KETONE BODIES

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Introduction

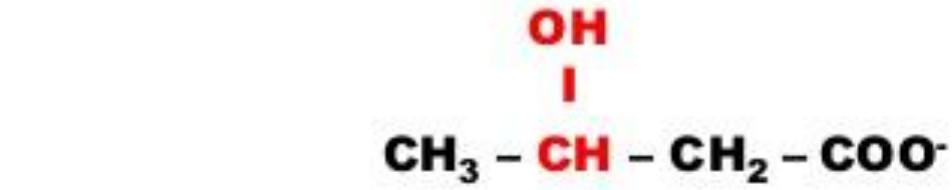
- Carbohydrates are essential for the metabolism of fat or FAT is burned under the fire of carbohydrates.
- Acetyl CoA formed from fatty acids can enter & get oxidized in TCA cycle only when carbohydrates are available.
- During starvation & diabetes mellitus, acetyl CoA takes the alternate route of formation of ketone bodies.

- **Acetone, acetoacetate & β-hydroxybutyrate (or 3-hydroxybutyrate) are known as ketone bodies**
- **β-hydroxybutyrate does not possess a keto (C=O) group.**
- **Acetone & acetoacetate are true ketone bodies.**
- **Ketone bodies are water-soluble & energy yielding.**
- **Acetone, it cannot be metabolized**

Ketone bodies

Acetone

Acetoacetate



β-Hydroxybutyrate

Ketogenesis

- Acetoacetate is the primary ketone body.
- β-hydroxybutyrate & acetone are secondary ketone bodies.
- 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

Reactions

- Ketone body biosynthesis occurs in 5 steps as follows.

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.**

- **Acetoacetate may also be formed by the degradation of carbon skeleton of ketogenic amino acids like leucine, lysine, phenyl alanine & tyrosine.**
- **HMG CoA lyase is present only in liver.**

