

Metabolism of ketone bodies

Ketogenesis

localisation liver mitochondria

process: formation of ketone bodies is a normal process
 (normal conc: < 0,2 mM)
 pathological: increased formation

II. Utilitation of ketone bodies

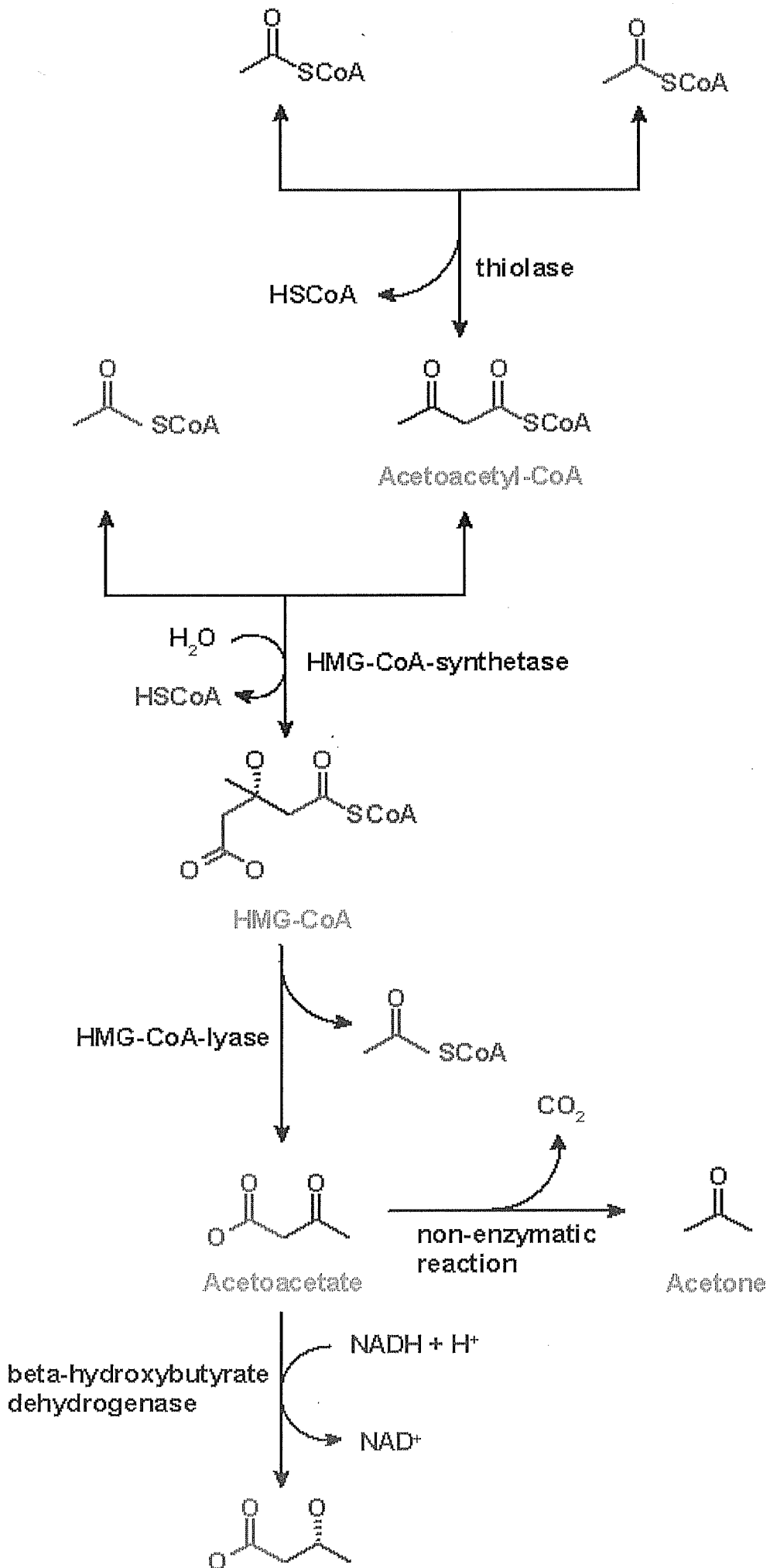
Ketone bodies are utilized by extrahepatic tissues through the conversion of β -hydroxybutyrate to acetoacetate and of acetoacetate to acetoacetyl-CoA. The first step involves the reversal of the β -hydroxybutyrate dehydrogenase reaction, and the second involves the action (shown below) of ***acetoacetate:succinyl-CoA transferase***, also called ***ketoacyl-CoA-transferase***.



