PHARMACOGENETICS OF ALCOHOL RESPONSE AND ALCOHOLISM: THE INTERPLAY OF GENES AND ENVIRONMENTAL FACTORS IN THRESHOLDS FOR ALCOHOLISM

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ABSTRACT:

Recent advances in neuroscience and genetics have enabled a better understanding of genetically influenced differences in ethanol (“alcohol”)–related responses and differential vulnerability to alcohol dependence at the cellular and molecular levels. Heritability studies reveal that the role of genetic factors in alcoholism is largely substance-specific, with the exception of nicotine. One focus of genetic research in alcoholism is the study of functional polymorphisms influencing alcohol metabolism, such as the aldehyde dehydrogenase type 2 Glu487Lys and alcohol dehydrogenase type 2 His47Arg polymorphisms, which affect vulnerability to alcoholism via pharmacokinetic mechanisms, and cross-population studies have begun to reveal important gene-environment interactions. The other focus is on functional genetic variants of proteins involved in the neuronal response to alcohol, including alcohol sensitivity, tolerance, and withdrawal. Studies on the roles of GABA\textsubscript{A} \textalpha\textsubscript{6}-amino acid substitutions in rodents in alcohol and benzodiazepine sensitivity, and potential roles in human alcohol and benzodiazepine sensitivity are reviewed. These studies, together with recently developed knowledge on a GABA\textsubscript{A} receptor gene cluster at a quantitative trait loci for alcohol withdrawal on mouse chromosome 11, indicate that research investigation of variation at GABA\textsubscript{A} neurotransmission is a promising area in the pharmacodynamics of alcohol and in differential susceptibility to alcoholism. Genes for proteins involved in alcohol-mediated reward include genes for transporters and receptors for dopamine, serotonin, opioids, and GABA. These genes and their functional variants also represent important targets for understanding alcohol's effects in humans. Identification of genes for alcoholism vulnerability is important in the near future, not only for prevention, but also for development and targeting treatments.

Heritability and Gene-Environment Interaction in Alcoholism

Alcohol dependence (“alcoholism”) is a common etiologically complex disorder, affecting about 10% of males and 4% of females in the United States (Kessler et al., 1994). An estimated 40 to 60% of the individual variation in alcohol preference and vulnerability to alcoholism is genetic in origin as revealed by adoption studies (e.g., Goodwin et al., 1977; Bohman et al., 1981; Cloninger et al., 1981) and by studies on large samples of cross-sectionally ascertained twin pairs (e.g., Heath et al., 1997; Kendler et al., 1997).

The largest portion of the genetic vulnerability to alcoholism is substance-specific; vulnerability is largely unshared with other drugs except for nicotine (Goldman and Bergen, 1998). Relatives of probands with other substance dependence disorders are not at substantial increased risk for alcoholism (Merikangas et al., 1998). On the other hand, alcoholism and nicotine addiction are frequently comorbid and tend to be coinherited. According to Patten and collaborators (1996), approximately 80% of alcoholics, as compared with 30% of nonalcoholics, smoke. A genetic correlation was detected in several large twin studies (Swan et al., 1997; Hettema et al., 1999). For example, in 3356 Vietnam veteran twin pairs, heritabilities for nicotine addiction and alcoholism were 0.60 and 0.55, respectively, and the genetic correlation between the two disorders was 0.68 (True et al., 1999). These studies point directly to the need to identify pharmacokinetic and pharmacodynamic vulnerability factors specific to alcohol, as well as factors shared with other substances, particularly nicotine (Goldman and Bergen, 1998).

