

Ketone Bodies Metabolism

Students Learning outcomes

At the end of this lecture students will be able to:

1. Recognize the sites, causes, the reactions for ketone bodies formation (**ketogenesis**).
2. Explain how ketone bodies are utilized by extrahepatic tissues (**ketolysis**).
3. Define terms: **ketonemia**, **ketonuria** and

Contents

I. Ketone Bodies

II. Ketogenesis

III. Ketolysis

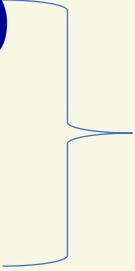
IV. Ketosis

I. Ketone Bodies

1. Types of Ketone bodies
2. Significance of ketone bodies

1.Types of Ketone bodies

Ketone bodies are three types

1. **Acetoacetic acid (AAA)**  **Primary ketone body**
 2. **β -hydroxyl butyric acid (BHBA)**
 3. **Acetone**
- 
- Secondary ketone body**

2. Significance of ketone bodies

- ❖ They act as a **Source of energy** in peripheral extrahepatic tissues especially **Brain**.
- ❖ As they are **small**, water **soluble**, **Can cross the blood brain barrier (BBB)**.
- ❖ They are **easily to be formed** & **easily oxidized**.
- ❖ Important in case of unavailability of CHO and since the long chain fatty acids can not cross BBB, & KBs synthesized → cross BBB → oxidized → energy.

II. Ketogenesis

1. Definition
2. Site
3. Significance
4. Steps

Ketogenesis

❖ Definition of ketogenesis:

Ketogenesis is the formation of ketone bodies (KBs) (acetoacetic acid, β -hydroxyl butyric acid and acetone) **from acetyl-CoA.**

The source of acetyl CoA for ketogenesis:

β -oxidation of fatty acids in excess of optimal function of Krebs cycle.

