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Research advances in ethanol metabolism

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Summary
The pharmacokinetics of alcohol determines the time course of alcohol concentration in blood after the ingestion of an alcoholic beverage and the degree of exposure of organs to its effects. The interplay between the kinetics of absorption, distribution and elimination is thus important in determining the pharmacodynamic responses to alcohol. There is a large degree of variability in alcohol absorption, distribution and metabolism, as a result of both genetic and environmental factors. The between-individual variation in alcohol metabolic rates is, in part due to allelic variants of the genes encoding the alcohol metabolizing enzymes, alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH). This review summarizes recent developments in the investigation of the following influences on alcohol elimination rate: gender, body composition and lean body mass, liver volume, food and food composition, ethnicity, and genetic polymorphisms in alcohol metabolizing enzymes as well as in the promoter regions of the genes for these enzymes. Evaluation of the factors regulating the rates of alcohol and acetaldehyde metabolism, both genetic and environmental, will help not only to explain the risk for development of alcoholism, but also the risk for development of alcohol-related organ damage and developmental problems. © 2001 Éditions scientifiques et médicales Elsevier SAS

alcohol dehydrogenase / aldehyde dehydrogenase / ethanol metabolism / ethnic differences / gender differences / genetic polymorphism / pharmacokinetics

Résumé – État de la recherche sur le métabolisme de l'éthanol.
La pharmacocinétique de l'alcool détermine l'évolution dans le temps de la concentration d'alcool dans le sang après ingestion d'une boisson alcoolisée, ainsi que le degré d'exposition des organes à ses effets. L'interaction entre la cinétique de l'absorption, de la distribution et de l'élimination est donc importante dans la détermination des réponses pharmacodynamiques à l'alcool. Il existe un important degré de variabilité, qui résulte de facteurs à la fois environnementaux et génétiques, au niveau de l'absorption, de la distribution et du métabolisme. La variation interindividuelle des vitesses de métabolisme de l'éthanol est en partie due à des variants alléliques des gènes codant pour les enzymes métabolisant l'alcool, l'alcool deshydrogénase (ADH) et l'aldéhyde deshydrogénase (ALDH). Cette revue résume les derniers progrès dans l'investigation des influences suivantes sur le taux d'élimination de l'alcool : le sexe, la composition corporelle et la masse corporelle maigre, le volume du foie, l'alimentation et sa composition, les facteurs ethniques, ainsi que les polymorphismes génétiques au niveau des enzymes métabolisant l'alcool, de même qu'au niveau des promoteurs des gènes codant pour ces enzymes. L'évaluation des facteurs, aussi bien génétiques qu'environnementaux, qui régulent les vitesses de métabolisme de l'alcool et de l'acétaldéhyde, va aider non seulement à expliquer le risque de développement de l'alcoolisme, mais également le risque de développement des dommages causés par l'alcool sur les organes et les problèmes développementaux. © 2001 Éditions scientifiques et médicales Elsevier SAS

alcool deshydrogénase / aldéhyde deshydrogénase / différences ethniques / différences sexuelles / métabolisme de l'éthanol / pharmacocinétique / polymorphisme génétique

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The pharmacokinetics of alcohol determines the time course of alcohol concentration in blood after the ingestion of an alcoholic beverage and the degree of exposure of organs to its effects. The interplay between the kinetics of absorption, distribution and elimination is thus important in determining the pharmacodynamic responses to alcohol.

After oral ingestion, alcohol is almost completely absorbed, primarily from the small intestine, by passive diffusion [1, 2]. Alcohol, ingested on an empty stomach, is very rapidly absorbed with peak concentrations occurring between 30 to 90 minutes. The rate of alcohol absorption after oral administration is greatly influenced by the nature and concentration of the alcoholic beverage [2–4], the rate of ingestion [4], the fed or fasted state [5], the nature and composition of food [5], the rate of gastric emptying [6, 7], as well as other genetic and environmental factors.

The distribution of alcohol throughout the body is largely governed by the water content of various organs and tissues, especially at equilibrium, because ethanol is a small, polar, completely water soluble molecule. The volume of distribution of alcohol is comparable to total body water [1, 8]. No plasma protein binding has been reported for alcohol.

