11 Genetic Aspects of Alcohol Metabolism

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CONTENTS

11.1 INTRODUCTION

Ethanol (also referred to as alcohol in this chapter) is probably the most widely investigated drug in the world, not only because of its ubiquitous use and its widespread abuse, but also because of its unique pharmacological properties. Following administration, systemic concentrations of alcohol are a consequence of the absorption and metabolism of alcohol, which display unique characteristics and demonstrate substantial interindividual variability.[1] As the pharmacological effects of alcohol depend on its systemic concentrations, variability in the pharmacokinetics of alcohol can have a significant impact on its pharmacodynamic effects. Following oral ingestion, alcohol is absorbed by passive diffusion, primarily from the small intestine.[2,3] The rate of absorption depends on several factors, both genetic and environmental, and is highly variable.[1] Some of these factors include the volume, concentration and nature of the alcoholic beverage,[2,4,5] the rate of drinking,[4] the fed or fasted state,[6] the nature and composition of food,[6,7] rate of gastric emptying,[8,9] gender differences in first-pass metabolism,[10,11] and other drugs including histamine

0-8493-1680-4/04/$0.00+$1.50

(H1) receptor antagonists like cimetidine and ranitidine.[12,13] Ethanol is a small polar molecule and its volume of distribution is comparable to total body water.[3] 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%).[3] Alcohol metabolism 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 cytochrome P450 enzymes (CYP2E1) and catalase also contribute to alcohol metabolism and alcohol-related cytotoxicity in specific circumstances.[14]

Alcohol metabolic rates show a considerable degree of interindividual and ethnic variability, in part due to allelic variants of the genes encoding ADH and ALDH producing functionally different isozymes.[15–17] 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 threefold to fourfold variance in the alcohol elimination rate in humans.[18] Factors that have been shown to be important determinants of alcohol metabolism include age,[19,20] gender,[21,22] ethnicity and genetics,[21,23–26] and body mass and liver size,[27] as well as environmental factors such as food intake.[28]

This chapter will focus on genetic variation in the alcohol metabolizing enzymes and its impact on the metabolism of alcohol.

11.2 ALCOHOL METABOLIZING ENZYMES AND GENETIC ASPECTS

11.2.1 Alcohol Dehydrogenase

The alcohol dehydrogenase (*ADH*) gene family encodes oxidative enzymes that metabolize a wide variety of alcohols including ethanol, retinol, other aliphatic alcohols, hydroxysteroids, and lipid peroxidation products.[15] Currently, seven human ADH genes have been identified and organized into five classes based on amino acid sequence alignments, catalytic properties and patterns of tissue-specific expression.[29] Human ADH is a dimeric molecule, arising from the association of different subunits expressed by the seven genes. Thus, there are over 20 ADH isozymes that vary greatly with regard to the types of alcohols they preferentially metabolize and the maximal rate at which they oxidize ethanol.[15] The five classes of ADH are divided according to their subunit and isozyme composition (Table 11.1).

The Class I isozymes are found in liver, and consist of homo- and hetero-dimeric forms of the three subunits (i.e., $\alpha\alpha$, $\alpha\beta$, $\beta\beta$, $\beta\gamma$, $\gamma\gamma$, etc.). Classes II, III, and IV enzymes are homodimeric forms of the π, χ, and σ subunits, respectively. All the Class I ADHs metabolize ethanol and are inhibited by pyrazole derivatives.[30] The ADH1 subunits share about 94% sequence identity. The relative order of catalytic efficiency (k_{cat}/K_m) for ethanol oxidation at ethanol concentrations of about 100 mg% and saturating coenzyme NAD^+ concentration (0.5 m*M*) is: $\beta2 > \beta1 > \gamma1 > \gamma2 \approx \sigma$

TABLE 11.1
Nomenclature for Alcohol Dehydrogenase Genes

ADH Class	New *Gene Nomenclature*	Former *Gene Nomenclature*	Enzyme Subunit Nomenclature	K_m for Ethanol (m*M*)
I	ADH1A	ADH1	α	4.0
I	ADH1B*1	ADH2*1	β1	0.05
I	ADH1B*2	ADH2*2	β2	0.9
I	ADH1B*3	ADH2*3	β3	40
I	ADH1C*1	ADH3*1	γ1	1.0
I	ADH1C*2	ADH3*2	γ2	6.0
II	ADH4	ADH4	π	30
III	ADH5	ADH5	χ	>1000
IV	ADH7	ADH7	σ	30
V	ADH6	ADH6	Not identified	?

