetoacetate, forming water, ATP, and acetoacetyl-CoA.

Step 3

In the final step, acetoacetyl-CoA is **cleaved by thiolase with the use of 1 CoA to form two acetyl-CoA**.

Acetyl-CoA is now available for energy production in the citric acid cycle and for the synthesis of necessary reducing equivalents to keep the respiratory chain running. Figure 2 shows the most important chemical reactions in the utilization process of ketone bodies.

Ketoacidosis

A blood **pH level <7.35** is referred to as acidosis. Ketoacidosis is an acidosis caused by high blood concentrations of ketone bodies.

As all 3 types of ketone bodies are acidic, they can cause a reduction in blood pH, giving rise to acidosis. This is why we can develop ketoacidosis during periods of fasting.

References

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