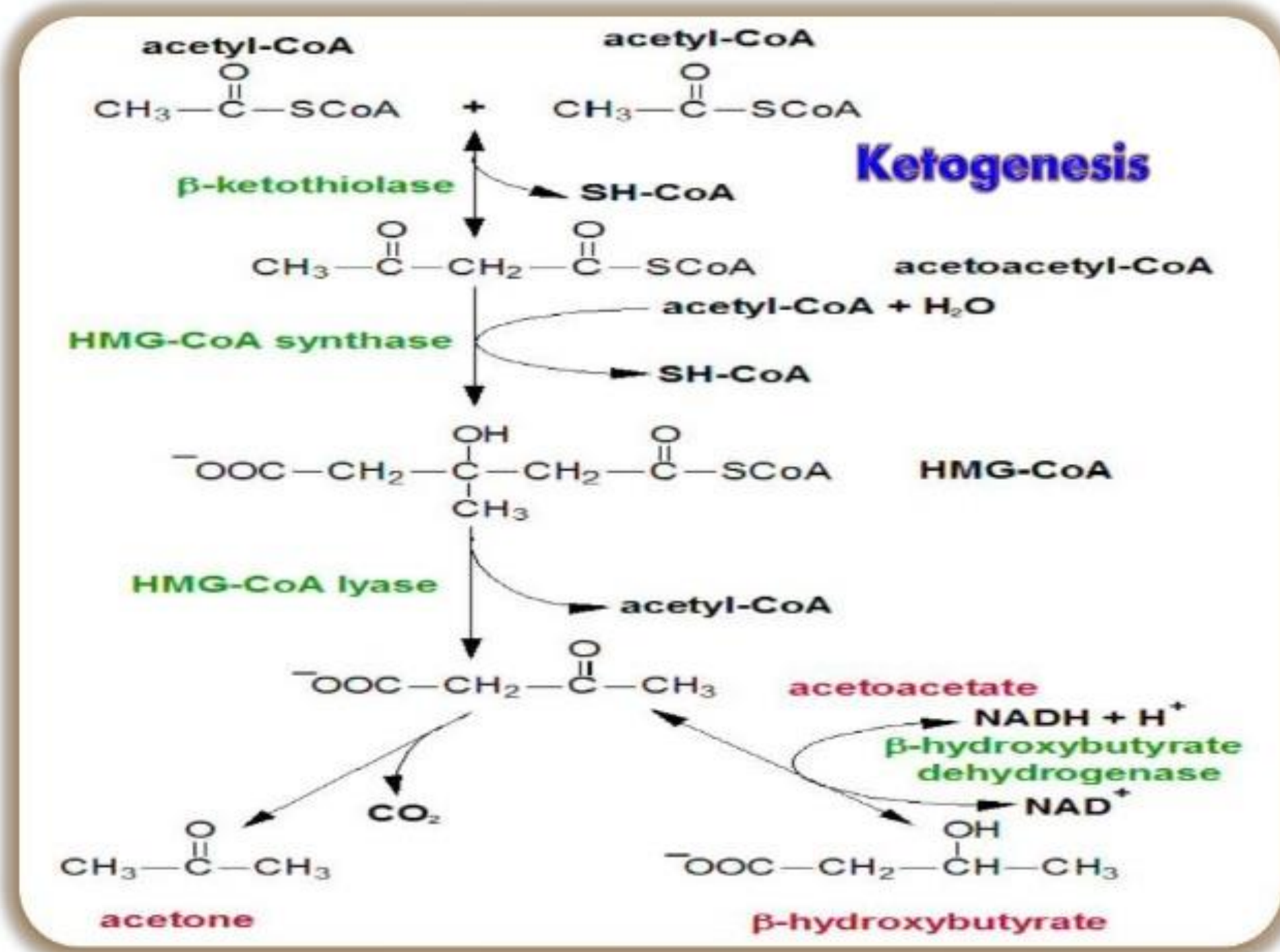
4. **Reduction:**

- **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.**


acetyl-CoA
acetyl-CoA
Ketogenesis
β-ketothiolase
SH-CoA
acetoacetyl-CoA
acetyl-CoA + H2O
HMG-CoA synthase
SH-CoA
HMG-CoA
HMG-CoA lyase
acetyl-CoA
acetoacetate
NADH + H+
β-hydroxybutyrate dehydrogenase
NAD+
CO2
acetone
β-hydroxybutyrate