Note: Human Genome Organization Gene Nomenclature Committee, Official gene nomenclature for ADH, http://www.gene.ucl.ac.uk/nomenclature/genefamily/ADH.shtml, 2001.

>> β3 > α >>π. However, the relative order of k_{cat} at saturating concentrations of both ethanol and NAD^+ is σ > β3 ≈ β2 > γ1 > γ2 ≈ π > β1. Thus, the relative contributions of each of the ADH isozymes to ethanol oxidation changes with the hepatic concentration of alcohol.[31]

The human ADH genes are differentially expressed in different tissues, and this is a very important determinant of the physiological consequences of alcohol metabolism in specific cells and tissues.[30,32] The liver contains a large amount of ADH (about 3% of soluble protein) and expresses the widest number of different isozymes. ADH4 (π-ADH) is solely expressed in liver. Only ADH7 (σ-ADH) is not highly expressed in liver. ADH5 (χ-ADH) is ubiquitously expressed in human tissues. ADH1C, ADH4, ADH5, and ADH7 are expressed in gastrointestinal tissues. The expression of ADH5 in humans and its role in ethanol metabolism remain to be elucidated. Also, the expression of ADH in other tissues such as skeletal muscle, and the quantitative significance of muscle ADH metabolism (because of the large proportion of muscle mass in the body), remains to be determined.[16]

In addition to ethanol, alcohol dehydrogenases 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.[30,33] Oxidation of these alcohols can be inhibited by ethanol, and therefore the role of ethanol substrate competition is an important issue in alcohol-related toxicology. Another important issue is the regional expression of ADHs in the brain and their potential role in the local formation of acetaldehyde, which may be psychoactive, possessing stimulant as well as sedative/hypnotic effects.[34–36]

11.2.1.1 Genetic Polymorphisms

Genetic polymorphism occurs at the *ADH1B* and *ADH1C* loci.[15,37] Variant alleles of *ADH1B* result in the β1, β2, and β3 subunits, while variants of *ADH1C* result in the γ1 and γ2 subunits. The resulting subunits have different catalytic activities for ethanol (see Table 11.1). Additionally, the *ADH1B* alleles appear with different frequencies in different racial groups, with the *ADH1B*1* form predominating in white and black populations, and *ADH1B*2* predominating in East Asian populations (e.g., Chinese and Japanese), and also found in about 25% of white subjects with Jewish ancestry. The *ADH1B*3* form is found in about 25% of black subjects. With respect to the *ADH1C* polymorphism, *ADH1C*1* and *ADH1C*2* appear with about equal frequency in white populations, but *ADH1C*1* predominates in black and East Asian populations.[18,38]

Recently, a novel single nucleotide polymorphism was identified in *ADH1C*. This polymorphism results in an allele that codes for a subunit with a proline → threonine substitution in position 351.[39] This variant is found to occur primarily in Native Americans with frequencies as high as 26%. However, the catalytic activity of the isozyme coded by this variant and its effect on the overall elimination of alcohol remain to be established.

11.2.2 Aldehyde Dehydrogenase

Acetaldehyde is the first metabolic product of ethanol metabolism, and is itself metabolized via oxidation by the NAD^+-dependent aldehyde dehydrogenase (ALDH). Several isozymes of ALDH, differing in kinetic properties and tissue distribution, have been detected in human organs and tissues.[15] Currently, 17 functional ALDH genes have been identified in the human genome.[40] However, only the *ALDH1* (*ALDH1A1*) and *ALDH2* genes encode the class I and class II isozymes that are involved in acetaldehyde oxidation. ALDH1 is the cytosolic form distributed ubiquitously in tissues including brain. It exhibits relatively low catalytic activity ($K_m \sim 30\ \mu M$) for acetaldehyde oxidation. ALDH2 is the mitochondrial enzyme that is highly expressed in liver and stomach.[41] It exhibits high catalytic activity ($K_m \sim 3\ \mu M$) for acetaldehyde oxidation and is primarily responsible for acetaldehyde oxidation *in vivo*.

