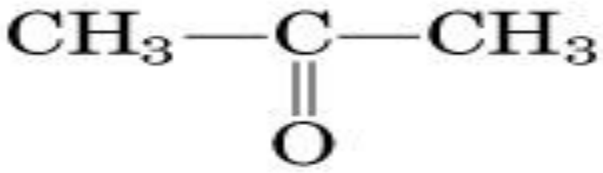
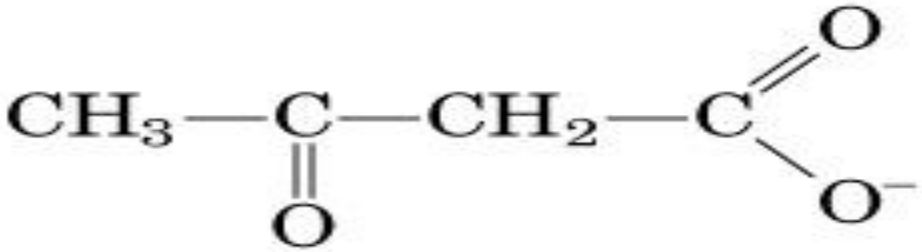
Ketone bodies and regulation

Dr.Sulieman Al-Khalil

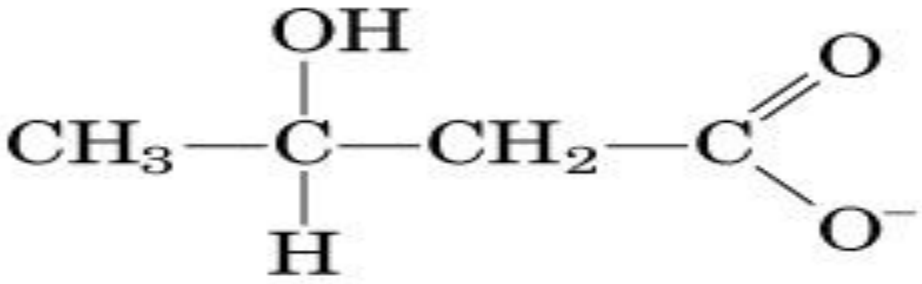
Ketone ‘bodies’



Acetone



Acetoacetate

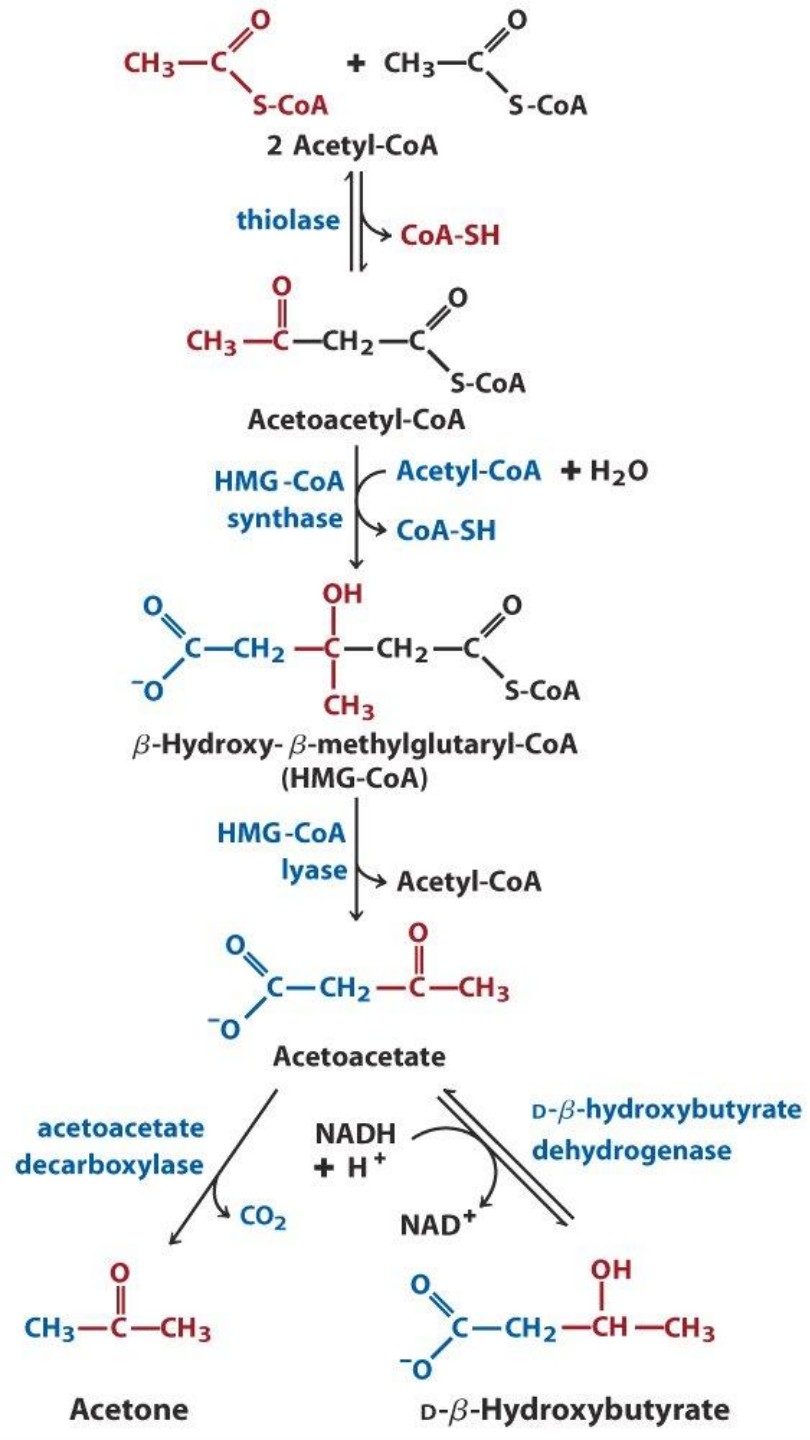


D-β-Hydroxybutyrate

- In the liver, acetyl-CoA can enter the citric acid cycle or it can be converted to ‘ketone bodies’ for export to other tissues (acetoacetate and D- b-hydroxybutyrate).
- In the tissues, acetyl-CoA is regenerated from the ketones and enters the citric acid cycle.
- The transport of ketone bodies allows continued oxidation of fatty acids in the liver even when acetyl-CoA is not entering the citric acid cycle in the liver.

