
بسم الله الرحمن الرحيم
السلام عليكم ورحمة الله وبركاته

رَبَّنَا آتِنَا فِي الدُّنْيَا حَسَنَةً وَفِي الآخِرَةِ حَسَنَةً وَقِنَا عَذَابَ النَّارِ

[البقرة :201]

Our Lord! Grant us good in this world and good in the Hereafter, and save us from the chastisement of the fire

[2:201]

Your patient

- 5 year old Amena was brought to the Paeds Emergency with high fever, excessive thirst, frequent urination, extreme fatigue and sleepiness

On Examination

- Fruity odour in breath (ketosis)
- Tachycardia
- Low volume pulses
- Hypotension
- Impaired skin turgor
- Sunken eyes
- Delayed capillary refill time
- Absence of tears
- Weight loss (if premorbid weight known)

Indicate dehydration or hypovolemia

- Rapid deep sighing breathing, Kussmaul respiration (metabolic acidosis)

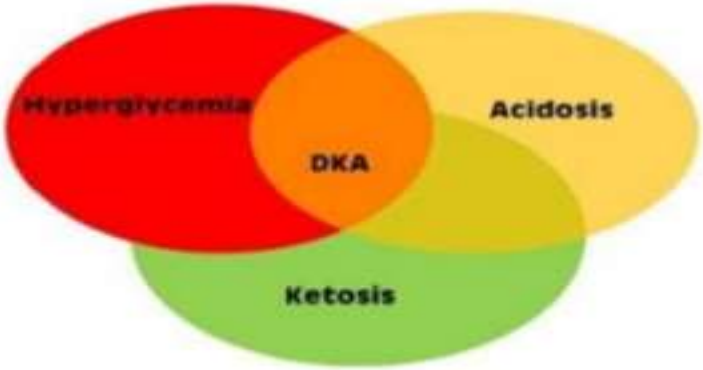
- Changes in sensorium, coma
- Bradycardia, hypertension
- Papilledema
- Abnormal pupillary reflexes, cranial nerve palsies
- Posturing: decerebrate, decorticate

Indicate cerebral edema

DIABETIC KETOACIDOSIS

CLASSICAL TRIAD IN DKA

- **Hyperglycemia** - blood glucose greater than 200 mg/dL
- **Ketosis** - ketones present in blood and/or urine
- **Acidosis** - pH less than 7.3 and/or bicarbonate less than 15 mmol/L

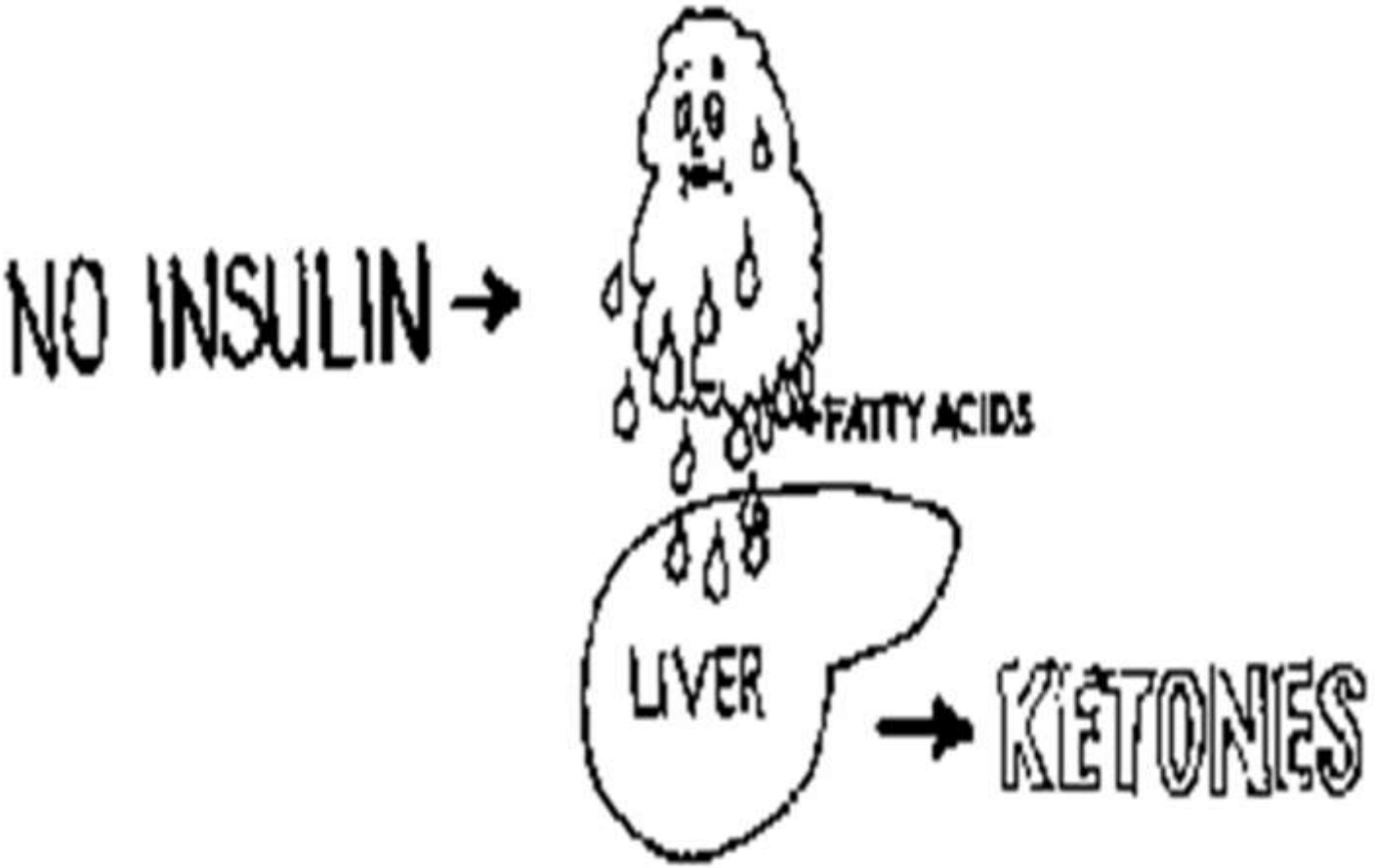


Medical Biochemistry
Metabolism with Clinical Correlations

LIPID METABOLISM

KETONE BODY METABOLISM

KETONE BODIES



LEARNING OBJECTIVES

- KETONE BODIES LIST
- WHEN ARE THEY SYNTHESISED
- WHY ARE THEY SYNTHESISED
- HOW ARE THEY SYNTHESISED
- WHICH TISSUES USE THEM
- HOW ARE THEY USED BY THE TISSUES
- COMPLICATIONS OF EXCESS

LEARNING OBJECTIVES

- Definition
- Significance
- Synthesis
- Utilization
- Ketosis

DEFINITION

Ketone bodies are ketones that are produced during excessive breakdown of fatty acids.

KETONE BODIES

Ketone Bodies

High rate of Fatty Acid Oxidation in Liver

↓

Produces considerable amount of **Acetoacetate, 3-hydroxybutyrate**

↓

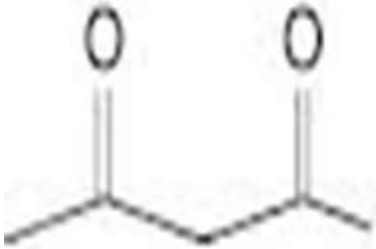
Acetoacetate continuously undergoes decarboxylation to form **acetone**

