
BIOCHEMICAL MECHANISMS OF AVERSION TO ALCOHOL

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In considering factors influencing alcohol intake, attention is often focused on those which may tend to increase consumption. However, protective factors also exist which are not just the opposite or the absence of risk factors, but which have a physical basis through producing unpleasant and ultimately aversive effects when alcohol is consumed.

Three main biochemically based routes to alcohol avoidance have been proposed; they each involve acetaldehyde, the first product of alcohol metabolism.

Acetaldehyde is produced in the liver cell cytoplasm under the action of alcohol dehydrogenase (ADH), or under some circumstances by microsomal enzymes (MEOS). It is converted to acetate by two forms of aldehyde dehydrogenase (ALDH); a predominantly cytoplasmic form with an intermediate K_m for acetaldehyde (ALDH1) and a predominantly mitochondrial form with a low K_m (or high affinity) (ALDH2). These ALDHs are found in other tissues as well as in the liver, but it appears that only very small amounts of acetaldehyde circulate from the liver to other tissues in normal circumstances.

Reactions to Alcohol

The best-explored example of unpleasant reactions to alcohol is the 'alcohol flush reaction' which occurs in many Japanese and other Asian subjects. This phenomenon was first systematically studied by Woolf (1,2), who found that small doses of alcohol (around 0.25 g/kg body weight) could produce objectively measurable changes in skin colour and temperature, and in pulse pressure, in many Asian and North American Indian subjects. Since then a number of other studies have been carried out on the prevalence of the flush reaction in different ethnic groups (eg. 3-5). There appears to be a gradient of flushing frequency across Asia, with the highest reported frequencies in Japan and China (70-80%) and lower frequencies in countries to the south. Europeans were reported in these studies to have flushing frequencies of around 5% but even in these subjects the flush reactions were less severe than in the Asians. Native North American groups may show a flushing frequency of up to 50%, but this varies among different groups (nations or tribes).

There is a difference in the incidence of alcohol problems between flushers and non-flushers, both within and between ethnic groups. Woolf (2) noted that alcohol consumption was inversely related to the intensity of the vasomotor response to alcohol in the American Indian subjects (in whom there was quite a wide range of alcohol intakes). This association has more recently been reinforced by studies which include ALDH phenotyping or genotyping as well as observation of reactions to test doses of alcohol (see below).

Genetics, Biochemistry and Molecular Biology of the Asian Alcohol Flush Reaction

The alcohol flush reaction in Asians is associated with higher than normal acetaldehyde concentrations during alcohol metabolism (6,7). This is due to inheritance of an inactive form of ALDH2 (8); the deficiency is a dominant characteristic (9). This is said to be because ALDH2 is a tetramer and even one affected subunit is enough to inactivate the enzyme molecule, but if the sub-units associate randomly then heterozygotes should have about 6% of the activity of the non-deficient subjects. There may be some difference in acetaldehyde metabolism between homozygous and heterozygous affected individuals, at least with low doses (0.1 g/kg) of alcohol (10), but further investigation of this aspect is needed.

Effect of ALDH2 Deficiency on Alcohol Use in Asia

There is good, but not perfect, concordance between ALDH2 deficiency and the alcohol flush reaction in Asians (11). Where subjects have been phenotyped (by enzyme activity measurements) or genotyped (by DNA techniques) for ALDH2 and the results related to prevalence of alcoholism, then a significant association between active enzyme and alcoholism has been found. For example, the prevalence of the inactive ALDH was much lower among Japanese alcoholics (4%) than in the general Japanese population (42%) (12) and similar results were obtained in Taiwan (12,13). The role of ALDH2 deficiency as a protective factor against alcoholism has been reviewed by Agarwal and Goedde (14).

Although few Asian alcoholics have ALDH2 deficiency, some do. It would be of interest to determine whether such subjects have high acetaldehyde levels during alcohol metabolism, if so how they tolerate them, and if not then what alternative routes of aldehyde metabolism are active. Also, alcohol-abusing subjects with inactive ALDH2 might be expected to suffer more commonly from liver disease and possibly other organ damage if acetaldehyde is involved in the pathogenesis of alcohol-related disease, as many authors have speculated.

