Biochemistry of Cardiac Muscle-2

The PC-CK system in cardiomyocytes

- CK synthesizes PC from creatine and a phosphate group from ATP in a reversible reaction, acting as a functional ATP reserve.
- CK associated with myofilaments catalyzes the transference of the phosphate from phosphocreatine towards ADP, replenishing ATP in ATPase active sites, such as myosin heads.

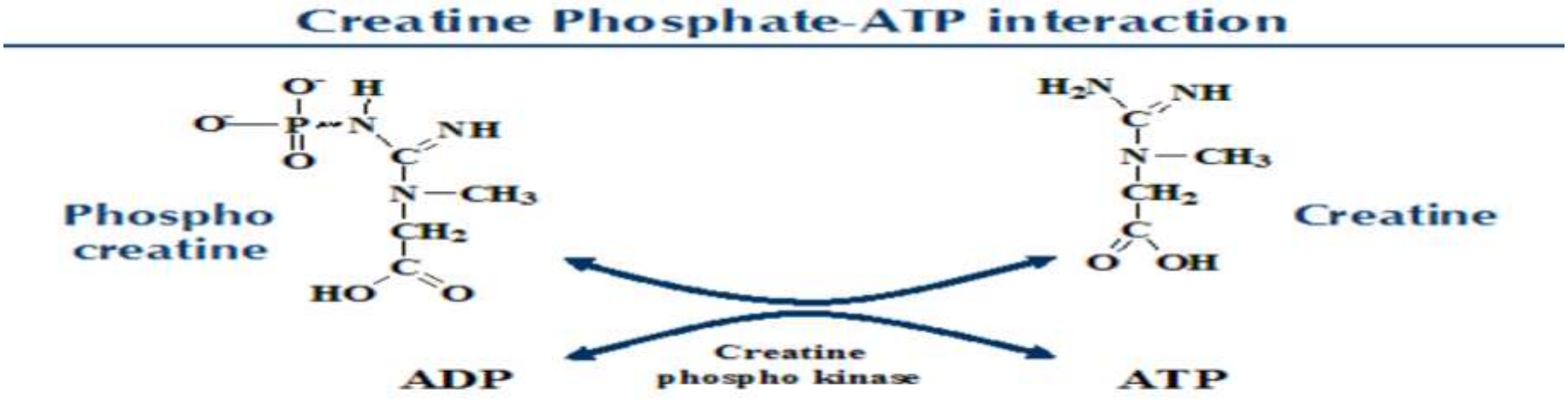
- The PC-CK system represents the first line of energetic reserves in cardiomyocytes, providing a quick source of ATP and favoring its transportation to its utilization sites, especially myofilaments.

- The disruptions in the PC-CK system have been linked to impaired myocardial contractility and increased risk for arrhythmias. Moreover, alterations in the functionality of CK have been identified as an independent risk factor for heart failure.

- CK is composed of dimers, which consist of subunits M and B, and originate three isozymes: CKMM, -MB and -BB.

- A fourth isozyme is found in mitochondria (mi-CK) and accounts for 20%-40% of all CK activity in the heart.

- The mi-CK isoform is coupled to the external surface of the internal mitochondrial membrane, near the ATP/ADP translocases.



- During oxidative phosphorylation, the ATP generated in the mitochondrial matrix is exported by ANT to the inter-membrane space and transphosphorylated by mi-CK to PC and ADP, with the latter being immediately available for oxidative phosphorylation, stimulating cellular respiration.

- In a healthy heart, approximately two thirds of all creatine is phosphorylated by CK to yield PC.
- In heart failure, the level of PC is lower in relation to the concentrations of ATP, with a lower PC/ATP index.

- Lower values of this index have been related to increased mortality.