- Acetoacetate
- 3 Hydroxy butyrate
- Acetone

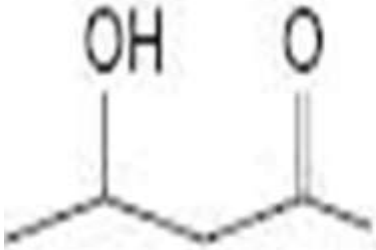
Are called ketone bodies

3 KETONE BODIES

Acetone – $(CH_3)_2CO$



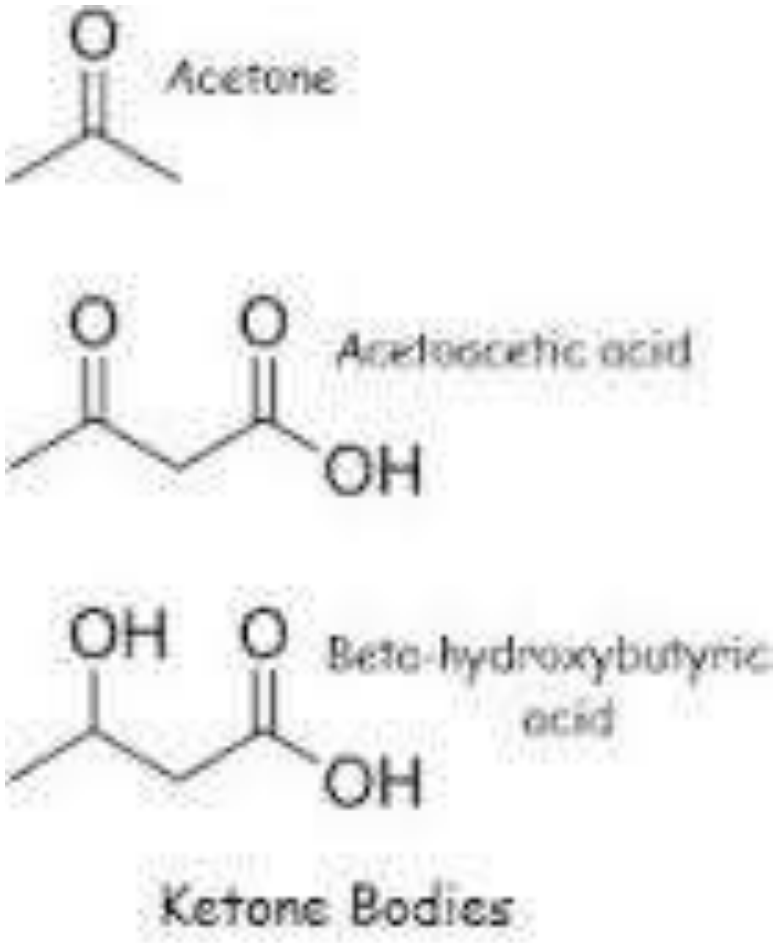
Acetoacetic acid – $CH_3C(O)CH_2CO_2H$



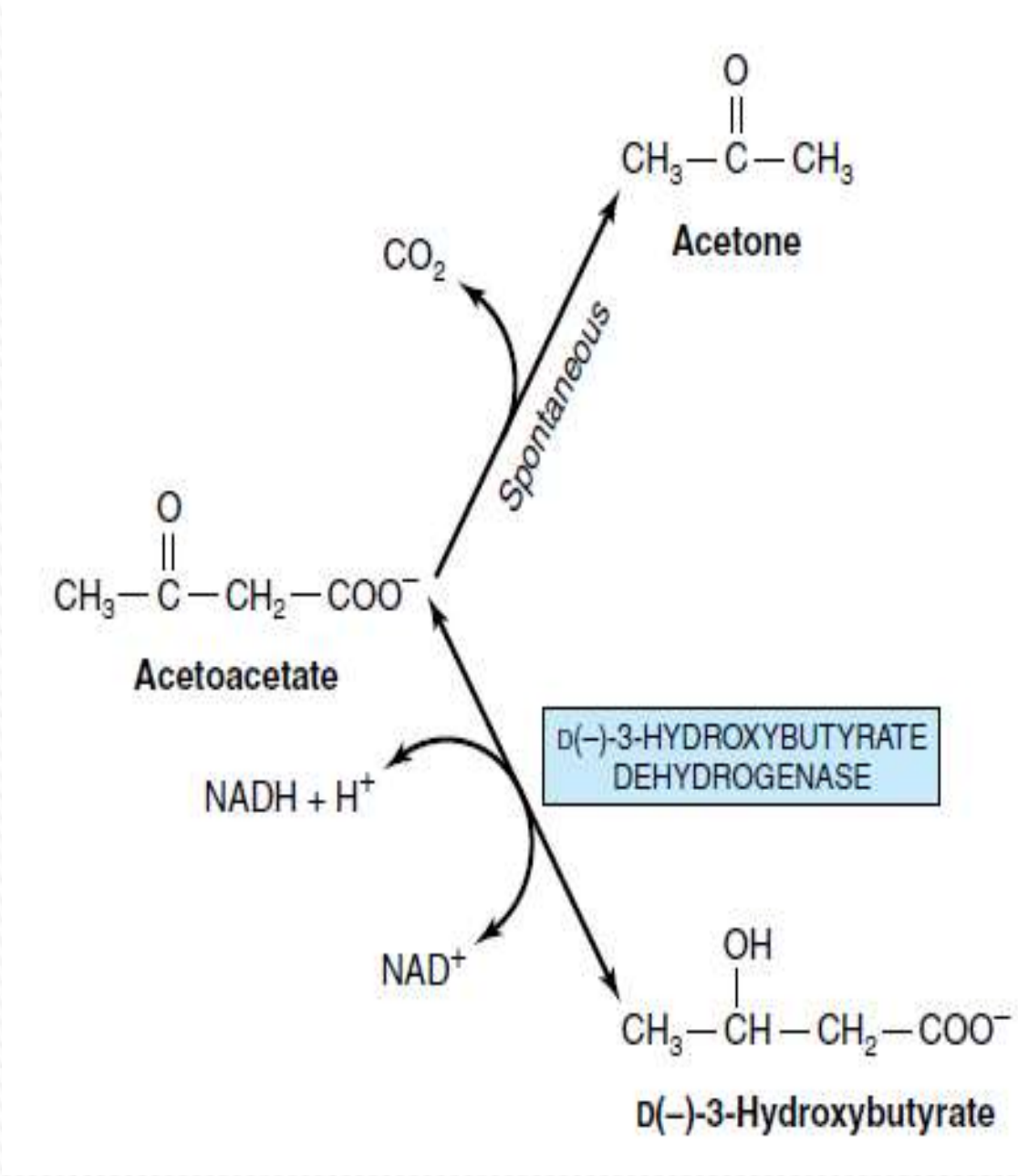
β-hydroxybutyric acid – $CH_3C(OH)CH_2CO_2H$

KETONE BODIES

- 3 types:-
  1. Acetone
  2. Acetoacetate
  3. 3-Hydroxybutyrate / β-hydroxybutyrate



Interrelation ship of ketone bodies



WHY ARE KETONE BODIES SYNTHESISED

Lack of Insulin
Excess Glucagon, Catehcolamines

↓

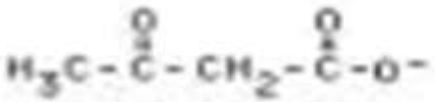
Excess Breakdown of Triglycerides

↓

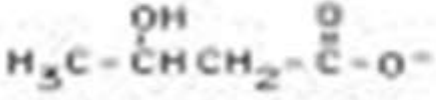
Increased Free Fatty Acids

↓

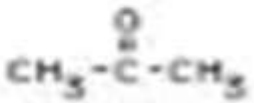
Formation of Ketone Bodies



acetoacetate



β-hydroxybutyrate



acetone

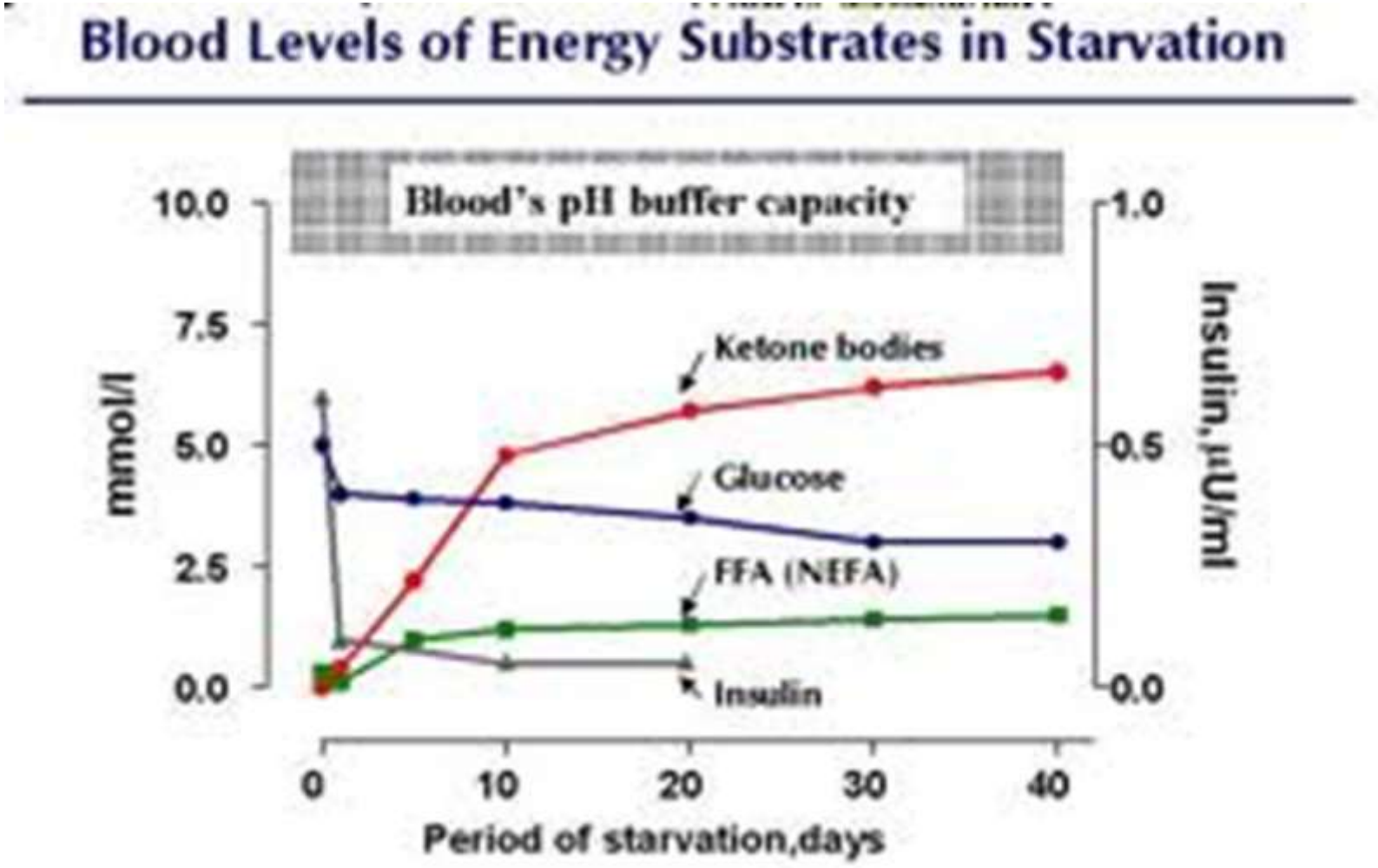
Alternate source to glucose for energy

Production of ketone bodies under conditions of cellular energy deprivation

Utilization of ketone bodies by the brain

SIGNIFICANCE

KETONE BODIES AS AN ALTERNATE ENERGY SOURCE



SYNTHESIS

- Liver mitochondria
- β oxidation of Fatty acids→ Acetyl CoA

  →Ketone bodies
- →transported in blood

  →peripheral tissues

  →Acetyl CoA

  →TCA cycle

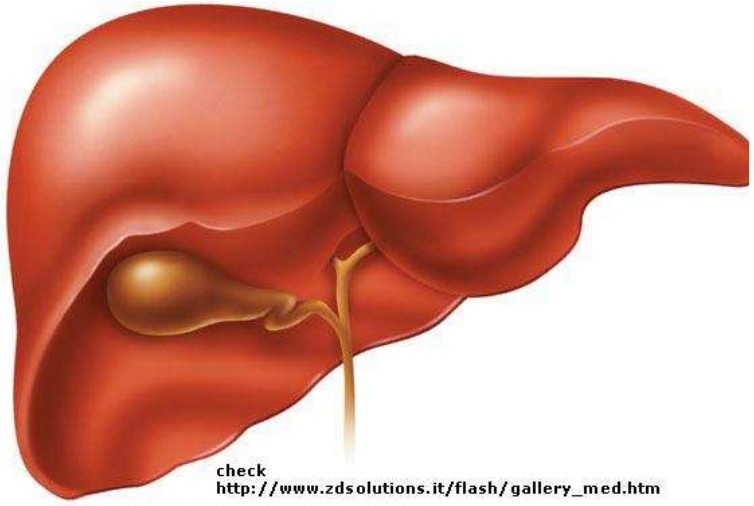
  →Energy

KETOGENESIS

Site

Pathway

Regulation



Ketone bodies are synthesized only in liver

SITE OF KETOGENESIS

IMPORTANT ENERGY SOURCE FOR PERIPHERAL TISSUE

1. Water soluble → do not need to be carried as lipoproteins/ with albumin
2. Produced when ↑Fatty acids >liver can oxidize
3. Used by extra hepatic tissue in place of glucose during fasting