- **Under these conditions there is a shortage of CoA for fatty acid oxidation.**
- **The brain relies on glucose for its fuel, but under conditions of glucose depletion it can instead function by converting ketone bodies to acetyl-CoA.**
- **The production of ketone bodies is basically a means of transporting acetyl-CoA throughout the body.**

Formation of ketone bodies from acetyl-CoA



Ketone formation in the liver

- **First step is condensation of two molecules of acetyl-CoA to give acetoacetyl-CoA. (Reverse of the last step of b-oxidation).**

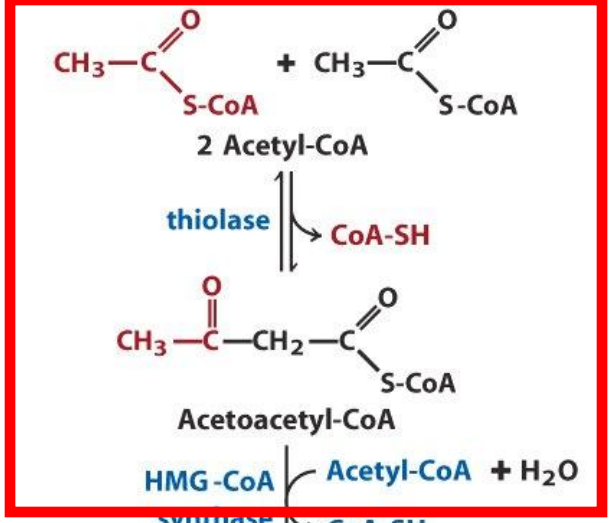
Catalyzed by thiolase

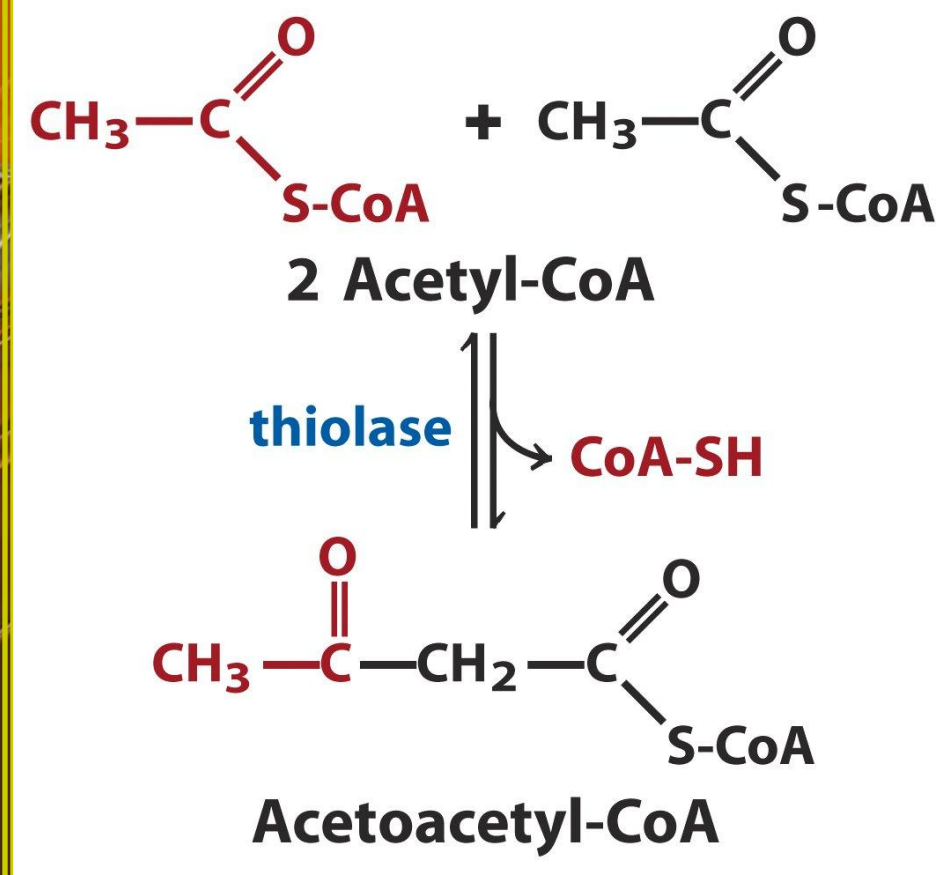
- **Acetoacetyl-CoA then condenses with another molecule of acetyl-CoA to give b-hydroxy- b-methylglutaryl-CoA (HMG-CoA).**