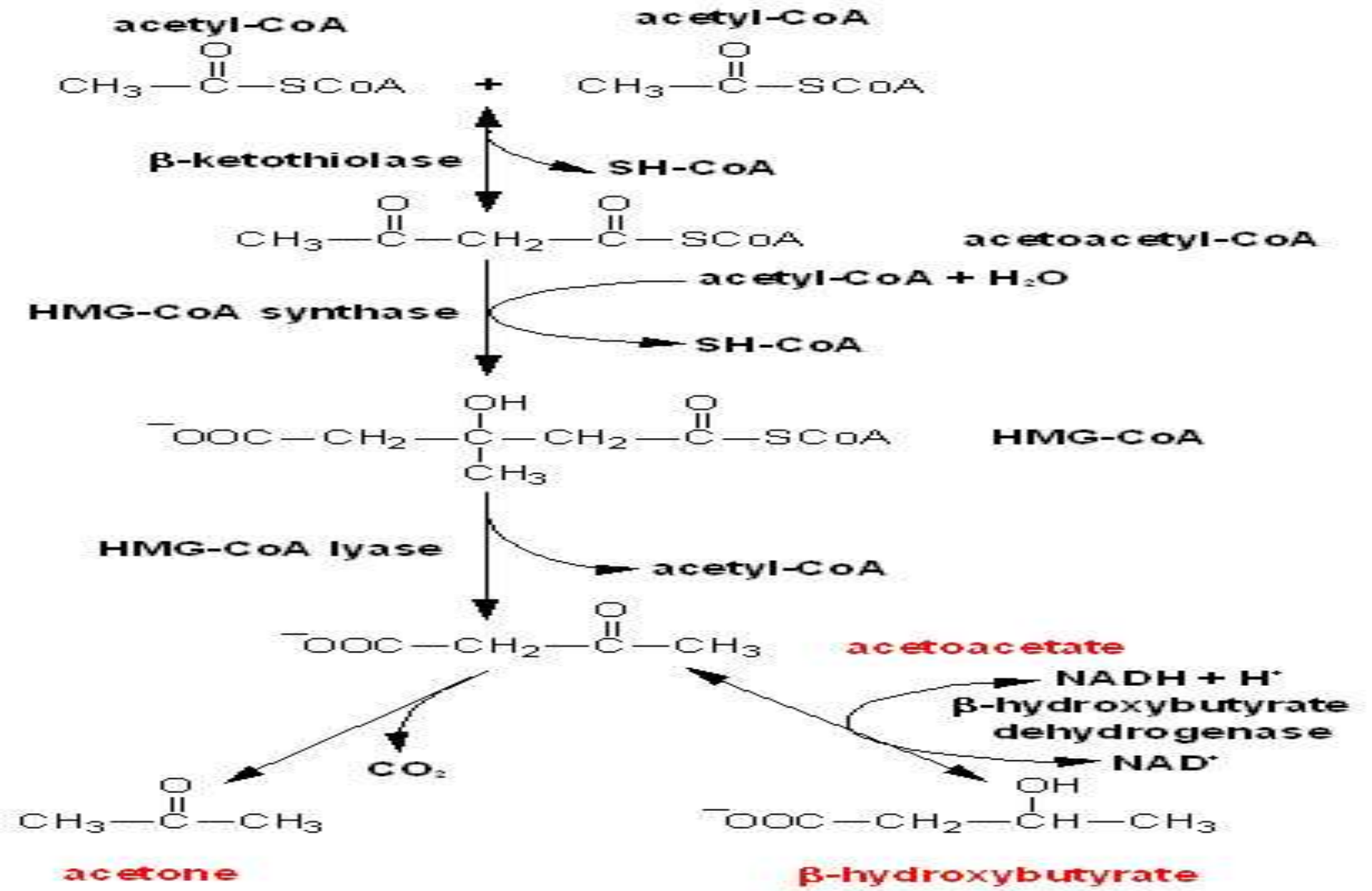
Ketone bodies

- A special source of fuel and energy for certain tissues.
- Some of the acetyl-CoA produced by FAs oxidation in liver mitochondria is converted to acetone, acetoacetate and β- hydroxybutyrate.
- Source of fuel for brain, heart and muscle.
- Major energy source for brain during starvation.