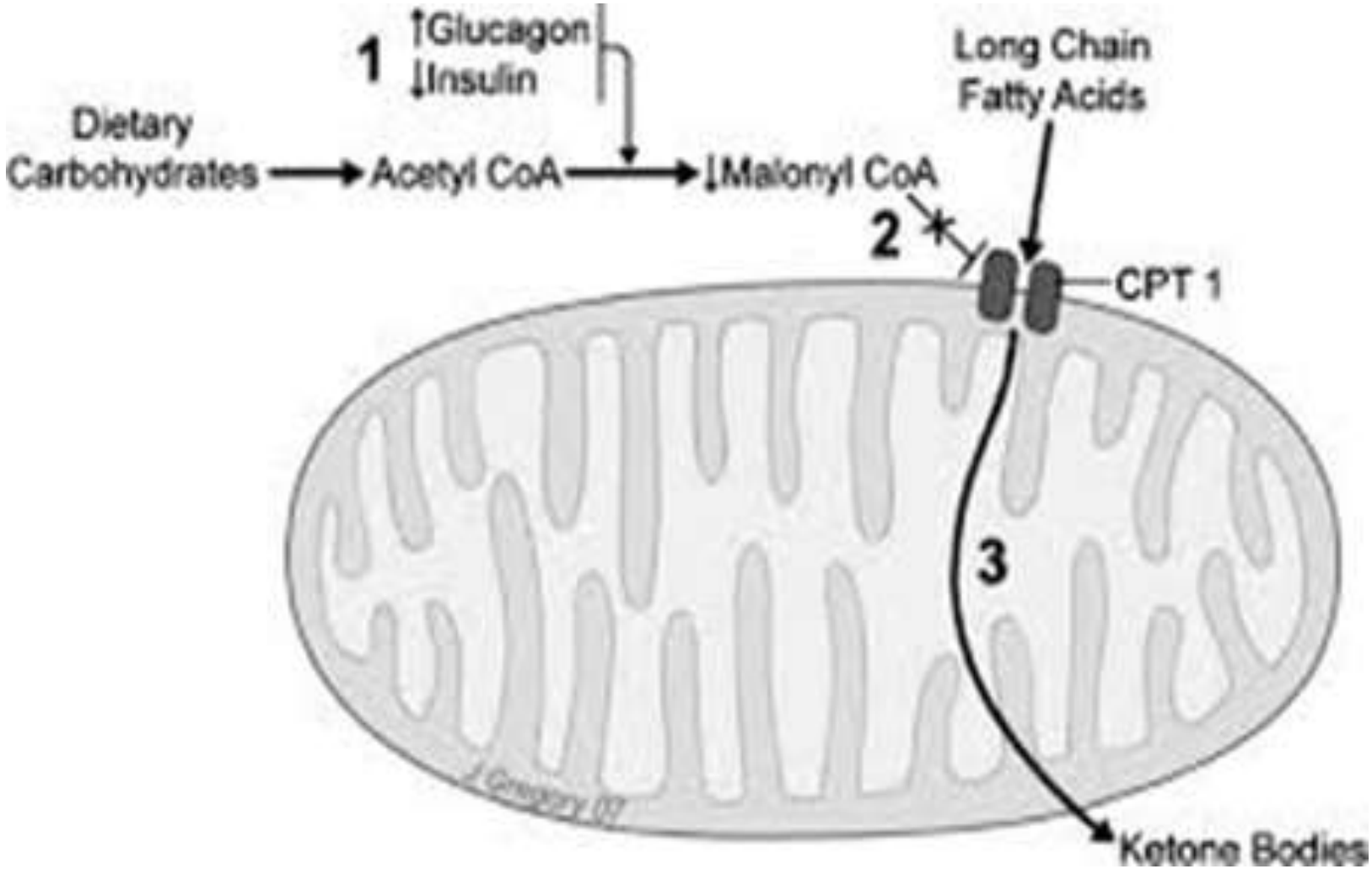
KETOGENESIS

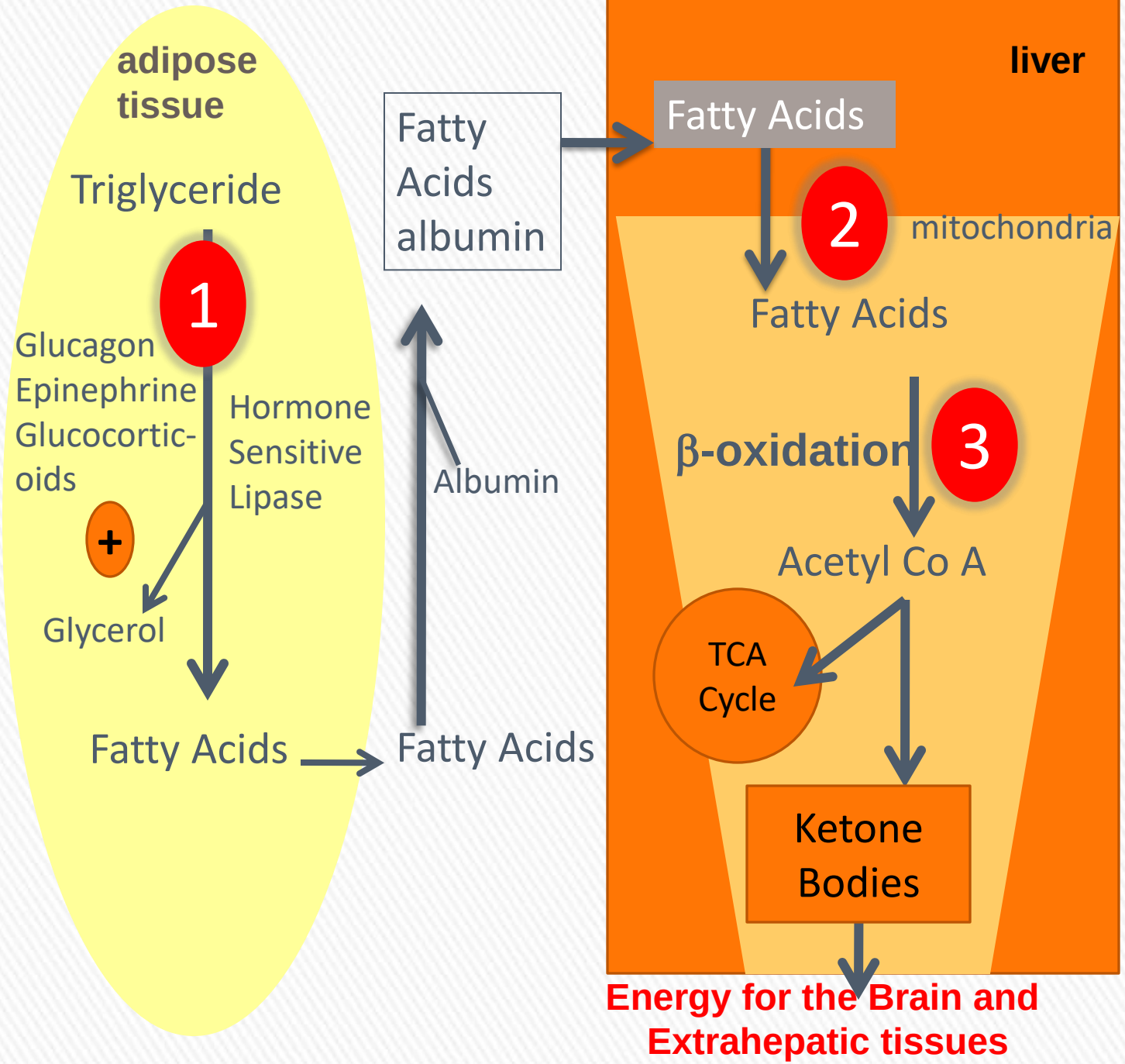
Formation of Ketone Bodies

Occurs in hepatic mitochondria.

Results from over production of Acetyl CoA formed during β oxidation.

HEPATIC MITOCHONDRIA




adipose tissue
Triglyceride
1
Glucagon
Epinephrine
Glucocortic-oids
+
Hormone Sensitive Lipase
Glycerol
Fatty Acids
Fatty Acids albumin
Albumin
Fatty Acids
liver
Fatty Acids
2
mitochondria
Fatty Acids
β-oxidation
3
Acetyl Co A
TCA Cycle
Ketone Bodies
Energy for the Brain and Extrahepatic tissues

KETOGENESIS

- Fasting→

  Adipose tissue→FFA→Liver

  →↑βoxidation of FFA

→↑hepatic acetyl CoA

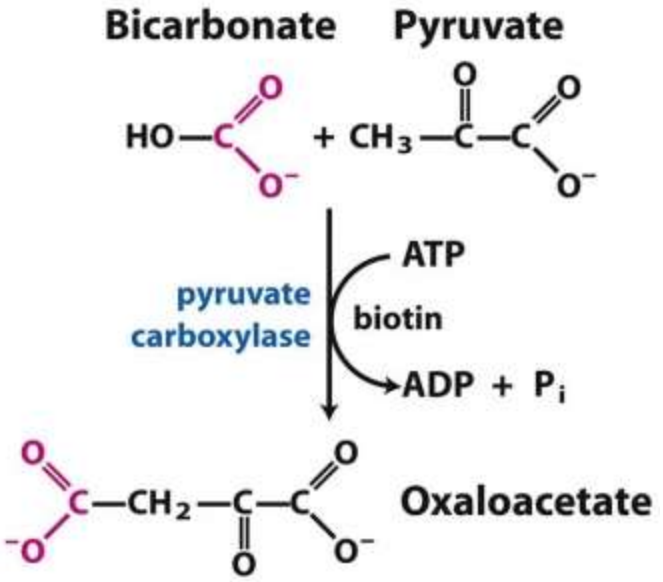
→↓PyruvateDehydrogenase

+ ↑Pyruvate Carboxylase

→↑OAA→Liver

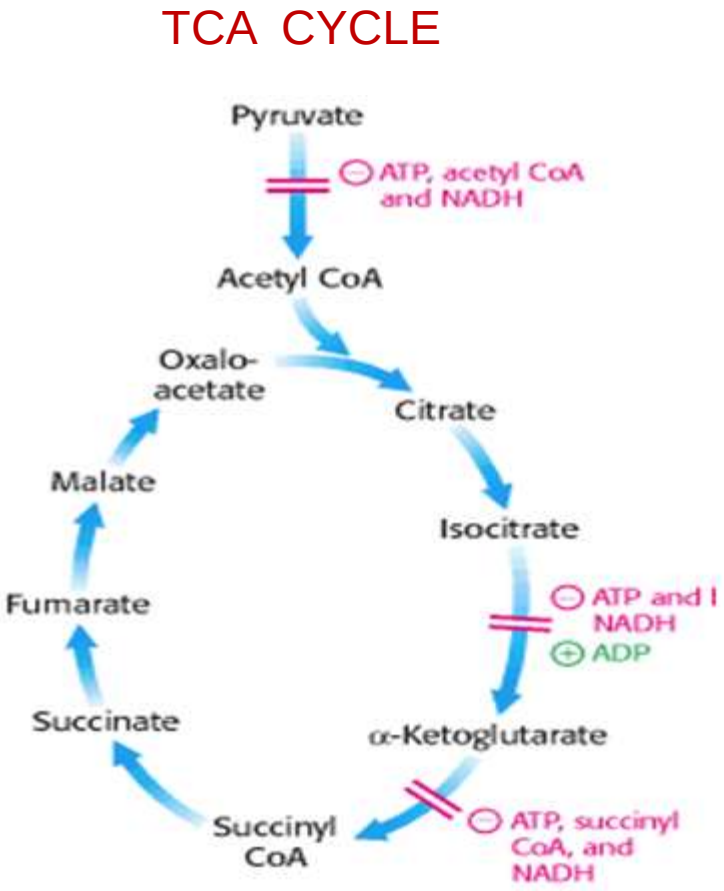
gluconeogenesis (not TCA)