Catalyzed by HMG-CoA synthase

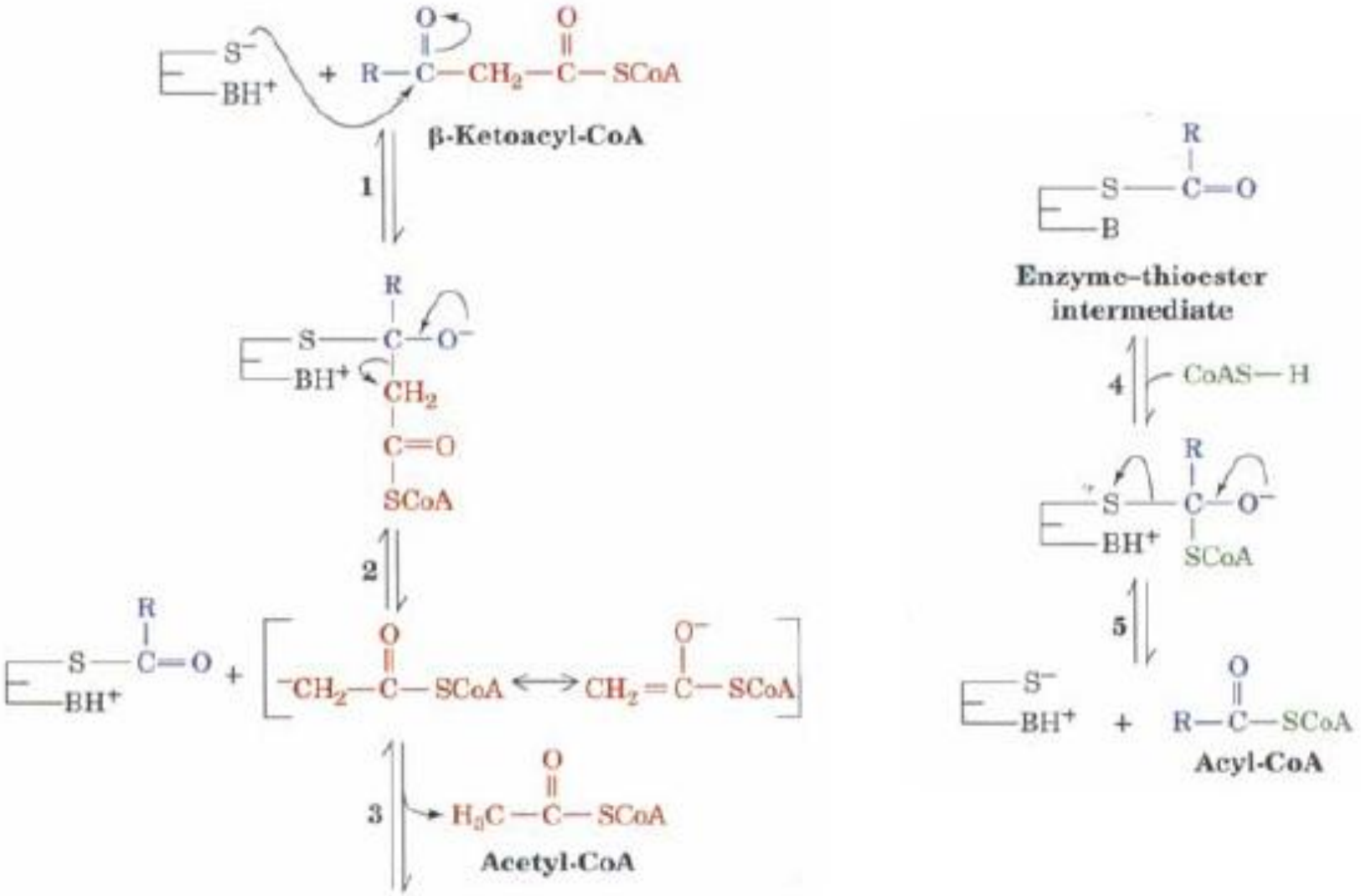
- **HMG-CoA is then cleaved to give acetoacetate, catalyzed by HMG-CoA lyase.**

