Ketone Bodies Biosynthesis Of Fatty Acids

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Introduction

- In humans and most other mammals, acetyl-CoA formed in the liver during oxidation of fatty acids can either enter the citric acid cycle or undergo conversion to the "ketone bodies" for export to other tissues.
- ketone bodies made through oxidation of fatty acids are- **acetone, acetoacetate,** and **D-hydroxybutyrate.**
- β-hydroxybutyrate does not possess a keto (C=O) group. Acetone & acetoacetate are true ketone bodies.

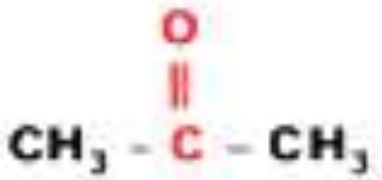
Introduction

- Ketone bodies are water-soluble & energy yielding.
- During starvation & diabetes mellitus, acetyl CoA takes the alternate route of formation of ketone bodies.
- Acetone, produced in smaller quantities than the other ketone bodies, is exhaled.
- Acetoacetate is the primary ketone body.
- β-hydroxybutyrate & acetone are secondary ketone bodies.

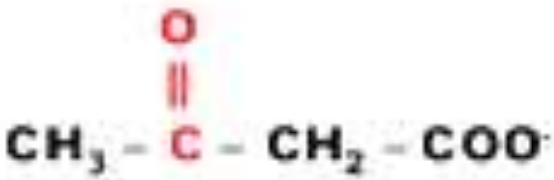
Introduction

- Acetoacetate and D--hydroxybutyrate are transported by the blood to tissues other than the liver (extrahepatic tissues), where they are converted to acetyl-CoA and oxidized in the citric acid cycle, providing much of the energy required by tissues such as skeletal & heart muscle and the renal cortex.
- The **brain, which preferentially uses glucose as fuel**, can adapt to the use of acetoacetate or D--hydroxybutyrate under starvation conditions, when glucose is unavailable.

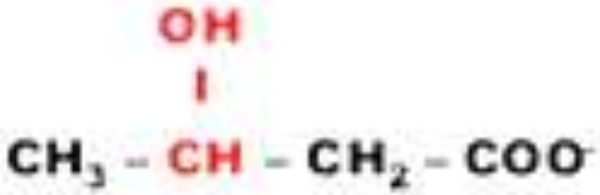
Ketone Bodies



Acetone



Acetoacetate



β-Hydroxybutyrate

Ketone Body Biosynthesis

- **Site:** Synthesized exclusively by the liver mitochondria.
- The enzymes are located in mitochondrial matrix.
- **Precursor:** Acetyl CoA, formed by oxidation of fatty acids, pyruvate or some amino acids.
- Ketone body **biosynthesis occurs in 5 steps-**
  1) Condensation
  2) Production of Hydroxy--methylglutaryl-CoA (HMG CoA)
  3) Lysis
  4) Reduction
  5) Spontaneous decarboxylation

1. Condensation

- Two molecules of acetyl CoA are condensed to form acetoacetyl CoA.
- This reaction is catalyzed by thiolase, an enzyme involved in the final step of β- oxidation.
- Acetoacetate synthesis is appropriately regarded as the reversal of thiolase reaction of fatty acid oxidation.

2. Production of HMG CoA

- Acetoacetyl CoA combines with another molecule of acetyl CoA to produce β-hydroxy β-methyl glutaryl CoA (HMC CoA).
- This reaction is catalyzed by the enzyme HMG CoA synthase.
- Mitochondrial HMG CoA is used for ketogenesis.
- Cytosolic fraction is used for cholesterol synthesis.
- HMG CoA synthase, regulates the synthesis of ketone bodies.

3. Lysis

- HMG CoA is lysed to form acetoacetate & acetyl CoA.
- HMG CoA lyase is present only in liver.