In ketogenesis:

- Large amounts of acetyl CoA accumulate.
- Two acetyl CoA molecules combine to form acetoacetyl CoA.
- Acetoacetyl CoA hydrolyzes to acetoacetate, a ketone body.
- Acetoacetate reduces to β-hydroxybutyrate or loses CO_2 to form acetone, both ketone bodies.

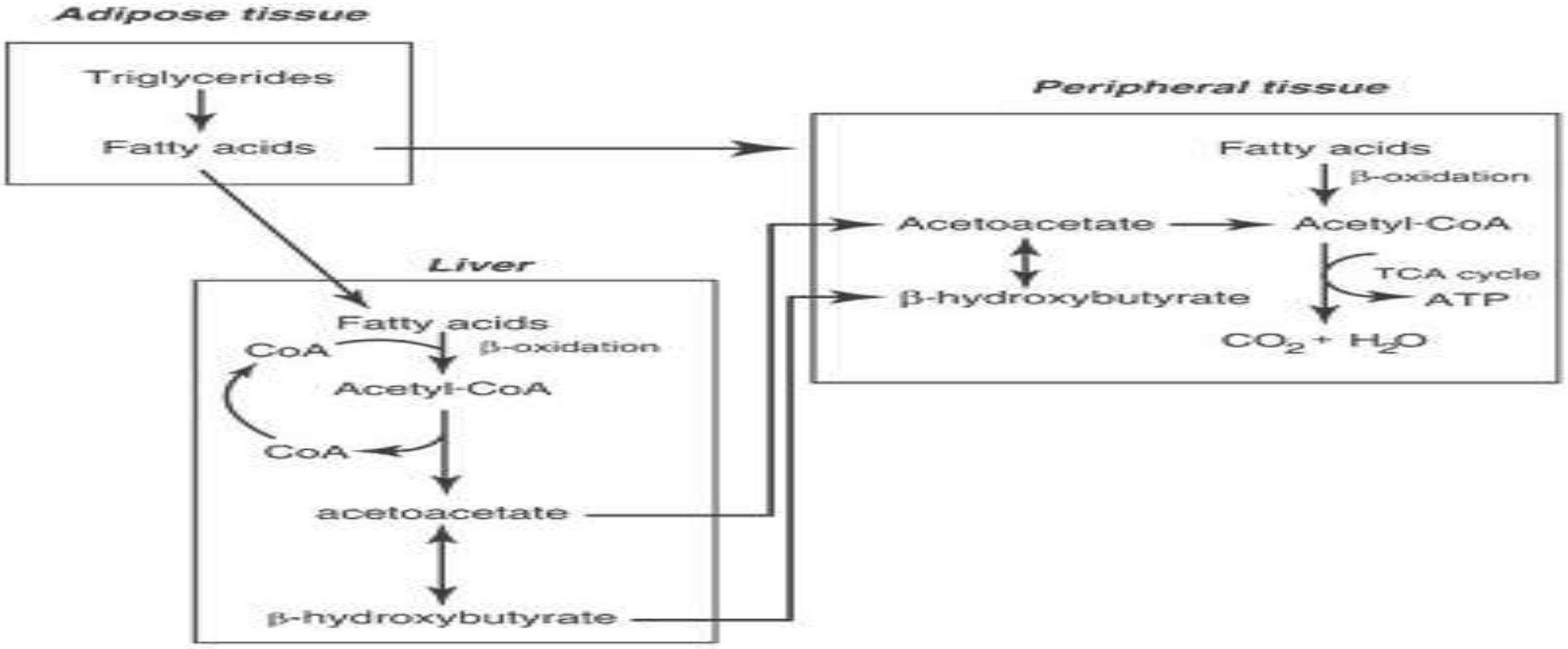
Reactions of Ketogenesis



Production

- Ketone bodies are produced mainly in the mitochondria of liver cells.
-Their synthesis occurs in response to low glucose levels in the blood and after exhaustion of cellular carbohydrate stores, such as glycogen.
- Fatty acids are enzymatically broken down in β-oxidation to form acetyl-CoA.
- Under normal conditions, acetyl-CoA is further oxidized and its energy transferred as electrons to NADH, $FADH_2$, and GTP in TCA cycle.
-The production of ketone bodies is then initiated to make available energy that is stored as fatty acids.

