

Ketone Body Metabolism

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OBJECTIVES

- Ketone bodies and their biological significance.
- Ketogenesis and its regulation.
- Utilization of ketone bodies.
- Disorders associated with ketone bodies.

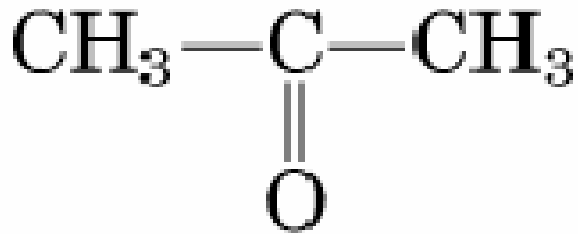


Introduction

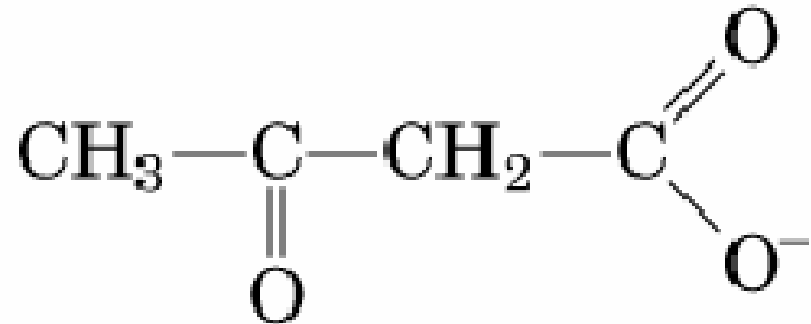
- **Ketone bodies** are three chemicals that are produced when fatty acids are broken down in excess.
- Production of these compounds is called “**ketogenesis**”, and this is necessary in small amounts.



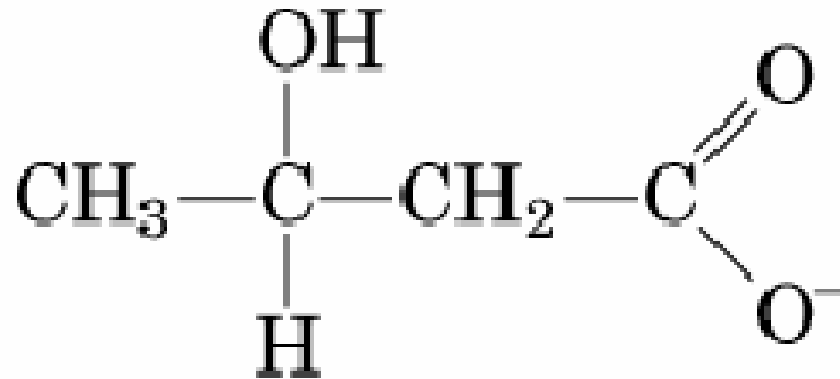
Ketone bodies



Acetone



Acetoacetate



β - Hydroxybutyrate

Introduction



- The three ketone bodies are
 - Acetoacetate, β -Hydroxy butyrate and Acetone.
- Ketone bodies are produced from acetyl-CoA, mainly in the mitochondrial matrix of liver cells when carbohydrates are so scarce that energy must be obtained from breaking down of fatty acids.

Ketone Bodies as Fuel



- water soluble
- transported across the inner mitochondrial membrane as well as across the blood-brain barrier and cell membranes.
- Source of fuel for brain, heart and muscle
- Major energy source(75%) for brain during starvation



Introduction

- when excess ketone bodies accumulate, this abnormal (but not necessarily harmful) state is called ketosis.
- When even larger amounts of ketone bodies accumulate such that the body's pH is lowered to dangerously acidic levels, this state is called ketoacidosis.



Introduction

- Ketone bodies are used for energy.
- Ketone bodies are transported from the liver to other tissues, where acetoacetate and β -hydroxybutyrate can be reconverted to acetyl-CoA to produce energy.
- The heart gets much of its energy from ketone bodies, although it also uses a lot of fatty acids



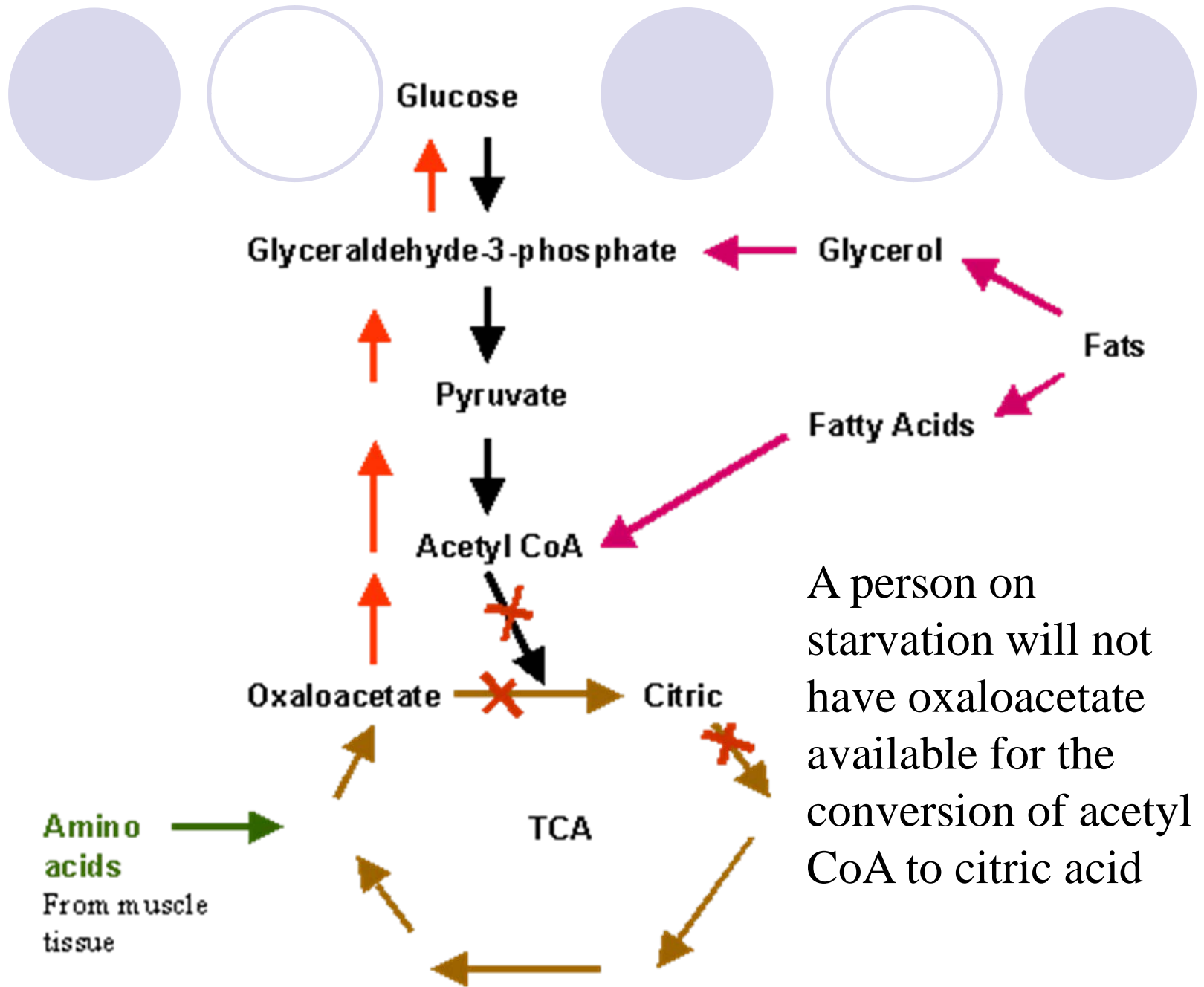
Introduction

- The brain gets its energy from ketone bodies when insufficient glucose is available (e.g. fasting).
- In the event of low blood glucose, most other tissues have additional energy sources besides ketone bodies (such as fatty acids) but the brain does not.

