

Cysteine Peptide Scientific Review, Dr. S. Dudek, DMV International

Ethanol and Glutathione

Reduced glutathione plays a critical role in cellular detoxification processes including the metabolism of peroxides, the conjugation with electrophils and the scavenging of free radicals. The relevance of glutathione in ethanol metabolism consists mainly in compensating for alcohol-related oxidative stress. Oxidative stress is a disturbance in the pro-oxidant/antioxidant balance (increased pro-oxidant levels), that may be achieved by either an enhancement of oxidative reactions leading to the increased formation of reactive oxygen species (ROS) or by a decrease of the antioxidant defense.

The metabolism of alcohol

Three routes of ethanol metabolism exist in the human body (figure 1).

- the oxidation of alcohol by alcohol dehydrogenase (ADH) in the liver, and, with less relevance, in the stomach
- the microsomal cytochrome P450 system (MEOS) especially at higher alcohol concentrations
- the oxidation by catalase (minor importance)

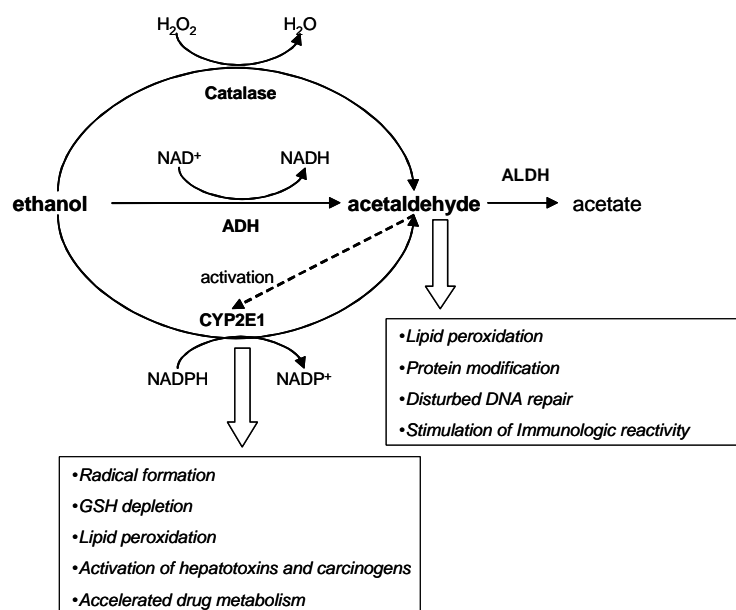


figure 1: The main routes of alcohol metabolism

The first metabolite of these pathways is **acetaldehyde** – a very toxic substance with a high chemical reactivity towards proteins, DNA and lipids that induce a number of physiological impairments. Acetaldehyde also reacts directly and non-enzymatically with GSH or cysteine in vivo, (therefore it depletes GSH and cysteine supply) although the detection of the respective intermediates is rather difficult.

The efficacy with which a person metabolizes alcohol depends on individual parameters, among others on the concentration of the crucial enzymes: alcohol dehydrogenase (ADH) and acetaldehyde dehydrogenase (ALDH).

Human males have more ADH in the stomach than females leading to a more active so-called first-pass metabolism of alcohol. Due to the lack of ADH, women must rely primarily on the detoxification capacity of their livers, and so they are more affected by equivalent doses of alcohol. Having less ADH than men, they are more susceptible to alcohol related liver damage like fatty liver, liver cirrhosis and cancer. A slower metabolism of acetaldehyde is accompanied with more severe acute acetaldehyde-related and hangover symptoms. Many Asian people possess a ALDH phenotype that has a low affinity for acetaldehyde, so they suffer more from acetaldehyde-related symptoms and are prone to liver damage from acetaldehyde

Beside its direct toxicity, ethanol activates the microsomal cytochrome P450-dependent enzyme system, especially the subclass **CYP2E1**, that plays an important role in the liver detoxification system [1,2].

The microsomal route of alcohol oxidation via CYP2E1 is accompanied with the **formation of free radicals** challenging the natural antioxidant defense of the body [3]. The liver and brain are especially affected by alcohol related oxidative stress because these organs have an abundance of this enzyme. As an example, the hydroxyethyl-radical that is derived from alcohol, is even more reactive than the hydroxyl radical, but has a much higher lifetime, and so remains in the body with potentially damaging effect [4]. These radicals may interact with lipids, proteins or other macromolecules, damaging the biological system. The oxidative stress is compounded by the induction of the microsomal CYP2E1 system which enhances the formation of reactive oxygen species (**ROS**), increasing the pro-oxidative pressure especially in the liver and the brain.

A **depletion of GSH in the liver**, but also in other organs in the body, e.g. in the lung, is **evident after acute alcohol ingestion**. GSH depletion occurs mainly in the liver because of an increased biliary excretion of GSH which lowers the intrahepatic GSH concentration. Inhibition of the γ -glutamylcysteine synthetase (GCS), the rate-limiting enzyme for the hepatic GSH synthesis, by alcohol, and an increased GSH consumption because of alcohol related oxidative stress further aggravates the GSH depletion. A direct conjugation of GSH with acetaldehyde was also observed in acute models [5].