→Acetyl CoA → Ketone bodies

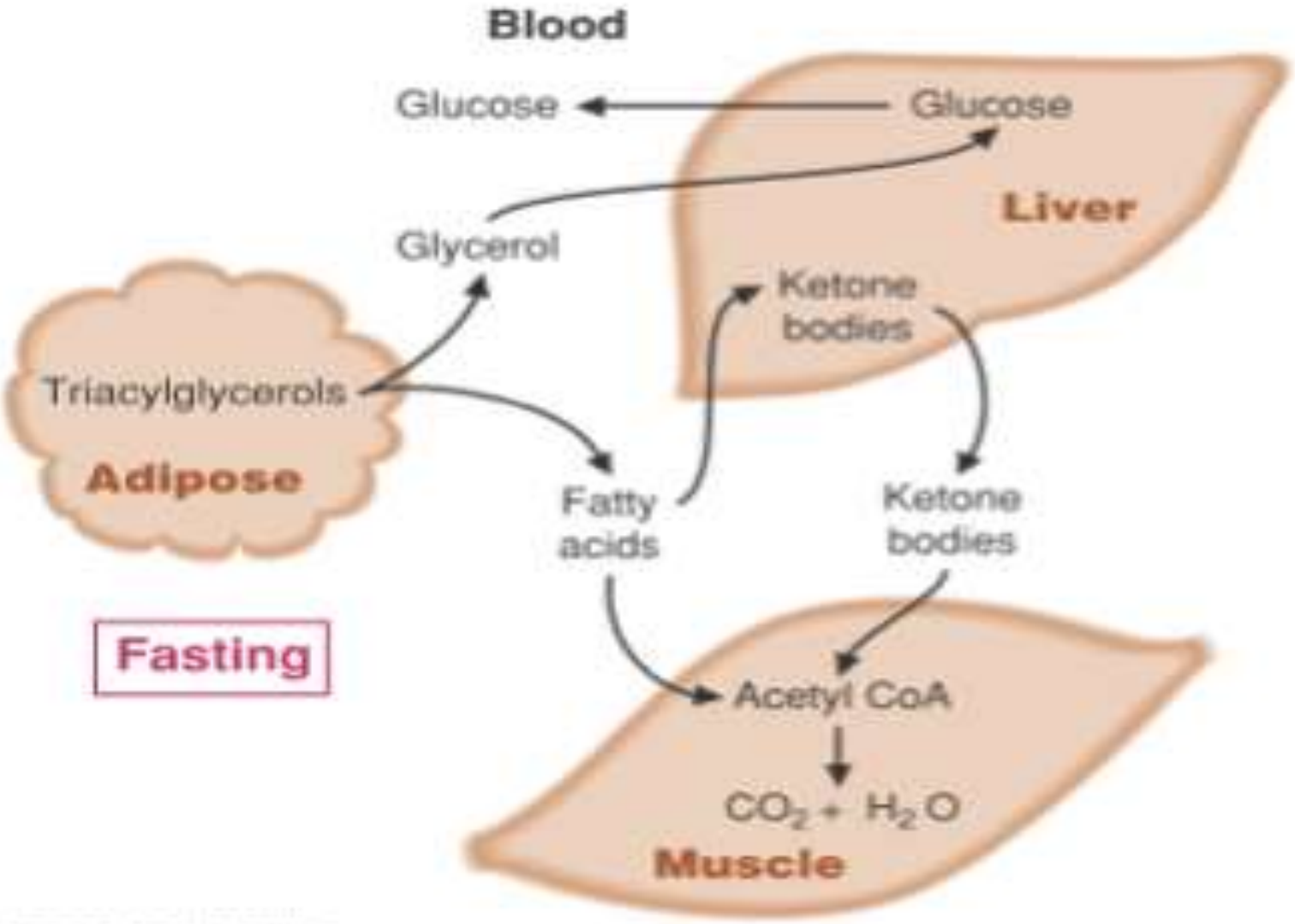


KETOGENESIS

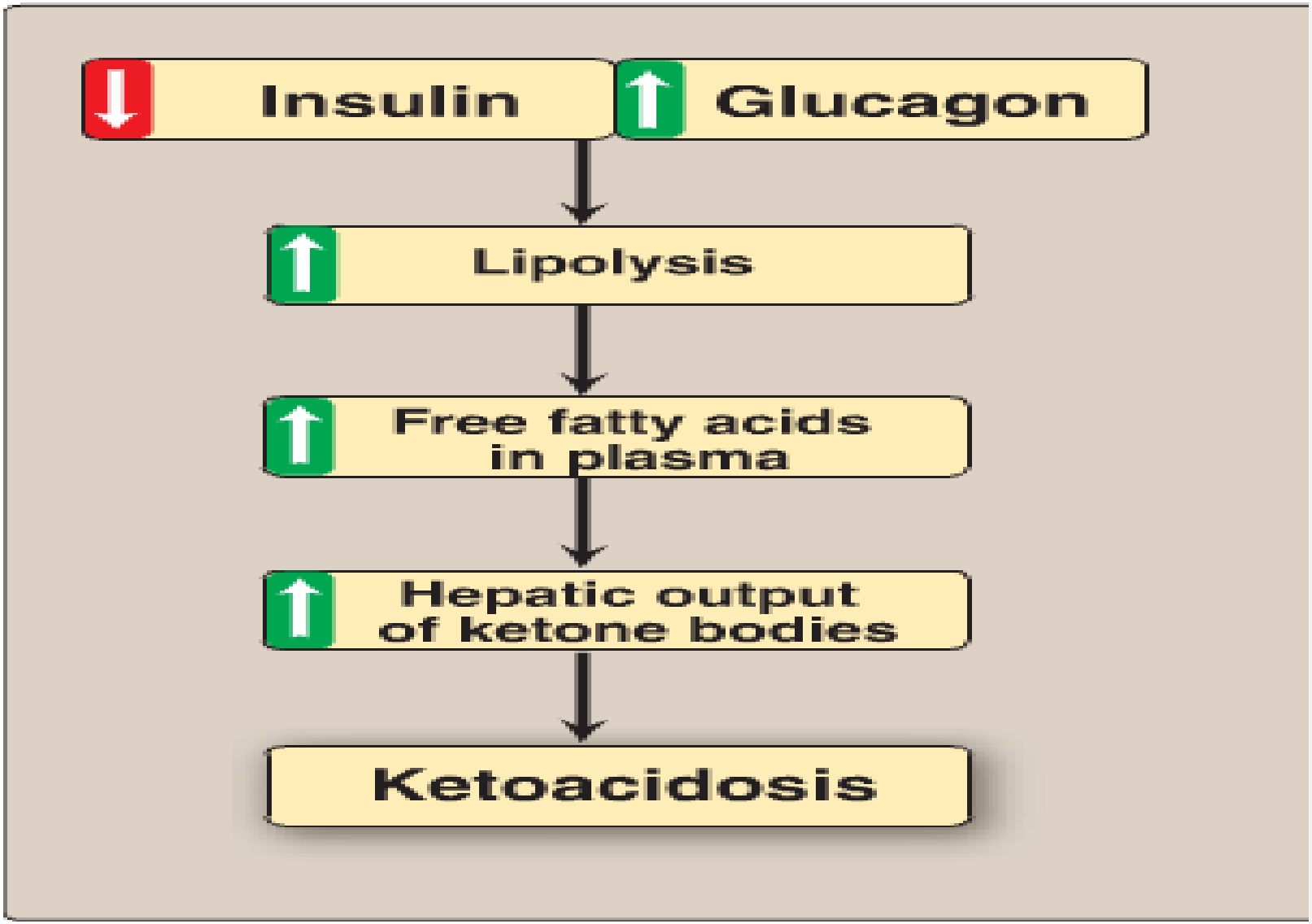
- ↑ATP and NADH
- →inhibits Isocitrate Dehydrogenase in the TCA cycle
- →↑ Malate.
- → leaves the mitochondrion →gluconeogenesis.
- Excess acetyl CoA → rerouted to ketogenesis



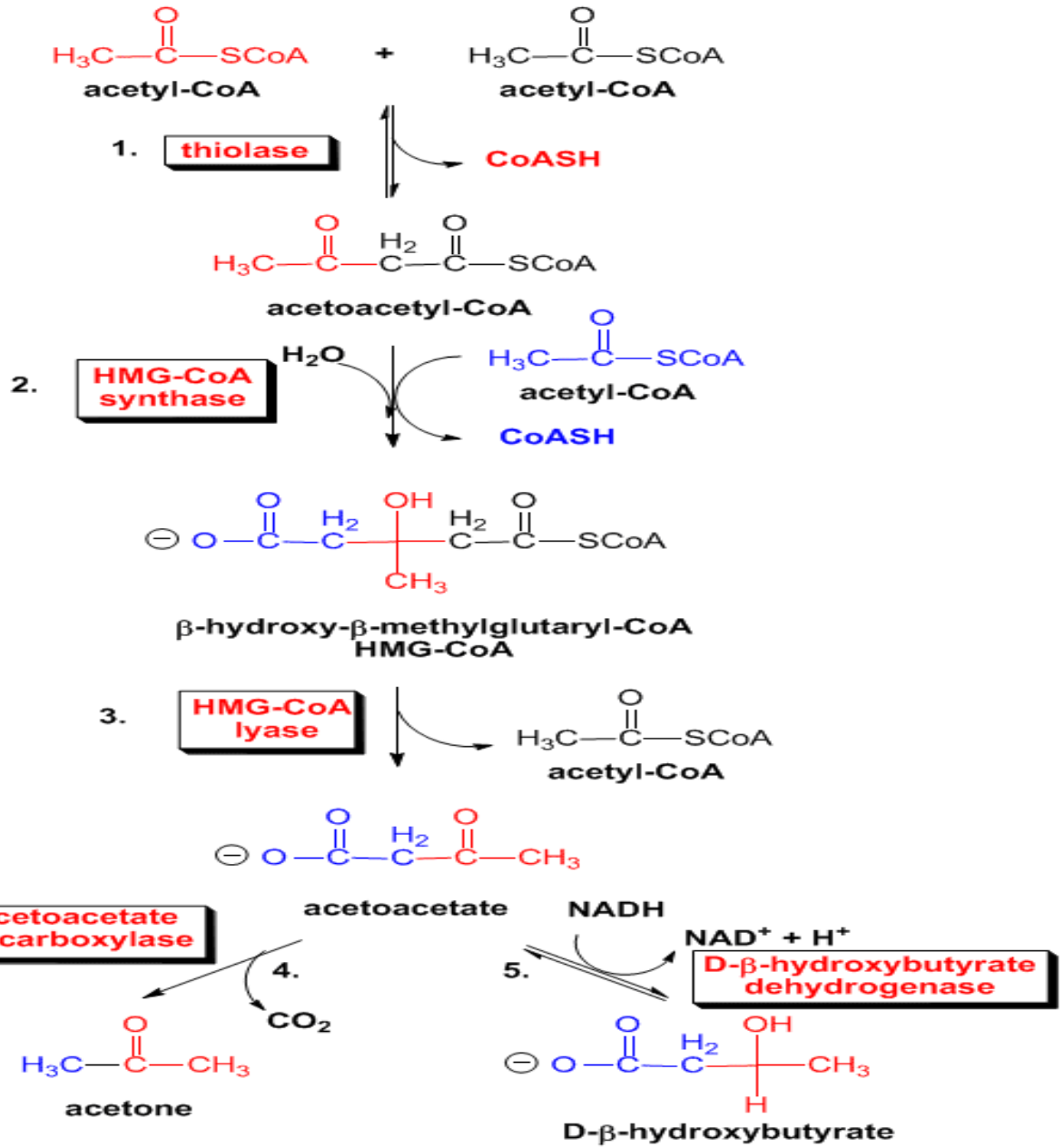
KETOGENESIS

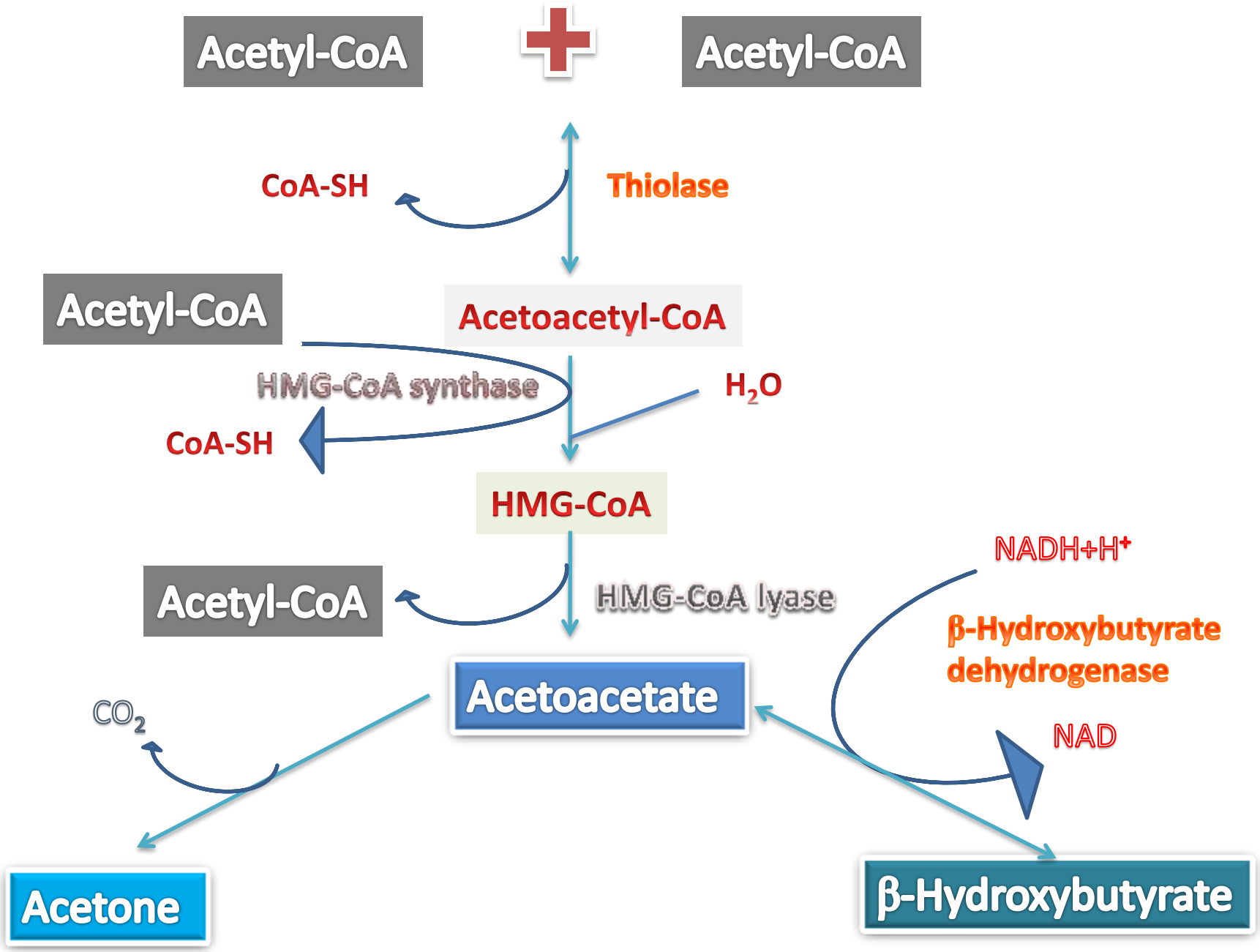


KETOGENESIS



Ketogenesis




Acetyl-CoA
Acetyl-CoA
CoA-SH
Thiolase
Acetyl-CoA
Acetoacetyl-CoA
HMG-CoA synthase
H_2O
CoA-SH
HMG-CoA
Acetyl-CoA
HMG-CoA lyase
NADH+H+
β-Hydroxybutyrate dehydrogenase
NAD
Acetoacetate
CO_2
Acetone
β-Hydroxybutyrate