11.2.2.1 Genetic Polymorphisms

There is one known functionally significant genetic polymorphism of the *ALDH2* gene. The allelic variants are *ALDH2*1* and *ALDH2*2*, encoding for the high activity and low activity forms of the subunits respectively. The low activity form arises from a single amino acid exchange (glutamine to lysine substitution at position 487) at the coenzyme binding site of the enzyme subunit.[15] This results in a 100-fold increase in the K_m for NAD^+.[42] This very prominent variant allele has been seen in about half of the East Asian populations studied (including the Han Chinese, Taiwanese, and Japanese).[43,44] It has not been observed in populations of Caucasian origin. It exhibits virtually no acetaldehyde oxidizing activity *in vitro*, and represents the "deficient" phenotype seen in these Asian populations.[45] Individuals who are

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heterozygous or homozygous for *ALDH2*2* show the characteristic sensitivity reaction (facial flushing, increased skin temperature and heart rate) following alcohol intake.[26,46]

11.2.3 Microsomal Ethanol Oxidizing System (MEOS)

A small fraction of an ingested dose of ethanol is metabolized by enzymes other than ADH. Metabolism of ethanol by microsomal enzymes, particularly the cytochrome P450 enzymes, accounts for the major non-ADH system. The cytochrome P450 isoform, P4502E1 (CYP2E1), is the major alternative system that catalyzes the NADPH- and O_2-dependent oxidation of ethanol to form acetaldehyde, $NADP^+$, and water. As many as 13 different *CYP2E1* polymorphisms have been identified.[15] A polymorphism has been reported in the 5′-flanking region of the *CYP2E1* gene. This polymorphism is differentially expressed in different racial populations, and the rare mutant allele (*c2* allele) has been found to be associated with higher transcriptional activity, protein levels, and enzyme activity than the common wild-type *c1* allele.[15,47] The influence of *CYP2E1* genotypes on alcohol elimination was examined in one study in Japanese alcoholics and control, and indicated that the presence of the *c2* allele (heterozygous or homozygous) may be associated with higher alcohol metabolic rates but only at blood alcohol levels greater than 0.25% (g/dl).[48]

While MEOS accounts for a much smaller fraction of ethanol oxidation than the ADH system under normal conditions, it represents a major adaptive response of alcohol metabolism with chronic ethanol consumption.[14] This is due to the direct effect of chronic ethanol consumption on the expression of hepatic CYP2E1. In humans, there is an induction of CYP2E1 with chronic alcohol consumption that can be followed by a decrease in activity associated with generalized hepatic injury and loss of function. There are two mechanisms postulated for CYP2E1 induction: (1) a posttranslational mechanism involving mRNA stabilization and protection of the expressed protein against degradation and (2) a direct transcriptional regulation of CYP2E1 expression, generally following high exposures to ethanol. The expression of CYP2E1 is influenced by factors such as diet (lipids, carbohydrates) and hormones (thyroid hormones, glucocorticoids, steroids, pituitary hormones). However, much work needs to be done to understand mechanisms for transcriptional and posttranslational regulation of the MEOS genes, and their role in alcohol metabolism and alcohol-related liver disease.[14]

11.2.4 Catalase

Catalase is an enzyme that catalyzes the H_2O_2-dependent oxidation of ethanol yielding acetaldehyde and two molecules of water. It is found in the cytosol and mitochondria but its main expression and function is in peroxisomes. Most studies indicate that it contributes very little to total ethanol elimination because of the limited availability of hydrogen peroxide.[14,49] However, the activation of peroxisomal catalase by increased generation of hydrogen peroxide via peroxisomal β-oxidation leads to a hypermetabolic state and a swift increase in alcohol metabolism.[50] This state may contribute to alcohol-related inflammation and necrosis in alcoholic liver disease.

