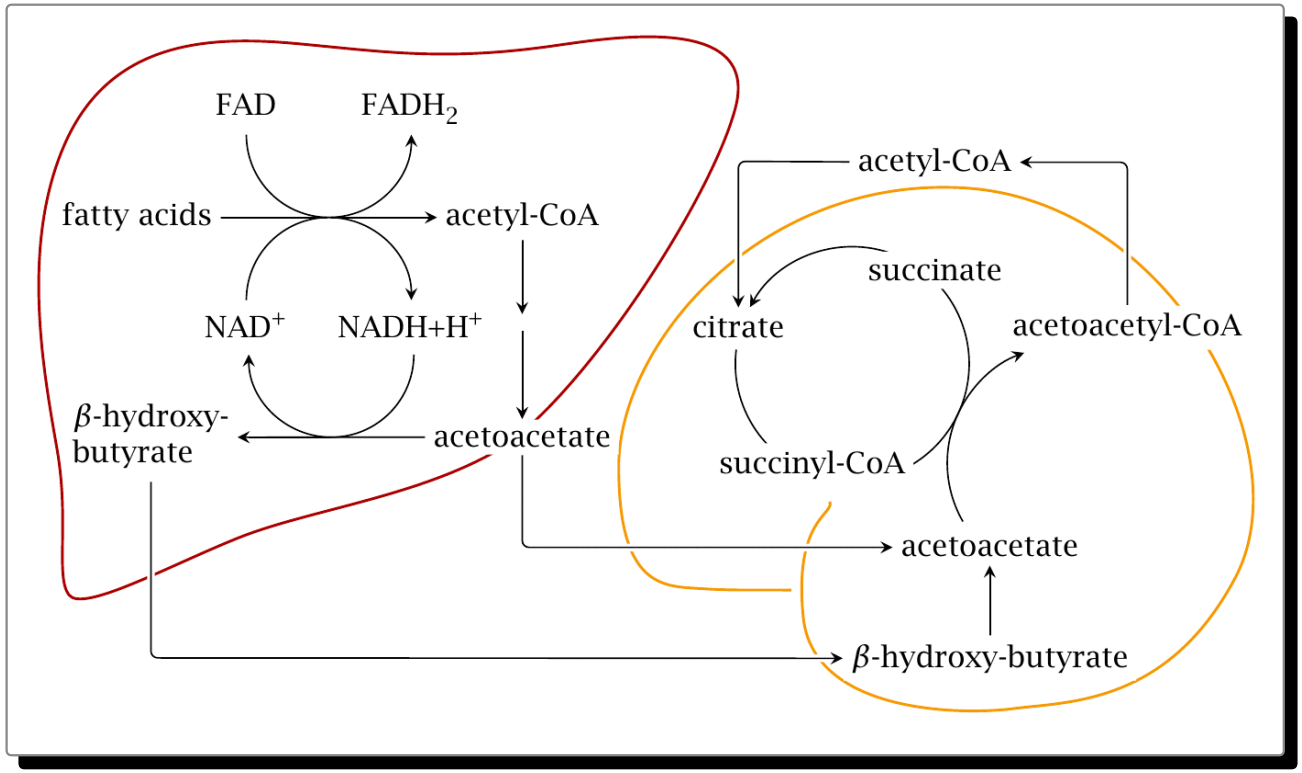
10.4 Ketone body metabolism

- Synthesis of acetoacetate and β-hydroxybutyrate
- Decarboxylation of acetoacetate
- Acetone can serve as a precursor for gluconeogenesis
- Anticonvulsant effects of acetone and acetol