Elimination of alcohol occurs primarily through metabolism, with small fractions of the administered dose being excreted in the breath (0.7%), sweat (0.1%), and urine (0.3%) [1]. Alcohol elimination occurs mainly via hepatic oxidation and is governed by the catalytic properties of the alcohol metabolizing enzymes, alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH). The microsomal ethanol oxidizing system (MEOS) also contributes to alcohol metabolism and alcohol-related cytotoxicity in specific circumstances [9].

Alcohol metabolic rates show a considerable degree of inter-individual and ethnic variability, in part due to allelic variants of the genes encoding ADH and ALDH producing functionally different isozymes. The functional polymorphisms of the *ADH1B* and *ALDH2* genes have been shown to increase the variance in alcohol metabolism among individuals. Additionally, a multitude of environmental factors can influence the metabolic regulation of alcohol metabolism, which results in a large 3- to 4-fold variance in the alcohol elimination rate in humans [10].

Alcohol dehydrogenase

There are multiple molecular forms of human ADH, which is a dimeric molecule. At present, seven human ADH genes and subunits have been identified. The genes were initially named according to the sequence of their discovery [11, 12]. There is now a new nomenclature that organizes the seven genes into five classes based on amino acid sequence alignments, catalytic properties and patterns of tissue-specific expression [13]. *Table I* gives the new and previous nomenclature for ADH genes and isozymes and the relative catalytic efficiency for ethanol. The new nomenclature for genes and the shorthand Greek subunit nomenclature will be used in this review.

Within the Class I isozyme subunit forms, there is random recombination of the protein subunits. Therefore, homo- and heterodimeric enzyme forms, viz., $\alpha\alpha$, $\alpha\beta$, $\beta\beta$, $\alpha\gamma$, $\beta\gamma$ and $\gamma\gamma$ are found. All the Class I ADHs are active with ethanol as substrate and are inhibited by pyrazole derivatives [11]. These six different ADH1 subunits that form heterodimers have about 94% sequence identity. Polymorphism occurs at the *ADH1B* and *ADH1C* loci, resulting in the β_1, β_2, and β_3, and the γ_1 and γ_2 subunits, respectively. The *ADH1B* alleles appear with different frequencies in different racial groups, with the β_1 predominating in Caucasian and African-American populations, β_2 predominating in the Japanese and Chinese, and β_3 appearing in 25% of the African-American population. With respect to the *ADH1C* polymorphism, the two γ alleles appear with approximately equal frequencies in Caucasian populations, but γ_1 predominates in Japanese, Chinese and African-American populations [10, 14].

The human ADH genes are differentially expressed in different tissues, which is a very important feature for the physiological consequences of alcohol metabolism in specific cells and tissues [11, 12]. Liver contains a large amount of ADH (about 3% of soluble protein) and expresses the widest number of different isozymes. *ADH2* (π-ADH) is solely expressed in liver. Only *ADH4* (σ-ADH) is not highly expressed in liver. *ADH3* (χ-ADH) is ubiquitously expressed in human tissues. *ADH1C*, *ADH2*, *ADH3* and *ADH4* are expressed in gastrointestinal tissues. The question of expression of *ADH5* and its role in ethanol metabolism needs further examination. Also, the expression of ADHs in other tissues such as skeletal muscle, and the quantitative significance of muscle ADH metabolism (because of muscle mass), is yet to be determined.

In addition to ethanol, alcohol dehygrogenases also oxidize several "physiological" alcohols with high catalytic efficiency including retinol, ω-hydroxy fatty acids, hydroxy steroids, and hydroxy derivatives of dopamine and epinephrine metabolites [11, 15]. Oxidation of these alcohols can be inhibited by ethanol. Hence the role of ethanol substrate competition is an important issue in alcohol-related toxicology.

Another important question is the regional expression of ADHs in brain and the potential role in the localized generation of acetaldehyde, which may have CNS stimulant as well as sedative/hypnotic effects [16, 17]. As acetaldehyde levels in the systemic circulation are usually very low, it is doubtful if peripheral acetaldehyde would reach the brain. On the other hand, a recent study has shown that the brain can oxidize ethanol to acetaldehyde,

Table I. Nomenclature for ADH genes and enzyme subunits.