- However, if the amounts of acetyl-CoA generated in fatty acids β-oxidation exceeds the capacity of the TCA cycle or if activity in the TCA cycle is low due to low amounts of intermediates such as oxaloacetate, acetyl-CoA is then used instead in biosynthesis of ketone bodies via acetoacyl -CoA ß-hydroxy-ß- methylglutaryl - CoA (HMG-CoA), which is also an intermediate in the synthesis of cholesterol.



Ketosis or keto-Acidosis

- A large accumulation of ketone bodies is dangerous, because it leads to profound metabolic acidosis.
-The physiologic ketogenesis of fasting and the adaptive ketosis in starvation never progress to acidosis.

Ketonemia

- It is increased concentration of ketone bodies in blood due to increased their production by the liver rather than to a deficiency in their utilization by extra hepatic tissues.
-The production of ketone bodies occurs at a relatively low rate during normal feeding and under conditions of normal physiological status.
- Normal physiological responses to carbohydrate shortages cause the liver to increase the production of ketone bodies from the acetyl-CoA generated from fatty acid oxidation.

Causes of ketosis:

- Uncontrolled diabetes mellitus
- Starvation
- Chronic alcoholism
- Von Gierke's disease
- Heavy exercise
- Low carbohydrate diet
- Phosphorylase kinase deficiency
- Pyruvate carboxylase deficiency
- Prolonged ether anesthesia
- Toxemia of pregnancy
- Nonpathologic due to high-fat feeding and
- After severe exercise in the post absorptive state

Starvation induced ketosis

In prolonged fasting:

-There will be drop in the levels of plasma glucose, amino acids, triacylglycerols and decline in insulin level and an increase in glucagon release (decreased insulin /glucagon ratio), makes this period of nutritional deprivation a catabolic state, characterized by glycogenolysis, triacylglycerol and protein degradation.

-There will be an exchange of substrates between liver, adipose tissue, muscle and brain that is guided by two priorities:

1- The need to maintain glucose level to sustain the energy metabolism of brain, red blood cells and other glucose requiring cells, and;

2- To supply energy to other tissues by mobilizing fatty acids from adipose tissues and converting them to ketone bodies to supply energy to other cells of the body.

- In early stages of starvation , heart and skeletal muscle consume primarily ketone bodies to preserve glucose for use by the brain.
- After several weeks of starvation, ketone bodies become the major fuel of the brain.

Diabetic ketoacidosis (DKA)

- It is a state of inadequate insulin levels resulting in high blood sugar and accumulation of ketone bodies in the blood.
- It is a potentially life-threatening complication.
- It happens predominantly in type 1 diabetes mellitus, but can also occur in type 2 under certain circumstances, which may be due to intercurrent illness (pneumonia, influenza, gastroenteritis, a urinary tract infection), pregnancy, inadequate insulin intake , myocardial infarction, eating disorder , stroke or the use of drugs.
- DKA results from relative or absolute insulin deficiency combined with counter regulatory hormone excess (glucagon, catecholamines, cortisol, and GH).
- In 5% of cases, no cause for the DKA is found.