Ketolysis

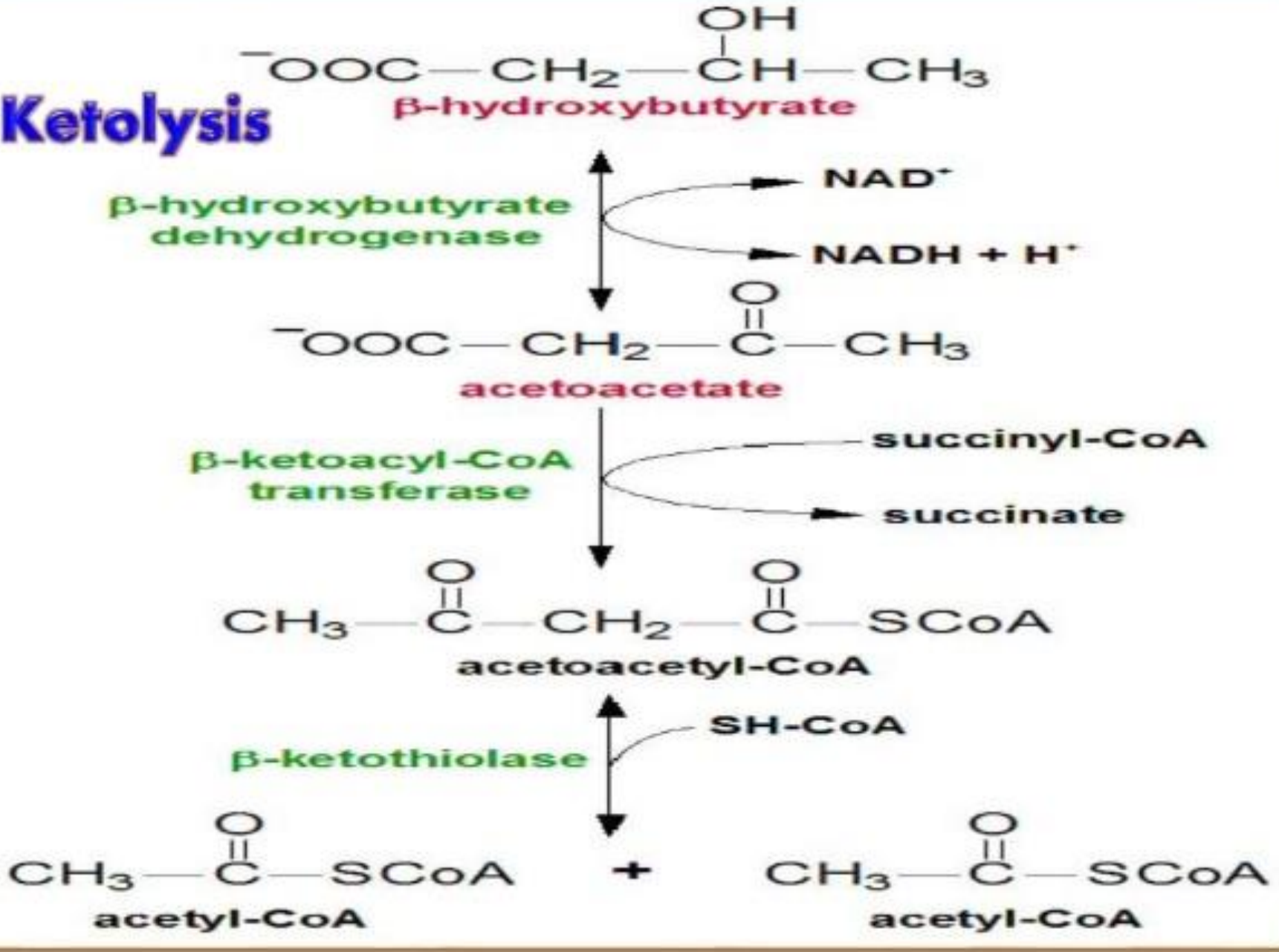
- Ketone bodies are formed in the liver, but utilized by the extrahepatic tissues.
- Heart muscle & renal cortex also utilizes ketone bodies as fuel, if glucose is not available.
- Almost all tissues (intestinal mucosal cells, placenta & adipocytes) & cells utilizes ketone bodies as fuel, except liver & RBC.

Reactions of ketolysis

- β-Hydroxybrutyrate is first converted to acetoacetate (reversal of synthesis) & metabolized.
- Acetoacetate is activated to acetoacetyl CoA by a mitochondrial enzyme thiophorase (succinylCoA acetoacetate CoA transferase).

- Coenzyme A is donated by succinyl CoA
- Thiophorase is absent in liver, hence ketone bodies are not utilized by the liver.
- Thiolase cleaves acetoacetyl CoA to two moles of acetyl CoA.
- Enters in TCA cycle.