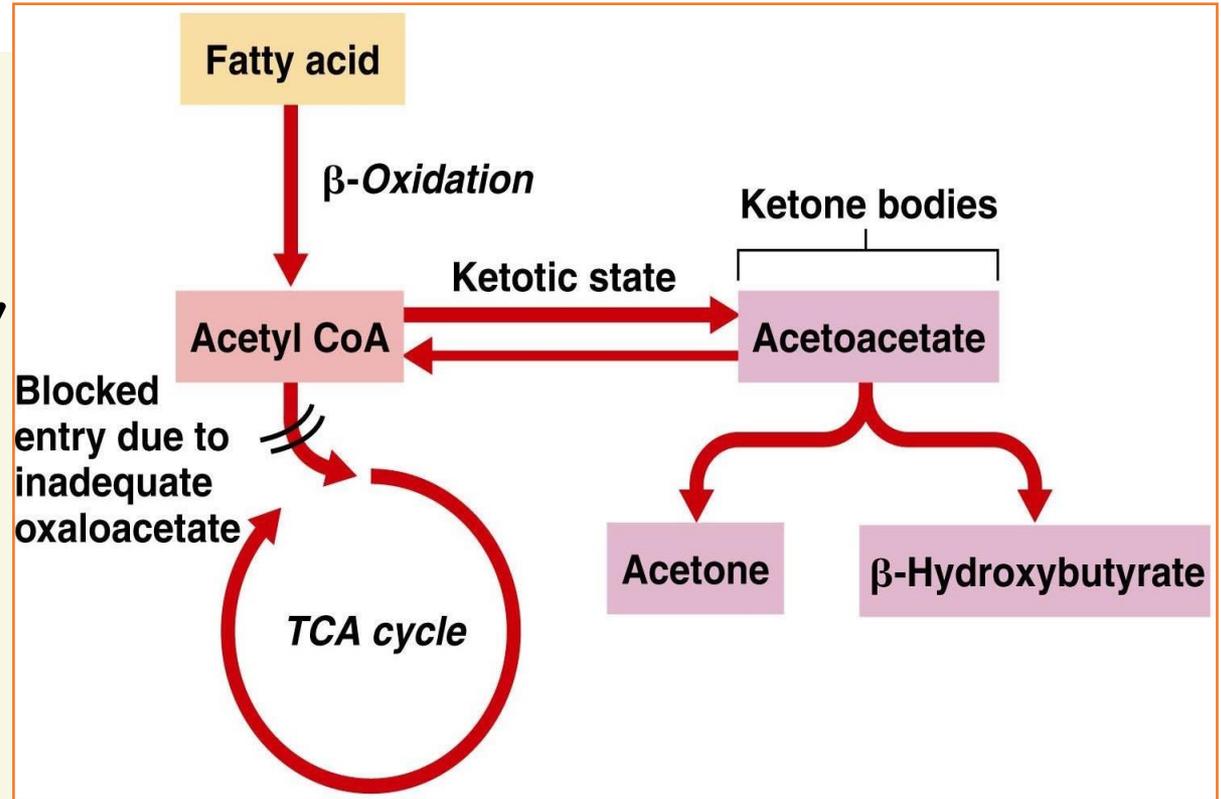
❖ Site of ketogenesis

Mitochondria of the **liver only.**

Ketone bodies are **produced in the liver** to be **used in peripheral tissues**

Ketogenesis

- During high rates of fatty acid oxidation, primarily in the **liver**, large amounts of **acetyl-CoA** are generated.
- These exceed the capacity of the TCA cycle, and result in synthesis of **ketone bodies** (**ketogenesis**).



Ketone body synthesis is promoted by:

- ✓ saturation of citric acid cycle.
- ✓ low mitochondrial oxaloacetate concentrations.

❖ Significance ketogenesis:

- ❑ The acetyl CoA formed from β oxidation of FA can enter and get oxidized to CO_2 and water in TCA cycle only when carbohydrates are available.
- ❑ So, during carbohydrates deficiency, starvation and DM, the acetyl CoA will direct to KBs formation to be utilized for energy production.

❖ Steps of ketogenesis:

Step 1: Condensation

- Two molecules of acetyl CoA are condensed to form aceto-acetyl CoA (Thiolase).

Step 2 : Production of HMG CoA

- One more acetyl CoA is added to aceto-acetyl CoA to form HMG CoA.
- The enzyme is mitochondrial HMG CoA synthase.

Step 3: Lysis

- HMG CoA is lysed to form acetoacetate (AAA).
- HMG CoA lyase is present only in liver.

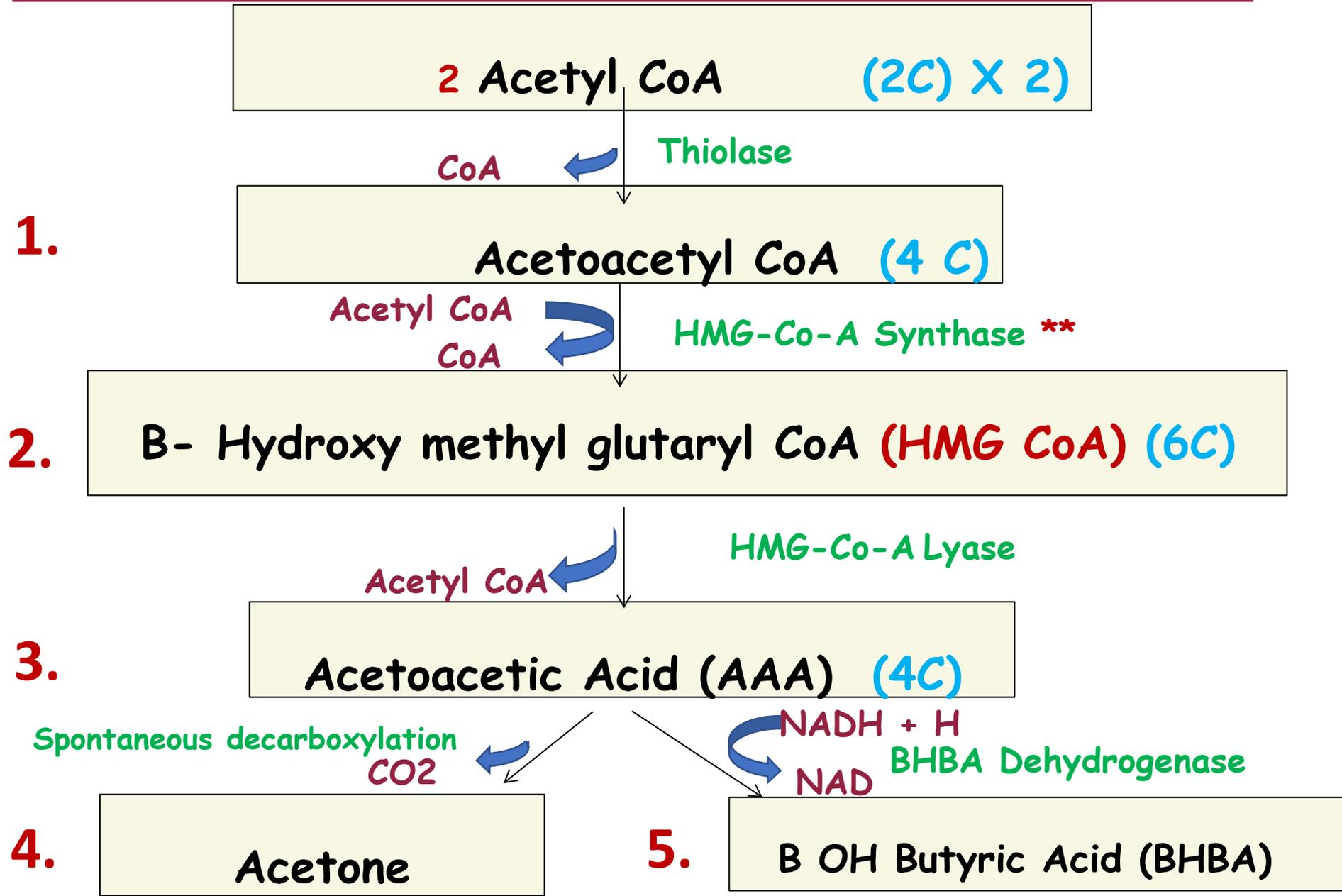
Step 4:Reduction:

