FORMATION OF KETONE BODIES

INTRODUCTION:

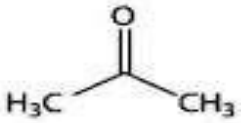
Ketone bodies are metabolic products that are produced in excess during excessive breakdown of fatty acids.

Acetoacetate, acetone and βhydroxybutyrate are collectively known as ketone bodies (acetone bodies).

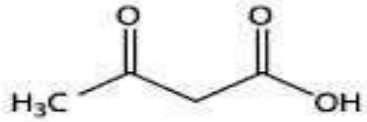
Only the first two are true ketones while β-hydroxybutyrate does not possess a keto (C=O) group.

Ketone bodies are water-soluble and energy yielding.

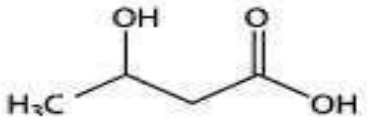
In a normal man, concentration of ketone bodies in the blood is usually less than 3 mg/100ml.



Acetone



Acetoacetate



2-Hydroxybutyric acid

SIGNIFICANCE OF KETONE BODIES

- **Alternate source to glucose for energy needs**

Ketone bodies represent an alternative to glucose for the provision of energy to the cells.

- **Production of ketone bodies under conditions of cellular energy deprivation**

Ketone bodies are produced when excessive fatty acids are being oxidized (because of increased adipose tissue lipolysis) and glucose availability to the cells is limited.

Such situations are seen in conditions such as diabetes mellitus and starvation.

- **Utilization of ketone bodies by the brain**

Brain normally utilizes glucose for energy needs.

Although ketone bodies cannot completely replace glucose for energy needs in the brain, brain gets adapted to oxidize ketone bodies during prolonged fasting and starvation.

Ketogenesis

DEFINITION

The process of the formation of ketone bodies is collectively called as ketogenesis.

TISSUES

Ketone bodies are synthesized only in liver.

LOCALIZATION OF REACTIONS

The synthetic reactions occur in mitochondria since enzymes are localized in the mitochondria.

REACTIONS

The major pathway of ketone body formation is HMG CoA lyase pathway.

The reactions of this pathway are:

1. Formation of acetoacetyl CoA

- Two molecules of acetyl CoA condence to form acetoacetyl CoA.
- This reaction is catalyzed by thiolase, an enzyme involved in the final step of β- oxidation.

2. Formation of β-hydroxymethyl glutaryl CoA

Acetoacetyl CoA combines with another molecule of acetyl CoA to produce β-hydroxy β-methyl glutaryl CoA (HMG CoA).

HMG CoA synthase, catalysing this reaction, **regulates the synthesis of ketone bodies**.

3. Formation of acetoacetate

HMG CoA lyase cleaves HMG CoA to produce acetoacetate and acetyl CoA.

4. Formation of β-hydroxybutyrate

Acetoacetate can undergo spontaneous decarboxylation to form acetone.