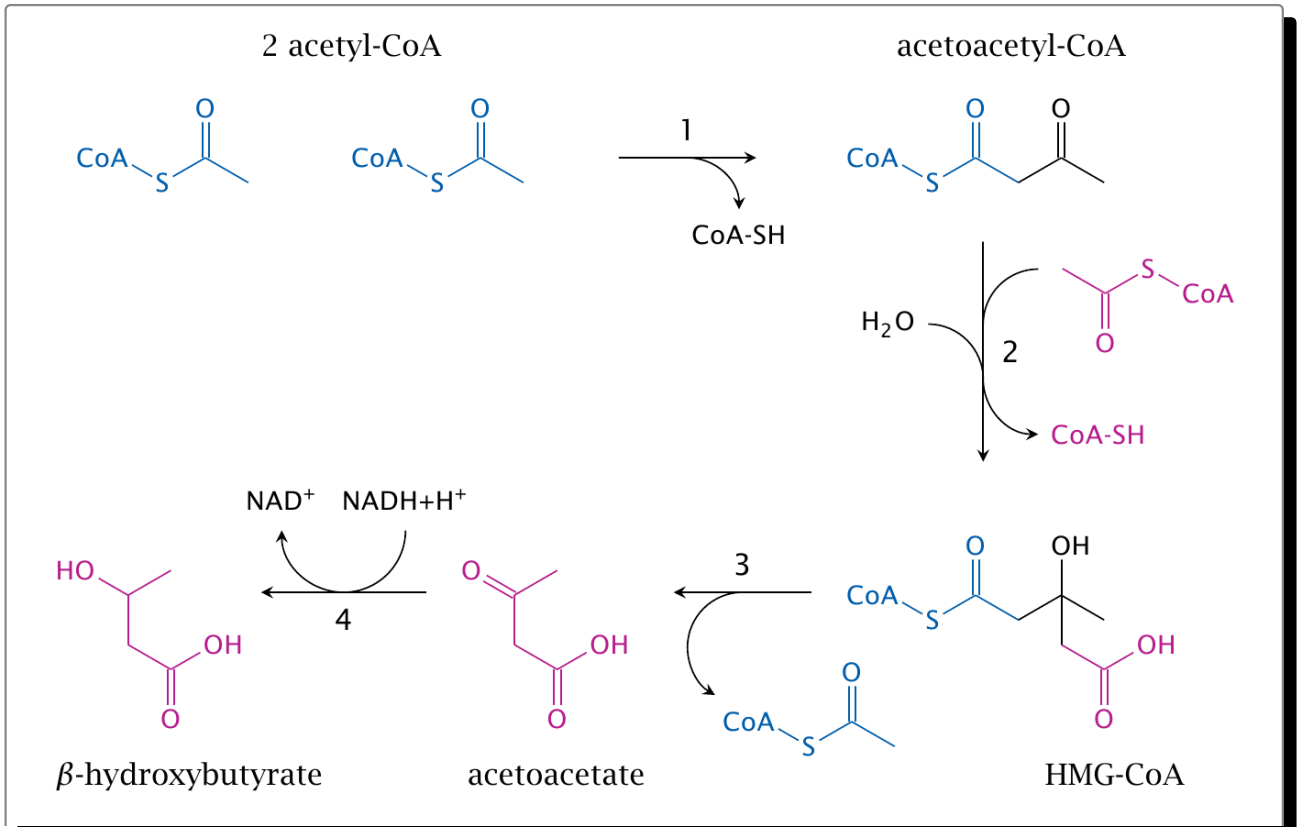


The key idea of ketone body metabolism is to convert free fatty acids into more water-soluble substrates that are easier to transport and to metabolize. This scheme gives an overview of organ relationships and pathways; note that the reactions are not stoichiometrically balanced.

Ketone bodies are formed mostly in the liver. As stated earlier, the first stage of ketogenesis consists in β-oxidation. The resulting acetyl-CoA is turned into acetoacetate along the pathway detailed in the next slide. The subsequent reduction of acetoacetate to β-hydroxybutyrate allows the liver to dispose of some of the surplus hydrogen that accumulates during β-oxidation. Both acetoacetate and β-hydroxybutyrate are released into the circulation.

Utilization of ketone bodies in the brain, muscle and other tissues is quite straightforward. β-Hydroxybutyrate is dehydrogenated again to acetoacetate, which steals coenzyme A from succinyl-CoA to become acetoacetyl-CoA. Thiolase then cleaves acetoacetyl-CoA to two molecules of acetyl-CoA, which enter the TCA cycle.