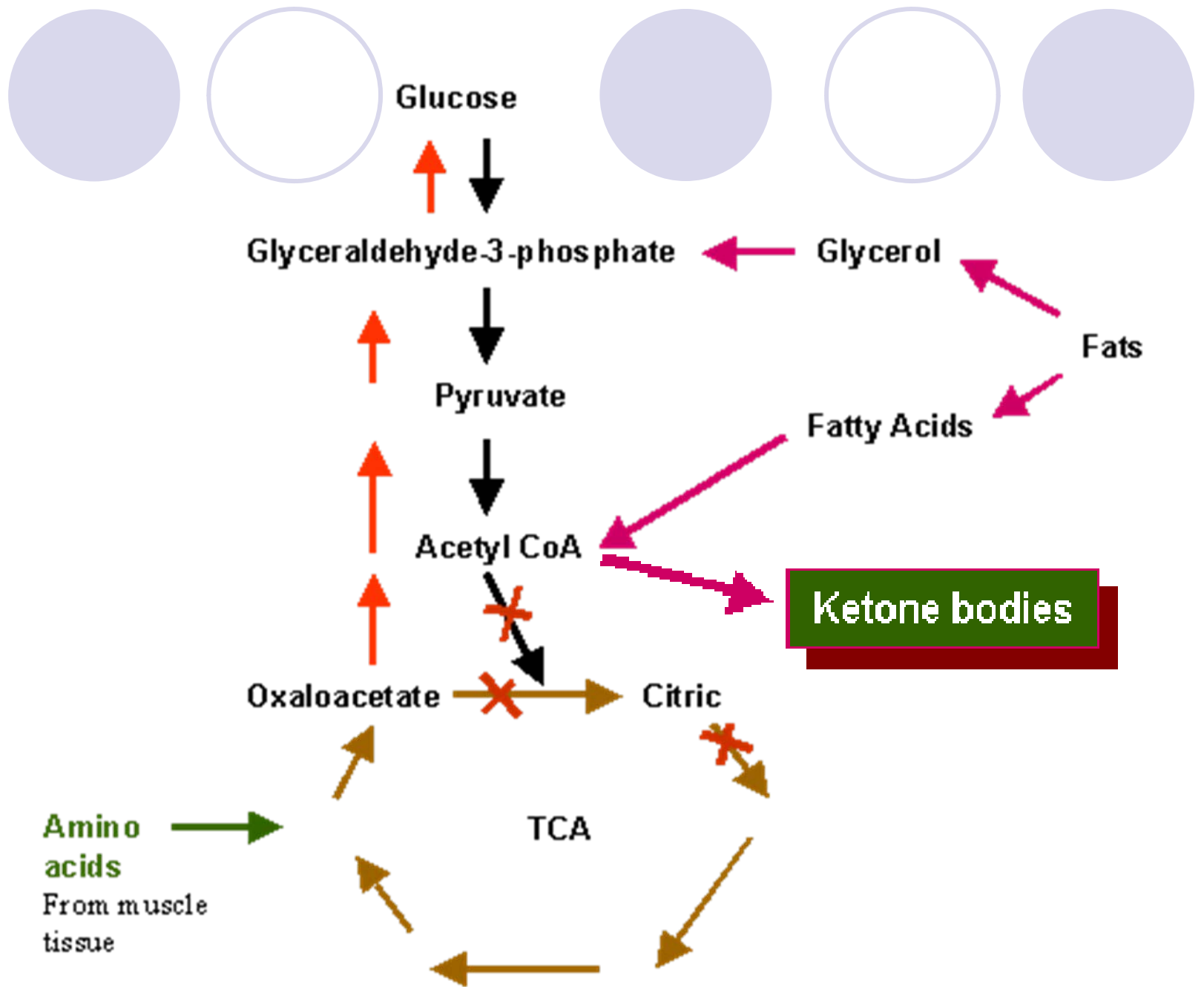
Ketone body synthesis



- Liver – Mitochondria
- Some of the Acetyl-CoA produced by fatty acid oxidation in liver mitochondria is converted to Acetone, Acetoacetate and β -hydroxybutyrate.
- Ketone bodies are produced when glucose is not available as fuel source.
- Transport of fatty acids through the mitochondrial membrane is an important regulatory point.



A person on starvation will not have oxaloacetate available for the conversion of acetyl CoA to citric acid





Ketogenesis

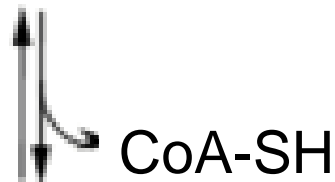
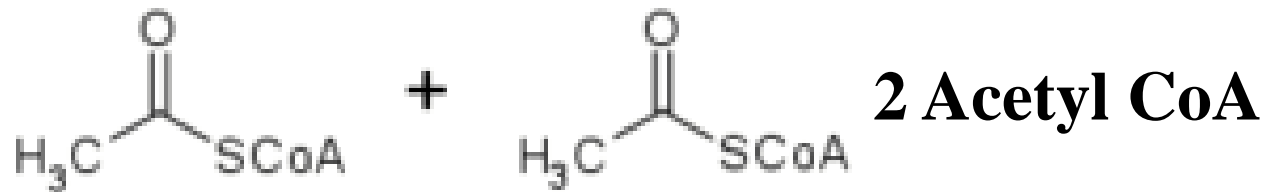
1. First step – Reverse of Thiolyase.
2. Second step – Synthesis of HMG CoA.

These reactions are mitochondrial analogues of the (cytosolic) first two steps of cholesterol synthesis.

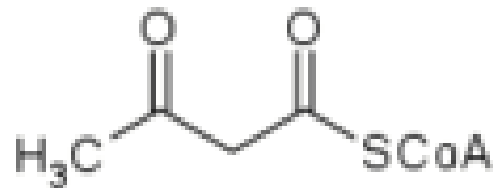
3. Third step – HMG CoA Lyase.