5. Formation of acetone

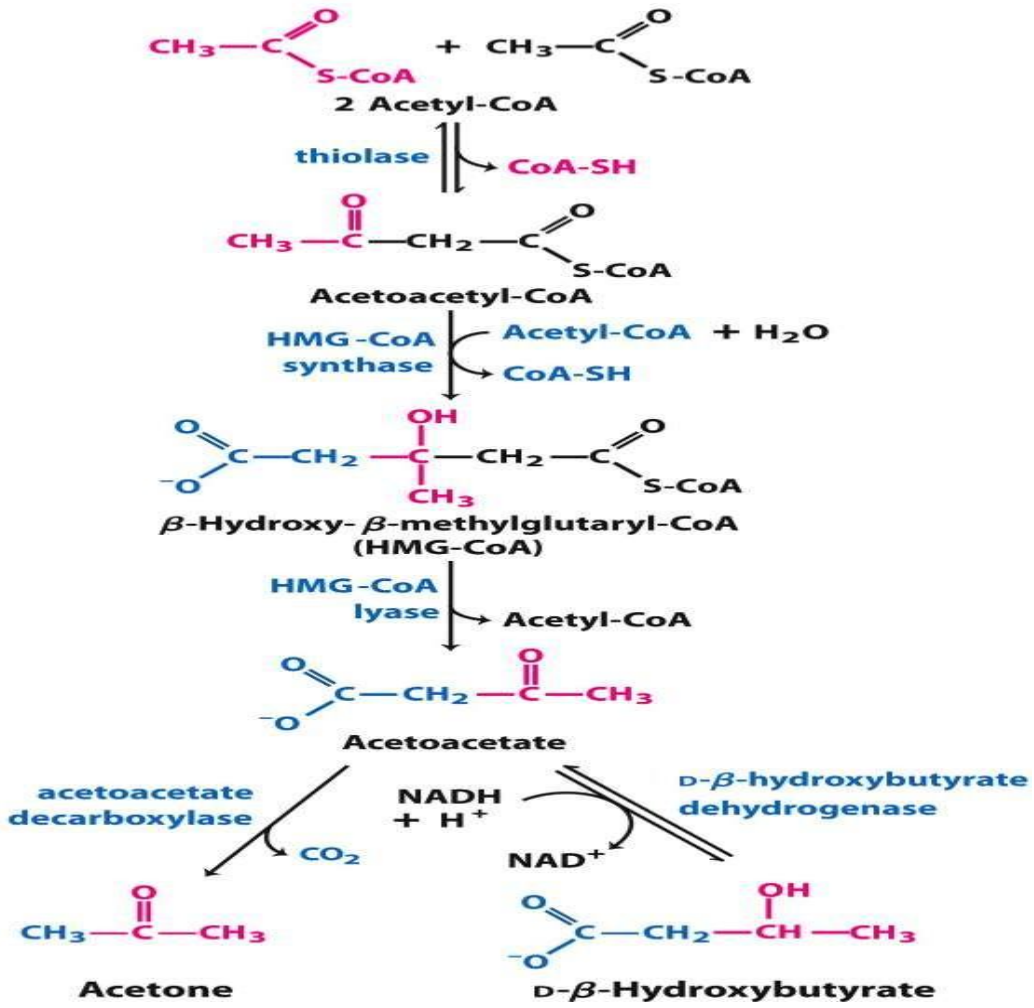
Acetoacetate can be reduced by a dehydrogenase to β-hydroxybutyrate.

CONDITIONS FOR KETONE BODIES OVERPRODUCTION:

In certain conditions, such as during prolonged starvation or impairedglucose oxidation (diabetes mellitus), fat becomes the source of energy and its degradation is greatly accelerated.

It results in excessive production of acetyl CoA which cannot be fully utilized through Kreb's cycle (due to lack of oxaloacetate) and therefore is converted to ketone bodies.

Formation of ketone bodies from acetyl CoA:



REGULATION OF KETOGENESIS

Ketogenesis is regulated mainly by:

1. Substrate availability

Increased ketogenesis occurs when there is excessive availability of fatty acids for oxidation. Thus, increased ketogenesis occurs during starvation or diabetes mellitus.

2. Regulation of β-oxidation

Increased glucagon and decrease insulin in fasting result in inhibition of acetyl CoA carboxylase. This results in decrease in malonyl CoA.

Decreased malonyl CoA results in increased β-oxidation of fatty acids (activtion of carnitine palmitoyl transferase I).

3. Availability of ATP

Increased β-oxidation results in more production of ATP through citric acid cycle in liver. This results in increased availability of acetyl CoA for ketogenesis.

4. Induction of HMG CoA synthase

HMG CoA synthase is the rate limiting enzyme in ketogenesis. The synthesis of HMG CoA synthase is stimulated by fasting, increased intake of fatand diabetes mellitus.

Fatty acids are strong inducers of HMG CoA synthse. The increased synthesis of enzyme occurs by increased transcription.

UTILISATION OF KETONE BODIES

INTRODUCTION:

Ketone bodies are utilized for energy needs in the extrahepatic tissues such as brain, heart,skeletal muscle and kidney.

The two ketone bodies-acetoacetate and β-hydroxybutyrate serve as important sources of energy for the peripheral tissues.

The tissues which lack mitochondria (e.g. erythrocytes) however, cannot utilize ketone bodies.

During prolonged starvation, ketone bodies are the major fuel source for the brain and other parts of CNS.