Ketone Bodies

- Acetone is volatile – Expelled → Lungs
- Acetoacetate and 3 Hydroxybutyrate excreted →urine
- Ketone bodies are **produced in Liver**
- **Liver is not able to utilize** ketone bodies due to the absence of the enzyme THIOPHORASE required to activate acetoacetate
- **Extrahepatic tissues** contain the enzyme THIOPHORASE required to activate acetoacetate (They are able to **utilize ketone bodies**)

Acetyl CoA enters TCA cycle - Oxidized → energy

After 3 days of starving → liver forms lots of ketone bodies

- Brain fulfils 1/3 of its energy needs from Acetoacetate.
- Heart also uses Ketone bodies

After several weeks of starvation → ketone bodies become major fuel of brain (60-75% energy from ketone bodies)

Now only 40gm glucose / day is needed by brain compared to 120 gm/day on 1st day of starvation

1. SYNTHESIS OF HMG CoA

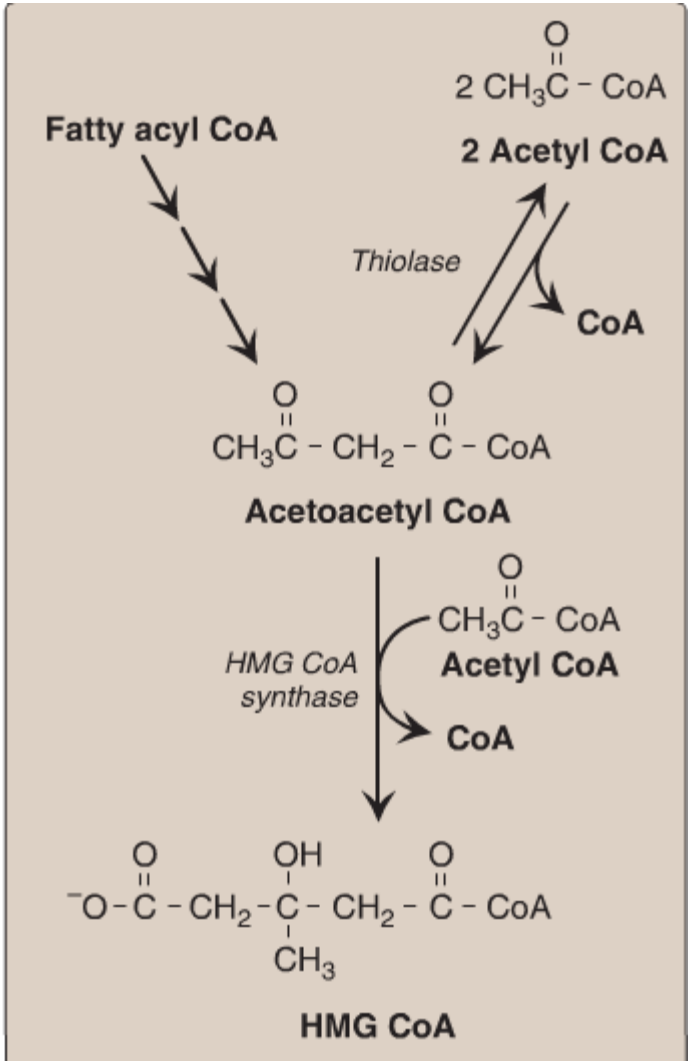
- 2 Acetyl CoA condense → Acetoacetyl CoA

  Enzyme = Thiolase

- Acetoacetyl CoA +

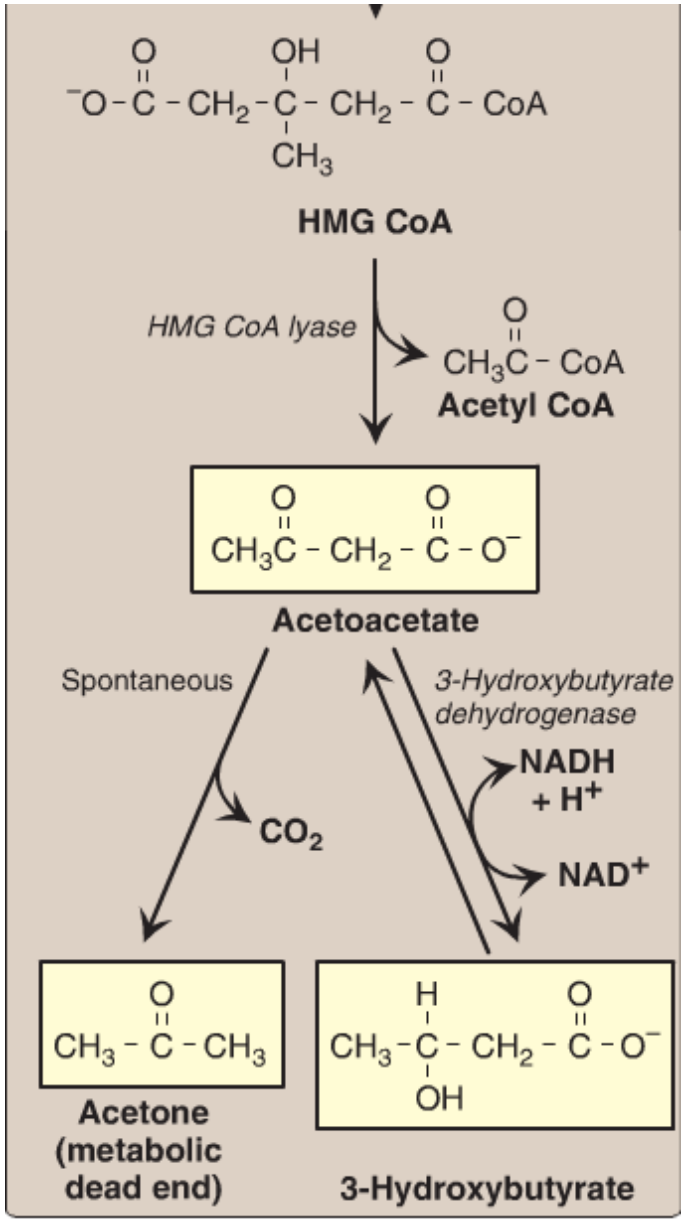
Acetyl CoA→HMG CoA

Enzyme=Mitochondrial HMG CoA Synthase



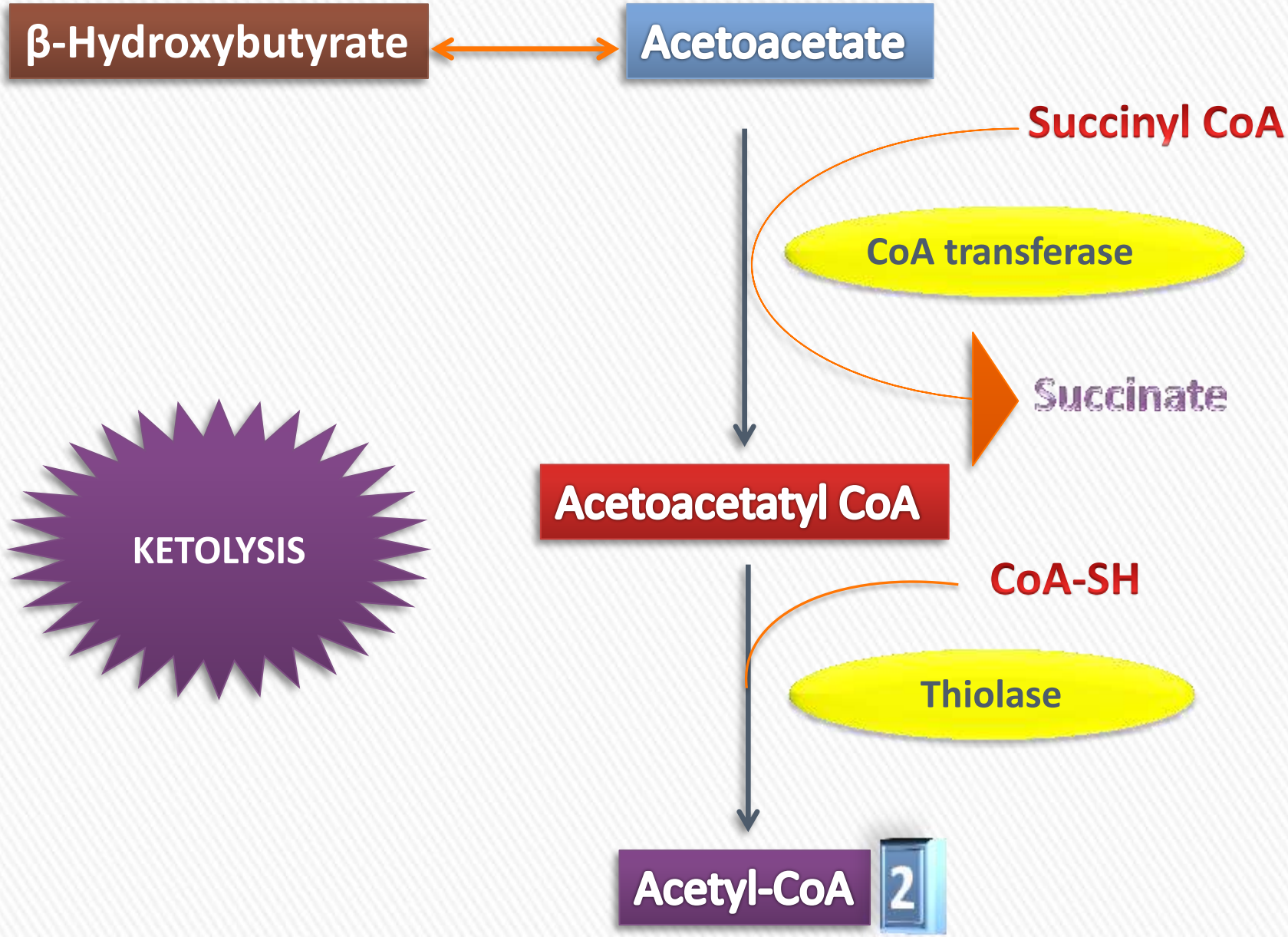
2. SYNTHESIS OF KETONE BODIES

- HMGCoA→AcetylCoA
  + Acetoacetate
  Enzyme=HMG CoA Lyase
- Acetoacetate→ (reduced with NADH)→ 3-hydroxy Butyrate / (decarboxylated)→ Acetone(breath)
- ↑with →↑FA oxidation →↑NADH:NAD