Ketogenesis

Reverse of Thiolase step



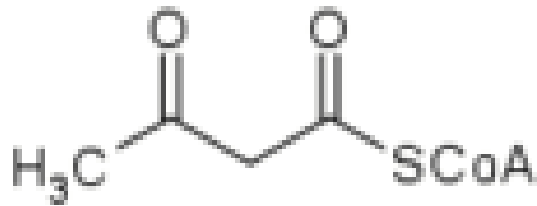
Thiolase



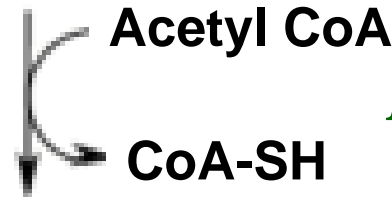
Acetoacetyl CoA

Ketogenesis

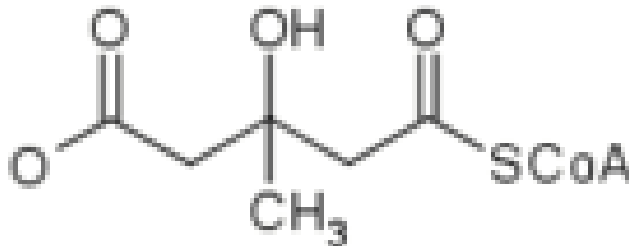
Synthesis of HMG CoA



Acetoacetyl CoA



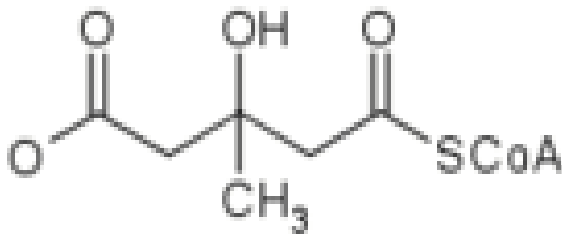
HMG CoA synthase



**β -Hydroxy- β -Methyl Glutaryl CoA
(HMG CoA)**

Ketogenesis

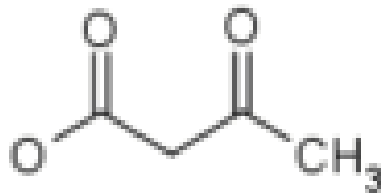
Lysis of HMG CoA



**β -Hydroxy- β -Methyl Glutaryl CoA
(HMG CoA)**



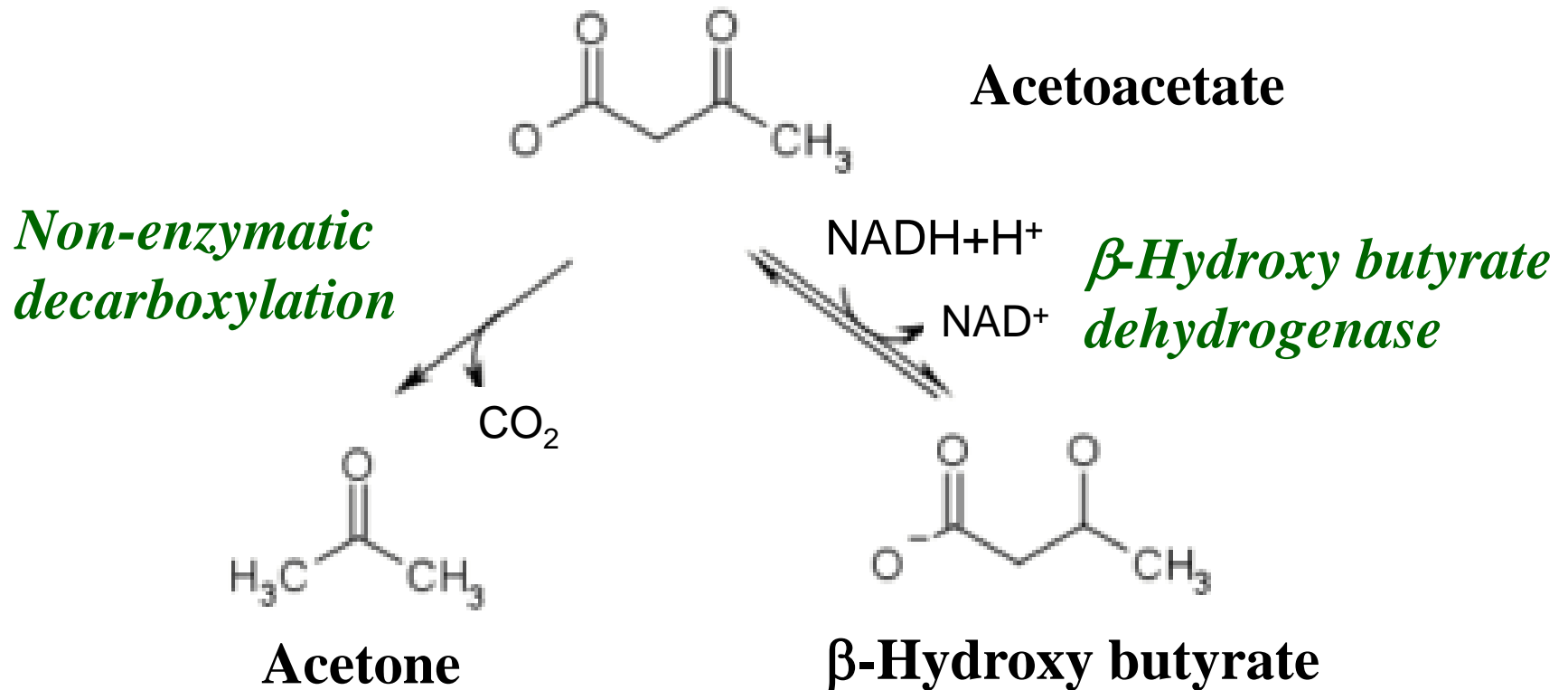
HMG CoA Lyase

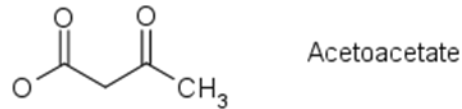
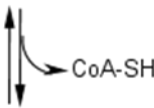
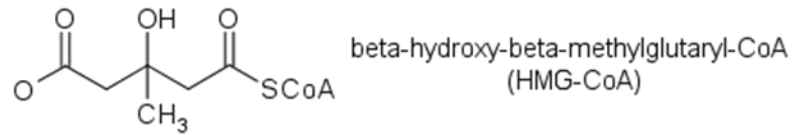
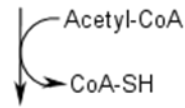
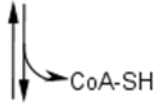
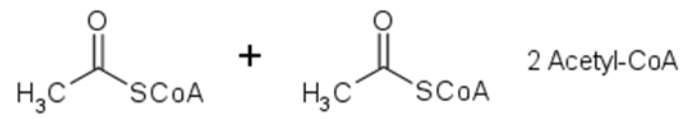


Acetoacetate

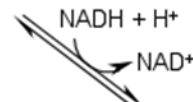
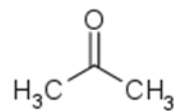
Ketogenesis

Parent ketone body producing
other ketone bodies

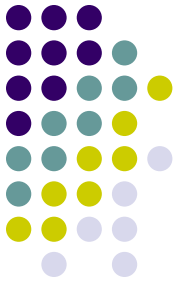
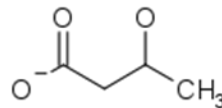