The latter enzyme is present in all tissues except the liver. Importantly, its absence allows the liver to produce ketone bodies but not to utilize them. This ensures that extrahepatic tissues have access to ketone bodies as a fuel source during prolonged starvation. Acetoacetyl-CoA is converted into two molecules of acetyl-CoA by a ***thiolase*** :



localisation: skeletal muscle
 heart
 brain (especially: in fetus and newborn babies)
 kidney
 mitochondria



importance of ketone bodies: energy source! (fuel)

during starvation: - brain $\frac{3}{4}$ of total energy source!
(after the 3rd day)

glucose requirement (brain) ↓ (50%)
balance of ketogenesis and
utilization of ketone bodies ↓

III. Circumstances of ketogenesis

cause: low i.c. glucose concentration.

increased lipid mobilization

- consequence:

pyruvate

gluconeogenesis

- citric acid cycle ↓
- acyl – CoA transport into mitochondria ↓

⇒ ketone bodies (3-5 mM) physiological
(ketogenesis) (20 mM) pathological

ketonemia (hyper)
ketonuria
acetone in breath

ketosis



ketoacidosis (coma)

states occurrence:

- starvation - diabetes mellitus
- quick switch in diet:
(from carbohydrate – poor to extremely lipid – rich)
- in childhood gastrointestinal problems
(vomiting diarrhoea)
- renal glucosuria -- loss of glucose
(e.g. in pregnancy)
- extremely intensive exercise, sports

Regulation of Ketogenesis

The fate of the products of fatty acid metabolism is determined by an individual's physiological status. Ketogenesis takes place primarily in the liver and may be affected by several factors:

- 1. Control in the release of free fatty acids from adipose tissue directly affects the level of ketogenesis in the liver. This is, of course, substrate-level regulation.
- 2. Once fats enter the liver, they have two distinct fates. They may be activated to acyl-CoAs and oxidized, or esterified to glycerol in the production of triacylglycerols. If the liver has sufficient supplies of glycerol-3-phosphate, most of the fats will be turned to the production of triacylglycerols.
- 3. The generation of acetyl-CoA by oxidation of fats can be completely oxidized in the TCA cycle. Therefore, if the demand for ATP is high the fate of acetyl-CoA is likely to be further oxidation to CO₂.
- 4. The level of fat oxidation is regulated hormonally through phosphorylation of ACC, which may activate it (in response to glucagon) or inhibit it (in the case of insulin).

Ketoacidotic coma

IDDM ~ type I
 β -cells - \emptyset

Primary: in untreated juvenile diabetes (under age 40)

catabolic metabolic state

- glycogen decreases
 - protein degradation
 - lipid store decreases
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- ketogenesis increases
acetone in breath

 - metabolic acidosis
compensation: breathing (Kussmaul's resp.)
nausea vomiting

 - loss of Na^+ , K^+
ketone bodies are excreted in the form of Na^+ , K^+ salts
(+ vomiting)

 - dehydration
 Na^+ ↓ (e. c. dehydration)
 K^+ ↓ (i. c. dehydration)
-
- osmotic diuresis: poliuria, polydipsia
- circulating blood volume decreased:
 - hypotension (collapse)

 - coma
(loss of consciousness)
main cause: dehydration of brain
cerebral circulation decreased

Symptoms of acute diabetic syndrome

polyuria	osmotic diuresis
polydypsia	exciccosis
glucosuria	hyperglycemia
	gluconeogenesis ↑
	glucose uptake ↑
	(GLUT4 muscle, adipose tissue)
muscle weakness	glycogen ↓
	glucose uptake ↓
	K ⁺ loss (from cells) K ⁺ increases in blood
loss of weight	proteolysis ↑
	lipolysis ↑
nause, vomiting	ketogenesis ↑ (ketonemia, ketonuria)
	metabolic acidosis
deep breathing	Kussmaul's respiration
	severe metabolic acidosis
	(blood plasma pH ↓)
consciousness ↓	dehydration of brain