KETONE BODY UTILIZATION

Ketone bodies are not oxidized in the liver or RBCs
Utilized in extrahepatic tissues such as brain, heart, skeletal muscle and kidney


β-Hydroxybutyrate
Acetoacetate
Succinyl CoA
CoA transferase
Succinate
KETOLYSIS
Acetoacetatyl CoA
CoA-SH
Thiolase
Acetyl-CoA
2

KETOLYSIS (USE OF KETONES BY PERIPHERAL TISSUE)

- Liver continuously makes low levels of Ketone bodies
- ↑secretion during fasting

  / Diabetes Mellitus (Type 1 uncontrolled)

  → provides energy to peripheral tissues
- Liver cannot use Ketone bodies as fuel because it lacks Thiophorase

KETOLYSIS (USE OF KETONES BY PERIPHERAL TISSUE)

All extrahepatic tissue having mitochondria can use Ketone bodies

- 3-Hydroxybutyrate (oxidized) + NAD →Acetoacetate + NADH + H^+

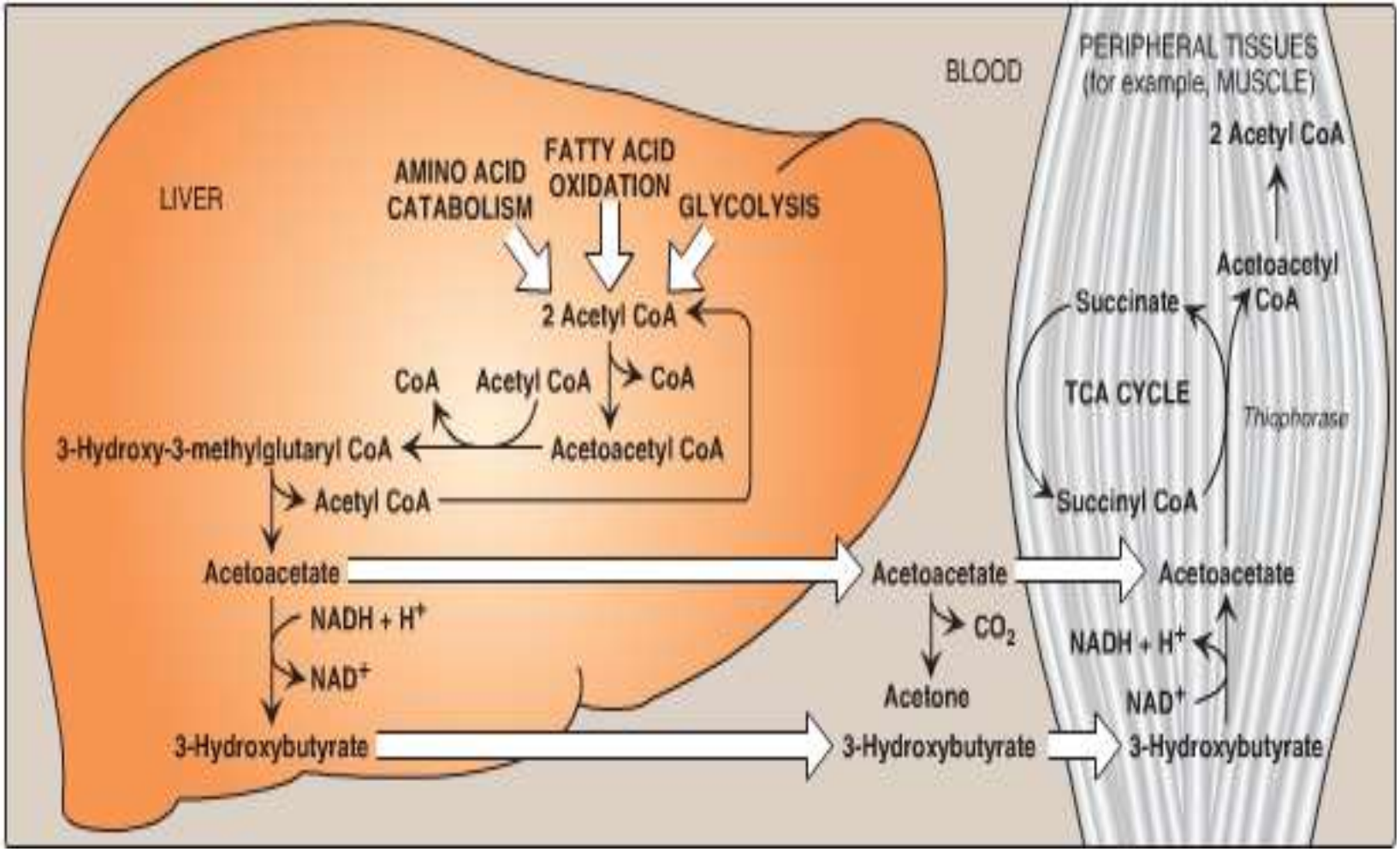
  Enzyme = 3-Hyroxybutyrate dehydrogenase

- Acetoacetate + CoA (from Succinyl CoA by

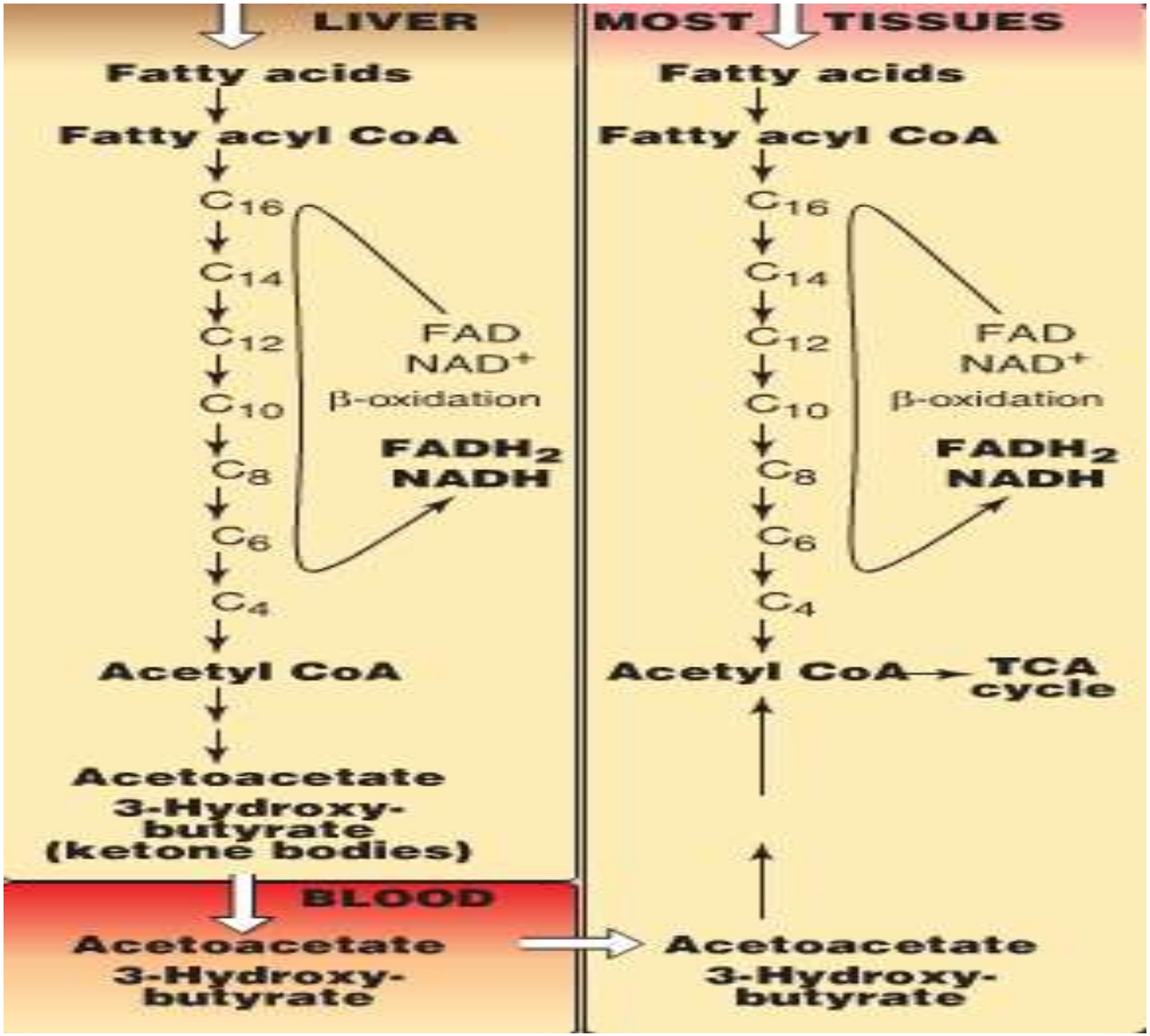
  Sucinyl CoA:Acetoacetate CoA transferase/ Thiophorase) →Acetoacetyl CoA