11.3 ADH AND ALDH POLYMORPHISMS: INFLUENCE ON ALCOHOL METABOLISM

Functional polymorphisms of the alcohol metabolizing enzymes ADH and ALDH2, and differences in the prevalence of the polymorphic alleles in different ethnic populations, have resulted in several studies examining ethnic differences in alcohol metabolism and the influence of *ADH1B*, *ADH1C*, and *ALDH2* genotypes. The isozymes encoded by the polymorphic alleles have very different catalytic properties *in vitro*,[30,31] and would be expected to exert influences on an individual's alcohol metabolic rate.

One of the first studies examining the influence of *ADH* and *ALDH* polymorphisms on alcohol metabolism was done by Mizoi et al.[23] in 68 healthy Japanese subjects. Subjects were genotyped for *ADH1B* as well as *ALDH2* polymorphisms and alcohol disappearance rates (mg/ml/h) and elimination rates (mg/kg/h) were compared among the groups classified, based on zygosities of both *ADH1B* (*ADH1B*1/*1*, *ADH1B*1/*2* and *ADH1B*2/*2*), and *ALDH2*. Results indicated that there were no differences in alcohol metabolism among the *ADH1B* genotypes; however, there were marked differences among the *ALDH2* genotypes with regard to alcohol metabolism. This is discussed further below.

In another study, Neumark et al.[51,52] found differences in alcohol elimination rates in Jewish subjects with different *ADH1B* genotypes following alcohol administration using the alcohol clamp method.[53,54] The authors found significantly higher alcohol elimination rates in subjects carrying the *ADH1B*2* allele (heterozygotes and homozygotes) compared with *ADH1B*1* homozygotes. As the Jewish do not show polymorphisms of the *ALDH2* genes, this appears to be a direct effect of *ADH1B* genotypes on alcohol metabolism.

Thomasson et al.[21] examined the influence of the other *ADH1B* polymorphism (*ADH1B*3*) on alcohol metabolism in a sample of 112 African-American subjects selected by genotype. In this study, subjects received an oral dose of alcohol and alcohol disappearance rates were determined from the slope of the pseudo-linear portion of the blood ethanol concentration vs. time curves. Results revealed that subjects who had β3-containing ADH isozymes showed a higher alcohol disappearance rate (mg% per h) compared to those with β1β1-ADH isozymes. 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*.[24] However, this difference was not statistically significant probably because of the small number of subjects possessing the *ADH1B*3* genotype in the study and the low frequency of occurrence of this genotype (~7%) in this ethnic group. Earlier studies in Native Americans had also demonstrated higher alcohol elimination rates compared to those reported in Caucasians; however, *ADH* genotypes were not determined in these studies.[55–57]

The influence of *ALDH2* polymorphisms on alcohol metabolism has been studied more extensively, although almost exclusively in Asian subjects, mainly because of the high frequency of the polymorphism in this population. Most of these studies have compared peak concentrations of alcohol and acetaldehyde as well as peak responses on subjective and cardiovascular measures and flushing across *ADH1B*

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and *ALDH2* genotypes, with generally consistent results. In general, individuals who are heterozygous or homozygous for *ALDH2*2* show increased acetaldehyde levels following alcohol administration.[25,26,46,58–60] Some studies have also demonstrated significant increases in ethanol concentrations and area under the ethanol concentration time curves,[46,60] possibly due to product inhibition of ADH activity by acetaldehyde. However, other studies have shown accumulation of acetaldehyde in subjects carrying the *ALDH2*2* allele without any alterations in alcohol concentrations or elimination rates.[25,26]