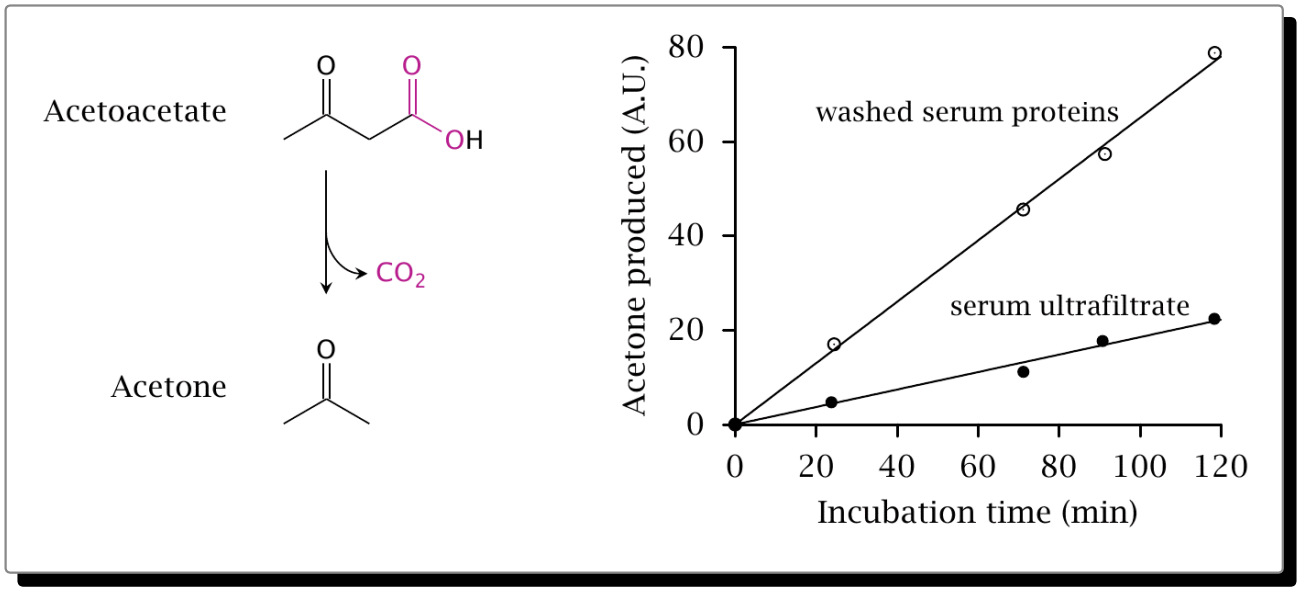
10.4.1 Synthesis of acetoacetate and β-hydroxybutyrate



This slide details the mitochondrial pathway that converts acetyl-CoA to ketone bodies. It involves the following steps:

1. formation of acetoacetyl-CoA from two molecules of acetyl-CoA by thiolase. This step is the reversal of the final step in β-oxidation;
2. formation of -CoA (HMG-CoA) by HMG-CoA synthase;
3. release of acetoacetate by HMG-CoA lyase; and
4. reduction of acetoacetate to β-hydroxybutyrate by β-hydroxybutyrate dehydrogenase.

