Research on Alcohol Metabolism Among Asians and Its Implications for Understanding Causes of Alcoholism

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Synopsis

Research into the causes of alcoholism is a relatively recent scientific endeavor. One area of study which could lead to better understanding of the disease is the possibility of a genetic predisposition to alcoholism. Recent work has demonstrated that people have varying complements of enzymes to metabolize alcohol. Current knowledge is examined about the influence of various ethanol metabolizing enzymes on alcohol consumption by Asians and members of other ethnic groups. The two principal enzymes involved in ethanol oxidative metabolism are alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH). ADH is responsible for the metabolism of ethanol to acetaldehyde. ALDH catalyzes the conversion of acetaldehyde to acetate. The different isozymes account for the diversity of alcohol metabolism among individuals.

An isozyme of ADH ($\beta_2\beta_2$) is found more frequently in Asians than in whites, and an ALDH isozyme ($ALDH_2$), although present in Asians, often is in an inactive form. The presence of an inactive form of $ALDH_2$ is thought to be responsible for an increase in acetaldehyde levels in the body. Acetaldehyde is considered responsible for the facial flushing reaction often observed among Asians who have consumed alcohol. A dysphoric reaction to alcohol, producing uncomfortable sensations, is believed to be a response to deter further consumption. Although the presence of an inactive $ALDH_2$ isozyme may serve as a deterrent to alcohol consumption, its presence does not fully explain the levels of alcohol consumption by those with the inactive isozyme. Other conditions, such as social pressure, and yet undetermined biological factors, may play a significant role in alcohol consumption.

THE PROBLEMS of alcohol abuse and alcoholism have been with mankind for as long as alcohol has been available to drink. Alcoholism has been viewed as a moral, or alternatively, as a character defect which could be resolved if the alcoholic or abuser truly wanted to stop using alcohol. The current view of alcoholism as a disease is supported by recent research (*1*).

Although research on causes of alcoholism is a relatively new field, major findings have occurred in the last 10 or 15 years. One important area of inquiry is the way alcohol is metabolized in the body. Of special interest is the finding that the metabolism of alcohol varies among people and that variations in metabolism are particularly noticeable for certain ethnic groups. Because alcohol abuse and alcoholism have been perceived as occurring less among Asians than the general white population, possible reasons for differences have generated considerable interest. Differences between Asians and whites in how they metabolize alcohol may help explain differences between the groups in alcohol consumption. Research on this question could lead to the identification of genetic predisposition to alcoholism among certain ethnic groups.

Routes of Ethanol Metabolism

Elimination of ethanol from the human body occurs through several pathways, including oxidative metabolism, and in pulmonary and renal excretion. Only about 10 percent of the body's ethanol intake is directly eliminated by the lungs and urine (*2*). By far the most important route of ethanol elimination is oxidative metabolism in the liver (see chart).

In each of the three mechanisms shown, ethanol is first oxidized to acetaldehyde by either alcohol dehydrogenase (ADH), the microsomal ethanol oxidizing system (MEOS), or catalase activity. Acetaldehyde is oxidized to acetate by aldehyde dehydro-

Table 1. Kinetic characterization of selected human ADH isozymes

Isozyme	Km alcohol (mM)	Km NAD (μM)	Optimum pH
β1β1	0.049	7.4	10.5
β2β2	0.94	180	8.5
γ1γ1	1.0	7.9	10.5
γ2γ2	0.63	8.7	10.5

SOURCE: Reference *16*. Km = Michaelis-Menton constant; mM = millimolar; μM = micromolar.

genase (ALDH). Acetate thus produced is converted to acetyl coenzyme A (CoA) and enters either the citric acid cycle, where it is ultimately oxidized to carbon dioxide and water, or is involved in other metabolic functions. Thus, the routes of oxidative metabolism differ only in the first step, the metabolism of ethanol to acetaldehyde. Considerable interest has focused on each of the pathways and the question of whether they have specialized roles to play in alcohol metabolism.

The principal pathway involved in the oxidation of ethanol to acetaldehyde is through alcohol dehydrogenase. Alcohol dehydrogenase is a NAD^+-dependent cytosolic enzyme principally in the liver but found to a lesser degree in the stomach, lungs, and kidneys. The enzyme is a zinc-containing, dimeric molecule, with a molecular weight of 80,000, which catalyzes the oxidation of ethanol by the reaction

$$CH_3CH_2OH + NAD^+ \rightarrow CH_3CHO + NADH + H^+$$

Note that oxidation of alcohol results in the accumulation of NADH. As the reaction proceeds, the available NAD^+ decreases and the continued oxidation of ethanol depends on the reoxidation of NADH to NAD^+. The reoxidation of NADH can become a rate-limiting step in the metabolism of alcohol. In addition, the change in ratio of available NAD^+ to NADH can have a profound influence on other metabolic functions of the liver (*3,4*).

