9.2: Alcohol metabolism

Metabolism of alcohol occurs primarily in the liver through two different oxidative pathways. The activity of each pathway depends on the ethanol concentration and the frequency of ethanol consumption.
Figure 9.5: Overview of ethanol metabolism. The pathway spans the cytosol and the mitochondria, and NADH is produced in both steps of the pathway.

At low concentrations, oxidation of ethanol is a two-step process that occurs in both the cytosol and the mitochondria (figure 9.5). The first step of the reaction by alcohol dehydrogenase (ADH) occurs in the cytosol and produces acetaldehyde. Acetaldehyde is converted into acetate in the mitochondria by acetaldehyde dehydrogenase (ALDH) and can be transported in the blood to be used as an energy source for peripheral tissues (figure 9.5). The acetate can be converted to acetyl-CoA by acetyl-CoA synthetase (figure 9.6), and this will be oxidized in the TCA cycle. Each step in the oxidation of ethanol produces NADH, which increases the ratio of NADH/NAD⁺. The increase in this ratio can alter metabolism of other substrates and cause metabolic dysfunction, which will be discussed below.
Consequences of ethanol metabolism in the liver

At each step in ethanol oxidation, NADH is generated in both the mitochondrial and cytosolic compartments (figure 9.5). This can have major metabolic ramifications depending on the underlying metabolic environment (figure 9.7).

1. Hypoglycemia: High NADH produced by alcohol metabolism (figure 9.7; label 1) contributes to the diversion of the gluconeogenic substrates OAA and pyruvate. The higher NADH/NAD⁺ ratio drives the reactions toward malate and lactate, respectively. This can lead to the presentation of fasting hypoglycemia (figure 9.7; labels 4, 6, and 8).

2. Fatty steatosis: High NADH/NAD⁺ ratio also increases the conversion of dihydroxyacetone phosphate to glycerol 3-phosphate, contributing to increased synthesis of triacylglycerol. Additionally, increases in reactive oxygen species, which can impair protein synthesis, prevent the assembly and secretion of VLDLs. This can ultimately contribute to fatty liver disease (figure 9.7; label 3).
3. Acidosis: Increases in alternative substrates for peripheral tissues (acetate from alcohol oxidation) can cause an elevation of ketones leading to ketoacidosis (figure 9.7; label 5).

4. Hyperlipidemia: The elevated NADH will negatively impact flux through the TCA by reducing the activity of the two key regulatory enzymes. This can lead to an increased shunting of citrate for fatty acid synthesis (figure 9.7; labels 2 and 3).

5. Acetaldehyde is a toxic compound that forms adducts with other proteins reducing their ability to function.

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**Excessive alcohol consumption**

At higher concentrations of ethanol, the microsomal ethanol oxidizing system (MEOS) becomes activated (figure 9.7; label 9). This pathway consists of a series of cytochrome P450 enzymes, which have a relatively high \(K_m\) for ethanol and are located in the hepatic smooth endoplasmic reticulum (SER). This microsomal-ethanol oxidizing system also detoxifies drugs such as barbiturates (figure 9.8).

![Figure 9.8: Ethanol detoxification by MEOS.](https://med.libretexts.org/Bookshelves/Basic_Science/Cell_Biology_Genetics_and_Biochemistry_for_Pre-Clinical_Students/0...)

1. Chronic consumption of alcohol will increase the expression of the MEOS and proliferation of hepatic SER. Increases in expression of both CYP2E1 (P450 enzyme) and gamma-glutamyltransferase (GGT), an enzyme located in the SER, are excellent markers of alcohol ingestion.

2. Ethanol oxidation by MEOS does not affect the NADH/NAD\(^+\) ratio substantially, therefore, it does not have the metabolic effects described for low concentrations of ethanol.

Although the MEOS system does not impact the NADH/NAD\(^+\) ratio, that is not to suggest that induction of this system is without metabolic consequences. Induction of the P450 system can negatively impact the metabolism of other drugs causing serious side effects. One example of this is altered metabolism of acetaminophen (Tylenol). Acetaminophen can be glucuronylated or sulfated in the liver for safe excretion by the kidney. However, the cytochrome P450 system can metabolize acetaminophen to the toxic intermediate N-acetyl-p-benzoquinone imine (NAPQI), which requires conjugation with glutathione prior to excretion. The enzyme that produces NAPQI, CYP2E1, is induced by alcohol through the MEOS. Thus, individuals who chronically abuse alcohol have increased sensitivity to acetaminophen toxicity because a higher percentage of acetaminophen metabolism is directed toward NAPQI, compared with an individual with low levels of CYP2E1.
Ethanol is also an inhibitor of the phenobarbital-oxidizing P450 system. When large amounts of ethanol are consumed, the inactivation of phenobarbital is directly or indirectly inhibited. Therefore, when high doses of phenobarbital and ethanol are consumed at the same time, toxic levels of the barbiturate can accumulate in the blood.

References and resources

Text


Figures

Grey, Kindred, Figure 9.5 Overview of ethanol metabolism. The pathway spans the cytosol and the mitochondria and NADH is produced in both steps of the pathway. 2021. https://archive.org/details/9.5_20210926, CC BY 4.0.


Lieberman M, Peet A. Figure 9.7 Clinical consequences of alcoholism. Adapted under Fair Use from Marks’ Basic Medical Biochemistry. 5th Ed. pp 709. Figure 33.6 Acute effects of ethanol metabolism on lipid metabolism in the liver. 2017.

Lieberman M, Peet A. Figure 9.8 Ethanol detoxification by MEOS. Adapted under Fair Use from Marks’ Basic Medical Biochemistry. 5th Ed. pp 704. Figure 33.3 The reaction catalyzed by the microsomal ethanol-oxidizing system (MEOS; which includes CYP2E1) in the endoplasmic reticulum (ER). 2017. Chemical structure by Henry Jakubowski.