- Acetoacetyl CoA → 2 Acetyl CoA

KETOGENESIS AND KETOLYSIS



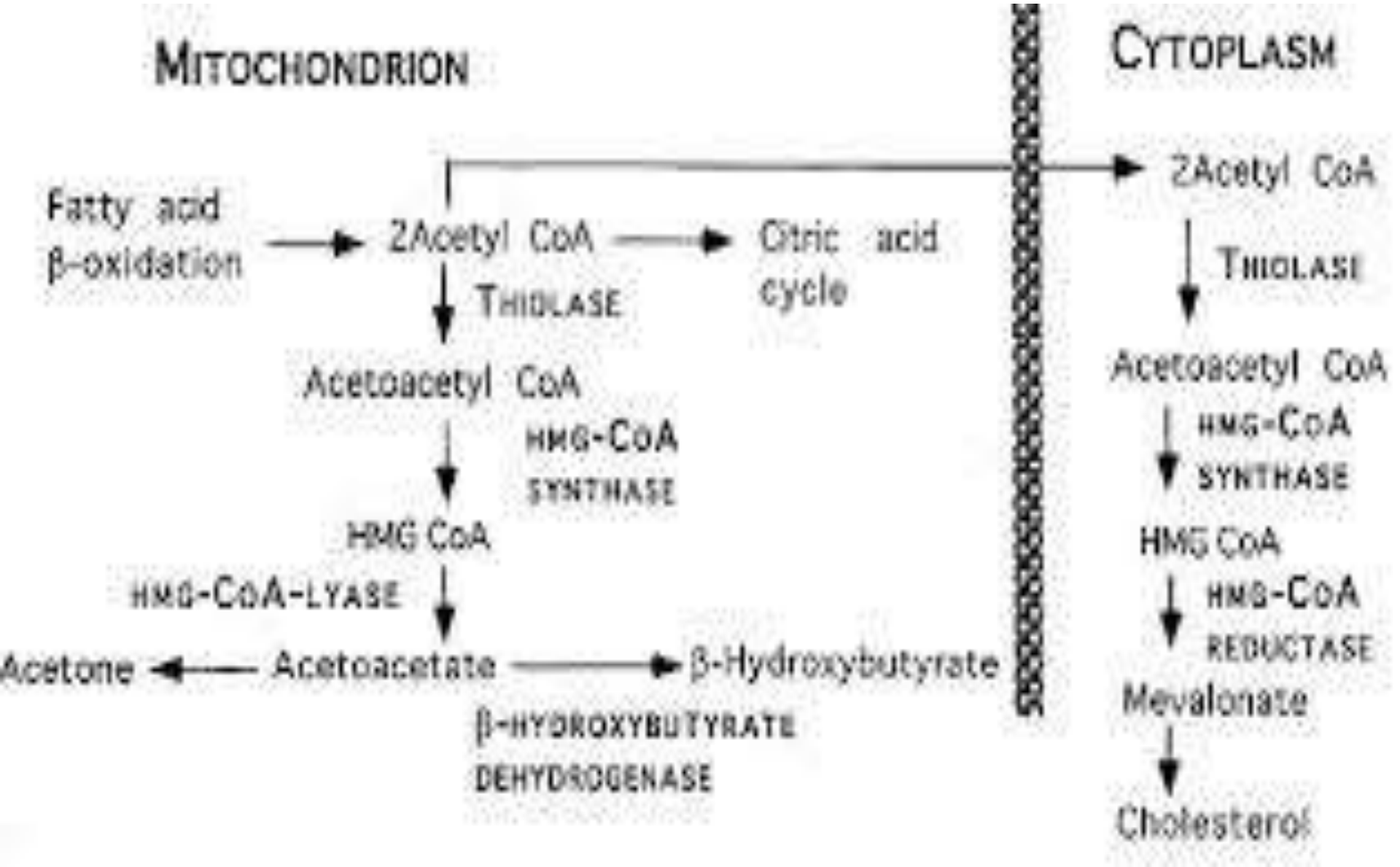
KETOGENESIS AND KETOLYSIS



ENERGY YIELD FROM KETONE BODIES

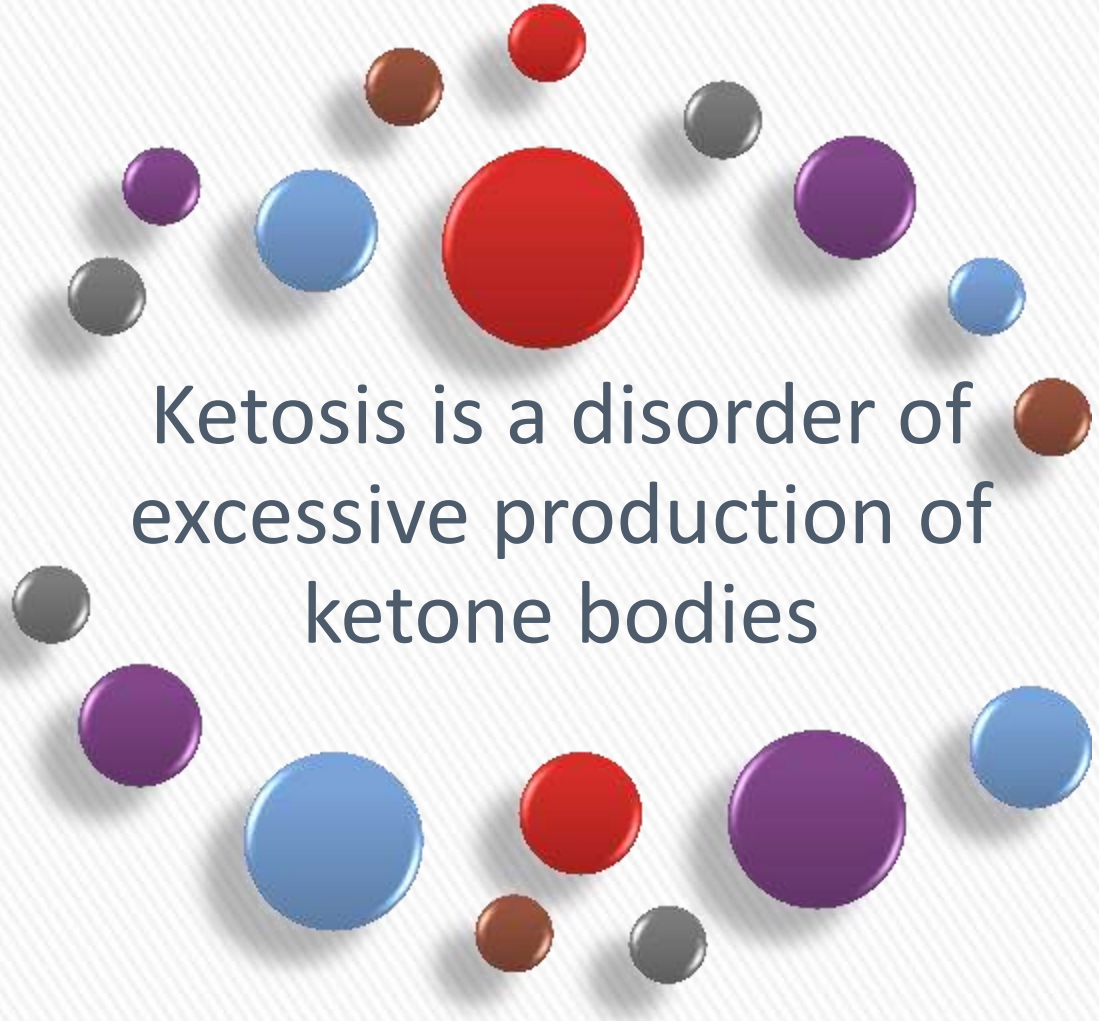
Ketone bodies are used as fuel, yielding 2 GTP and 22 ATP molecules per Acetoacetate molecule when oxidized in the mitochondria.

OTHER USES OF KETONE BODIES




Definition
Causes
Biochemical findings
Diagnosis
management

KETOSIS



Ketosis is a disorder of excessive production of ketone bodies

KETOSIS - DEFINITION ›

Prolonged starvation

- Carbohydrate deprivation

Uncontrolled diabetes mellitus

- Impaired uptake of glucose by the peripheral tissues

KETOSIS - CAUSES

Ketonemia

Acetone breath

Hyperkalemia

Ketonuria

Metabolic acidosis

KETOSIS – BIOCHEMICAL FINDINGS

KETOSIS – BIOCHEMICAL DIAGNOSIS

β hydroxybutyrate

- In plasma

Acetoacetate

- In urine
- Rothera's test

KETOACIDOSIS

- In normal individuals → constant production and utilization of Ketone Bodies
- Normal Ketone body level < 3mg%
- When Ketogenesis > Ketolysis

→Ketonemia (90mg/dl)

→Ketoacidosis

→Fruity odor in breath (Acetone)

→Ketonuria (5000mg/ day)

- Diabetic ketoacidosis (Type 1- uncontrolled) /Starvation

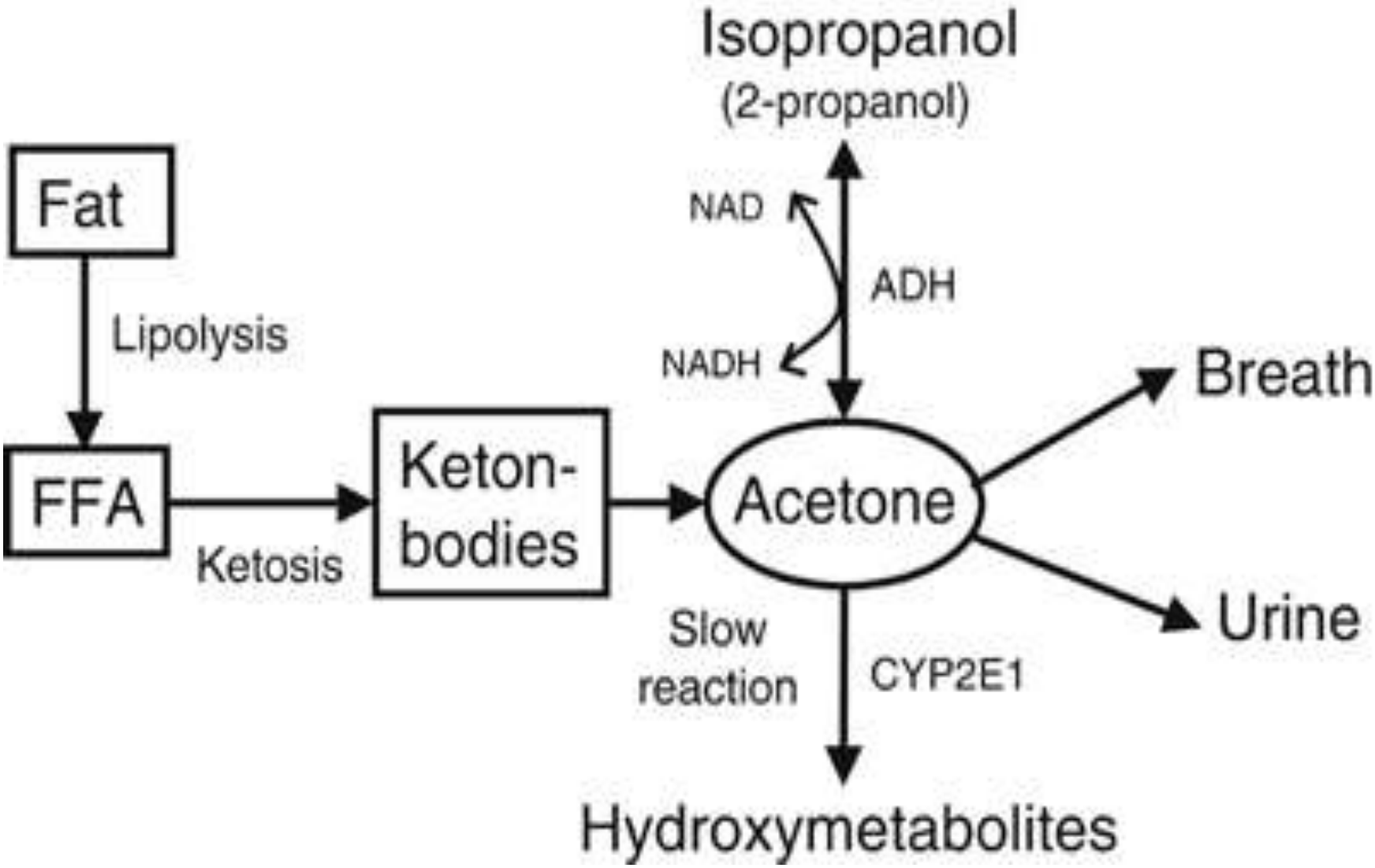
→Ketoacidosis→Ketonuria (+ Glucosuria)

→ Dehydration

Ketosis and ketoacidosis

- Ketonemia → *Ketonuria* (excretion of ketone bodies in urine)
- Ketonemia + Ketonuria = KETOSIS
- Smell of acetone in breath→ Ketosis.
- When a DMT1 suffers a biological stress event (sepsis, heart attack, infection) → Ketosis

Ketosis and Ketoacidosis



Ketosis ; Ketoacidosis

Ketonemia + Ketonuria = **Ketosis**

Ketone bodies (acetoacetic acid & 3-OH Butyric acid) are acidic in nature

↓

Hydrogen ions are neutralized by bicarbonate (HCO_3^-) of the blood

↓

Bicarbonate (HCO_3^-) level of the blood decreases – metabolic acidosis

↓

Metabolic acidosis is due to accumulation of ketone bodies so it is called ketoacidosis

Diabetic Ketoacidosis

Relative or absolute deficiency of insulin combined with counter regulatory hormone excess

[INSULIN] / [GLUCAGON] ↓

↓

Excess mobilization of fatty acids

↓

Hyperglucagonemia alters hepatic metabolism to favor ketone body formation, through activation of the enzyme carnitine palmitoyltransferase I.