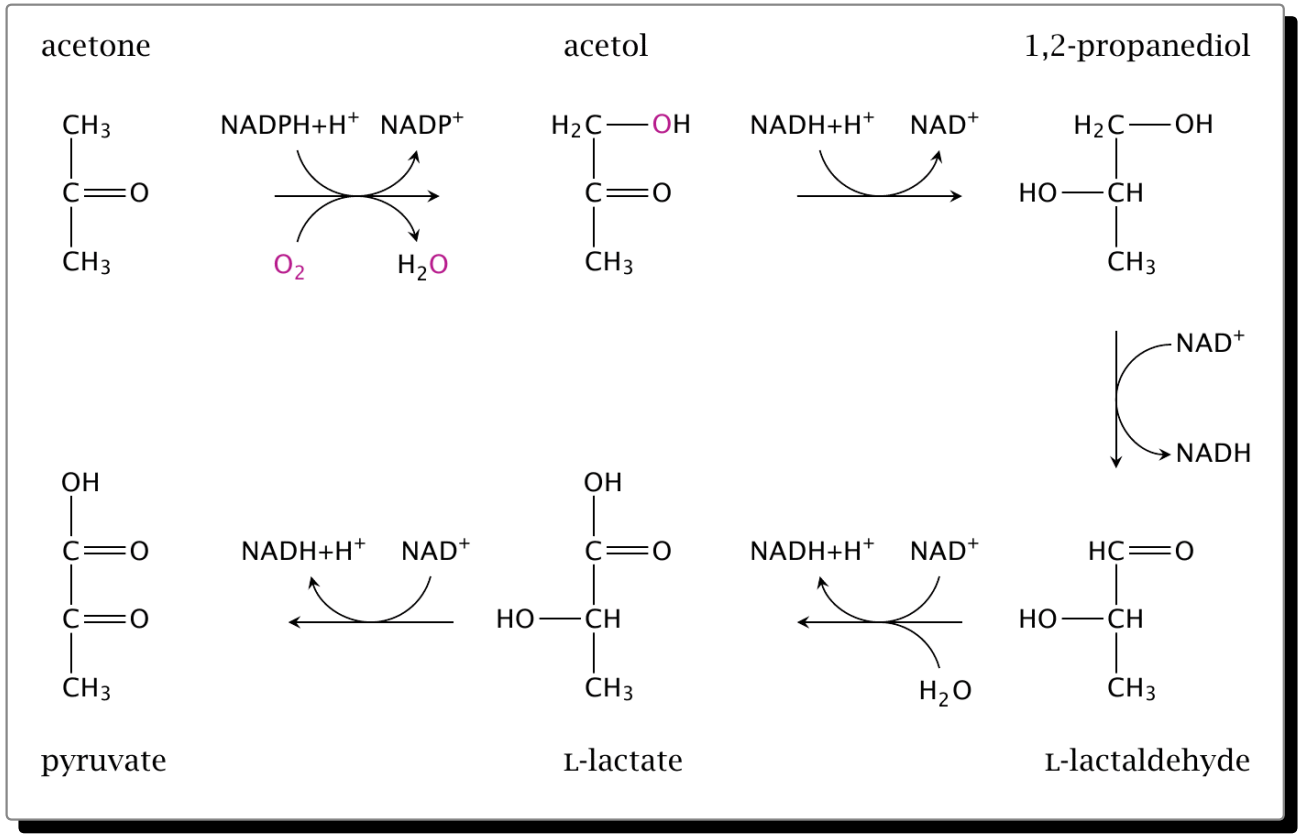
10.4.2 Decarboxylation of acetoacetate



Acetone can form from acetoacetate through spontaneous, non-enzymatic decarboxylation. As shown in this plot (redrawn from [1]), the rate of decarboxylation is enhanced by unfractionated serum proteins. The catalytic activity of serum is greater when ketogenesis has been induced, suggesting the existence of a specific enzyme

activity. A bacterial acetoacetate decarboxylase is known and has been studied in molecular detail; however, the hypothetical mammalian enzyme remains incompletely characterized [2].