Ketolysis

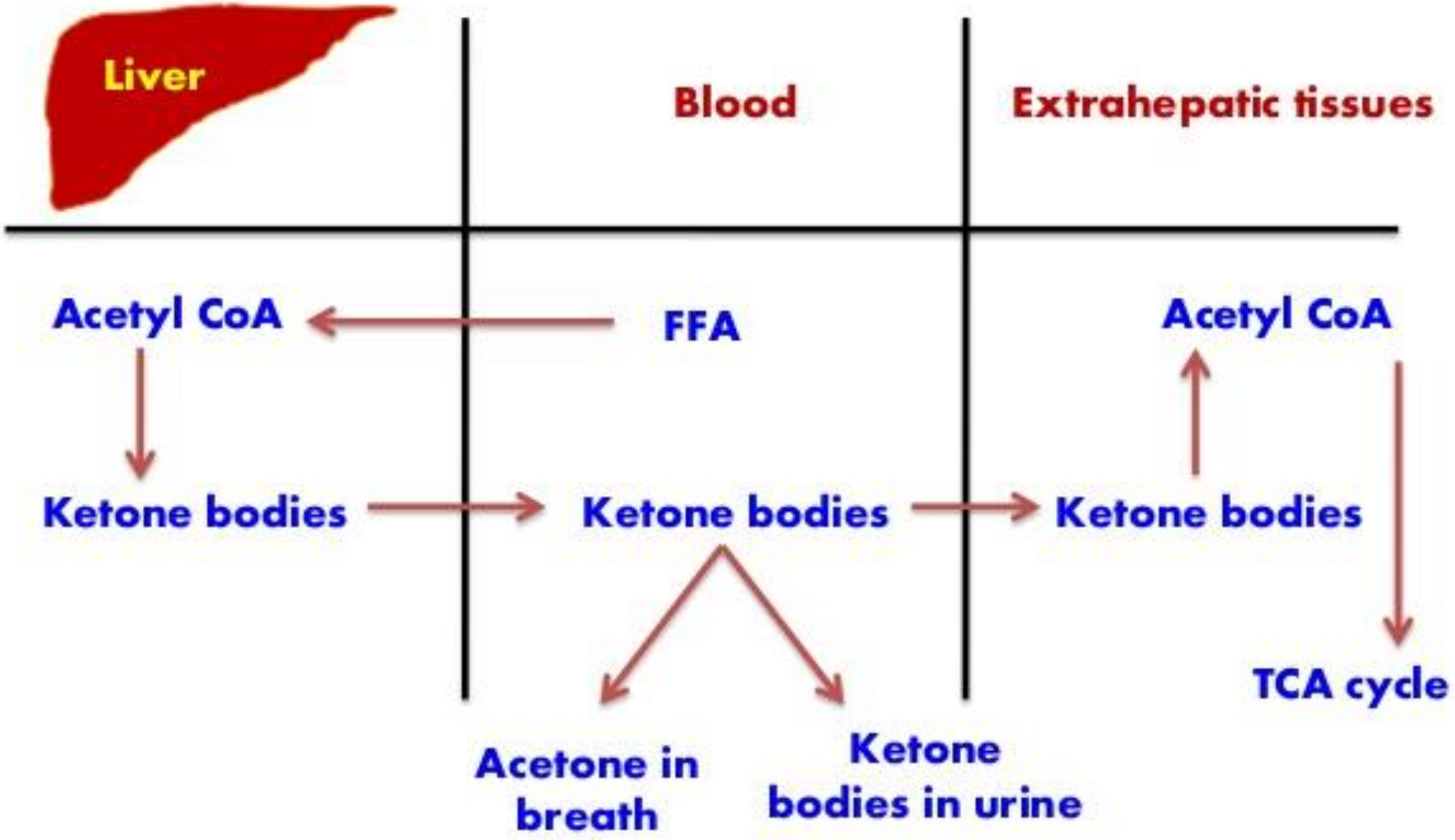

OH
⁻OOC — CH₂ — CH — CH₃
β-hydroxybutyrate
β-hydroxybutyrate dehydrogenase
NAD⁺
NADH + H⁺
O
⁻OOC — CH₂ — C — CH₃
acetoacetate
β-ketoacyl-CoA transferase
succinyl-CoA
succinate
O O
CH₃ — C — CH₂ — C — SCoA
acetoacetyl-CoA
β-ketothiolase
SH-CoA
O
CH₃ — C — SCoA
acetyl-CoA
+
O
CH₃ — C — SCoA
acetyl-CoA

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 (eg. erythrocytes) cannot utilize ketone bodies.
- 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

Formation, utilization & excretion of ketone bodies



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/dl.
- Ketonemia:
- When the rate of synthesis of ketone bodies exceeds the rate of utilization, their concentration in blood increases - ketonemia.