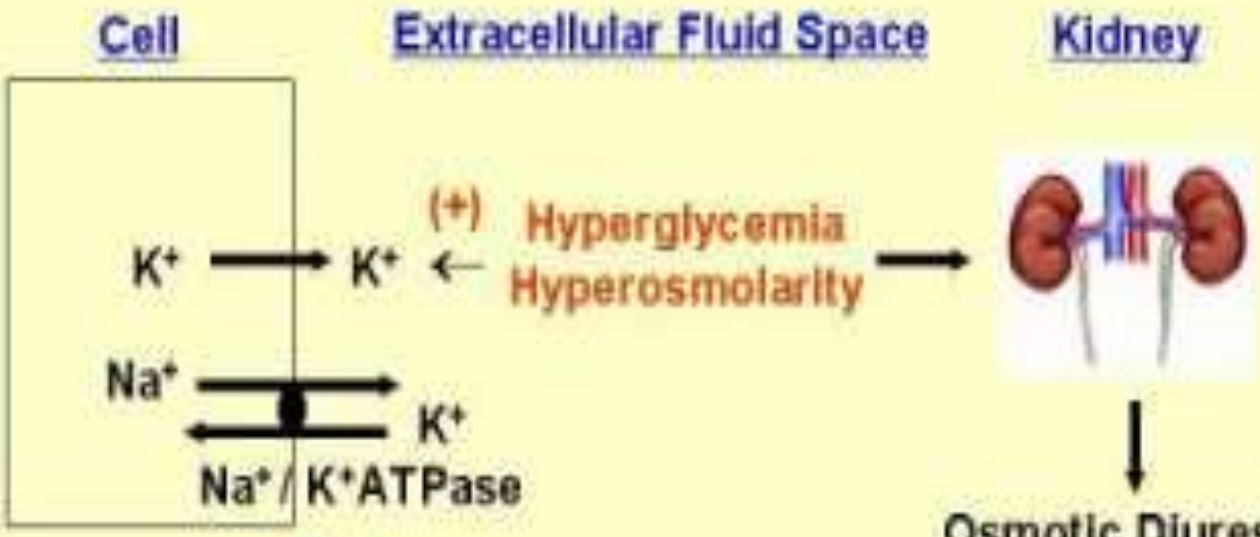
↓

Excess **β-oxidation of fatty acids in the hepatocytes**

↓

Excess ketone body formation

Diabetic Ketoacidosis
Consequences



Signs and Symptoms

Signs and Symptoms

Initial symptoms of DKA

Anorexia, nausea, vomiting, abdominal pain

Polyuria, polydipsia

Dehydration --) dry mucous membranes, tachycardia, hypotension

Alterated mental function--) somnolence, stupor,coma

Fever is not a sign of **DKA** --)signifies underlying infection

Classic signs of DKA

Kussmaul`s respirations (deep) to

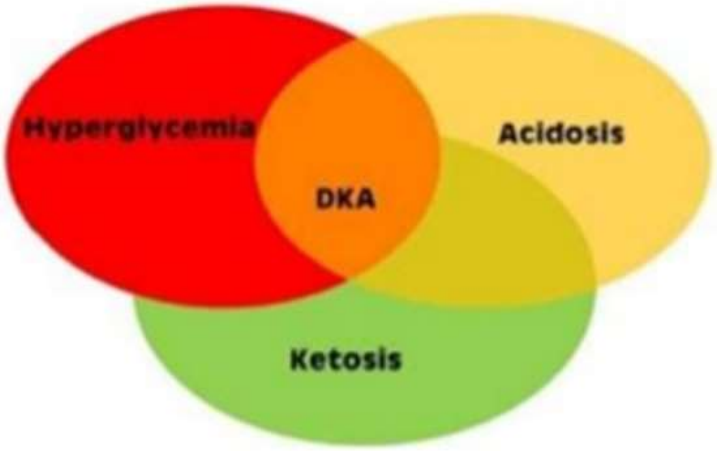
Signs and Symptoms of DKA

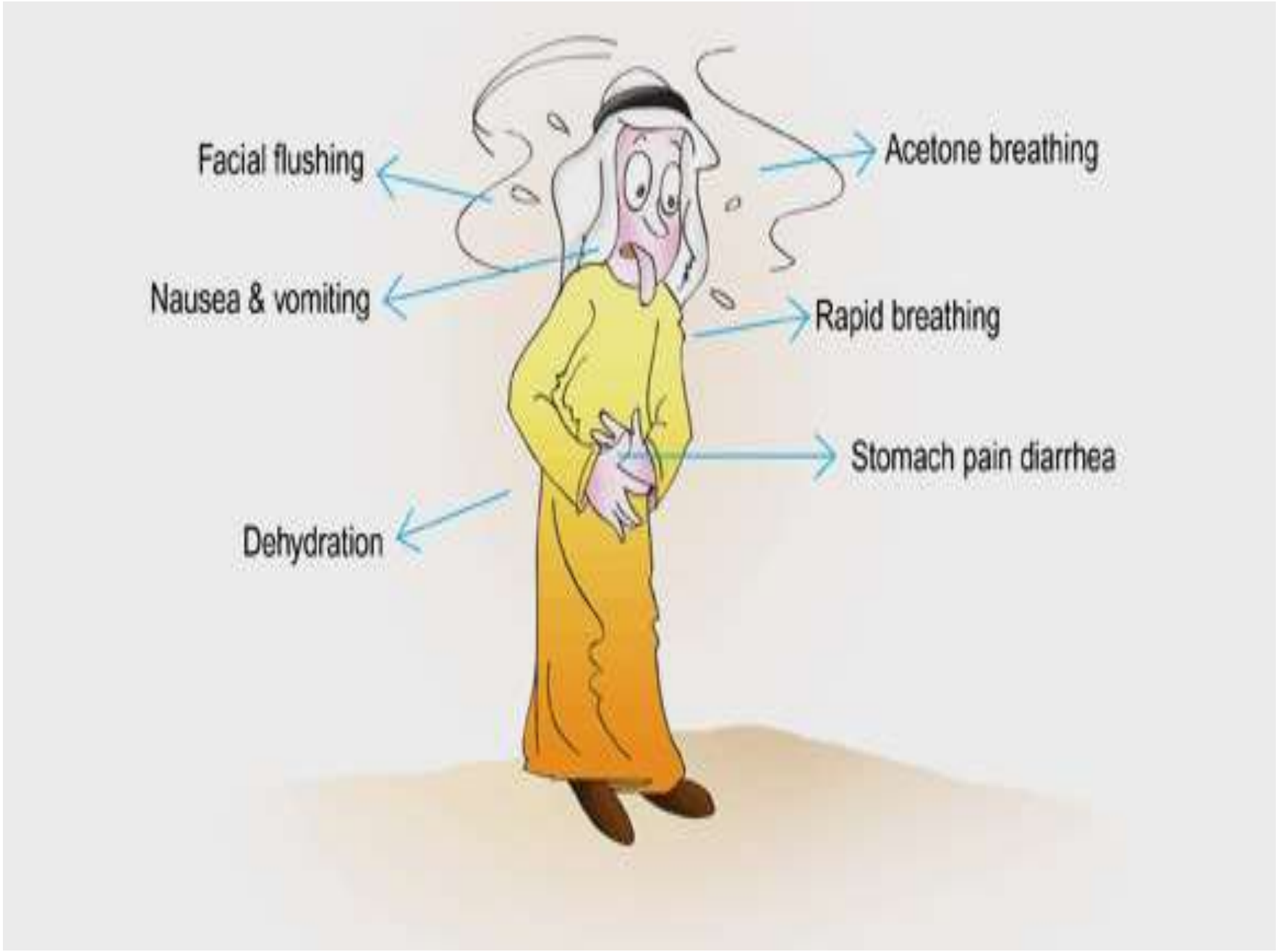
- Polyuria, polydipsia
  - Enuresis
- Dehydration
  - Tachycardia
  - Orthostasis
- Abdominal pain
  - Nausea
  - Vomiting

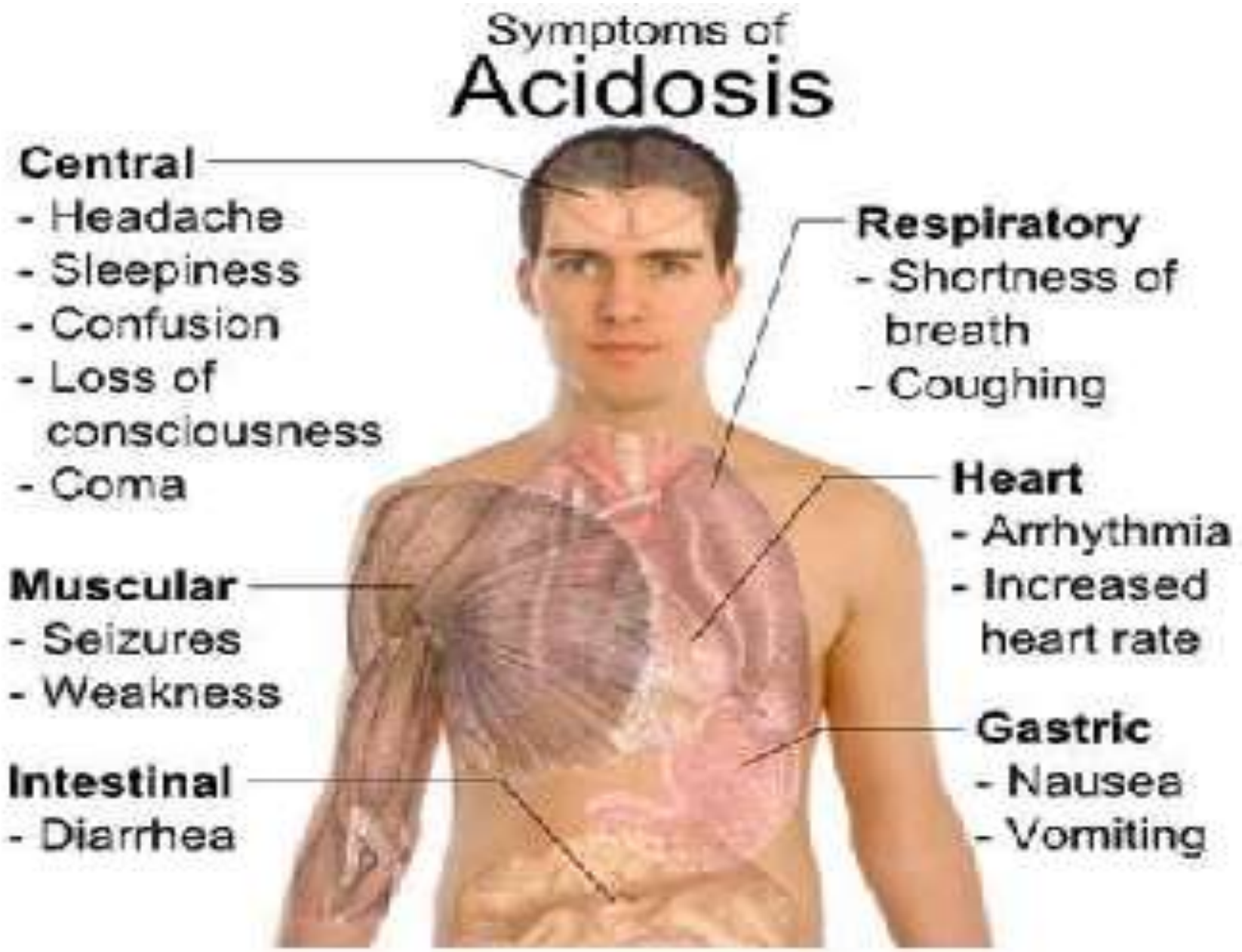
- Fruity breath
  - Acetone
- Kussmaul breathing
- Mental status changes
  - Combative
  - Drunk
  - Coma

CLASSICAL TRIAD IN DKA

- **Hyperglycemia - blood glucose greater than 200 mg/dL**
- **Ketosis - ketones present in blood and/or urine**
- **Acidosis - pH less than 7.3 and/or bicarbonate less than 15 mmol/L**




Facial flushing
Acetone breathing
Nausea & vomiting
Rapid breathing
Stomach pain diarrhea
Dehydration


Symptoms of
Acidosis
Central
- Headache
- Sleepiness
- Confusion
- Loss of consciousness
- Coma
Muscular
- Seizures
- Weakness
Intestinal
- Diarrhea
Respiratory
- Shortness of breath
- Coughing
Heart
- Arrhythmia
- Increased heart rate
Gastric
- Nausea
- Vomiting

HISTORY OF DKA