The ketone bodies can meet 50-70% of the brain's energy needs.

REACTIONS:

The major pathway of ketone bodies utilization is Transacylase pathway.

- ***Formation of acetoacetate from β-hydroxybutyrate***

β-hydroxybutyrate is converted to acetoacetate by β-hydroxybutyrate dehydrogenase.

- ***Formation of acetoacetyl CoA***

Acetoacetate is activated to form acetoacetyl CoA by the transfer of CoA molecule from succinyl CoA.

The reaction is catalyzed by succinyl CoA:Acetoacetate CoA transferase.

- ***Formation of acetyl CoA***

Acetoacetyl CoA is cleaved to form acetyl CoA and acetyl CoA in a reaction catalyzed by thiolase.

Formation of Acetyl CoA from Ketone bodies:

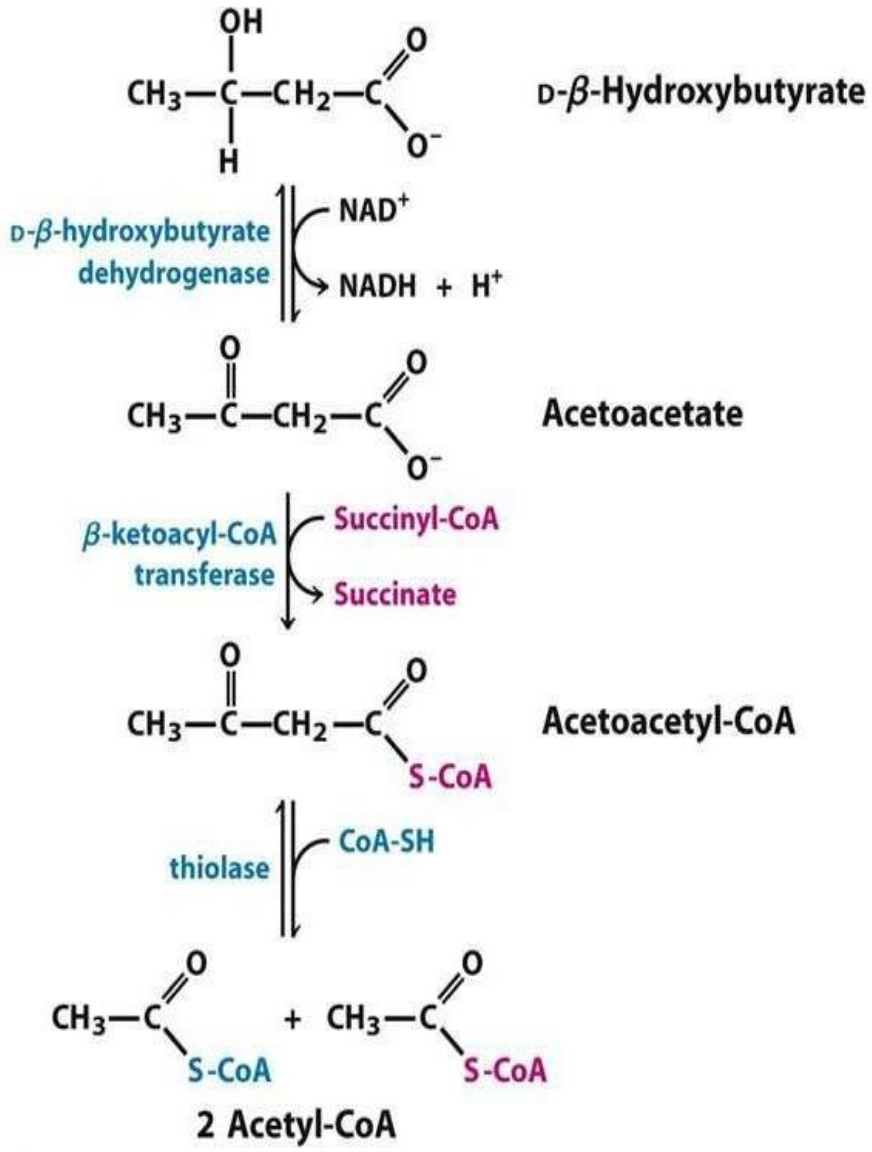
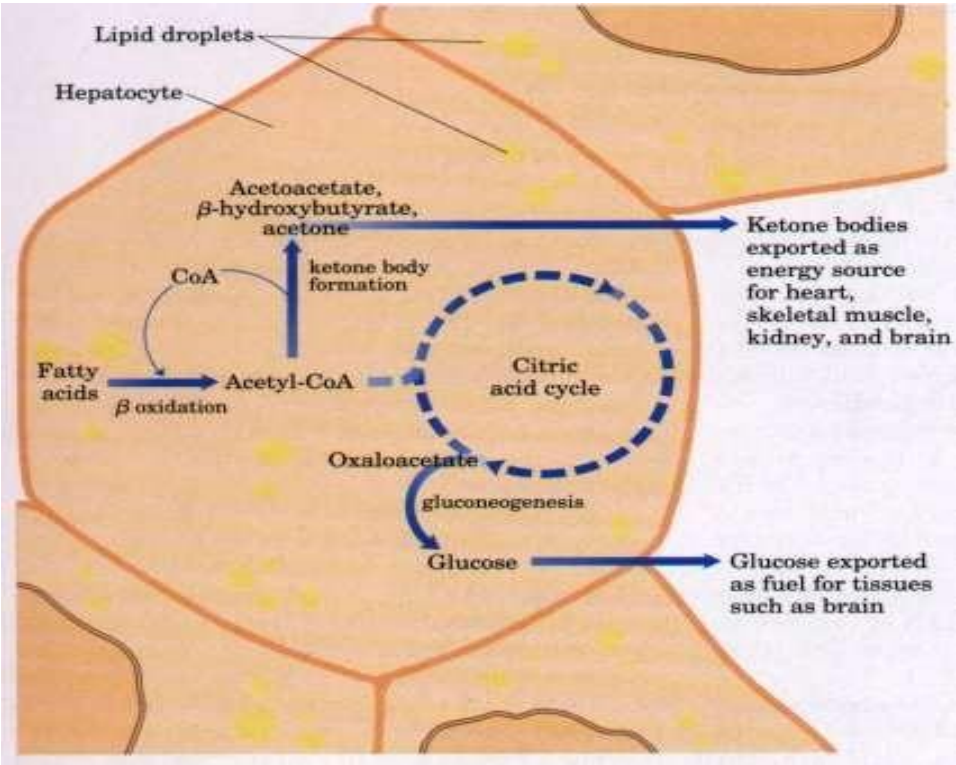