Although alcoholism is substantially heritable across cultures and in both males and females, thresholds for disease expression vary across time, across different cultures, and between the two sexes. The lifetime prevalence of alcoholism differs dramatically between cultures, as well as between the two sexes within the same culture. In the United States and other Western societies where alcohol is available to both sexes and the prevalence of alcoholism is high, the lifetime risk for alcohol dependence is 2 to 3 times higher in men than in women. However, the male:female ratio is considerably higher in Japan, where alcoholism is less common and females’ access to alcohol is more restricted (Schuckit, 1995). Meanwhile, in a Southwestern American Indian tribe the male:female ratio is only 1.7, whereas in this population the lifetime prevalence of alcoholism is approximately 85% in males and 50% in females (Robin et al., 1998). Consistent with varying environmental liability thresholds, genotype at aldehyde dehydrogenase type 2 differentially impacts the risk for alcoholism between populations (Tu and Israel, 1995). In the United States, prevalence of alcoholism and associated problems diminished during the Prohibition years and substantially rose thereafter.

Physiology of Specific and Nonspecific Alcoholism Vulnerability

Factors involved in the substance-specific inheritance of alcoholism include both pharmacokinetic and pharmacodynamic genetic variation. The specific behavioral and physiologic effects of ethanol (alcohol) depend on dose, distribution, and metabolism of alcohol, prior drinking experience, mood, concurrent use of other drugs, and the
presence of other medical problems (Schuckit, 1995). Although some of these factors may be largely environmentally determined, several are genetically influenced (e.g., alcohol metabolism).

The body adapts metabolically and neurally to repeated alcohol exposure, compensating in at least three ways to increase tolerance. First, after 1 to 2 weeks of daily drinking, the rate of hepatic ethanol metabolism increases by as much as 30%. This is metabolic or pharmacokinetic tolerance. Second, pharmacodynamic tolerance occurs via neuroadaptation, forming the primary basis for dependence and withdrawal. Neuroadaptation may in part provide the mechanism for craving and rapid reinstatement to high levels of alcohol consumption after relapse. Some components of the neuroadaptation to alcohol are long lasting if not permanent (Schuckit, 1995).

Pharmacogenetics of Alcohol Metabolism

Although there is a great deal of evidence for genetic predisposition in alcoholism, the only well-established genetic factors for differential susceptibility are polymorphisms of two major enzymes of alcohol metabolism. These are ALDH2 Glu487Lys, and following in importance, ADH2 Arg47His. Quantitatively, the most important component of alcohol metabolism occurs in the stomach (class IV subunits, ADH1D–7), and in hepatocytes (class I subunits, ADH1D–ADH3). Alcohol is oxidized to a toxic intermediate, acetaldehyde, by homodimeric and heterodimeric ADH isozymes (Bosron and Li, 1986). Under normal conditions, acetaldehyde is rapidly oxidized to acetate, primarily by tetrameric aldehyde dehydrogenase enzymes located in the cytosol (ALDH1) and in mitochondria (ALDH2). Other enzymes that play a quantitatively much smaller role in alcohol and acetaldehyde metabolism are P450 2E1 and catalase.

Functional polymorphisms in two alcohol metabolic enzymes (i.e., ADH2 and ALDH2) are found in about half the population of Southeast Asian countries including China, Japan, and Korea. These variants are rare in Caucasian and African populations (Enomoto et al., 1991; Yoshida et al., 1991; Goede et al., 1992; Bosron et al., 1993) except for ADH2 Arg47His, for which the His47 allele is abundantly present in the Jewish population of Israel (Monteiro et al., 1991). The ADH2 His47 allele increases the rate of acetaldehyde formation, and the ALDH2 Lys487 allele decreases the rate of removal of acetaldehyde, so that the altered enzymatic functions due to these polymorphisms lead to an accumulation of acetaldehyde after alcohol intake. The acetaldehyde causes a flushing reaction very similar to that produced if alcohol is consumed following drugs that block aldehyde dehydrogenase (for example, disulfiram—used for alcoholism treatment—and the antiprotozoal drug metronidazole and congeners).

Because the ALDH2 Lys487 and ADH2 His47 alleles are common and aversive for alcohol intake, several studies have investigated their relationship to alcoholism (Harada et al., 1982; Shibuya and Yoshida, 1988; Thomasson et al., 1994; Osier et al., 1999).