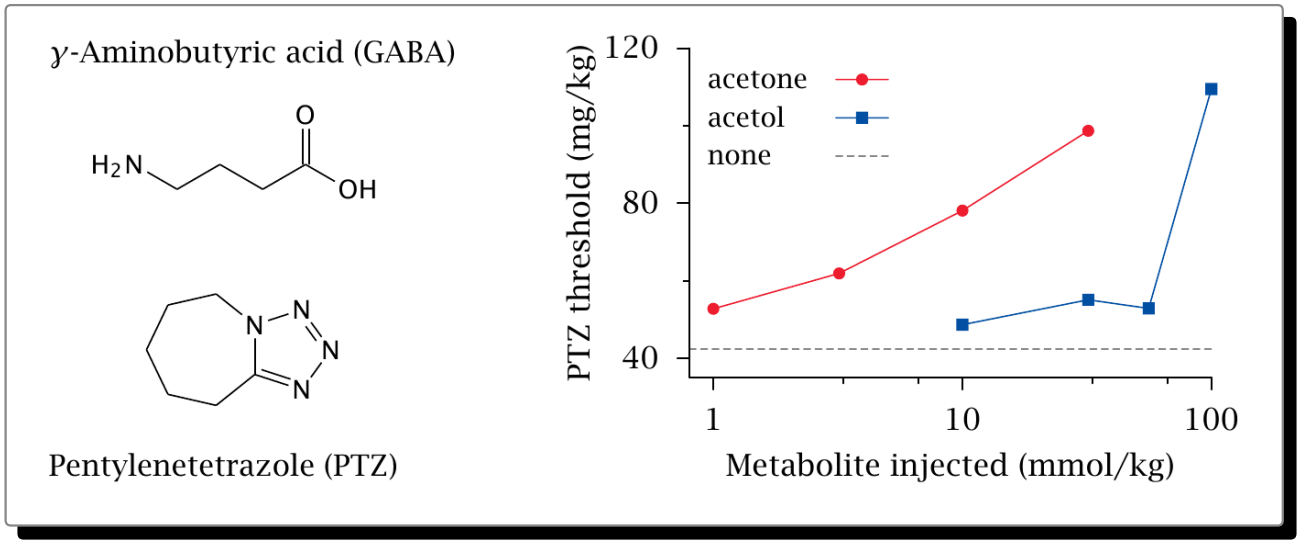
10.4.3 Acetone can serve as a precursor for gluconeogenesis



While many textbooks, even ones of recent vintage, continue to spread the myth of acetone being a useless metabolic dead end, it has been known for some time that acetone can be converted to pyruvate, which can then enter gluconeogenesis [3]. Thus, acetone provides a back door for fatty acyl carbon to be turned back into glucose. The capacity of this pathway appears to be limited; it has been estimated that up to 11% of endogenously produced glucose may be derived from acetone in fasting humans [4].

The first step of the pathway shown here is catalyzed by the enzyme cytochrome P450 type 2E1. This enzyme can also metabolize ethanol and is transcriptionally induced by both acetone and ethanol. The enzyme that converts acetol to propanediol has not been characterized; the subsequent steps are catalyzed by alcohol dehydrogenase and aldehyde dehydrogenase, respectively, which also function in the major pathway of ethanol degradation (see slide 7.4.2).*[3].

10.4.4 Anticonvulsant effects of acetone and acetol



At higher than physiological plasma concentrations, acetone acts like a general anesthetic, as do many organic solvents (e.g. chloroform and diethylether). This is also the case for some antiepileptic drugs. An important common target for anesthetics and antiepileptic drugs is the $GABA_A$ receptor, which is one of the two major inhibitory neurotransmitter receptors in the central nervous system.*[5]. Accordingly, acetone has been proposed to be responsible for the effectiveness of the *ketogenic diet* in epilepsy. This diet was the first effective treatment of this disease [6], and it remains in use in a significant number of patients, particularly children, who don't respond to antiepileptic drugs.

The ketogenic diet restricts carbohydrates and protein, and it supplies most calories as triacylglycerol, much of which is then converted to ketone bodies. In animal experiments, acetone has greater antiepileptic potency than the two other ketone bodies and, as illustrated here, also than the metabolites formed in its own breakdown. In the experiment shown here [7], the $GABA_A$ receptor antagonist pentylenetetrazole was used to induce epileptic seizures. Injection of acetone raises the dosage of pentylenetetrazole necessary to trigger seizures. It does this at lower concentrations than its metabolite acetol, indicating greater anticonvulsant potency.

The ketogenic diet does not work in all patients, and it seems desirable to increase its effectiveness. A possible strategy to achieve this might be to combine the diet with inhibitors of metabolic breakdown of acetone [8]. This approach is currently undergoing experimental evaluation.