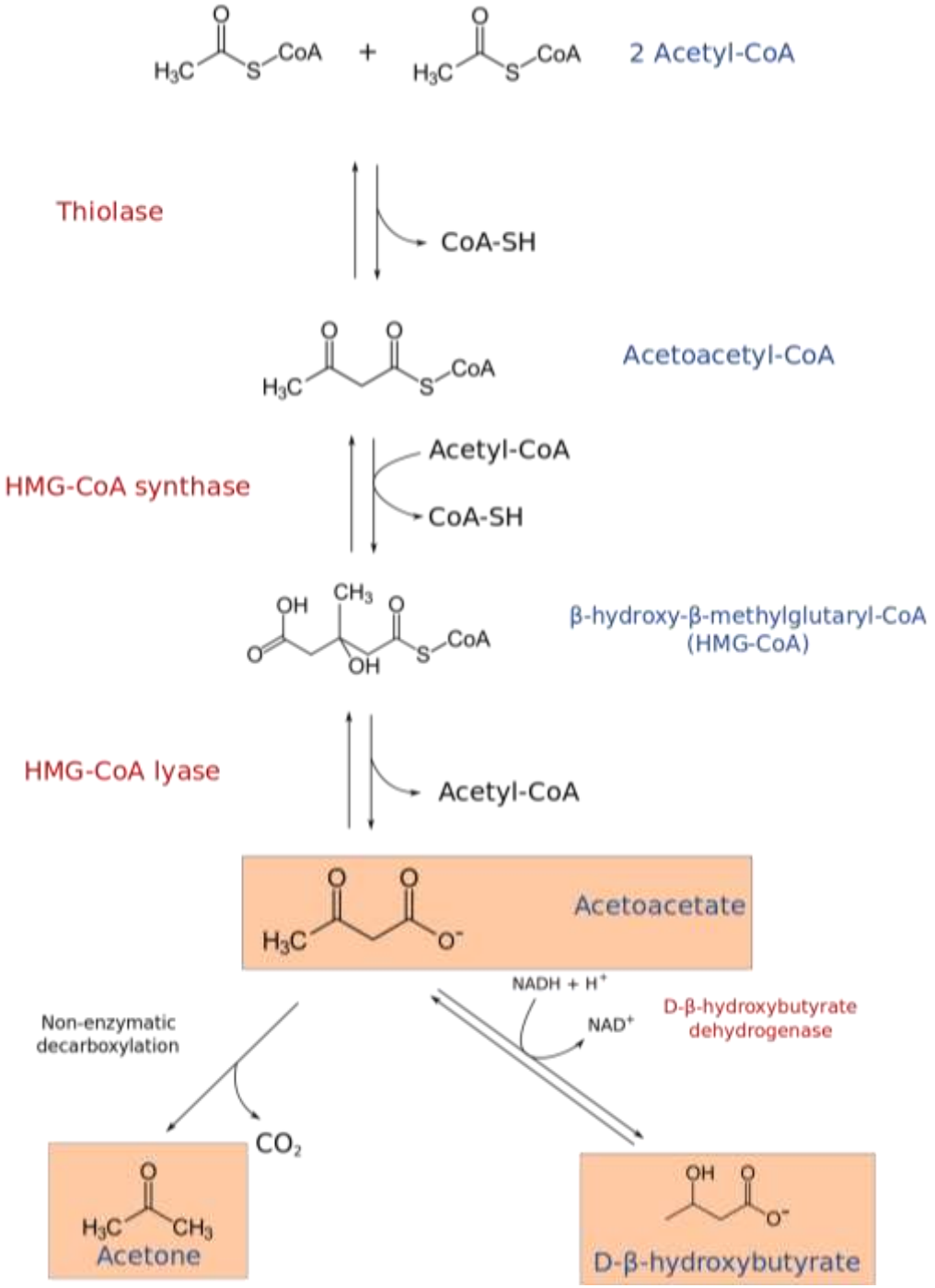
4. Reduction

- β-hydroxybutyrate is formed by the reduction of acetoacetate.
- Ratio between acetoacetate & β- hydroxybutyrate is decided by cellular NAD:NADH ratio.

5. Spontaneous decarboxylation

- Acetoacetate can undergo spontaneous decarboxylation to form acetone.

Ketogenesis



Utilization of Ketone Bodies

- The ketone bodies, are easily transported from the liver to various tissues.
- Acetoacetate & β-hydroxybutyrate serve as important sources of energy for the peripheral tissues such as skeletal muscle, cardiac muscle, renal cortex etc.
- The tissues which lack mitochondria cannot utilize ketone bodies (eg. erythrocytes) .
- The production & utilization of ketone bodies is more significant when glucose is in short supply to the tissues.
- During starvation & diabetes mellitus ketone bodies production & utilization is more significant.

Ketosis

- The rate of synthesis of ketone bodies by the liver is such that they can be easily metabolized by extrahepatic tissues.
- Blood level of ketone bodies is **<1 mg/decilitre**.
- **Ketonemia:** When the rate of synthesis of ketone bodies exceeds the rate of utilization, their concentration in blood increases.
- **Ketonuria:** The term ketonuria represents the excretion of ketone bodies in urine
- **Ketosis:** Ketonemia, ketonuria & smell of acetone in breath. All these three together known as ketosis

Regulation of Ketogenesis

- The ketone body formation (particularly overproduction) occurs primarily due to non-availability of carbohydrates to the tissues.
- The hormone glucagon stimulates ketogenesis whereas insulin inhibits.
- The ketone body formation is regulated at 3 levels.

  Level 1 : Lipolysis

  Level 2 : Entry of FA to Mitochondria

  Level 3 : Oxidation of Acetyl CoA

Level 1 : Lipolysis

- Free fatty acids are the precursors of ketone bodies.
- Factors regulating the mobilization of fatty acid from adipose tissue will also control ketogenesis.
- Insulin inhibits lipolysis, while glucagon favors lipolysis.

Level 2 : Entry of FA to Mitochondria

- The mobilized fatty acid then enters mitochondria for β-oxidation.
- CAT-1 regulates this entry.
- Malonyl CoA is the major regulator of CAT-1(carnitine acyltransferase I) activity.
- In diabetes & starvation, glucagon is increased, which decreases malonyl CoA & β- oxidation is stimulated.

Level 3 : Oxidation of Acetyl CoA

- When the first two steps are increased, more acetyl CoA is produced.
- Acetyl CoA is completely oxidized in TCA cycle.
- In DM & starvation, glucagon/insulin ratio is increased & key gluconeogenic enzymes are activated. TCA cycle cannot function optimally.
- Acetyl CoA is generated in excess & its utilization is reduced.
- This excess acetyl CoA is channeled into ketogenic pathway.

THANK YOU