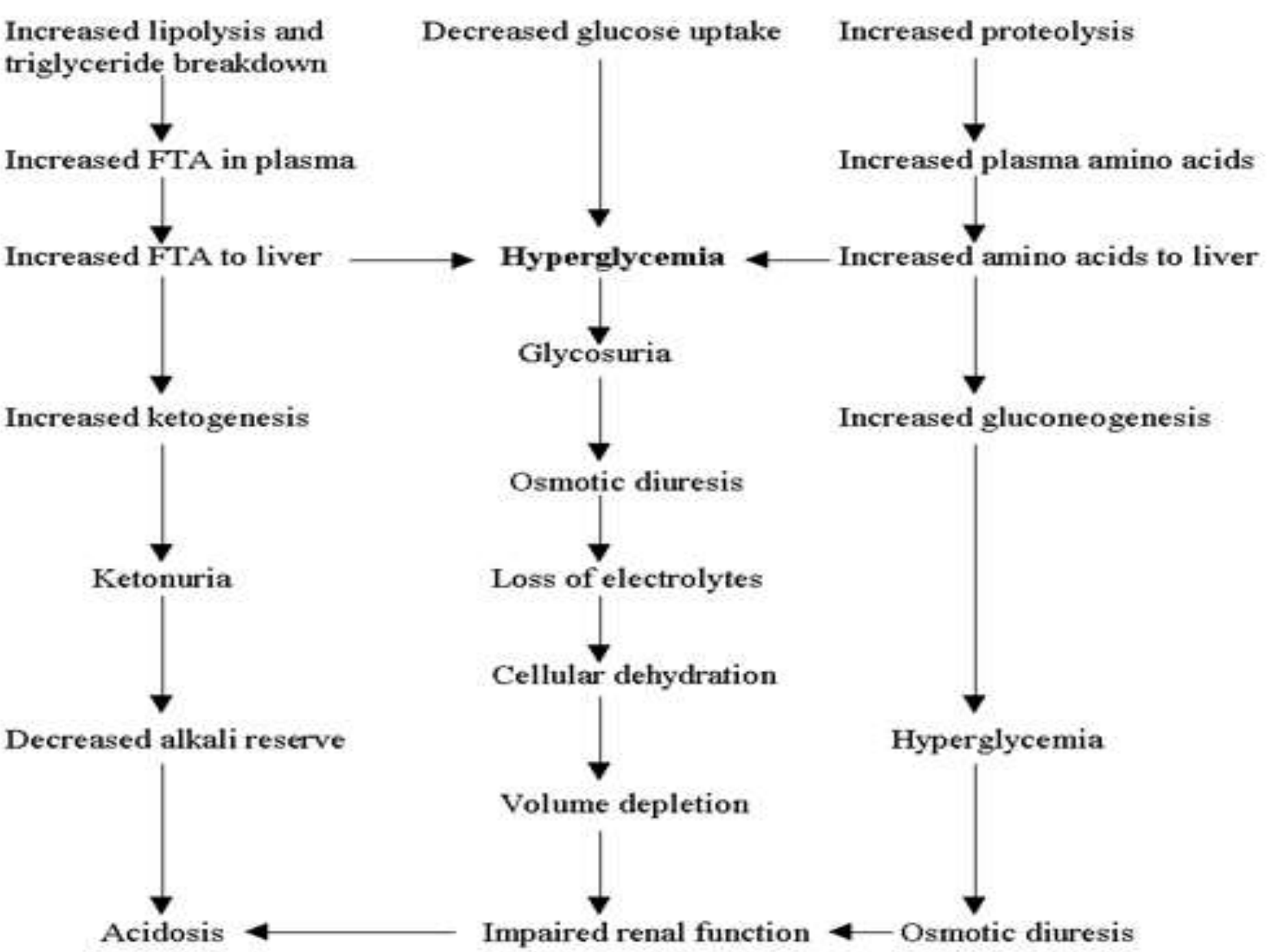
- Decreased ratio of insulin/glucagon ratio promotes gluconeogenesis, glycogenolysis, and ketone bodies formation in the liver, as well as increases in substrate delivery from adipose and muscle tissues (free fatty acids, amino acids) to the liver

-The ketone bodies have a low pH → metabolic acidosis.

-The body initially buffers these with the bicarbonate buffering system, and other mechanisms to compensate for the acidosis, such as hyperventilation (Kussmaul respiration) to ↓ blood CO_2 levels.

- Ketone bodies lead to electrolyte losses due to osmotic diuresis.

- Diabetic ketoacidosis may be diagnosed when the combination of hyperglycemia, ketones on urinalysis and acidosis are demonstrated.