Such a group could provide a useful natural experiment to test the importance of acetaldehyde. The best test of such a hypothesis, comparison of ALDH2 deficiency frequencies in alcoholics with and without liver disease, does not appear to have been carried out, but Yoshihara et al (15) reported that chronic alcoholics with and without ALDH2 deficiency did not differ in their histologically and biochemically assessed liver function. Naturally enough, there were only a very small number of ALDH2-deficient alcoholics, and no assessment of life-time alcohol intake in the two groups was made.

Other ALDH Deficiencies

Similar alcohol flush reactions, but caused by different mutations in either mitochondrial or cytosolic ALDHs, have been described in a small number of European subjects (16,17) and in some American native populations (2,18).

The nature, prevalence and effects of ALDH deficiency in Europeans have not been thoroughly investigated. Studies by Peters et al (16,17) have shown that some subjects have a deficiency of ALDH1, the mainly cytoplasmic form. Even within this group there is heterogeneity at the molecular level, with varying kinetic and electrophoretic characteristics of the enzyme between subjects. In one family a restriction fragment length polymorphism has been shown to be associated with the enzyme deficiency (16).

What the ALDH1 deficiencies do show, however, is that absence of the cytoplasmic, higher-K_m, enzyme is associated with adverse reactions to alcohol in humans so it presumably does have a role in normal alcohol metabolism.

The molecular basis of the flush reaction seen in some native American populations is even less well-documented. At first it was thought that these people had the Asian form of ALDH2 deficiency, inherited because of the original population of the Americas from north Asia, but it has been shown that some other mutation must be responsible (19).

There are also suggestions that variation in ALDH1 (the cytosolic form) occurs in Asians (20) and may affect the severity of the alcohol flush reaction. It does seem that even within Asian flushing subjects there are differences in the speed and degree of response to ethanol and acetaldehyde (21).

What can be said of the ALDH deficiencies is that they seem to have no adverse effects at the evolutionary level. They are present at high frequency in some very large populations and one can only speculate on whether this is due to neutrality of their effects or to balanced advantage and disadvantage.

Other Forms of Reaction to Alcohol

The reactions discussed so far seem to be based on classical 'inborn errors of metabolism'; for each affected subject there is a gene, an abnormal enzyme, and a metabolic effect. Other people seem to have reactions to alcohol of a different nature, probably related to allergic reactions.

Edfors-Lubs (22) conducted a survey of allergies in Swedish subjects around 1970. As well as asking about conditions such as asthma, hay fever or dermatitis, enquiry was made about the occurrence of 'alcohol allergy'. This included symptoms such as 'swelling or itching in the throat or eyes, severe headache, urticaria, nausea with vomiting or unconsciousness'. 4.5% of subjects reported such symptoms after taking alcohol and the rate of such reactions was about twice as great in subjects with classically allergic conditions. Unfortunately, although the subjects were all pairs of twins and the main allergic conditions were analysed for MZ and DZ pairwise concordance, this was not done for the so-called alcohol allergies. This study strongly suggests a mechanism of an immunological nature for at least some alcohol reactions in Europeans.

These reactions may perhaps be based on the formation of antibodies to acetaldehyde-modified proteins (23), but at present there is no proof that such a mechanism operates in humans.

Studies in Australia

Recent studies on the prevalence and effects of unpleasant reactions to alcohol in Sydney have shown that an appreciable proportion of the Australian population of European descent report such reactions, either every time they drink or sometimes.

Subjects were participants in a ten-year follow-up of a twin study of alcohol metabolism and susceptibility to intoxication (24). Among other questions about alcohol use they were asked whether they experienced unpleasant reactions after small amounts of alcohol, and of the first 200 subjects 5.5% answered that they always do (25). Moreover, these reacting subjects reported significantly lower values for customary alcohol intake, frequency and quantity of alcohol use, and alcohol use in the last seven days than the other subjects.

Our study has shown a prevalence of alcohol reactions in Europeans similar to that of other studies. It would be expected that reacting subjects avoid alcohol, but ours seems to be the first study to have shown this association in European subjects. Further work is in progress to characterise the biochemical basis of these reactions, which seem to be heterogeneous in their enzymology.

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