ADH Class	*New Gene Nomenclature*	*Former Gene Nomenclature*	*Enzyme Subunit Nomenclature*	*Ethanol Catalytic Efficiency*
I	*ADH1A*	*ADH1*	α	Low
I	*ADH1B*1*	*ADH2*1*	β_1	High
I	*ADH1B*2*	*ADH2*2*	β_2	High
I	*ADH1B*3*	*ADH2*3*	β_3	Low
I	*ADH1C*1*	*ADH3*1*	γ_1	High
I	*ADH1C*2*	*ADH3*2*	γ_2	High
II	*ADH2*	*ADH4*	π	Low
III	*ADH3*	*ADH5*	χ	Very Low
IV	*ADH4*	*ADH7*	σ	High
V	*ADH5*	*ADH6*	Not identified	Not identified

although the enzyme systems that affect this transformation remain unsettled [18].

The proximal promoter regions for *ADH1-5* have been mapped [12]. *ADH1* and *ADH2* promoters have a high level of expression in liver. The *ADH3* promoter is characteristic of "housekeeping genes" with wide expression. There is a very interesting promoter polymorphism in *ADH2* that leads to a two-fold difference in promoter expression assays [19]. It is likely that there are more polymorphisms that influence ADH gene expression and more research is needed on the regulation of expression of the gene family, especially in developmental expression and cell-specific expression.

Aldehyde dehydrogenase

There are also multiple molecular forms of aldehyde dehydrogenase (ALDH) in human liver, but only class I and class II isozymes, encoded by *ALDH1* (or *ALDH1A1* in the new nomenclature) [20] and *ALDH2*, respectively, are thought to be involved in acetaldehyde oxidation. ALDH1 is the cytosolic ALDH enzyme ubiquitously distributed in tissues including brain. It exhibits relatively low catalytic efficiency (k_{cat}/K_m) for acetaldehyde oxidation. ALDH2 is the mitochondrial enzyme that is highly expressed in liver and stomach [21]. It exhibits high catalytic efficiency for acetaldehyde oxidation and is primarily responsible for acetaldehyde oxidation in vivo.

A very predominant variant of *ALDH2* has been detected in about half of the Japanese and Chinese populations and characterized biochemically. It exhibits virtually no acetaldehyde oxidizing activity in vitro, and represents the "deficient" phenotype seen in Asian populations [22]. Individuals who are heterozygous or homozygous for *ALDH2*2* show the characteristic alcohol sensitivity reaction (facial flushing, increased skin temperature and heart rate). This is discussed in a later section of this review.

Pharmacokinetic models for alcohol

Several pharmacokinetic models for alcohol have been published. These models quantify the time course of alcohol concentrations in the body using compartments with combinations of zero-order and first-order rate constants along with saturable (Michaelis-Menten) kinetics to characterize the processes of absorption, distribution and metabolism [2, 23 – 27]. Compartmental pharmacokinetic models typically do not provide a great degree of physiological validity to the volumes and rate constants. On the other hand, physiologically-based pharmacokinetic (PBPK) models, as the name implies, quantitatively characterize the pharmacokinetics in terms of physiologically-relevant compartments and relevant flow rates and volumes [28, 29].

PBPK models typically employ a series of mass balance equations to predict the concentration of the drug in various physiological compartments over time for a given input regimen [30]. Current published models use estimates of overall metabolic capacities and rate constants (V_{max} and K_m) [31]. For ethanol metabolism, individual K_m constants are known for all alcohol and aldehyde dehydrogenase isozymes [11, 32]. Further development of more complete PBPK models that allow prediction of alcohol concentrations in different tissues (such as brain and skeletal muscle) will require determination of the content of individual alcohol metabolizing isozymes in these tissues (compartments) to evaluate V_{max} values. Thus there is a need for further research in this area. PBPK models can be scaled among species, and provide a comprehensive approach to the evaluation and estimation of specific factors that influence alcohol metabolism [29, 31, 33, 34].