A second important pathway in the metabolism of ethanol is MEOS. MEOS, found in the smooth endoplasmic reticulum, has been suggested as responsible for the metabolism of 10 to 20 percent of alcohol in the liver (*5,6*). MEOS is a NADPH-dependent system that catalyzes the metabolism of ethanol by the reaction

$$CH_3CH_2OH + NADPH + H^+ + O_2 \rightarrow CH_3CHO + NADP^+ + 2H_2O$$

Note that the activity of MEOS increases after chronic consumption of ethanol. The increase results from induction of a unique P-450 isozyme with great propensity for alcohol oxidation (*7*). Thus, the importance of the system in alcohol metabolism may be greater at high concentrations of alcohol.

The third pathway involved in ethanol metabolism is catalyzation by catalase in the reaction

$$CH_3CH_2OH + H_2O_2 \rightarrow CH_3CHO + 2H_2O$$

The amount of ethanol metabolized by this pathway is thought to be only 1 or 2 percent of the alcohol in the body and is thus insignificant, relative to the other pathways.

Each of the pathways metabolizes ethanol to acetaldehyde. Once produced, acetaldehyde is metabolized to acetate by aldehyde dehydrogenase in the reaction

$$CH_3CHO + NAD^+ + H_2O \rightarrow CH_3COOH + NADH + H^+$$

While the enzymes responsible for the oxidation of alcohol are mainly in the liver, those responsible for oxidation of acetaldehyde are throughout the body. However, because the acetaldehyde level found in blood is low, even with a high blood alcohol level, the principal site for acetaldehyde metabolism must be at the same location as the oxidation of ethanol, that is, in the liver (*8*).

A nonoxidative pathway for alcohol metabolism is known, which results in the formation from ethanol of fatty acid ethyl esters (FAEE). The formation of FAEEs is catalyzed by fatty acid ester synthase. There are two forms of the enzyme (major and minor), which are found primarily in the brain, pancreas, and heart. Note that those organs do not have the capacity to oxidize ethanol to acetate through alcohol dehydrogenase and aldehyde dehydrogenase. Thus, this system provides an alternative pathway for alcohol metabolism (*9–11*).

Although everyone has the described fundamental pathways for ethanol metabolism, the enzymes responsible for the metabolism can be in different forms, called isozymes, which result from the substitution of one or more amino acids in the polypeptide chain. Both alcohol dehydrogenase and aldehyde dehydrogenase exist as isozymes with

different catalytic characteristics. The presence of multiple forms of the enzymes results in rates of alcohol metabolism that vary among persons. The difference in the complement of enzymes offers a possible source for a marker for susceptibility to particular alcohol problems, and potentially even to alcoholism itself.

Isozymes of Alcohol Dehydrogenase

In humans, alcohol dehydrogenase exists as a highly polymorphic dimeric enzyme. Five different polypeptide subunits (α, β, γ, π, and χ) combine in various dimeric combinations to complete an active enzyme molecule. Studies of the enzyme, with respect to its electrophoretic mobility, substrate specificity, stability, and inhibition characteristics, have placed it in three classes (*12–15*):

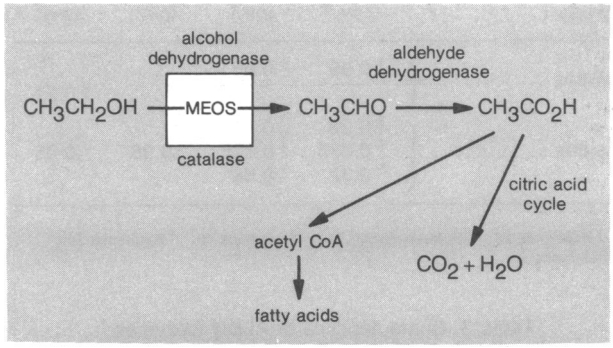
Class I: homo and heterodimers of α, β, and γ subunits
Class II: dimers of π
Class III: dimers of χ

Each subunit in ADH is encoded for by a specific gene, with the gene serving as the blueprint to specify which amino acids will be contained in the subunit. Thus the α, β, γ, π and χ subunits are encoded for by the ADH_1–ADH_5 genes, respectively. In addition, the ADH_2 and ADH_3 loci exhibit polymorphism with the presence of ADH_2^1, ADH_2^2, ADH_2^3, ADH_3^1 and ADH_3^2 alleles coding for β_1, β_2, β_3, γ_1, and γ_2 subunits, respectively. The occurrence of such polymorphism creates the potential for the presence of a wide range of isozymes in different persons.