- Beta-hydroxy butyrate (BHBA) is formed by reduction of acetoacetate.

Step 5: Spontaneous decarboxylation

- Acetone is formed (a side product excreted via lungs).

Ketogenesis



III. Ketolysis

(Ketone bodies activation)

1. Definition
2. Site
3. Significance
4. Steps

Ketolysis

❖ Definition of ketolysis:

Ketolysis is the lysis (degradation, breakdown, oxidation) of ketone bodies to provide **energy + CO₂ + water**.

❖ Site of ketolysis

- Mitochondria of the **extrahepatic tissues** especially **(Brain, Muscles & Heart)**.
- **Not in the liver:** due to absence of **thiophorase (thiokinase)**

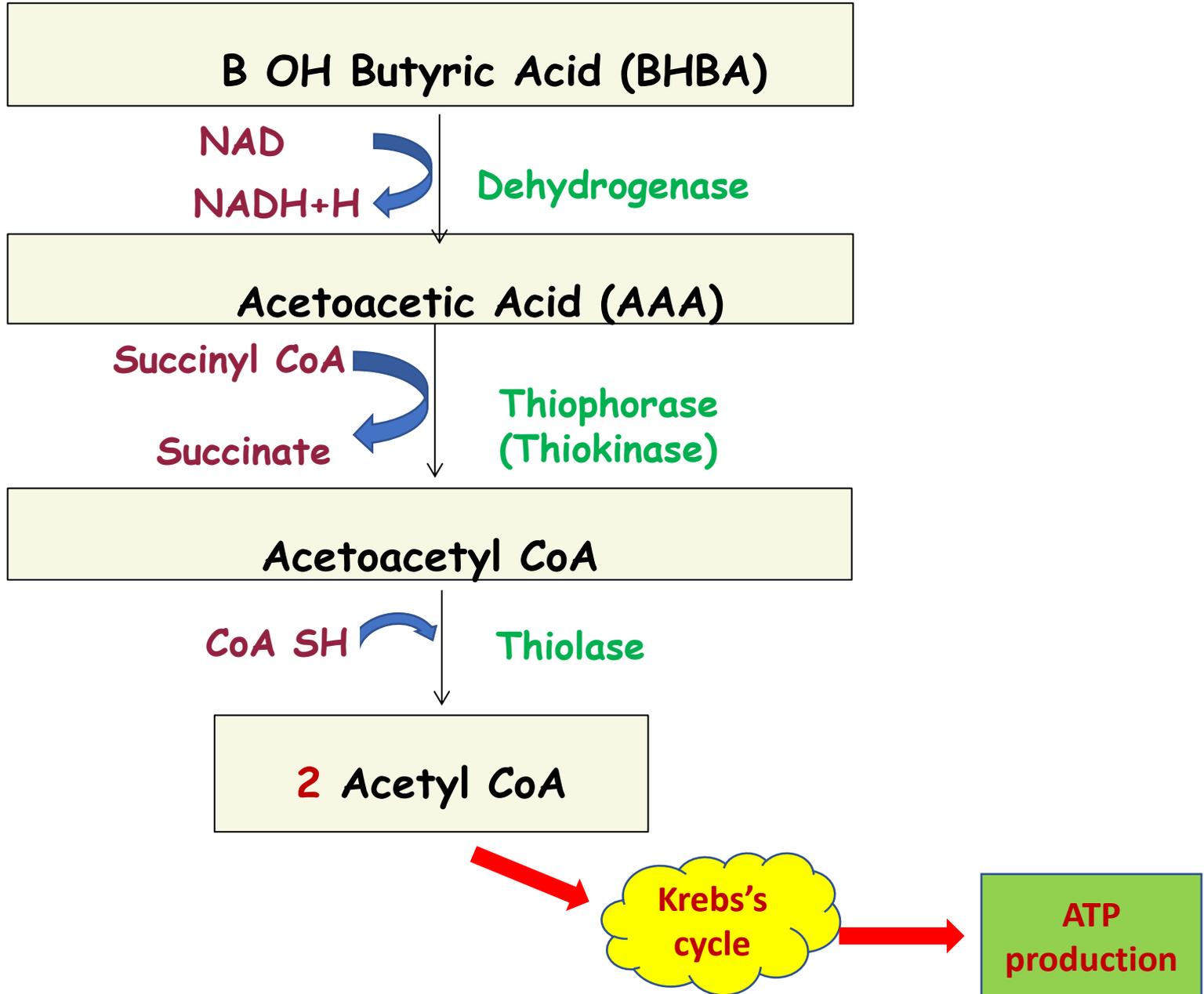
Ketone bodies are produced in the liver to be used in peripheral tissues