Increased lipolysis and triglyceride breakdown
Decreased glucose uptake
Increased proteolysis
Increased FTA in plasma
Increased plasma amino acids
Increased FTA to liver
Hyperglycemia
Increased amino acids to liver
Glycosuria
Increased ketogenesis
Increased gluconeogenesis
Osmotic diuresis
Ketonuria
Loss of electrolytes
Cellular dehydration
Decreased alkali reserve
Hyperglycemia
Volume depletion
Acidosis
Impaired renal function
Osmotic diuresis

Regulation

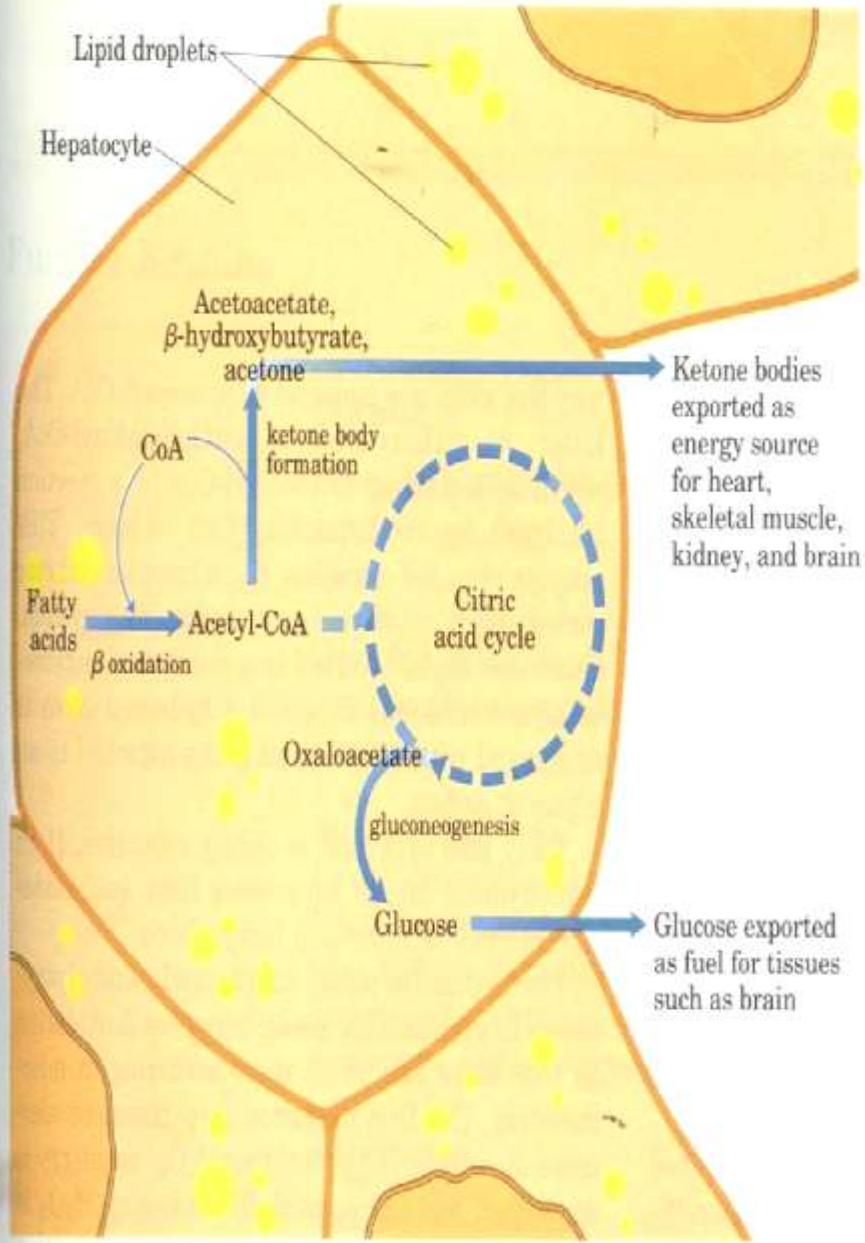
- Ketogenesis may or may not occur, depending on levels of available carbohydrates in the cell or body.