Table 1 shows some of the variations in kinetic parameters between selected isozymes. The kinetic characteristics for the homodimer β isozymes exhibit a wide range of values with respect to their affinity for binding to substrate, as represented by the Michaelis-Menton constant (Km), ranging by almost two orders of magnitude. Because each of the isozymes has different kinetic properties, a wide variation in ethanol metabolism is possible, depending on the isozymes present (*6, 16–18*). Persons with different isozymes may be expected to show different characteristics with respect to their ability to metabolize ethanol. The possible significance of genetic polymorphism in ADH has been suggested in studies of the genetic makeup of whites and Asians with respect to ADH.

Stamatoyannopoulos and coworkers (*19*), analyzed 40 liver samples obtained at autopsy from

Routes of ethanol oxidative metabolism in humans



Japanese subjects for ADH isozymes. They showed that 85 percent of the specimens were either homozygous or heterozygous for the ADH_2^2 allele, while 15 percent of the subjects were homozygous for the ADH_2^1 allele. Other work has included expanded studies to determine the frequency of other alleles in Japanese (*20,21*) and white subjects (*22–24*). This work is summarized in table 2. In addition to the β_1 and β_2 homodimers, a third homodimer ($\beta_3\beta_3$) has been identified (*18*). The isozyme is found with greater frequency (15 percent) in blacks than in either Asians or whites (5 percent). The significance of this isozyme, if any, to the black population has yet to be determined.

The interest generated by these data is obvious when the frequency of alleles in Japanese subjects is compared with the presence of the same alleles in white subjects. As table 2 shows, the ADH_2^2 allele occurs with much greater frequency in Asian subjects than in whites, while the situation is reversed with regard to ADH_2^1 allele. Because the ADH_2^1 allele codes for the β_1 subunit, and ADH_2^2 codes for the β_2 subunit, the difference in kinetics of the $\beta_1\beta_1$ and $\beta_2\beta_2$ isozymes may play a role in how whites and Asians metabolize alcohol. Table 1 shows that the $\beta_1\beta_1$ isozyme has a smaller Km for ethanol (0.049 millimolar [mM]) than the $\beta_2\beta_2$ isozyme (0.94 mM), as well as for NAD^+ (7.4 and 180 mM, respectively). In addition, the specific activity of the $\beta_2\beta_2$ isozyme is several times higher than that of the $\beta_1\beta_1$ isozyme (*25*). Based on the characteristics of the $\beta_2\beta_2$ isozyme, it would be expected that Asians who have this isozyme would metabolize ethanol at a greater rate than persons without the isozyme.

If this were to occur, the level of acetaldehyde might increase more rapidly in Asians than in whites. The presence of high levels of acetaldehyde has been implicated with dysphoric reaction to alcohol, including facial flushing commonly observed among Asians (*26*). The dysphoric reaction

Table 2. Frequency of ADH alleles in whites and Asians

Ethnicity	ADH_2[1]	ADH_2[2]	ADH_3[1]	ADH_3[2]
Whites	[1] 0.95	[1] 0.05	...	...
	...	...	...	[2] 0.37
Asians	[3] 0.39	[3] 0.61	...	...
	[4] 0.375	[4] 0.625	[4] 0.95	[4] 0.05
	[5] 0.32	[5] 0.68	...	...

[1] Reference 22. [2] References 23, 24. [3] Reference 19. [4] Reference 20. [5] Reference 21.

Table 3. Characteristics of ALDH isozymes [1]

Isozyme	Km acetaldehyde (μM)	Km NAD+ (μM)	Subcellular localization
$ALDH_1$	100	10	cytosol
$ALDH_2$	1	100	mitochondria
$ALDH_3$	1000	50	cytosol
$ALDH_4$	1000	50	cytosol

[1] References 31–34. Km = Michaelis-Menton constant; μM = micromolar.

is generally characterized by such effects as reddening of the face and skin, increased heart rate, warmth, sleepiness, dizziness, and light headedness. Because of its unpleasant feelings, the reaction is generally thought to be a deterrent to drinking. Thus, if the metabolism of alcohol in Asians is increased because of the presence of specific isozymes that increase the metabolism of alcohol, the alleles coding for the various isozymes might serve as markers for the development of alcoholism.