- **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.**

Causes for ketosis

- **Diabetes mellitus:**
- **Untreated DM is the most common cause.**
- **DM is associated with insulin deficiency, causes the accelerated lipolysis & more fatty acids are released into circulation.**
- **Oxidation of these FA increases Acetyl CoA.**

- Enhanced gluconeogenesis restricts the oxidation of acetyl CoA by TCA cycle.
- Since availability of oxaloacetate is less.
- Finally, acetyl CoA is diverted for ketone bodies synthesis in DM.

Starvation

- In starvation, the dietary supply of glucose is decreased in starvation.
- Starvation is accompanied by increased degradation of fatty acids.
- During prolonged starvation, ketone bodies are the major fuel source for the brain & other parts of central nervous system.

- Available oxaloacetate is channeled to gluconeogenesis.
- Increased rate of lipolysis is to provide alternate source of fuel.
- The excess acetyl CoA is converted to ketone bodies.
- The high glucagon favors ketogenesis.
- The brain derives 75% of energy from ketone bodies under conditions of fasting.

- Hypermesis (vomiting) in early pregnancy may also lead to starvation-like condition & may lead to ketosis.
- Glucagon-ketogenesis:
- During starvation & DM, level of glucagon is increased.
- Glucagon inhibits glycolysis, activates gluconeogenesis & lipolysis, decreases malonyl CoA level & stimulates ketogenesis.
- High glucagon-insulin ratio is ketogenic.

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 increased ratio of glucagon/insulin in diabetes mellitus promotes ketone body formation.
- This is due to disturbances caused in carbohydrate and lipid metabolisms in diabetes.
- The ketone body formation is regulated at 3 levels:

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 fatty acid 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 activity.
- In diabetes & starvation, glucagon is increased, which decreases malonyl CoA & β-oxidation is stimulated.

Level 3: Oxidation of acetyl CoA

- When above 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.

When oxaloacatate is diverted for gluconeogenesis

- TCA cycle cannot function optimally.
- Acetyl CoA is generated in excess & its utilization is reduced.
- This excess acetyl CoA is channeled into ketogenic pathway.

- In both DM & starvation, the oxaloacetate is channeled to gluconeogenesis.
- The availability of oxaloacetate is decreased.
- Hence acetyl CoA cannot be fully oxidized in the TCA cycle.

Salient features of ketosis

- **Metabolic acidosis (ketoacidosis):** Acetoacetate & β-hydroxy butyrate are acids, when they accumulate metabolic acidosis results.
- **Reduced buffers:** The plasma bicarbonate is used up for buffering of these acids.
- **Kussmaul's respiration:** Patients will have typical acidotic breathing due to compensatory hyperventilation.

- **Smell of acetone in patient's breath.**
- **Osmotic diuresis induced by ketonuria may lead to dehydration.**
- **Sodium loss: The ketone bodies are excreted in urine as their sodium salt, leading to loss of cations from the body.**
- **Dehydration: The sodium loss further aggravates the dehydration.**
- **Coma: hypokalemia, dehydration & acidosis contribute to the lethal effect of ketosis.**

Diagnosis of ketosis

- Detection of ketone bodies in urine by Rothera's test.
- Estimation of serum electrolytes, acid-base parameters, glucose & urea estimation.
- Management of ketoacidosis:
- Treatment is to give insulin & glucose.

- When glucose & insulin are given intravenously, potassium is trapped within the cells.
- Always monitor the electrolytes.
- Administration of bicarbnate, maintenance of electrolyte & fluid balance.