Non-enzymatic decarboxylation



D-beta-hydroxybutyrate dehydrogenase



Acetone

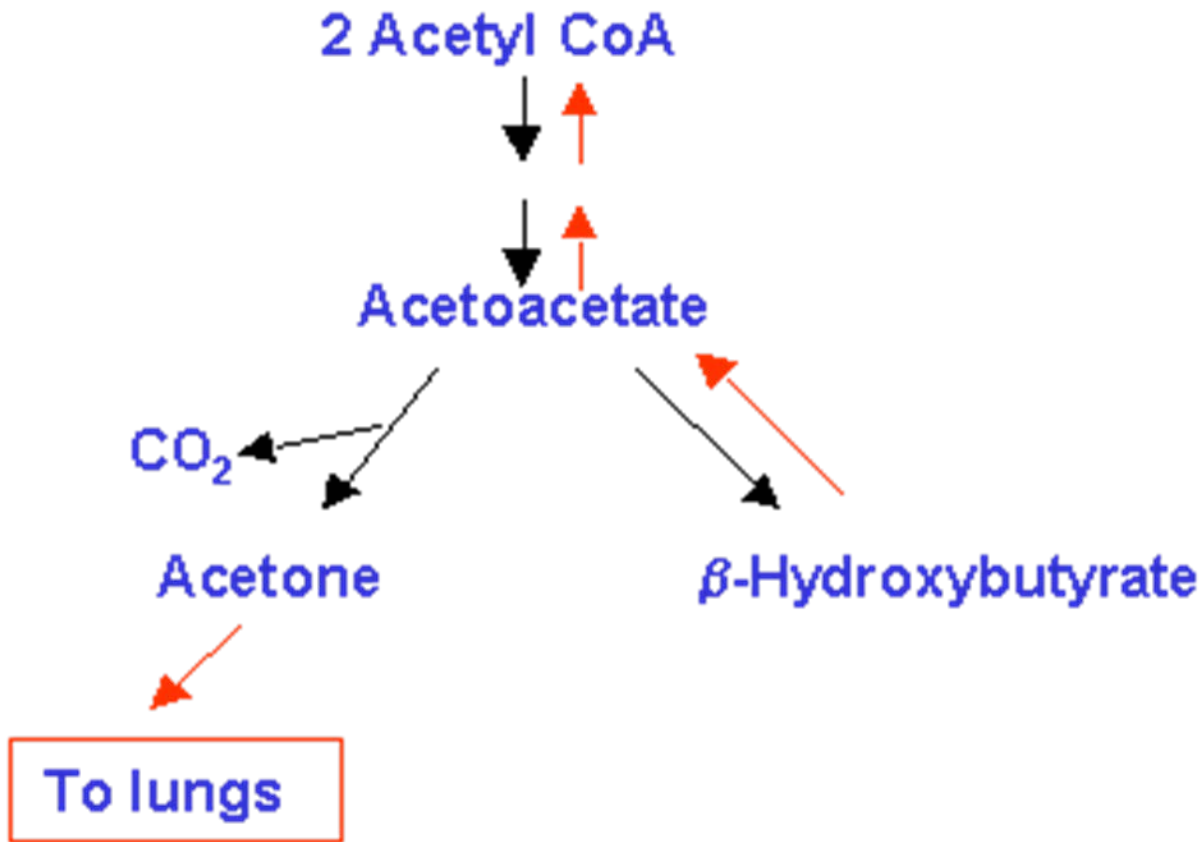
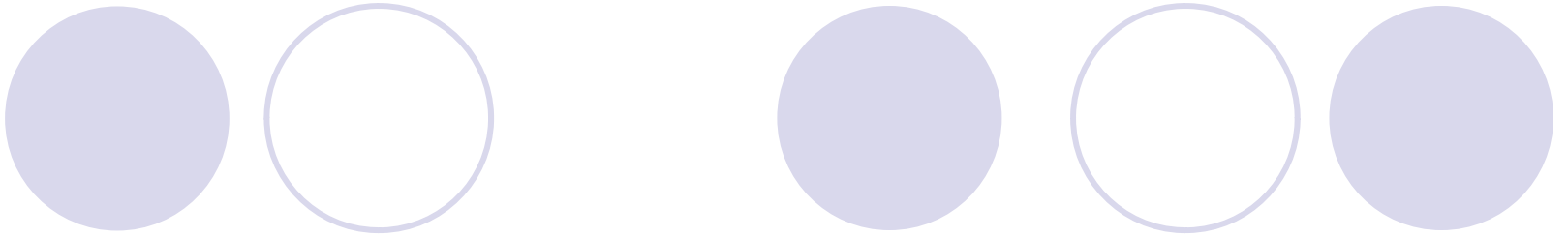


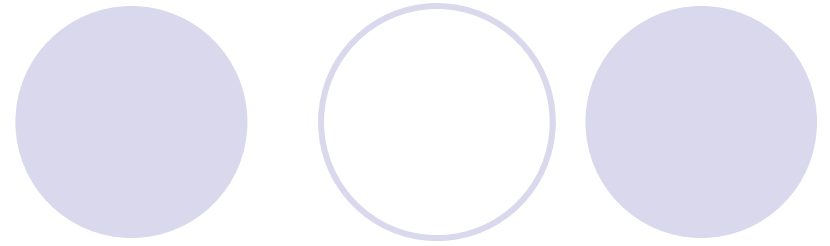
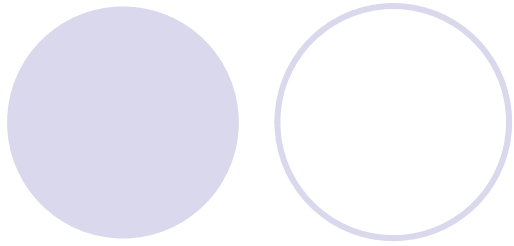
- Acetone is formed from spontaneous decarboxylation of acetoacetate.
- In a corresponding manner, the levels of acetone are much lower than those of the other two types of ketone bodies.
- Acetone is produced in small quantities; highly volatile. Hence it is not used by the body.

Acetone (Contd)



- Acetone cannot be converted back to acetyl-CoA, so it is excreted in the urine and exhaled (it can be exhaled because it has a high vapor pressure and thus evaporates easily).
- The exhalation of acetone is responsible for the characteristic "fruity" odour of the breath of persons in ketotic states.