There are only a few studies that have actually estimated and compared alcohol disappearance rates (beta-60) or elimination rates among *ADH1B* and/or *ALDH2* genotypes.[23,25,61] A study in Chinese men indicated that the presence of the *ALDH2*2* allele was associated with slower alcohol metabolism following oral administration.[61] In the study by Mizoi et al.[23] described above, peak acetaldehyde levels, alcohol disappearance rates (mg/ml/h), and elimination rates (mg/kg/h) were compared among subjects classified into groups based on zygosities of both *ADH1B* and *ALDH2* (*ALDH2*1/*1*, *ALDH2*1/*2*, and *ALDH2*2/*2*). Results indicated that subjects homozygous for *ALDH2*1/*1* showed no increase in acetaldehyde levels regardless of their *ADH1B* genotype. There was a progressive increase in peak acetaldehyde levels in subjects with the *ALDH2*1/*2* and *ALDH2*2/*2* genotypes. Both alcohol disappearance rates and elimination rates showed significant differences among the *ALDH2* genotypes and decreased in the following order: *ALDH2*1/*1* > *ALDH2*1/*2* > *ALDH2*2/*2*.

Thus, genetic polymorphisms of *ADH* and *ALDH* result in alterations in the metabolism of alcohol and/or acetaldehyde. Polymorphisms in *ADH* result in variants (*ADH1B*2* and *ADH1B*3*) that code for isozymes that tend to show a faster rate of alcohol metabolism, while the *ALDH2*2* polymorphism results in a "deficient" form of ALDH2 that causes an accumulation of acetaldehyde and its associated physiological effects.

11.4 ADH AND ALDH POLYMORPHISMS: ASSOCIATION WITH ALCOHOL DEPENDENCE

Functional polymorphisms of the alcohol metabolizing enzymes ADH and ALDH2 can also exert important effects on the biological effects of alcohol.[62] In fact, *ADH* and *ALDH* are the only genes which have been firmly established to influence vulnerability to alcohol dependence or alcoholism.[38] Studies have demonstrated unequivocally that the allele frequencies of *ADH1B*2*, *ADH1B*3*, and *ALDH2*2* are significantly decreased in subjects diagnosed with alcohol dependence as compared with the general population of East Asians, including the Japanese, Han Chinese, and Koreans.[43,44,63–67] The *ALDH2*2* allele and the *ADH1B*2* allele also significantly influence drinking behavior in nonalcoholic individuals. Association between reduced alcohol consumption or reduced risk of alcohol dependence and the *ADH1B*2* variant allele has recently been found in other ethnic groups that do not carry the *ALDH2*2* allele, including Europeans,[68–70] Jews in Israel,[71,72] as well as Mongolians in China,[44] and the Atayal natives of Taiwan.[73] A recent study has

also shown a protective association between the *ADH1B*3* allele and alcohol dependence in Native Americans.[74] Finally, studies have indicated that the *ADH1B*3* allele may be protective against alcohol-related problems in children born to African-American mothers who may have consumed alcohol during pregnancy.[75–78]

11.5 SUMMARY

There has been substantial progress in the field of alcohol pharmacogenetics to characterize differences in alcohol metabolism in subjects exhibiting polymorphic genotypes of the alcohol metabolizing enzymes. Studies are, however, 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 racial and ethnic groups, but large differences in alcohol elimination rates still exist between individuals within the various ethnic groups. Of potential significance in this regard may be the recent discovery of polymorphisms in the promoter regions of *ALDH2*[79,80] and *ADH4*,[81] as well as the recently identified *ADH1C*351Thr* polymorphism.[39] Studies are needed to evaluate the influence of these polymorphisms on the activity of ADH and ALDH 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 (i.e., genetic component of variance) of alcohol metabolic rates is about 50%.[82,83] Further evaluation of the factors, both genetic and environmental, regulating the rates of alcohol and acetaldehyde metabolism will help improve our understanding of the metabolic basis and consequences of alcohol's effects, including the risk and consequences of alcohol-related organ damage and developmental problems, as well as alcohol dependence.

ACKNOWLEDGMENTS

The author wishes to thank Dr. Ting-Kai Li, National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD, and Dr. William F. Bosron, Indiana University School of Medicine, Indianapolis, IN.

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