UNIT-3, Semester-3

Ketogenesis is a catabolic pathway of metabolism in which, fatty acids and certain ketogenic amino acids are broken down to derive energy by alternative means. Ketone bodies are produced in the ketogenesis process.

Our body continuously produces ketone bodies in low amounts, but in certain cases like starving, when carbohydrates are present in fewer amounts in diet, ketogenesis is preferred to compensate for the energy requirements. Ketone bodies accumulated in an excess amount may lead to a condition called **ketoacidosis,** which may be fatal.

Ketone Bodies

Fatty acids undergo β-oxidation in the liver mitochondria to generate a high amount of energy and form three compounds, that are known as "ketone bodies"**.** These ketone bodies are water-soluble and do not require lipoproteins for transportation across the membrane. Ketone bodies are lipid molecules having a carbonyl group attached to two -R groups.

The three ketone bodies formed are:

1. **Acetoacetate**
2. **D-3-hydroxybutyrate**
3. **Acetone**

Ketogenesis Pathway

Our body normally derives energy from stored carbohydrate by the process of glycogenolysis (glycogen → glucose) or from non-carbohydrate sources such as lactate by the process of gluconeogenesis**.**

Ketogenesis occurs continuously in a healthy individual, but under certain conditions, when there is an increased concentration of fatty acids or carbohydrate reserves are decreased, ketogenesis happens at a higher rate:

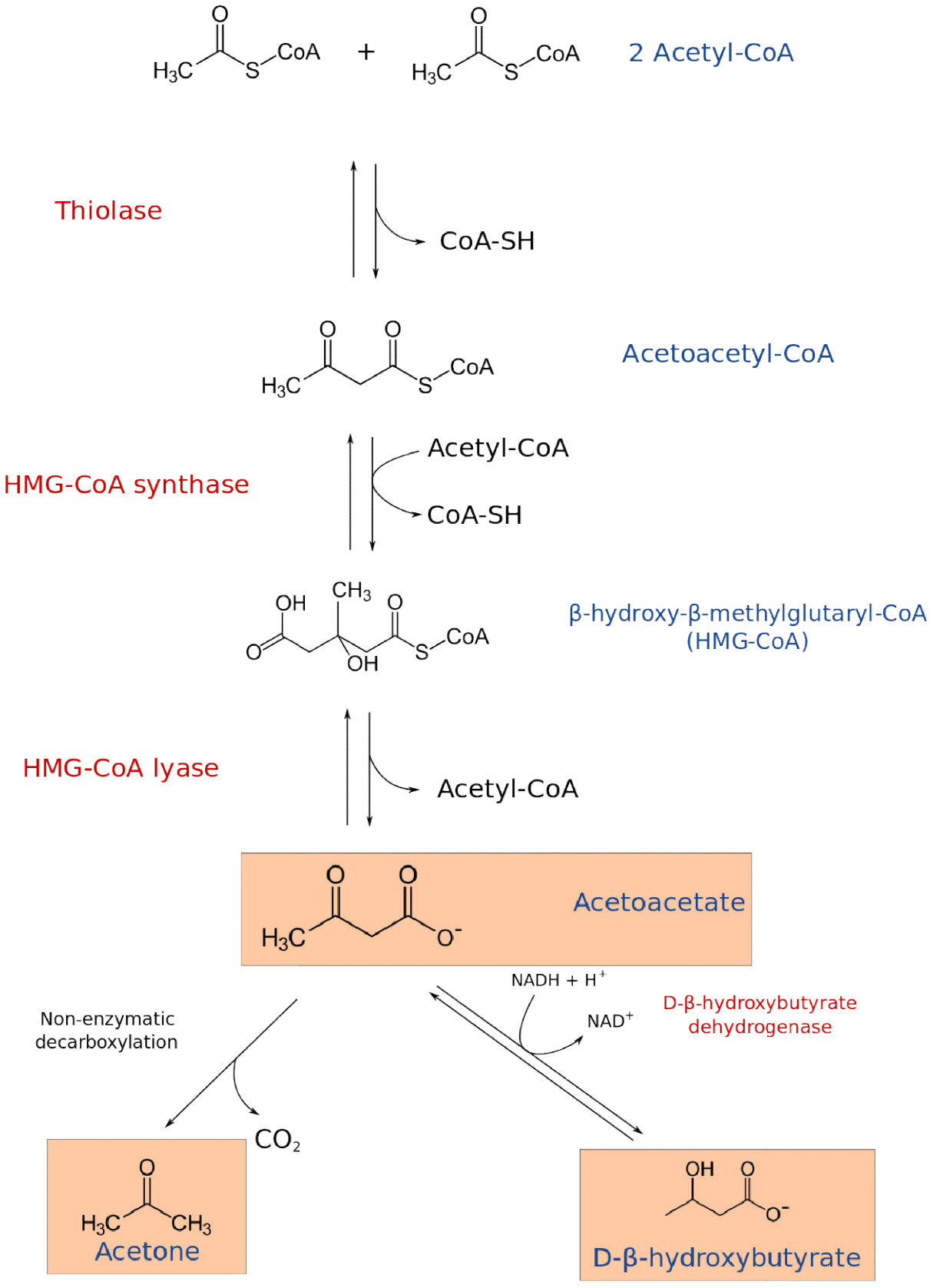
- Under low blood glucose level, e.g. during fasting or starvation
- On exhaustion of carbohydrate reserve, e.g. glycogen
- When there is insufficient insulin, e.g. Type-1 diabetes