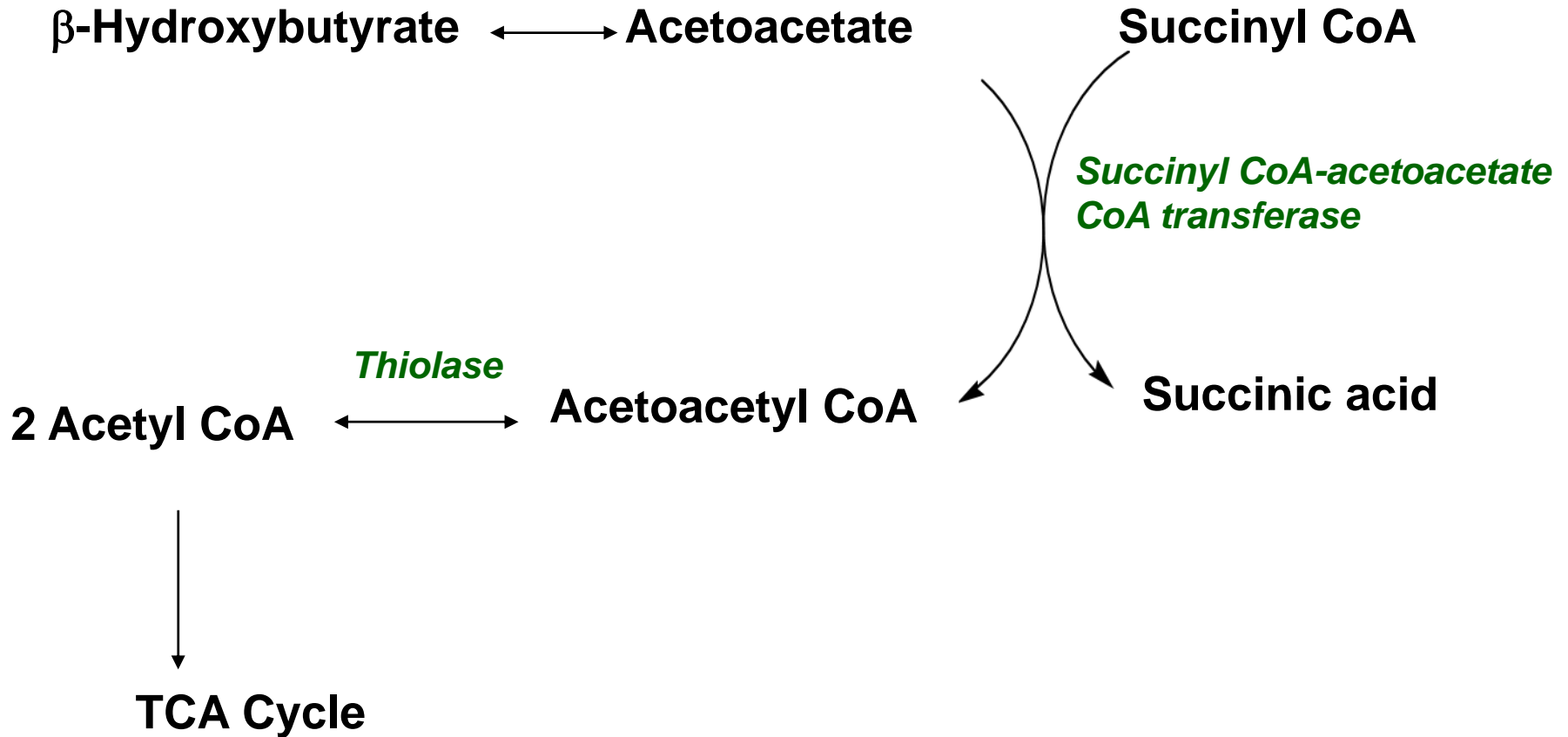


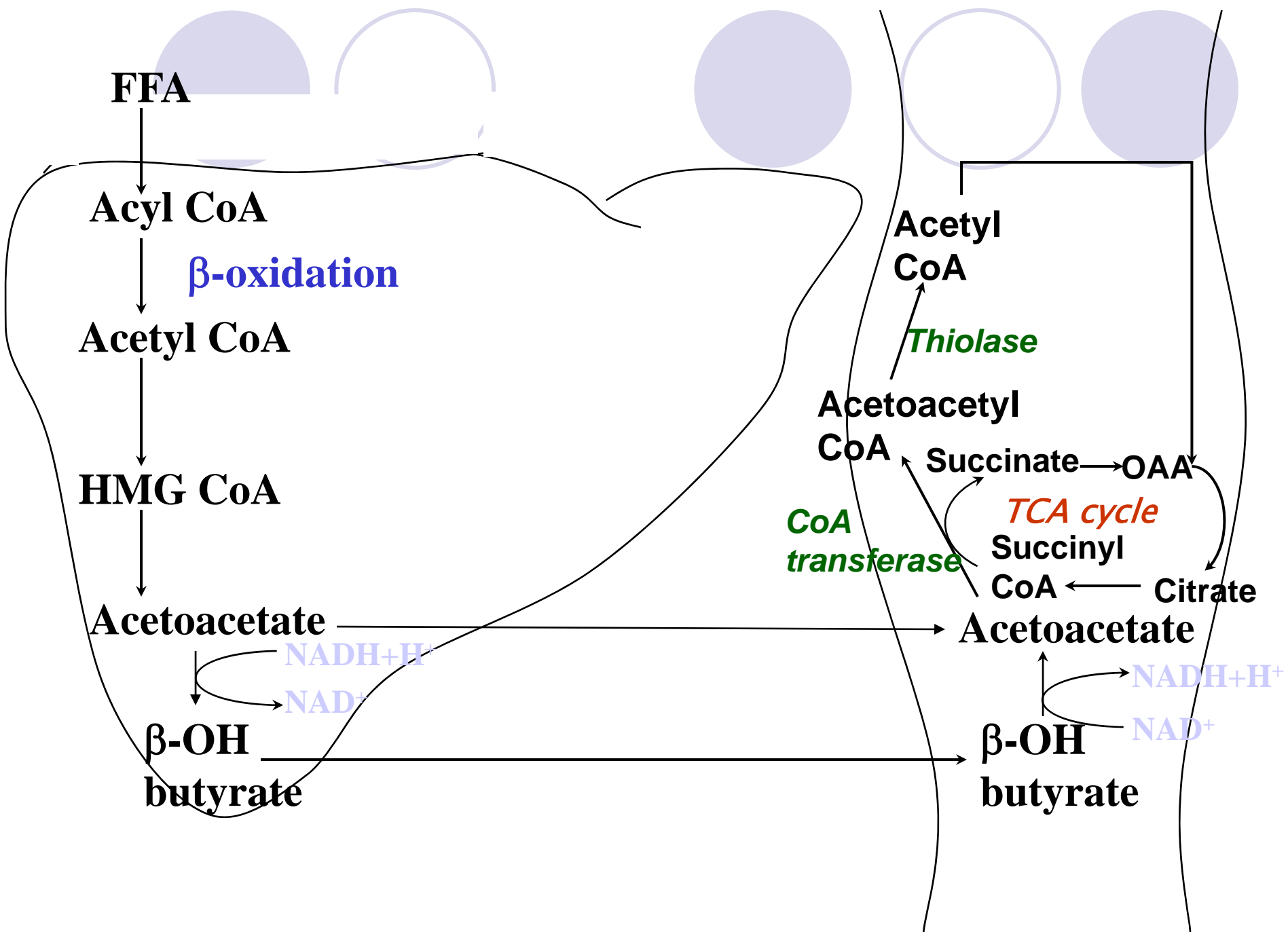
Utilization of Ketone bodies

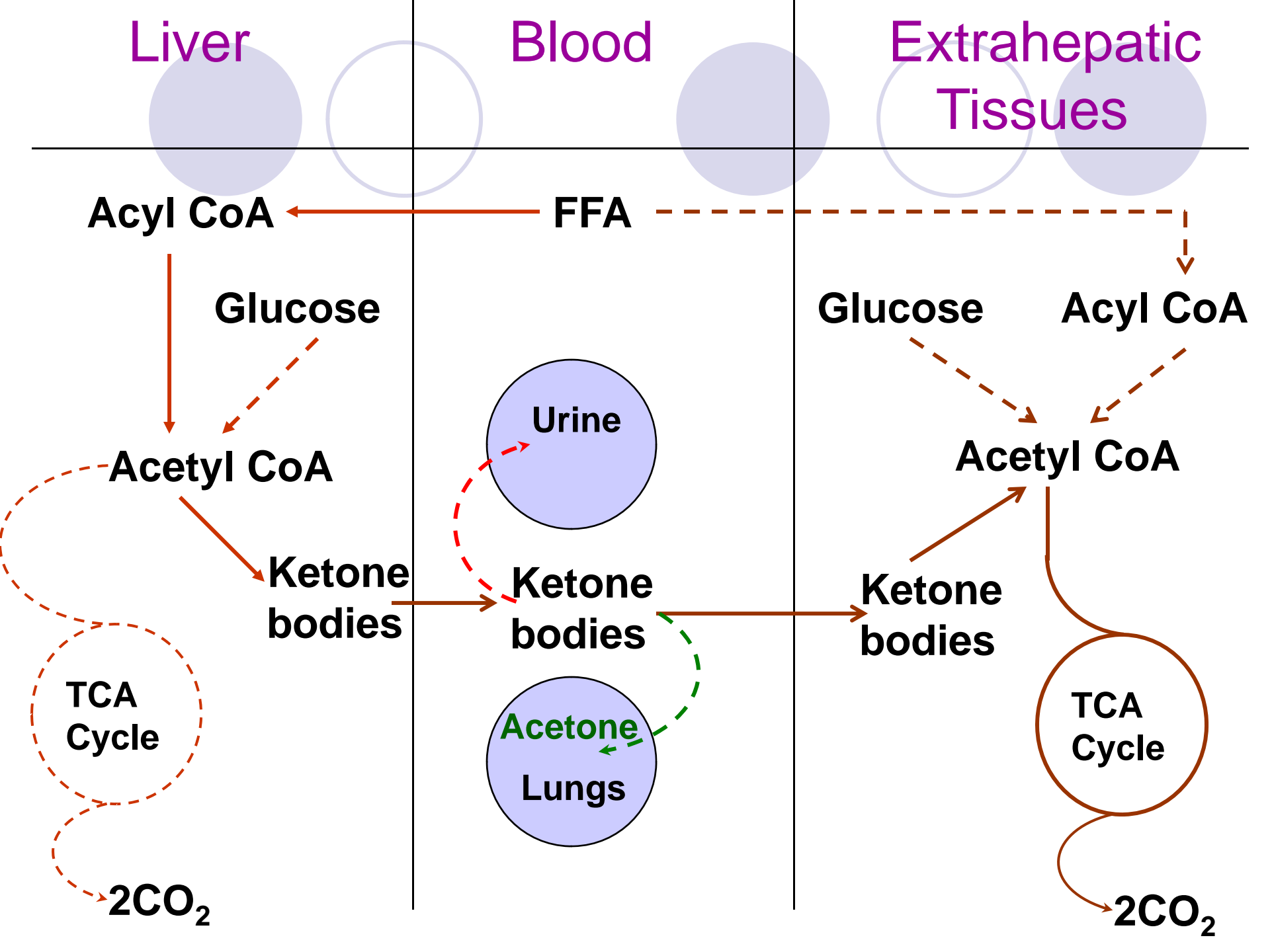
Liver cannot use ketone bodies

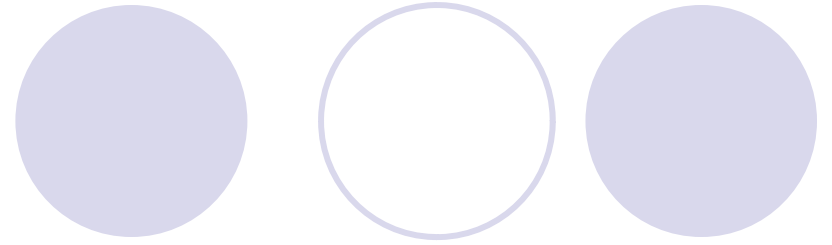
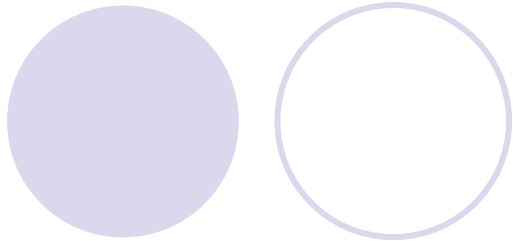
- β -hydroxy butyrate is converted to acetoacetate for energy.
- For oxidation of Acetoacetate, it has to be activated to Acetoacetyl CoA by “*succinyl CoA-acetoacetate CoA transferase*”.
- This transferase is absent in liver.