-This is closely related to the paths of acetyl-CoA:

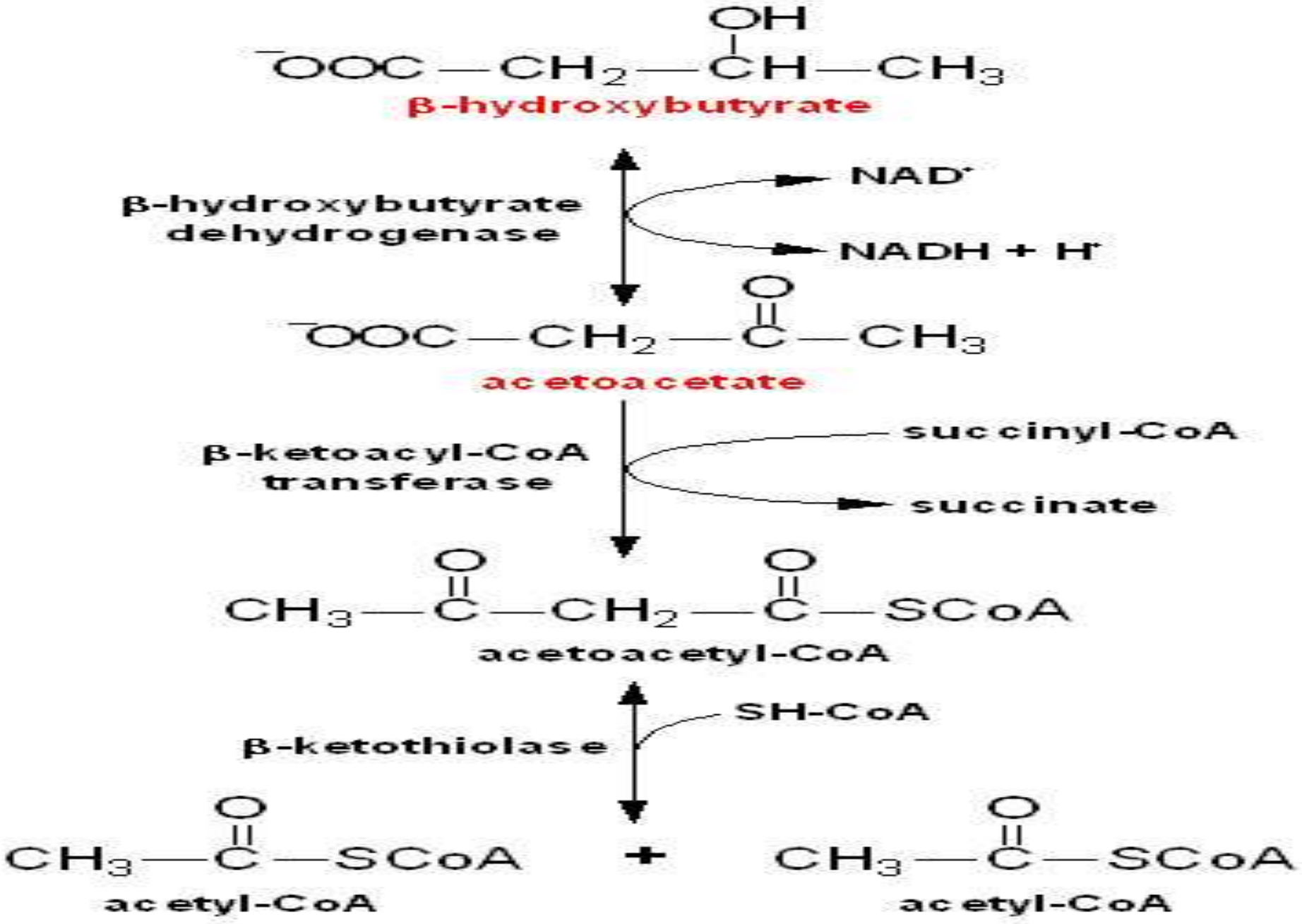
1- When the body has ample carbohydrates available as energy source, glucose is completely oxidized to CO2; acetyl-CoA is formed as an intermediate in this process, first entering the citric acid cycle followed by complete conversion of its chemical energy to ATP in oxidative phosphorylation.