Figure 17-19
Lehninger Principles of Biochemistry, Fifth Edition

Ketone body formation and export from the liver:



KETOSIS

DEFINITION:

Ketosis is a disorder of excessive production of ketone bodies.

CAUSE:

Excessive ketone bodies are produced mainly in two conditions:

- Starvation (carbohydrate deprivation)
- Uncontrolled diabetes mellitus (impaired uptake of glucose by the peripheral tissues).

BIOCHEMICAL AND CLINICAL FINDINGS

The important features of ketosis are ketonemia, ketonuria, acetone odor of breath, metabolic acidosis and hyperkalemia.

Ketonemia

In ketosis, the plasma concentration of ketone bodies is well above normal limits. The condition is called ketonemia.

Ketonuria

When the concentration of ketone bodies significantly increased (above 70mg/dl) in plasma, they appear in urine. The condition is called ketonuria.

Acetone in breath

Acetone is also excreted by the lungs and produces a characteristic odor in breath (acetone odor of breath).

Metabolic acidosis

Metabolic acidosis is caused by excessive accumulation of β-hydroxybutyrate and acetoacetate.

Hyperkalemia

Acidosis results in the shift of potassium from intracellular to extracellular compartment.

BIOCHEMICAL DIAGNOSIS

β-hydroxybutyrate in plasma, Acetoacetate in urine and Rothera's test

MANAGEMENT

- ✓ Provision of glucose to the tissues
- ✓ Ketosis is suppressed by restoring adequate level of carbohydrate metabolism.

- ✓ Correction of electrolyte imbalance and acid-base imbalance
- ✓ Metabolic acidosis is corrected by bicarbonate administration.
- ✓ Correction of metabolic acidosis also reverses hyperkalemia.