Formation of ketone bodies from acetyl-CoA

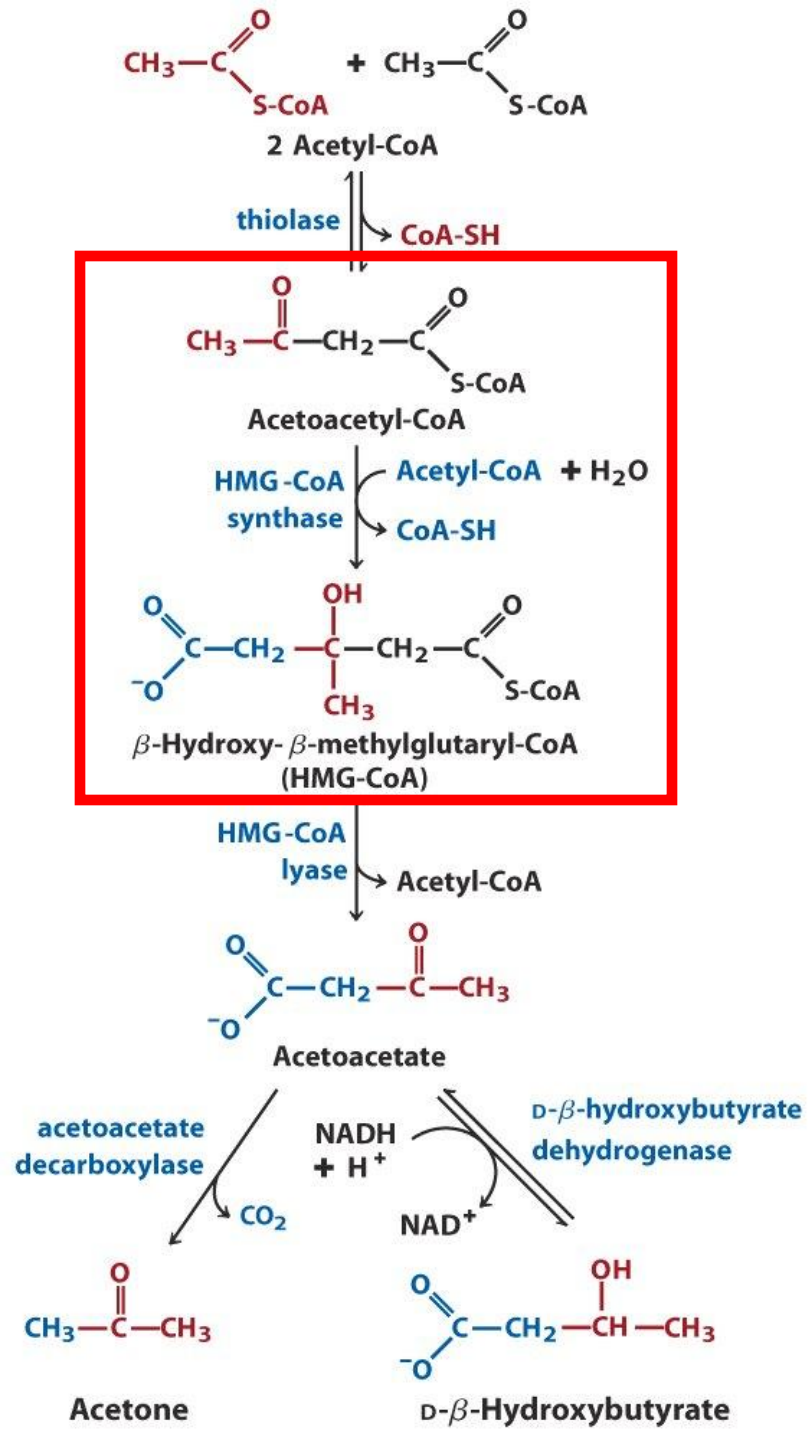


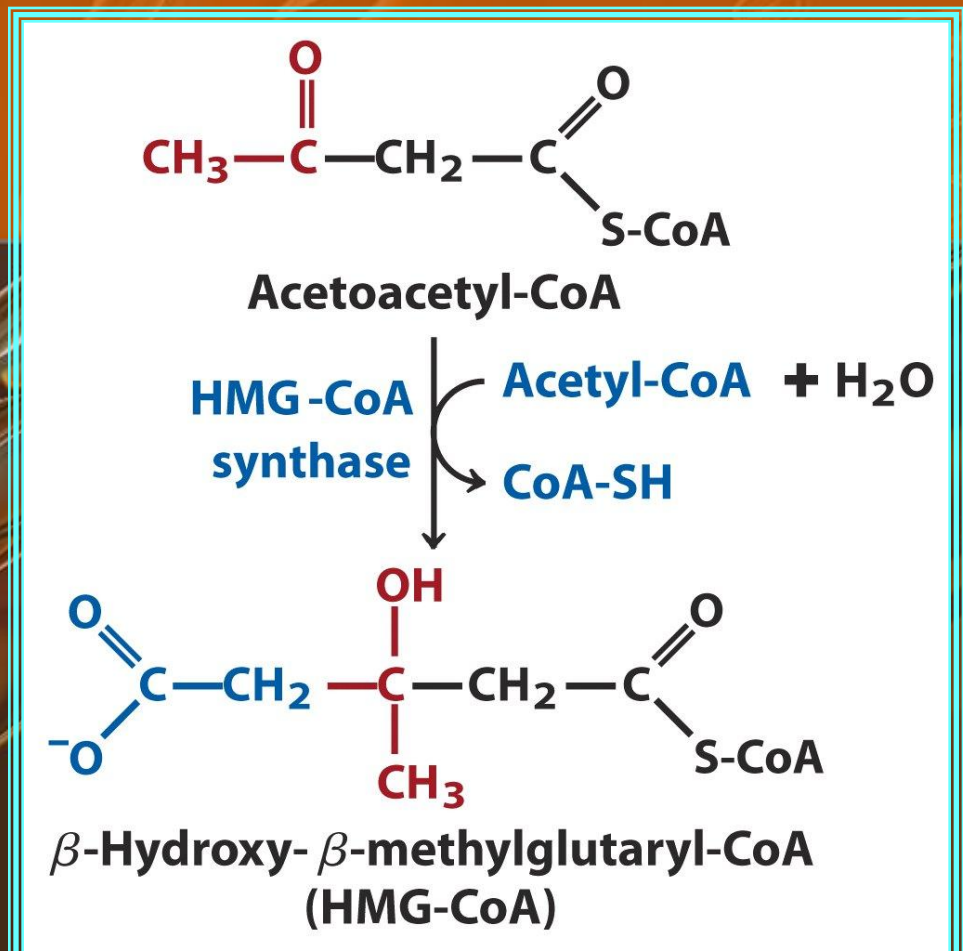