Ketolysis

❖ Significance ketolysis:

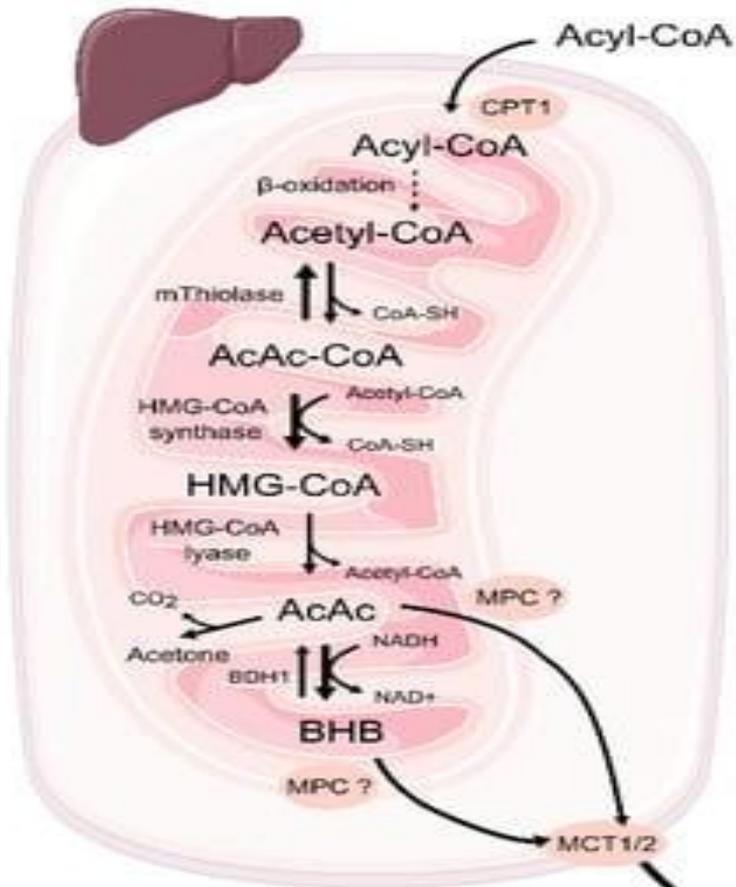
- It is a major source of energy to extrahepatic tissues during starvation, CHO deficiency as it completes the oxidation of FA, which started in the liver.
- To be used as an alternative fuel for other tissues and thus spare glucose for the brain
- During prolonged starvation KB can then become an alternative fuel for brain, as it can cross the blood brain barrier, so can be utilized by brain in fasting state (brain never oxidize FAs).
- Inhibits proteolysis thus prevent excessive degradation of body proteins.