Although differences in the metabolism of alcohol by various isozymes have been well established in vitro, corresponding differences have not been established in vivo for those of different ethnic backgrounds who are subject to flushing and those who are not (*27–30*). Thus, no clear correlation yet exists between the presence of specific ADH isozymes and the in vivo metabolism of alcohol in subjects with different ethnic backgrounds. Therefore, the use of ADH alleles as markers of potential alcohol abuse has not been verified.

Isozymes of Aldehyde Dehydrogenase

Human aldehyde dehydrogenase (ALDH) is a tetrameric enzyme with a molecular weight of approximately 230,000. There are at least four different ALDH isozymes found in the liver, which are designated $ALDH_1$, $ALDH_2$, $ALDH_3$, and $ALDH_4$. Each can be differentiated with respect to kinetic properties, localization within the cell, tissue distribution, and electrophoretic mobility. Table 3 summarizes some important characteristics of the ALDH isozymes (*31–34*). All the isozymes may be found in the cytosol, excepting $ALDH_2$, which is located in the mitochondria. The mitochondrial ALDH has a low Km (high affinity) for alcohol (1 micromolar [μM]), which distinguishes if from the other ALDH isozymes which have much greater Km for ethanol. After administration of ethanol, the acetaldehyde level in the liver does not generally exceed 100 μM(*35*). Because $ALDH_2$ is the only isozyme with a Km not exceeding the in vivo acetaldehyde level in the liver, it is probably the principal enzyme involved in acetaldehyde metabolism.

Studies of various ALDH isozymes in Asian and white populations have found (*20, 35–38*) that whites have two predominant ALDH isozymes, $ALDH_1$ and $ALDH_2$. The isozymes were present in 100 percent of those tested. However, about 50 percent of the Asian subjects tested did not have the active $ALDH_2$ isozyme. Further work on subjects deficient in the active $ALDH_2$ isozyme has shown that the enzyme is present, but not in the active form. Thus, a null-variant $ALDH_2$ has been found in those lacking the active form. The variant was found in about 50 percent of Japanese, 35 percent of Chinese, and 40 percent of Vietnamese and Indonesians tested (*39*). Additional work on the inactive variant has shown it to result from the substitution of lysine for glutamine in the protein (*40*).

Discussion

The absence of an active $ALDH_2$ isozyme in Asians is significant because the isozyme may provide a deterrent to abusive alcohol consumption and possibly serve as a marker for potential development of alcoholism. Increased levels of acetaldehyde can, in theory, occur when alochol is more rapidly metabolized to acetaldehyde or when acetaldehyde is metabolized more slowly than normal. As discussed, the former situation is not thought to occur in vivo. However, the later condition, where acetaldehyde levels increase because of decreased metabolism of the compound, is believed to be a viable, in vivo condition brought about in some Asians by the presence of an inactive form of $ALDH_2$.

The accumulation of acetaldehyde evokes the facial flushing reaction, producing, as described, uncomfortable sensations when alcohol is consumed. Such a reaction to the consumption of

alcohol is thought to act as a negative stimulus for further alcohol consumption. The occurrence of alcoholism in Asians historically has been viewed as less prevalent than in the general population (*41,42*). A possible explanation is that the absence of the principal acetaldehyde metabolizing enzyme ($ALDH_2$) among Asians increases the level of acetaldehyde in a substantial segment of the population, eliciting the dysphoric reaction, which acts as a deterrent to further alcohol consumption. Although backed by data, the actual story may be more complex than simply the absence of the active form of $ALDH_2$. Some recent work (*26*) suggested that the rate of alcohol abuse in young Chinese and Japanese women may be increasing, even though the flushing reaction appears to be present. A possible explanation for this seeming paradox is the phenomenon of drinking through, an unproven theory that proposes that some people can drink alcohol rapidly enough to negate the adverse effects of the facial flushing reaction. The reasons are unknown, but one possibility is that it may be a pharmacologic response, as for example euphoria produced by alcohol, which offsets the effects of the dysphoric reaction.

The ability to circumvent the deterrent effect of the dysphoric reaction may help to explain some apparent increases in alcohol consumption among Asians who continue to drink despite their flushing reactions. Nonbiological factors as well may contribute to alcoholism and help to determine why some people are at risk, while others are not. Such factors and the complex interaction of such variables will require comprehensive study. Although an inactive form of $ALDH_2$ present in Asians may discourage drinking by many, others will drink despite their flushing reaction, perhaps in response to social pressures.

The knowledge that biological and genetic differences exist among ethnic groups is a start on a study of the causes of alcoholism. That these genetic factors alone do not at this time fully explain the causes of alcoholism suggests that other factors, including psychological and social conditions, should be studied with respect to genetic variables before we are able to predict with confidence why, and in whom, alcoholism is likely to develop.

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