Mechanism of Thiolase –



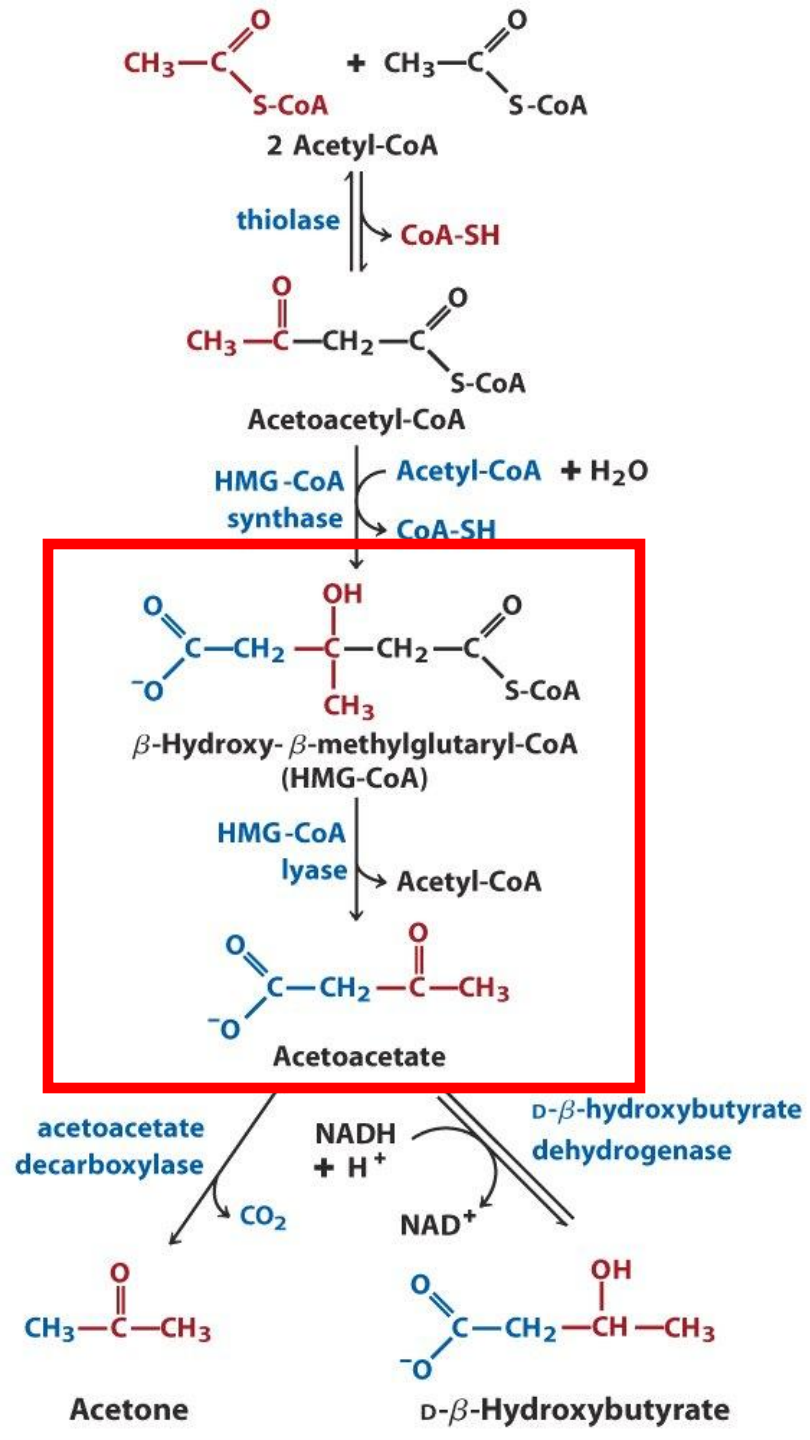
Formation of ketone bodies from acetyl-CoA