Ketone Bodies As energy sources

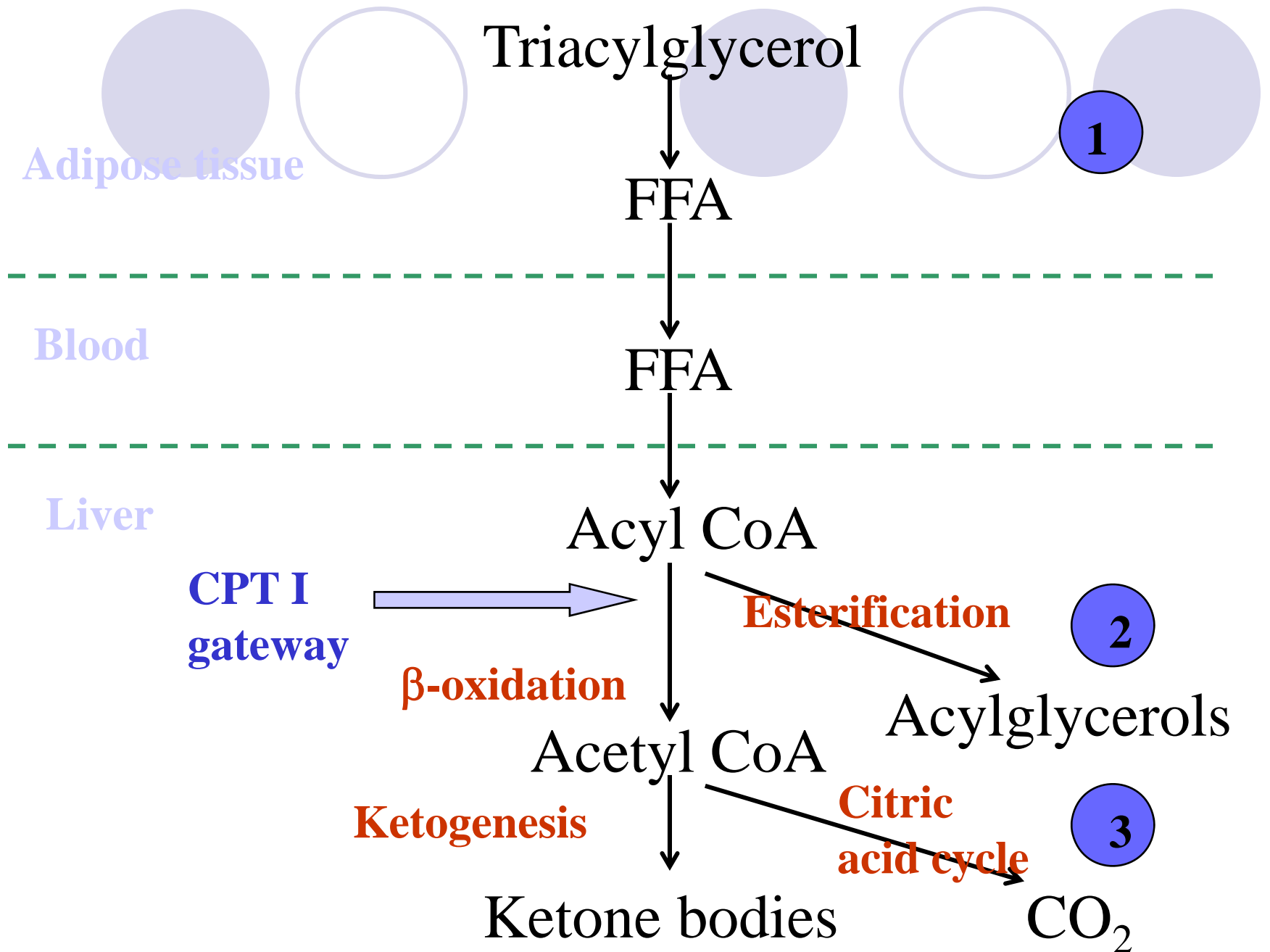








Regulation of Ketogenesis



Regulation of ketogenesis in adipose tissue :

- The factors regulating mobilization of FFAs from adipose tissue are important in controlling ketogenesis.
- The liver, both in fed and in fasting conditions, extracts about 30% of the FFAs passing through it.
 - At high concentrations of FFA, the flux passing through the liver is substantial.

Carnitine Palmitoyltransferase-I (CPT-I) Gateway

- *CPT-I* activity regulates the entry of long chain acyl groups into mitochondria.
- The activity of *CPT-I* is
 - Low in the fed state – depression of FA oxidation.
 - High in starvation – FA oxidation Increase.

Carnitine Palmitoyltransferase-I (CPT-I) Gateway

- Malonyl CoA is formed by acetyl CoA carboxylase in the fed state – potent inhibitor of *CPT – I*.
- In fed state, FFAs enter the liver cells in low conc. And are nearly all esterified to Acylglycerols and transported out of the liver in VLDL.
- ↓ [Insulin] / [Glucagon] ratio in starvation.

Partition of Acetyl CoA between the pathway of ketogenesis and oxidation to CO₂

- This partition is so regulated that the total free energy captured in ATP which results from the oxidation of FFAs remains constant.
- Ketogenesis allows liver to oxidize increasing quantities of FAs within a tightly coupled system of oxidative phosphorylation, without increasing its total energy expenditure.

Carnitine Palmitoyltransferase-I (CPT-I) Gateway

- With the onset of starvation, conc of FFA increase, *acetyl CoA carboxylase* is inhibited by acyl CoA, and [malonyl CoA] decreases.
- This decrease of [malonyl CoA] releases the inhibition on *CPT-I*, allowing more acyl CoA to be β -oxidized.

Partition of Acetyl CoA between oxidation and KB production

- Complete oxidation of palmitate: 129 ATP
- If acetoacetate is the end product :
 - 7 cycles of betaoxidation of palmitate forms 8 acetyl CoA, which join to form 4 acetoacetate.
 - 5 ATP for each cycle of betaoxidation. Total ATP formed 35.
 - 2 are used for initial activation.
 - Thus 33 ATP are formed if acetoacetate is the end product.
- If β -OH butyrate is the end product:
 - 4 acetoacetate form 4 β -OH butyrate using 4 NADH(i.e.,12 ATP)
 - Thus $33-12= 21$ ATP



2. OA is also used by gluconeogenesis.

3. Acetyl CoA is an allosteric activator of pyruvate carboxylase.



But pyruvate concentration is low due to decreased glycolysis as in starvation & DM



KB in blood & urine

- Normal KB in plasma: 0.2mmol/L
- Starvation : 3-5 mmol/L
- Diabetic ketoacidosis: >12mmol/L
- KB of >12mmol/L, saturates all oxidative pathways.
- Normal KB in urine: <1mg/day

Metabolic Acidosis due to KBs

- Both acetoacetate and beta-hydroxybutyrate are acidic, and, if levels of these ketone bodies are too high, the pH of the blood drops, resulting in **ketoacidosis**.
- This happens in untreated Type I diabetes, and also during prolonged starvation.

Excess of Ketogenesis (Cause)

Extreme starvation

Diabetes Mellitus
(Untreated)



Gluconeogenesis (Liver)

Oxaloacetate (TCA cycle intermediate) is used

Consumption of Acetyl CoA is slowed down

Excess of Acetyl CoA in Liver

Excess of Ketogenesis (Cause)- contd.

Liver catabolizes fatty acids to meet the energy demand by other tissues



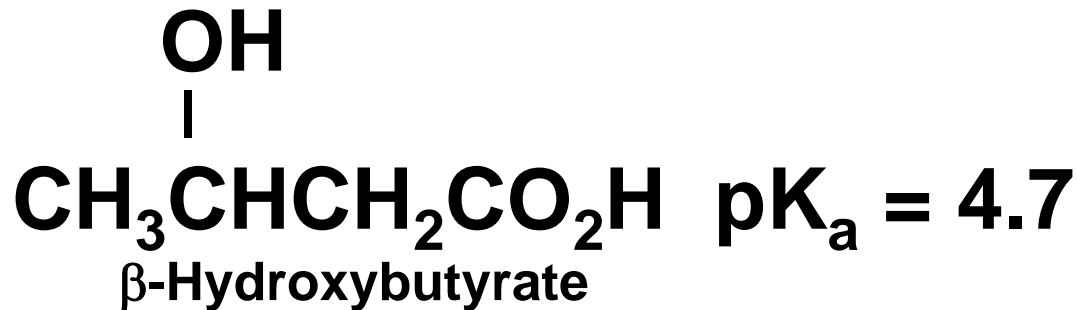
Excess of Acetyl CoA is produced, which are destined to form ketone bodies.



Ketone bodies are transported by blood to Muscle and Brain.

Ketone body formation regenerates free CoA, which is required for β -oxidation.