2- When the body has excess carbohydrates available, some glucose is fully metabolized, and some of it is stored by using acetyl-CoA to create fatty acids. (CoA is also recycled here).

3- When the body has no free carbohydrates available, fat must be broken down into acetyl-CoA in order to get energy. Acetyl-CoA is not being recycled through the citric acid cycle because the citric acid cycle intermediates (mainly oxaloacetate) have been depleted to feed the gluconeogenesis pathway, and the resulting accumulation of acetyl-CoA activates ketogenesis.



Ketolysis


β-hydroxybutyrate
β-hydroxybutyrate dehydrogenase
NAD+
NADH + H+
acetoacetate
β-ketoacyl-CoA transferase
succinyl-CoA
succinate
acetoacetyl-CoA
β-ketothiolase
SH-CoA
acetyl-CoA
acetyl-CoA

Ketolysis (ketone body utilization)

-Tissues that can use fatty acids can generally use ketone bodies in addition to other energy sources.

-The exceptions are the liver and the brain.

-The liver synthesizes ketone bodies, but has little α-ketoacyl-CoA transferase, and therefore little ability to convert acetoacetate into acetyl-CoA.

-The brain does not normally use fatty acids, which do not cross the blood-brain barrier; under ordinary circumstances, the brain uses glucose as its sole energy.

- The metabolic rate of the brain is essentially constant.

-While other tissues reduce their metabolic requirements during starvation, the brain is unable to do so.

- After a few days of fasting, the brain undergoes metabolic changes to adapt to the decreased availability of glucose.
- One major change is increased amounts of the enzymes necessary to metabolize ketone bodies.
-The utilization of ketone bodies requires one enzyme not present in the ketone body biosynthetic pathway, β - ketoacyl-CoA transferase (thiophorase), converts acetoacetate to acetoacetyl-CoA.
-The lack of thiophorase in the liver prevents the futile cycle of synthesis and breakdown of acetoacetate.
-The β- ketoacyl-CoA transferase uses succinyl-CoA as the CoA donor, forming succinate and acetoacetyl-CoA

-This reaction bypasses the succinyl-CoA synthetase step of the TCA cycle, although it does not alter the amount of carbon in the cycle.

-This implies that the TCA cycle must be running to allow ketone body utilization; a fact which is necessarily true, because the TCA cycle is necessary to allow generation of energy from acetyl-CoA.

-The other enzymes of the ketone body utilization pathway, β hydroxybutyrate dehydrogenase and thiolase, are identical to the enzymes used for ketone body synthesis.

Some aspects of myocardial biochemistry of heart failure

- Heart failure reduces the capacity to transduce the energy from foodstuff into ATP.

- In the advanced stage of HF→ → →
  - Down regulation in F.A.s oxidation;
  - Increased glycolysis and glucose oxidation
  - Reduced respiratory chain activity.

Cardiac muscle and Ischemia

- Coronary artery occlusion → ischemia → significant change in cell structure, chemistry and function
  - Loss of contractile function
  - Arrhythmias
  - Cell death

-The decrease of the ATP / ADP, the accumulation of AMP, inorganic phosphate, metabolic products are removed (lactate).

-The rapid decline in creatine phosphate (only short-term mechanism to compensate for reduced ATP production in mitochondria)

- Even mild ischemia reduces the concentration of ATP and creatinephosphate, increases the level of inorganic phosphate → activation of glycolysis (glucose needed from the bloodstream into the heart cells) → increase in the concentration of pyruvate → conversion by LDH to lactate.

- Prolonged ischemia - the accumulation of substrates (lactate, $NADH^+$ and H^+) → inhibition of glycolysis at the level of PFK-1 and glyceraldehyde-3-dehydrogenase.