❖ Steps of Ketolysis:



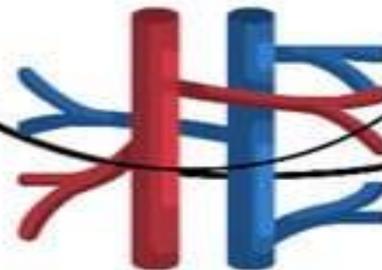
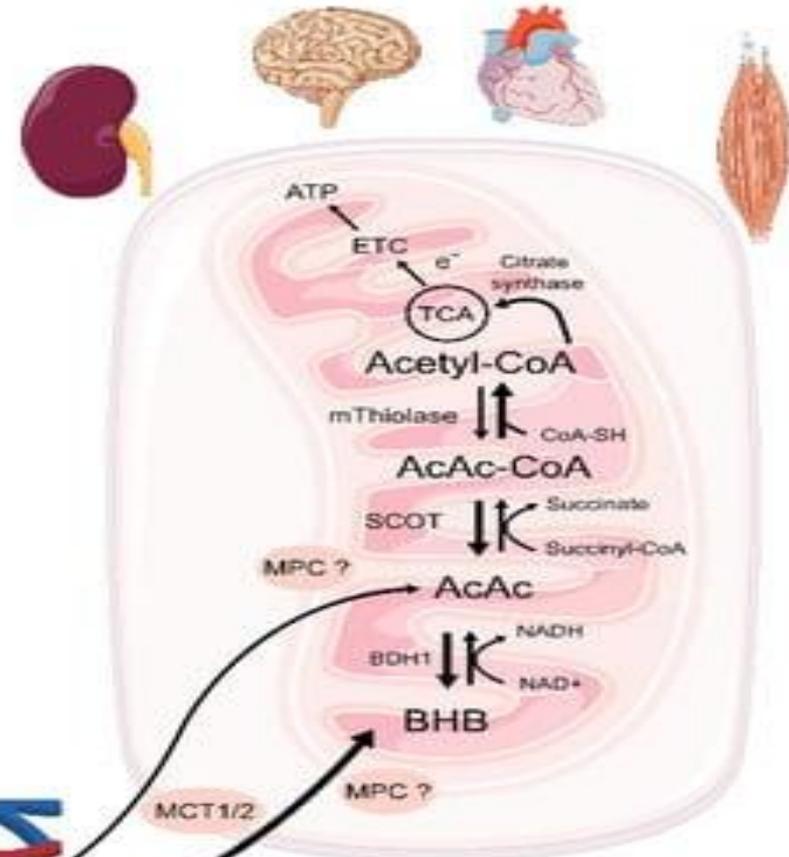
Ketogenesis

Liver mitochondria



Ketolysis

Extrahepatic mitochondria



Bloodstream

III. Ketosis

1. Definition
2. Causes
3. Conditions of active ketosis
4. Effect

Ketosis

❖ Definition

- **Ketosis:** Excessive production and circulation of excessive amount of ketone bodies (KBs) in blood leading to ketonemia & ketonuria
- **Ketonemia:** increased KBs concn. in blood over $1 \mu\text{g}/\text{dl}$
- **Ketonuria:** appearance of KBs in urine.

❖ Causes

- When the rate of KBs synthesis exceeds the ability of extrahepatic tissues to utilize them, there will be accumulation of ketone bodies in blood.
- This leads to **ketonemia**, excretion in urine (**ketonuria**) and smell of acetone in breath (**fruity odor**). All these **three together** constitute the condition known as **ketosis**.

❖ Condition characterized by active ketosis:

- 1- Low carbohydrate , high fat diet
- 2- Prolonged starvation
- 3- Uncontrolled DM.
- 4- Sever muscular exercise

❖ Effect of ketosis:

1. **Metabolic acidosis:** increased concn. Of AAA & BHBA (both are acids) → acidosis → if acidosis is not compensated by blood buffer system → acidemia.
2. **Rapid deep breathing** (Kussmaul breathing).
3. **Acetone smell** in patient's breath.
4. **Osmotic diuresis:** induced by ketonuria may lead to dehydration.
5. **Coma:** due to dehydration and acidosis → may be fatal.

References

- ✓1. Lippincott Illustrated Reviews: Biochemistry 7th Edition ISBN-10: 1-4963-6354-X
- ✓2. USMLE step 1 lecture Notes 2017 Biochemistry and medical genetics .
- ✓3. First AID Q& A for USMLE STEP 1 3rd Edition ISBN:978-0-07-174402-7 chapter 2 Biochemistry (page 17-page 52)
<https://medicombank.files.wordpress.com/2017/03/first-aid-qa-for-the-usmle-step-1-third-edition.pdf>

A bouquet of vibrant pink tulips with green leaves is arranged in a light-colored woven basket. In the foreground, a rustic wooden sign with a scalloped edge is placed on a piece of light-colored, textured paper. The sign has the words "THANK YOU" written on it in a bold, black, hand-drawn font. The background is a soft, out-of-focus white.

THANK
YOU