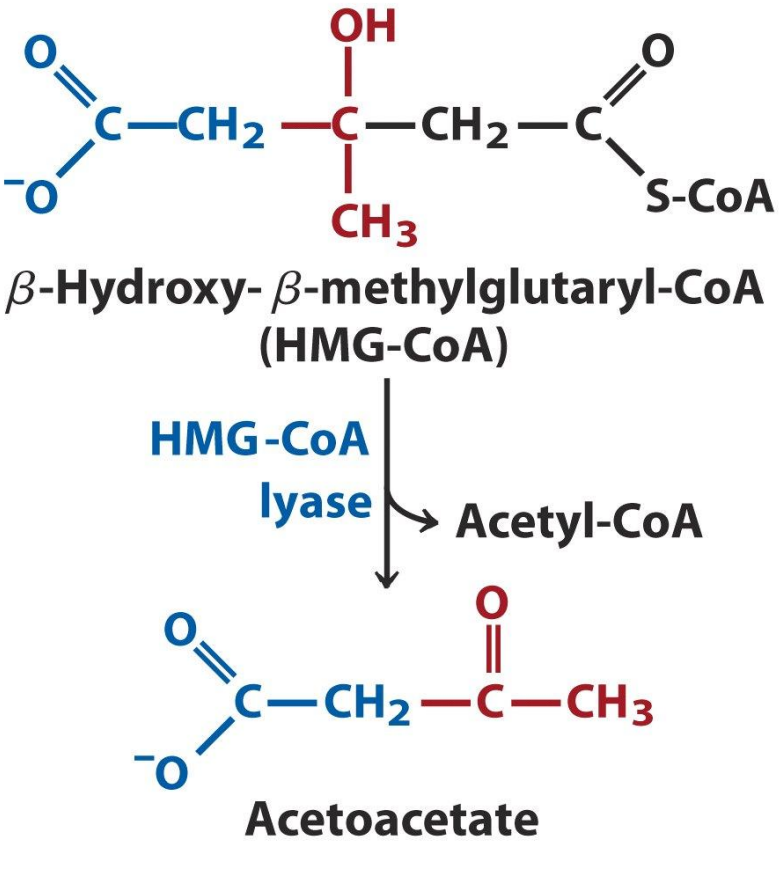




- Acetoacetate is reversibly reduced to D- b-hydroxybutyrate by D- b-hydroxybutyrate dehydrogenase.
- D- b-hydroxybutyrate and acetoacetate are both transported through the blood to other tissues.
- A fraction of the acetoacetate produced in the liver undergoes enzymatic or non-enzymatic decarboxylation to give acetone.
- Acetone is volatile, so it ends up being excreted from the lungs.
- People with untreated diabetes make large amounts of acetoacetate, and acetone can be smelled on their breath.
- This was used historically to diagnose diabetes.

Formation of ketone bodies from acetyl-CoA

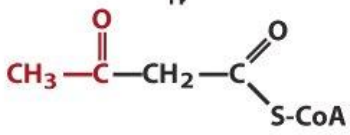




Formation of ketone bodies from acetyl-CoA

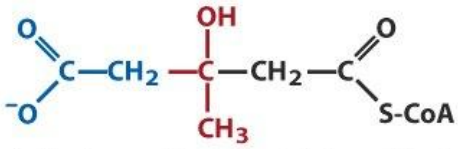
2 Acetyl-CoA

thiolase ⇌ CoA-SH



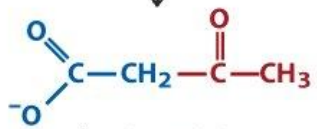
Acetoacetyl-CoA

HMG-CoA synthase: Acetyl-CoA + H_2O → CoA-SH



β-Hydroxy-β-methylglutaryl-CoA (HMG-CoA)

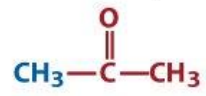
HMG-CoA lyase → Acetyl-CoA



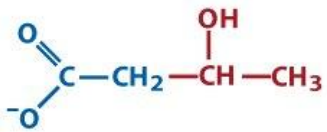
Acetoacetate

acetoacetate decarboxylase → CO_2

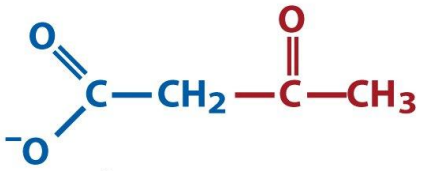
NADH + H^+ ⇌ NAD^+ (D-β-hydroxybutyrate dehydrogenase)



