Ketogenesis & ketolysis

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Metabolic Fates of Acetyl Co A

- Proteins (amino acids)
- Pyruvic Acid
- Fatty Acid Spiral
- Lipogenesis
- Cholesterol, steroids
- Citric Acid Cycle
- ATP (Energy)
- Ketone Bodies

Glycolysis
When fatty acid oxidation produces more acetyl-CoA than the capacity of TCA cycle to oxidize it (more than that can be combined with oxaloacetate to form citrate), then the "extra" acetyl-CoA is converted to acetoacetyl-CoA and ketone bodies, including acetone.

Ketogenesis (synthesis of ketone bodies) in the liver mitochondria as the enzyme responsible for ketogenesis are present in the liver mitochondria. It takes place when the rate of fatty acids oxidation in the liver is high.
Biological Significance

- Ketone bodies replace glucose as the major source of energy for many tissues especially the **brain**, **heart** and **muscles** during times of prolonged starvation.

- Normal physiological responses to carbohydrate shortages cause the liver to increase the production of **ketone bodies** from the acetyl-CoA generated from fatty acid oxidation.
Ketone Bodies

The **Brain** oxidizes KB but not Fat. **Other Tissues** oxidize KB and Fat.
**Ketogenesis:**

- **In Step 1**, two acetyl-CoA molecules combine in a reversible reaction catalyzed by **thiolase** to produce acetoacetyl-CoA.

- **In Step 2**, a third acetyl-CoA and a water molecule react with acetoacetyl-CoA to give 3-hydroxy-3-methylglutaryl-CoA (HMGCoA) in a reaction catalyzed by **HMGCoA synthase**.

  - HMGCoA synthase is the regulatory enzyme of ketone bodies synthesis, it is **induced** by **high fats** in blood and **inhibited** by CoASH.
In Step 3: 3-hydroxy-3-methylglutaryl-CoA lyase catalyzes the cleavage of HMGCoA. Removal of acetyl-CoA produces the first of the ketone bodies, acetoacetate, the precursor of the other two ketone bodies produced by ketogenesis, 3-hydroxybutyrate and acetone.
- **In Step 4**, the acetoacetate produced in Step 3 is reduced to **3-hydroxybutyrate** by β-hydroxy butyrate dehydrogenase.
- Note that 3-hydroxybutyrate and acetoacetate are connected by a **reversible** and **NADH-dependant** reaction.
- Both 3-hydroxybutyrate and acetoacetate can be transported across the mitochondrial membrane of liver cells → **blood stream** → used as fuel by other body cells.
Acetone is a spontaneous breakdown product of (a small amount) acetoacetate (decarboxylation) in the bloodstream, and is excreted primarily by exhalation, or it is formed by enzymatic cleavage of acetoacetate by the enzyme acetoacetate decarboxylase. Acetone formation is minimal under normal conditions, while in severe diabetes acetone odor may be detected in breath or urine.
Two molecules of acetyl-SCoA condense

\[
\text{CH}_3\text{C}-\text{SCoA} + \text{CH}_3\text{C}-\text{SCoA} \rightarrow \text{Acetoacetyl-SCoA}
\]

Step 1: thiolase

\[
\text{HS-SCoA} \rightarrow \text{Acetoacetyl-SCoA} \rightarrow \text{HMGCoA synthase}
\]

Step 2: HMGCoA synthase

\[
\text{HMGCoA} + \text{H}_2\text{O} \rightarrow \text{3-Hydroxy-3-methylglutaryl-SCoA}
\]

Step 3: HMGCoA lyase

\[
\text{3-Hydroxy-3-methylglutaryl-SCoA} \rightarrow \text{Acetoacetate}
\]

Step 4: \(\beta\)-hydroxy butyrate dehydrogenase

\[
\text{3-Hydroxybutyrate} \rightarrow \text{Acetoacetate} \rightarrow \text{Acetone}
\]

The 3 ketone bodies produced by ketogenesis.
Utilization of ketone bodies at extrahepatic tissues (Ketolysis):

Under well-fed, healthy conditions, skeletal muscles derive a small portion of their daily energy needs from acetoacetate, and heart muscles use it in preference to glucose.

During the early stages of starvation, heart and muscle tissues burn larger quantities of acetoacetate, thereby preserving glucose for use in the brain. In prolonged starvation, even the brain can switch to ketone bodies to meet up to 75% of its energy needs.

Ketolysis (utilization of ketone bodies) does not occur in liver because liver does not contain the enzymes responsible for this process.
Ketolysis

- β-hydroxybutyrate is reconverted to acetoacetate by β-hydroxybutyrate dehydrogenase

- Reactivation of acetoacetate by mitochondrial enzyme β-ketoacyl-CoA transferase (thiophorase), present in non hepatic tissues, that uses succinylCoA as source of CoA

- Then, acetoacetylCoA is cleaved into 2 acetyl-CoA molecules by thiolase

What happens to these two acetyl-CoA?
Ketones are an energy source for tissues

**How many total ATP from 2 acetyl-CoA?**

- 6 NADH
- 2 FADH2
- 2 GTP

18 ATP
4 ATP
2 ATP

**24 ATP**

Enter Kreb’s cycle with production of energy
The condition in which ketone bodies are produced faster than they are utilized (ketosis) occurs in diabetes. It is indicated by the odor of acetone (a highly volatile ketone) in the patient’s breath and the presence of ketone bodies in the urine (ketonuria) and the blood (ketonemia).
Ketoacidosis

- Two of the ketone bodies are carboxylic acids.
- **Ketoacidosis** results from increased concentrations of ketone bodies in the blood. The blood’s buffers mainly bicarbonate are depleted and blood pH drops.
- Ketoacidosis if untreated may lead to coma and death as in severe uncontrolled diabetes.

**Ketone bodies**

- **3-Hydroxybutyrate**: $\text{CH}_3\text{CHCH}_2\text{C} = \text{O}^-\text{OH}$
- **Acetoacetate**: $\text{CH}_3\text{C} = \text{CH}_2\text{C} = \text{O}^-$
- **Acetone**: $\text{CH}_3\text{C} = \text{CH}_3$
\[
\text{CH}_3\text{-CO-CH}_2\text{-COOH} + \text{NaHCO}_3 \rightarrow \text{CH}_3\text{-CO-CH}_2\text{-COONa} + \text{H}_2\text{CO}_3 \\
\text{H}_2\text{CO}_3 \rightarrow \text{H}_2\text{O} + \text{CO}_2
\]

**Causes of ketosis:** When there is high rate of fatty acid oxidation & lipolysis.

**I-Non-pathologic:**
- Starvation
- Carbohydrate poor diet
- High fat diet
- Severe exercise

**II-pathological:**
- Diabetes mellitus
  
  Increase glucagon & decrease insulin levels in blood will increase lipolysis & release of FFAs in blood that undergo β-oxidation in the liver.

When the amount of acetyl CoA increases above the capacity of TCA cycle to oxidize it, the excess amount will be directed to the formation of ketone bodies.