All the main body parts such as the brain, skeletal muscles, heart, etc. can utilise the energy formed by ketogenesis. Insufficient gluconeogenesis results in hypoglycemia and excessive production of ketone bodies resulting in a fatal condition called ketoacidosis**.**

Ketogenesis Steps

The first step in ketogenesis is the hydrolysis of triglycerides to yield fatty acids. In the liver, control of ketogenesis is largely due to the blocking of other pathways in the metabolism of the carbon product of fatty acid oxidation, acetyl-CoA (oxidation and fat synthesis). The ketoacids formed become the main fuel for the brain. In the process of ketogenesis, fatty acids are converted to ketoacids.

The ketogenesis process occurs primarily in the mitochondria of liver cells. Below are the steps in the process of ketogenesis:


2 Acetyl-CoA
Thiolase
CoA-SH
Acetoacetyl-CoA
HMG-CoA synthase
Acetyl-CoA
CoA-SH
β-hydroxy-β-methylglutaryl-CoA
(HMG-CoA)
HMG-CoA lyase
Acetyl-CoA
Acetoacetate
NADH + H+
NAD+
D-β-hydroxybutyrate
dehydrogenase
Non-enzymatic
decarboxylation
CO2
Acetone
D-β-hydroxybutyrate

1. Transfer of fatty acids in mitochondria by carnitine palmitoyltransferase CPT-1
2. β-oxidation of fatty acid to form acetyl CoA
3. Acetoacetyl-CoA formation: 2 acetyl CoA form acetoacetyl CoA. The reaction is catalyzed by the enzyme thiolase
4. 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) synthesis: the step is catalyzed by HMG-CoA synthase
5. Acetoacetate formation: HMG-CoA is broken down to acetoacetate and acetyl-CoA by the action of HMG-CoA lyase

Acetoacetate thus produced forms other ketone bodies, acetone by decarboxylation and D-3-hydroxybutyrate by reduction

Liver, which produces ketone bodies, primarily in the mitochondria, cannot utilise it due to lack of an enzyme β-keto-acyl-CoA transferase.

Acetoacetate and D-3-hydroxybutyrate are used by the body to get energy. These ketone bodies are circulated out of the liver cell.

In the extrahepatic tissues, the following reactions occur:

- D-3-hydroxybutyrate is converted back to acetoacetate by β-hydroxybutyrate dehydrogenase
- Acetoacetate is converted back to acetyl-CoA by β-keto-acyl-CoA transferase
- Acetyl-CoA enters the citric acid cycle (TCA or Kreb's cycle) and produces 22 ATP molecules
- Acetone is excreted out

Ketogenesis process is regulated by Insulin. Hormones such as glucagon, thyroid hormones, catecholamines, cortisol increase ketogenesis rate by stimulating the breakdown of free fatty acids.

Significance of Ketogenesis

- Ketogenesis is used to get energy by the brain, heart and skeletal muscles under fasting condition
- The ketogenic diet (low-carb, fat-rich diet) is used these days to lose weight. The idea is to utilise excess fat stored in the body to get energy, but excess ketone bodies production can lead to various complications and ketoacidosis
- In ketoacidosis condition, the kidneys excrete extra ketone bodies with the water resulting in fluid loss
- Diabetic patients are greatly affected by ketoacidosis because insulin hormone is the main regulator of the process
- Symptoms of ketoacidosis include frequent urination, breath smelling like fruits or acetone, nausea, shortness of breath, fatigue, excessive thirst, etc.
- Level of ketone bodies present in the body can be tested by blood serum or urine sample analysi

Regulation of ketogenesis

- The overproduction of ketone bodies is due to the un-availability of carbohydrates.
- This is the outcome of excessive utilization of fatty acids to meet the energy requirements
- Glucagon stimulates ketogenesis while on the other hand, insulin inhibits ketogenesis.
- Diabetes Mellitus also promotes ketogenesis Due to the disturbances caused in carbohydrate and lipid metabolism.
- Low concentration of oxaloacetate (an intermediate of TCA cycle) favors the ketogenesis.