Acetone



D-β-Hydroxybutyrate



Acetoacetate

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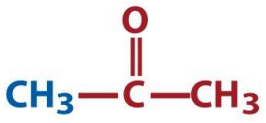
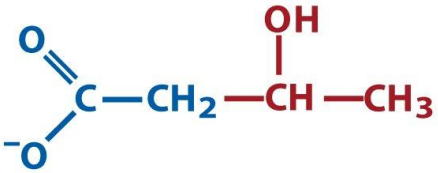
NADH + H^+ ⇌ NAD^+ (D-β-hydroxybutyrate dehydrogenase)



Acetone



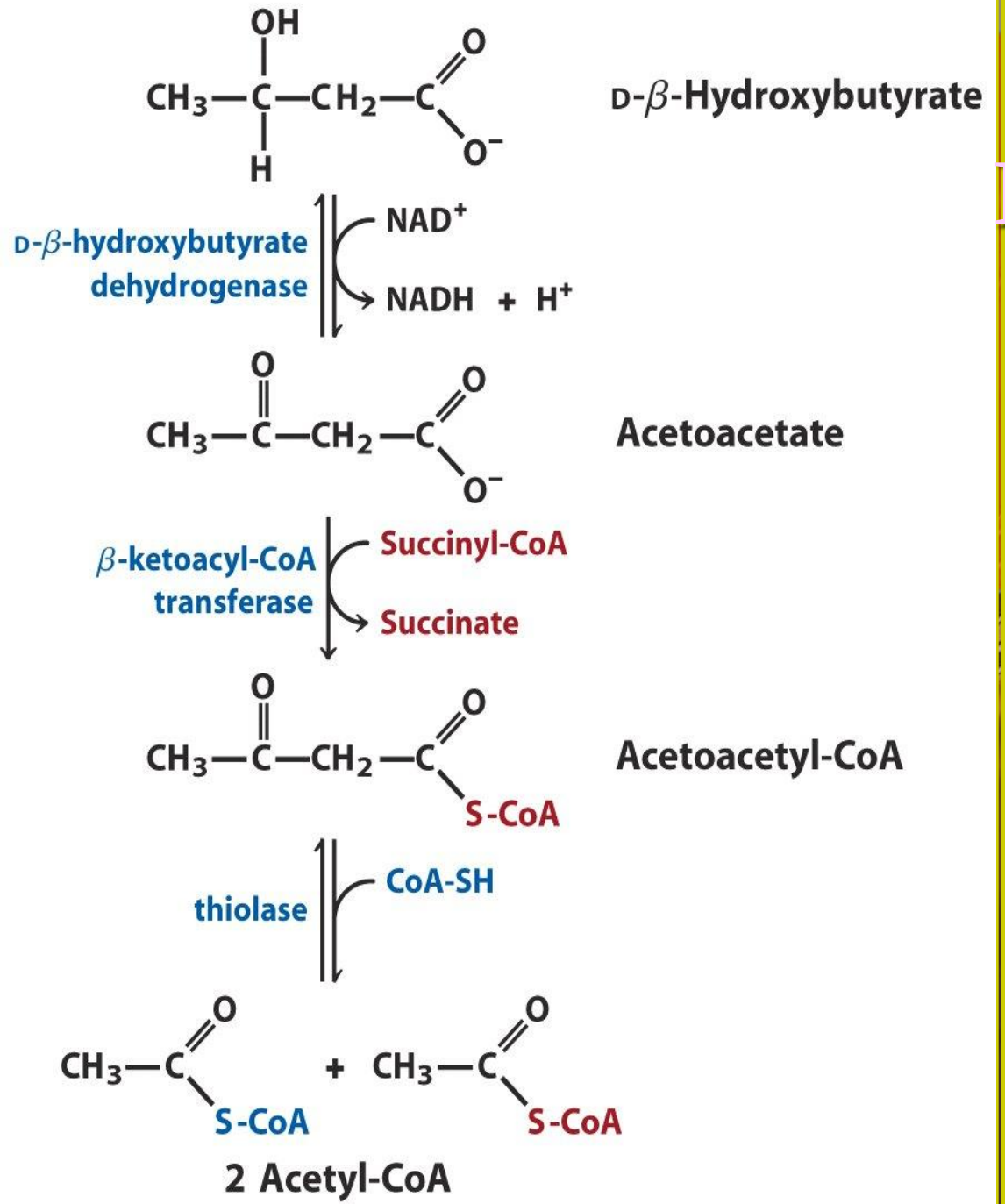
D-β-Hydroxybutyrate

Use of ketone bodies as fuel

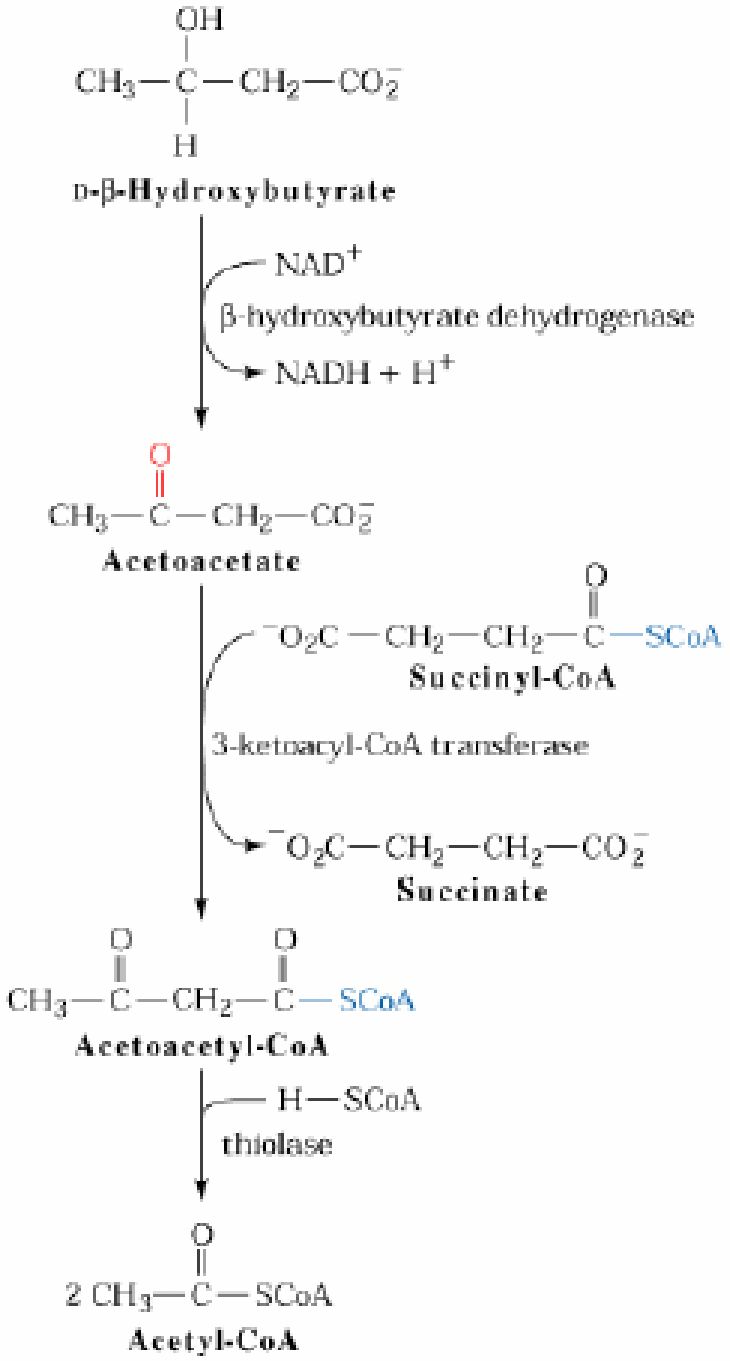
- In tissues outside the liver, D- b-hydroxybutyrate is oxidized to acetoacetate, which is then activated by transfer of CoA from succinyl-CoA.
- This reaction gives acetoacetyl-CoA, which then undergoes the last step of b-oxidation, catalyzed by thiolase, to give two molecules of acetyl-CoA.
- The acetyl-CoA generated can then enter the citric acid cycle.

Regeneration of acetyl-CoA

Occurs in tissues (brain, muscle)