Determinants of alcohol metabolism in humans

There are several factors that affect alcohol metabolism, including alcohol intake, food, other drugs, gender, body weight, body composition, as well as the genetic determinants of the alcohol metabolizing enzymes described above. The following sections will focus on recent developments in the investigation of the following influences on alcohol elimination rate: gender, body composition and lean body mass, liver volume, food and food composition, ethnicity, and genetic polymorphisms in alcohol metabolizing enzymes as well as the promoter regions of the genes for these enzymes.

Influence of gender and body composition

Women and men may differ in the absorption, distribution and metabolism of alcohol. Generally, women have a lower proportion of body water than men of similar body weight, so that women achieve higher concentrations of alcohol in the blood after drinking equivalent amounts of alcohol [35]. Other studies have reported that differences in peak concentrations following equivalent low doses of alcohol administered to men and women were due to differences in first-pass metabolism of alcohol in the gastrointestinal tract, which was significantly correlated with gastric ADH activity [36–38]. Some investigators concluded that females have lower gastric alcohol dehydrogenase activity resulting in a lower degree of first-pass metabolism and therefore in higher systemic concentrations compared to males. However, other studies have demonstrated no differences in the first-pass metabolism of alcohol between males and females [39], and first-pass metabolism is evident only with the ingestion of relatively low doses of ethanol and when gastric emptying is slow [40].

Gender differences in the elimination of alcohol have also been reported. This may be partly due to the differences in blood alcohol concentrations achieved following alcohol consumption and the nonlinear nature of alcohol pharmacokinetics, particularly at higher doses [25]. Thomasson et al., [41] have found a higher β_{60} (pseudo-zero-order disappearance rate calculated over 60 min) in women as compared with men with comparable ADH2 genotype following oral administration of alcohol to achieve similar peak concentrations. The authors speculate that these differences could be due to differences in daily alcohol intake, influence of sex hormones (estrogen and testosterone), or differences in liver size relative to body weight or lean body mass.

Because alcohol is almost completely metabolized by the liver, gender differences in liver size might explain the differences in alcohol elimination. To test this hypothesis, Kwo et al. [42], measured alcohol elimination rates using the breath alcohol clamp [43] in healthy male and female social drinkers. They also measured the liver volume of these subjects by computed tomography. Results revealed no gender difference in alcohol elimination rate (AER) between males and females when expresses in grams of ethanol eliminated per hour, and only a 4% higher mean liver volume in males than in females. However, the AER per unit lean body mass was 33% higher in females, and liver volume per unit lean body mass was 38% higher in females. Higher liver weight per unit body weight in females has also been seen in an autopsy study [44]. Thus, the higher liver volume per unit lean body mass in females might explain the equivalent AERs seen during clamping at 50 mg% [45].

Other gender-related studies, evaluating the effect of menstrual cycle and of oral contraceptives on alcohol pharmacokinetics in women were reviewed recently [35]. The authors concluded that the menstrual cycle had no effect on alcohol pharmacokinetics, and could not account for gender differences in alcohol disappearance rates in women. Studies of the effect of sex hormones and oral contraceptives on alcohol pharmacokinetics in women have been less conclusive, with some studies showing that women taking oral contraceptives have lower peak BACs and slower elimination as compared with women not taking oral contraceptives [35]. Other studies have shown no effect of oral contraceptives on alcohol pharmacokinetics. Further elucidation of the factors associated with gender differences in metabolism especially in relation to first-pass metabolism, as well as the greater vulnerability of women to alcohol-induced liver disease, is needed.

Influence of food and food composition

Most studies evaluating the effect of food and food composition on alcohol pharmacokinetics have shown a decrease in the rate of absorption and peak alcohol levels [5, 46–49]. This is probably due to food-induced delays in gastric emptying [50, 51]. Most of these studies were conducted using oral alcohol administration and therefore were unable to distinguish between the influence of food on the absorption (and bioavailability) and on the metabolism of alcohol. Breath alcohol clamping utilizes intravenous infusions of alcohol to achieve and maintain breath alcohol concentrations (BrAC) at a target level for prolonged periods of time [31, 43]. During this steady-state, the alcohol infusion rate is a direct measure of the alcohol elimination rate. Studies using the BrAC clamp thus allow the evaluation of the influence of food on alcohol elimination rates (AER) without the confounding effect on alcohol absorption.