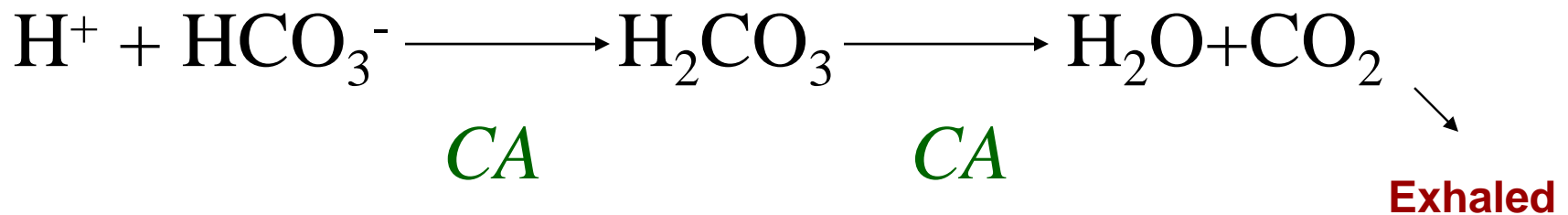
Metabolic Acidosis due to KBs



↑ Concentration of acetoacetic acid can result in metabolic acidosis (pH 7.1) → ↓affinity of Hb for O₂.

Metabolic Acidosis due to KBs

- Ketone bodies being acidic in nature, release H^+ ions into blood. They are buffered by HCO_3^- .



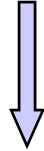
Continuous production of ketone bodies depletes alkali reserve resulting in ketoacidosis.

Ketone bodies in Starvation

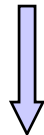
- After the diet has been changed to lower blood glucose for 3 days, the brain gets 30% of its energy from ketone bodies.
- After 40 days, this goes up to 70% (during the initial stages the brain does not burn ketones, since they are an important substrate for lipid synthesis in the brain).
- The brain retains some need for glucose, because ketone bodies can be broken down for energy only in the mitochondria, and brain cells' long thin axons are too far from mitochondria.

Starvation ketoacidosis

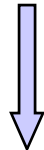
Absence of intake of food



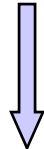
No stimuli from intestine to release insulin from pancreas.



↓ Insulin & ↑ glucagon



↑ Lipolysis & ↑ Oxidation of fatty acids



Ketoacidosis

Laboratory diagnosis of KA due to starvation.

- Blood glucose: low, may be < 50 mg/dl
- Serum bicarbonate: < 15 mEq/L
- pH: < 7.3
- Urine glucose: Nil
- Ketonuria: 3+

Diabetic ketoacidosis(DKA)

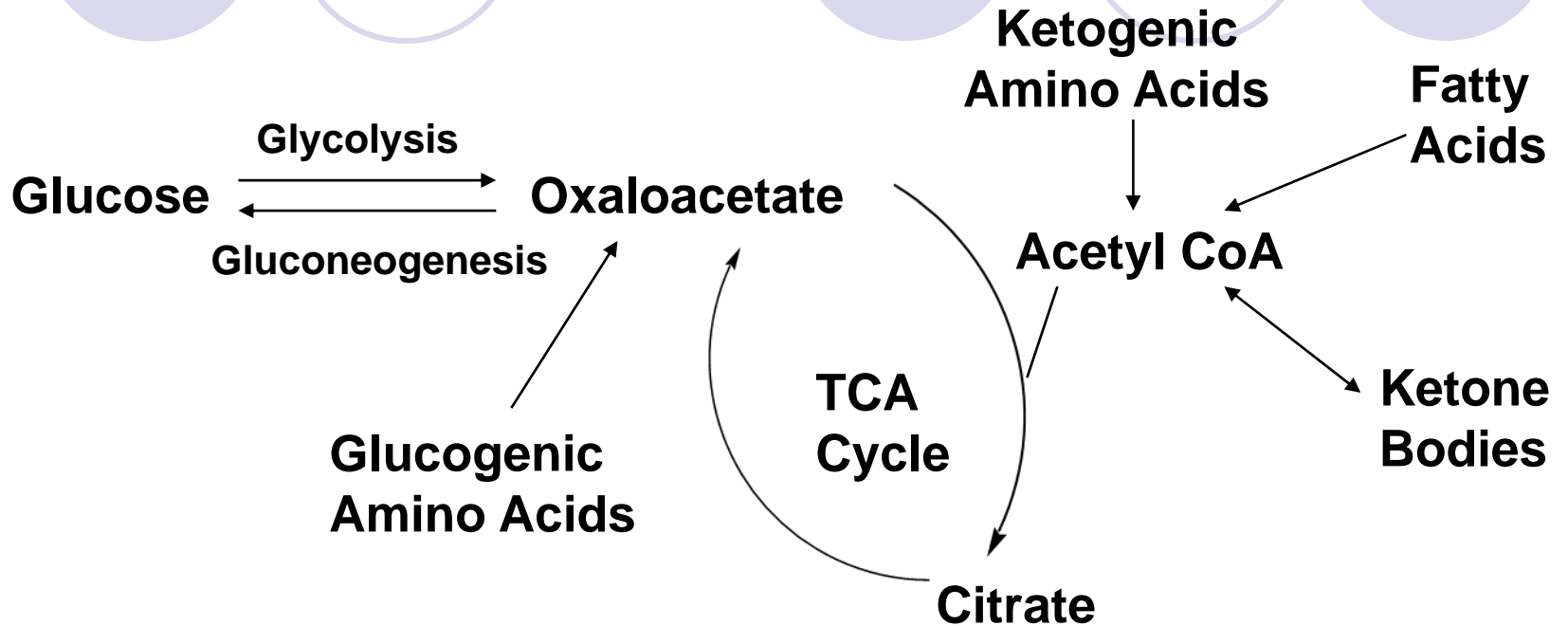
- DKA is due to a marked deficiency of insulin in the face of hormones that oppose the effects of insulin, particularly glucagon. Even small amounts of insulin can turn off ketoacid formation.
- Hormones that antagonise insulin action:
 - Glucagon
 - Cortisol
 - Oestrogens
 - Growth hormone
 - Catecholamines

Ketone Bodies and Diabetes

"Starvation of cells in the midst of plenty"

- Glucose is abundant in blood, but uptake by cells in muscle, liver, and adipose cells is low due to absence of insulin.
- Cells, metabolically starved, turn to gluconeogenesis and fat/protein catabolism
- In type I diabetics, OAA is low, due to excess gluconeogenesis, so Acetyl CoA from fat/protein catabolism does not go to TCA, but rather to ketone body production
- Acetone can be detected on breath of type I diabetics

Ketones in Diabetes Mellitus



↓ Glucose in cells \implies ↑ Gluconeogenesis \implies ↓ Oxaloacetate



↑ Fatty Acid breakdown \implies ↑ Acetoacetyl CoA \implies ↑ Ketone Bodies

Laboratory diagnosis of DKA

- Blood glucose: > 250 mg/dl
- Serum bicarbonate: < 15 mEq/L
- pH: < 7.3
- Urine glucose: +++
- Ketonuria: 3+