6 Metabolism and Toxicity of Acetaldehyde

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Metabolism of Acetaldehyde

Acetaldehyde is the first oxidation product of ethanol, and under normal conditions it is oxidized further so rapidly that significant acetaldehyde concentrations can only be found in the liver. Aldehyde oxidase, xanthine oxidases, and aldehyde dehydrogenases are all capable of catalyzing aldehyde oxidation. The first two enzymes, however, have a broad substrate specificity and a low affinity for acetaldehyde ($K_m > 1 \text{mM}$), and consequently their involvement in the metabolism of acetaldehyde is insignificant (Lundquist 1970; Lindros 1978). The main enzyme oxidizing acetaldehyde is aldehyde dehydrogenase (ALDH), which catalyzes the oxidation of acetaldehyde in the presence of nicotinamide-adenine dinucleotide (NAD) as follows:

$$\text{CH}_3\text{CHO} + \text{NAD}^+ \xrightarrow{\text{ALDH}} \text{CH}_3\text{COO}^- + \text{NADH} + \text{H}^+ .$$

Most of the acetaldehyde formed from ethanol is subsequently oxidized to acetate in the liver.

Aldehyde Dehydrogenases

In 1949 Rucker described a bovine liver NAD-dependent ALDH with a broad substrate specificity for aldehydes. Human ALDH was isolated from the liver about 20 years later (Kraemer and Deitrich 1968; Blair and Bodley 1969). The enzyme has very low $K_m$ values and is sufficiently active (Kraemer and Deitrich 1968) to explain why under normal circumstances only low concentrations of acetaldehyde are found outside the liver (Jacobsen 1952; Kiessling 1962). ALDH activity has been detected in various subcellular fractions, such as mitochondria (Walkenstein and Weinhouse 1953; Glenn and Vanko 1959), cytoplasm (Lundquist et al. 1962; Büttner 1965; Deitrich 1966), and microsomes (Tietz et al. 1964; Tottmar et al. 1973; Korsten et al. 1975). ALDH from the mitochondrial matrix has a low $K_m$ for acetaldehyde and is therefore responsible for the oxidation of most of the acetaldehyde present in the liver during ethanol oxidation (Grunnet 1973; Marjanen 1973; Lindros et al. 1974; Parrilla et al. 1974). At higher acetaldehyde concentrations ($> 0.4 \text{mM}$) the increase
in acetaldehyde oxidation is due to the activity of extramitochondrial ALDHs (Lindros et al. 1974; Parrilla et al. 1974).

Several molecular forms of ALDH exist in both the cytoplasm and the mitochondria (Marjanen 1973). More than ten ALDH isoenzymes have been demonstrated in rat liver by isoelectric focusing (Weiner et al. 1974). Multiple isoenzymes have also been found in horse and human liver (Koivula 1975; Eckfeldt et al. 1976), but the exact number of human liver isoenzymes has not been fully established (Kraemer and Deitrich 1968; Blair and Bodley 1969; Greenfield and Pietruszko 1977; Harada et al. 1980; Agarwal et al. 1981). ALDH isoenzymes can be specifically induced with various agents. Treatment with phenobarbital results in a twofold increase in the ALDH activity of mouse liver homogenate (Deitrich 1971) and in a tenfold increase in the cytosolic ALDH of rats of a certain genotype (Deitrich 1971; Deitrich et al. 1972). The induced isoenzyme has been partially purified and its properties clarified (Koivula and Kouvusalo 1975). Another cytosolic ALDH isoenzyme can be induced in rats by several drugs, regardless of the animal's genotype (Roper et al. 1976).

**Deficient ALDH and Oriental Flushing**

These multiple molecular forms of ALDH have certain physiological implications. About 50% of Japanese exhibit elevated blood acetaldehyde concentrations following alcohol ingestion (Mizoi et al. 1979). As a consequence of acetaldehyde-induced catecholamine release these individuals develop facial flushing and tachycardia (Ijiri 1974; Mizoi et al. 1979; Inoue et al. 1980) following alcohol ingestion. The acetaldehyde-mediated flushing occurs in individuals in whom one of the ALDH isoenzymes is physiologically inactive because of a genetically determined defect in the synthesis of the enzyme molecule (Agarwal et al. 1981; Ikawa et al. 1983). A direct relationship also exists among Japanese between the intensity of the alcohol-related facial flushing and tachycardia and the capacity of their red cells to oxidize acetaldehyde (Inoue et al. 1980). The high incidence of ALDH isoenzyme deficiency in Oriental communities and the effects of alcohol drinking in subjects who lack this isoenzyme have undoubtedly affected the epidemiology of alcohol abuse in these communities. Indeed, very few Japanese alcoholics have the inactive ALDH enzyme (Harada et al. 1982).

**ALDH Inhibitors and the Disulfiram-Alcohol Reaction**

A number of chemical compounds, including several naturally occurring substances such as those found in the fungus *Coprinus atramentarius*, are known to cause sensitizing reactions in the presence of ethanol (Fisher 1945; Barkman and Perman 1963; Genest et al. 1968). Calcinated bone meal fed to laboratory rats has been found to contain cyanamide – a powerful ALDH inhibitor (Lindros et al. 1975; Marchner and Tottmar 1976a, b). In 1937, a sensitization reaction to alcohol caused by tetramethylthiuram mono- and disulfide was described and the suggestion made that these compounds might be of use in the treatment of alcoholism (Williams 1937).