This depletion has a double effect:

- it affects the antioxidant defense network (GSH de-novo synthesis cannot be compensated by other antioxidants), and
- it lowers the availability of GSH for regulatory processes, enzyme function and for hepatic detoxification. This mechanism is already stressed by the alcohol induction of some of the cytochrome P450 dependent enzymes, like CYP2E1.

The **hepatic detoxification** proceeds in two steps. In the first reaction the substrates are oxidized by various cytochrom-P450 depending enzymes. The first metabolites are often more toxic than the original substrates. In the second step, the metabolites are conjugated with hydrophilic modifiers (hippuric acid, glucuronic acid and glutathione) making them less toxic and water-soluble, hence they may be excreted by the kidneys (figure 2). A depletion of the hepatic GSH store affects the effective metabolism and excretion of these hepatotoxins contributing further to the hepatotoxicity of these substances.

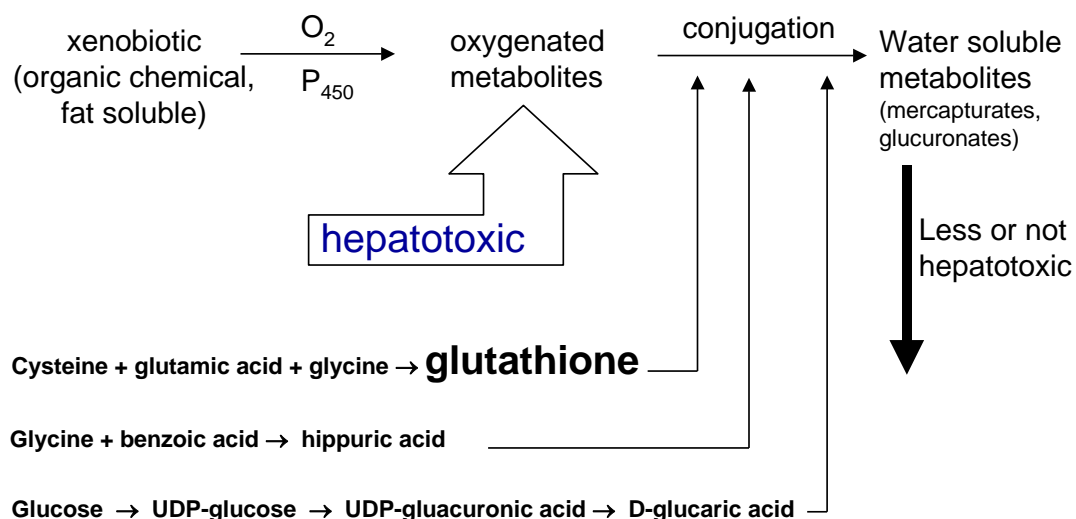


figure 2 Role of the P450 enzyme complex and the glutathione pool for the liver potential to effectively detoxify xenobiotics

Among the substrates of CYP2E1 are paracetamol and some anesthetics, but also caffeine, organic solvents like halogenated hydrocarbons (PCB and PBB) or aromatic hydrocarbons (benzene, toluene); pyridine, aniline, ethanol and acetaldehyde. The alcohol induction of CYP2E1 also has a toxicological impact. The activity of the drugs that are substrates for this enzyme may be decreased by an accelerated metabolism, and on the other hand toxic metabolites may be accumulated, with the potential to damage the liver.

Summary

Alcohol consumption leads to the formation of the toxic ethanol metabolite acetaldehyde and to increased oxidative stress, especially in the liver and the brain. Alcohol metabolism **increases the pro-oxidative pressure** by:

- generating free radicals and ROS which increase the pro-oxidative pressure on the anti-oxidant defense
- activating the metabolism of some drugs and chemicals increasing their hepatotoxicity

and **suppresses the intrahepatic GSH concentration** by:

- reducing the hepatic GSH concentration via an increased biliaric excretion.
- inhibiting the γ -glutamylcysteine synthetase activity
- increasing demand for GSH in the hepatic detoxification pathways

Antioxidants and GSH precursors were shown to protect the liver against alcohol-related damage, and the aggravation of the hepatotoxicity when alcohol and certain drugs, medications or chemicals are co-administered.

Restoring the glutathione homeostasis is essential because of the crucial role of GSH in the body as a regulatory factor, a co-factor for enzyme reactions and in the hepatic detoxification mechanism. Other antioxidants may restore the portion of GSH lost due to oxidation, but they cannot compensate for the lowered de-novo synthesis, or GSH excreted by the liver to other cells. Alterations in the liver GSH content may affect the systemic GSH homeostasis and affect the systemic antioxidant defense.

The administration of GSH precursors

- supports the hepatic GSH synthesis
- prevents liver cell damage
- supports the body to compensate for oxidative stress
- restores the essential GSH pool for other biological function where GSH is needed.

Cysteine Peptide is a natural food source of cysteine, the glutathione precursor.

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