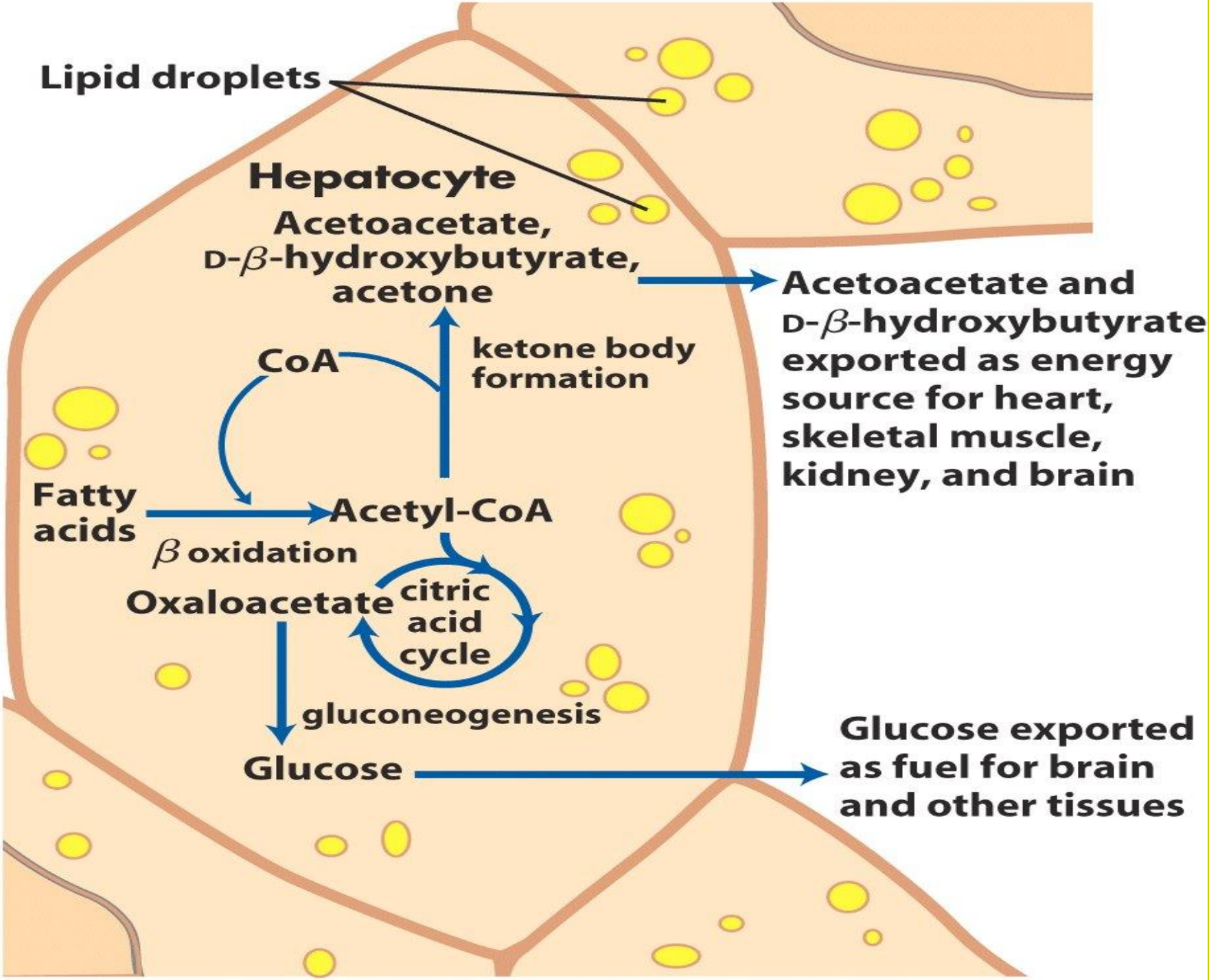


Conversion of Ketone Bodies to Acetyl-CoA



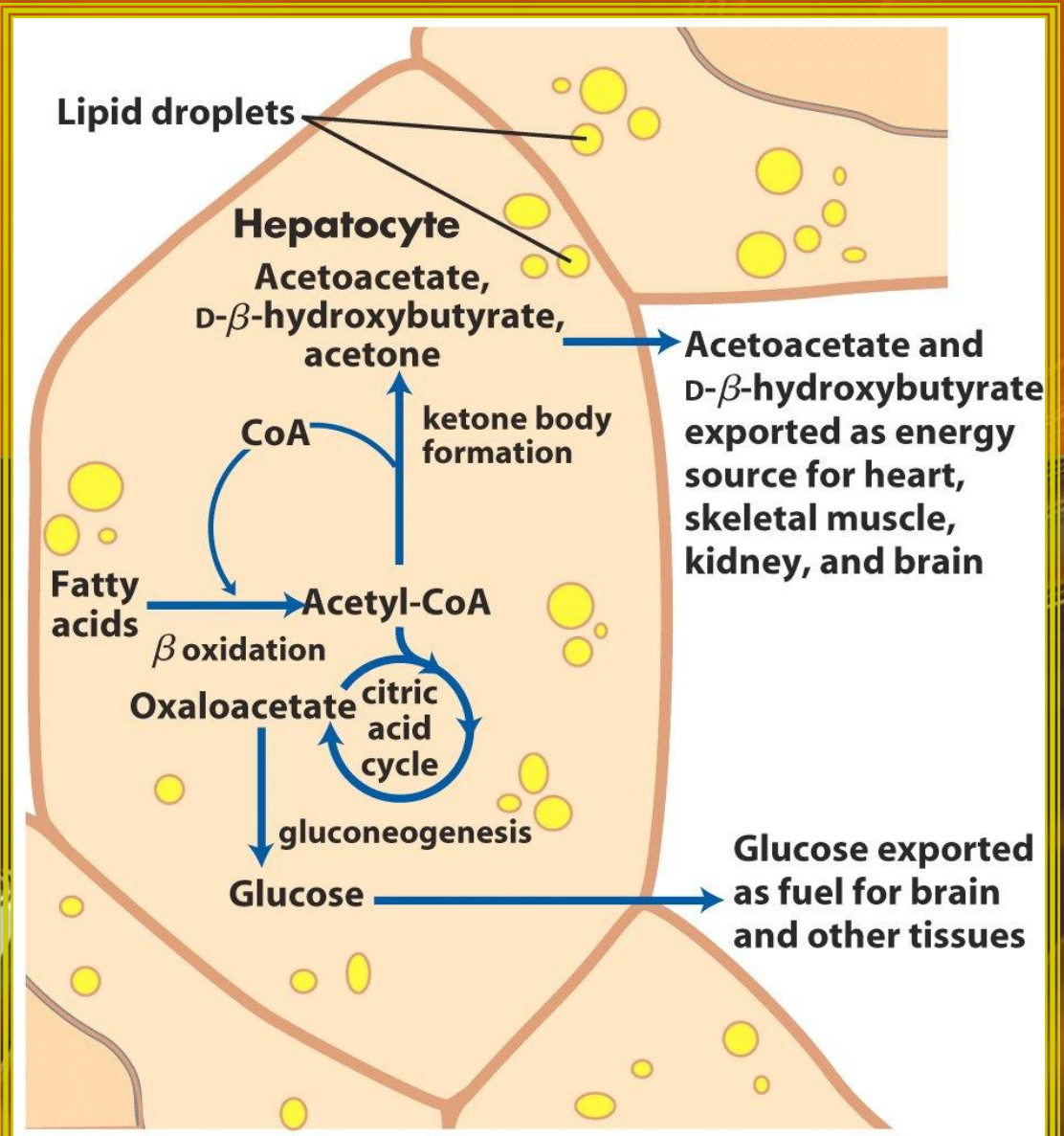
Ketone bodies are overproduced during starvation

- When other fuel sources have been depleted, there can still be some fat reserves.
- Production of ketone bodies can be thought of as an ‘emergency backup’ system for providing fuel for the body in times of severe stress.
- Production of ketone bodies in the liver allows continued oxidation of fatty acids when CoA is limiting.


Lipid droplets
Hepatocyte
Acetoacetate,
D-β-hydroxybutyrate,
acetone
Acetoacetate and
D-β-hydroxybutyrate
exported as energy
source for heart,
skeletal muscle,
kidney, and brain
CoA
ketone body
formation
Fatty
acids
Acetyl-CoA
β oxidation
Oxaloacetate
citric
acid
cycle
gluconeogenesis
Glucose
Glucose exported
as fuel for brain
and other tissues

- This is because the CoA is no longer present in the ketone bodies, so it can be recycled.
- When intermediates of the citric acid cycle are being siphoned off to function in gluconeogenesis, flux through the cycle decreases and acetyl-CoA accumulates, making free CoA vanishingly scarce.
- Ketone body production frees CoA, allowing b-oxidation to continue.

Ketone body formation and export from the liver



Ketone bodies are also overproduced in diabetes

- Diabetes mellitus (“sweetened with honey”).
- Metabolism is disrupted because of a lack of insulin.
- Insulin normally promotes glucose uptake and glycogen synthesis, essentially signaling that the levels of glucose are sufficient.

- In the absence of insulin, the body behaves as if it is starving even when it is well fed.
- fatty acids are broken down, leading to an overproduction of ketone bodies
- glycogen is continually broken down to glucose, further increasing glucose concentration
- Overproduction of ketone bodies lead to pH changes in the blood, which can be life-threatening

table 17–2

Ketone Body Accumulation in Diabetic Ketosis

	Urinary excretion (mg/24 h)	Blood concentration (mg/100 mL)
Normal	≤125	<3
Extreme ketosis (untreated diabetes)	5,000	90

Summary

1. When glucose is scarce, the liver can oxidize fatty acids to ketone bodies. These ketone bodies are transported through the body and converted back to acetyl-CoA to enter the citric acid cycle.

2. The brain normally uses only glucose, but when glucose in unavailable it can survive on ketone bodies.

3. Significant production of ketone bodies occurs principally in starvation and in untreated diabetes.