Two studies have been conducted to evaluate the effect of food and food composition on AER in healthy men and women, using alcohol clamping at 50 mg%. Results show a 25–30% increase in AER following consumption of a $\sim$ 530-calorie meal [52, 53]. The increase is similar for high-fat, high-carbohydrate and high-protein containing meals. Other studies using alcohol infusions have

shown similar results [46, 48]. Probable mechanisms for this increased alcohol elimination include food-induced increases in liver blood flow and increases in activity of ADH, perhaps through perturbation of the NAD^+/NADH ratio in the liver. However, further studies are needed to understand the mechanisms underlying this food-induced change in alcohol elimination.

Influence of ethnicity and genetic polymorphisms

Several studies have examined ethnic differences in alcohol metabolism and the influence of the ADH and ALDH2 genotypes, due to the resultant functional polymorphisms of the alcohol metabolizing enzymes ADH and ALDH2, and the differences in the prevalence of the polymorphic alleles in different ethnic populations. The isozymes encoded by the polymorphic alleles have very different catalytic properties in vitro [11, 32], and would be expected to influence individual pharmacokinetics of alcohol.

The influence of the *ADH1B* polymorphisms on alcohol pharmacokinetics was studied in 112 African-American subjects, selected by genotype [41]. Results showed a higher β_{60} for subjects who had β_3-containing ADH isozymes compared to those with β_1-ADH isozymes. The *ADH1B*3* allele also has been shown to be protective against alcohol-related birth defects among African-Americans [54]. The authors of this study speculated that this protective effect could be related to more efficient metabolism of alcohol particularly at high blood alcohol concentrations (BAC). A recent preliminary study also suggests that mothers who have the *ADH1B*3* allele also drink less than those who do not possess the allele [55]. A study in Native Americans also showed that subjects with *ADH1B*3* alleles had a trend toward higher alcohol elimination rates than subjects with *ADH1B*1* [56]. *ADH1B*3* occurs at a fairly low frequency ($\sim$ 7%) in this ethnic group. Overall, the study by Wall et al. [56] and others [57–59] have shown that alcohol elimination rates in Native Americans were higher than those reported in Caucasians.

Functional polymorphism of *ALDH2* results in a variant allele (*ALDH2*2*) that encodes a low-activity form of the mitochondrial ALDH2 enzyme. This has been shown to have a protective effect against the development of alcoholism in Asian populations [60–65]. A recent study also investigated alcohol and acetaldehyde pharmacokinetics in Asian subjects with different ALDH2 allelotypes and explored the correlation between alcohol and acetaldehyde blood levels and physiological/psychological responses to alcohol. Homozygous *ALDH2*2* individuals showed a substantial increase in blood alcohol levels and a higher and prolonged increase in blood acetaldehyde levels as compared with the homozygous *ALDH2*1* individuals and the heterozygous *ALDH2*1/*2* subjects [66]. These findings are consistent with product inhibition of the ADH enzyme by acetaldehyde and explain the hypersensitivity to alcohol as well as the strong protective effect against heavy drinking and alcoholism in these individuals who are homozygous for *ALDH2*2*. Progress in this field to characterize differences in alcohol metabolism in subjects exhibiting different polymorphic genotypes has been substantial. Further studies are needed to further evaluate these genetic determinants of alcohol metabolism, particularly differences arising from the polymorphisms of *ADH1C* and *ALDH2*.

Recent studies have characterized the genetic polymorphisms in different races and ethnic groups, but large differences in alcohol elimination rates still exist between individuals within different ethnic groups. Of potential significance in this regard is the recent discovery of polymorphisms in the promoter regions of the ALDH2 gene [67, 68] and the ADH2 gene [19]. Studies are needed to evaluate the influence of these promoter polymorphisms on the activity of ADH and ALDH in individuals and on alcohol levels and elimination rates in individuals, as well as on the physiological response to alcohol consumption and alcoholism.

Studies in monozygotic and dizygotic twins have shown that the heritability of alcohol elimination rate (i.e., genetic component of variance) is about 50% [69, 70]. Further evaluation of the factors regulating the rates of alcohol and acetaldehyde metabolism, both genetic and environmental, will help not only to explain the risk for development of alcoholism, but also the risk for development of alcohol-related organ damage and developmental problems.

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