In the epidemiology of alcoholism, the ALDH2 Glu487Lys polymorphism plays the most important role. ALDH2 is responsible for most acetaldehyde metabolism in hepatocytes, and the inactive allele Lys487 acts dominantly. Glu487/Lys487 heterozygotes have little residual enzyme activity because one Lys487 subunit is sufficient to largely inactivate the ALDH2 tetramer. The flushing reaction is evident in Glu487/Lys487 heterozygotes after consumption of even a single drink of alcohol with several aversive symptoms, including vasodilation, headache, nausea, and palpitations (Harada et al., 1982) and is most severe in Lys487/Lys487 homozygous individuals. While about 10% of Japanese are homozygous for the Lys487 allele, there has so far been only one reported case of an alcoholic Lys487/Lys487 homozygote, and this individual had an unusual drinking pattern in which small amounts of alcohol were imbibed throughout the day (Chen et al., 1999b). Lys487 has an abundance of approximately 0.30 in Japanese and Chinese (Bosron and Li, 1986; Thomasson et al., 1994; Higuchi et al., 1995; Chen et al., 1996). Therefore, approximately half the Japanese and Chinese populations experience flushing after alcohol consumption. In these Lys487/Glu487 heterozygotes, the risk of alcoholism is reduced 4–to 10-fold (Thomasson et al., 1994).

The action of the ALDH2 Lys487 allele is additive with the ADH2 His47 allele (Chen et al., 1996), a catalytically more active ADH2 allele that is independently associated with higher acetaldehyde levels and flushing (Impraim et al., 1982; Hsu et al., 1988). The His47 allele is also found in non-Oriental populations. Monteiro et al. (1991) estimated that His47 accounts for 20 to 30% of the variance in alcohol intake variance between two groups of light drinking and heavy drinking Israeli Jews, and proposed that the relatively high frequency of the His47 allele in that population might contribute to lower levels of alcohol consumption among Jews.

An ADH3 polymorphism Ile271Val also produces a difference in enzyme activity, and the superactive allele (Val271Ile) is again more abundant in East Asia (Tanaka et al., 1992; Edenberg and Bosron, 1997). However, findings of association of ADH3 to alcoholism vulnerability appear to be entirely attributable to linkage disequilibrium with ADH2, which is located in the same gene cluster on chromosome 4q, and at a distance of only 15 kb (Chen et al., 1999a; Osier et al., 1999).

It is of great interest that the protective effect of alcohol metabolic gene polymorphisms may be expressed differentially against varying environmental backgrounds, or thresholds (Goldman, 1993). Tu and Israel (1995) found that the ALDH2-specific odds ratio for alcoholism was only about 2:1 among individuals of Korean and Taiwanese ancestry born in North America. Acculturation accounted for 7 to 11% of the variance in alcohol consumption, and the ALDH2 polymorphism predicted two-thirds of the vulnerability to alcohol consumption and excessive alcohol use. Furthermore, in Southeast Asian populations with similar ALDH2 Glu487Lys allele frequencies there are large differences in the prevalence of alcohol dependence (i.e., 2.9% in Taiwan and 17.2% in Korea).

Genetics of Alcohol Sensitivity and Other Alcohol-Related Behaviors

Alcohol Sensitivity in Rodents. Alcoholism is a behavior uniquely defined in the human. However, animal genetic and pharmacobehavioral models offer new insights and convergent information on mechanisms and gene targets for alcohol-seeking behavior and response in the human. For example, the long-sleep and short-sleep lines of mice were initially selected for differential response to the acute sedative effects of alcohol (McClearn and Kakihana, 1981). They differ markedly in their genetic sensitivity to alcohol and intercrosses reveal that the difference is polygenic in origin. The LS and SS mice have also been found to differ in response to a variety of hypnotics and anesthetics (Miller et al., 1988).

LS versus SS and other mouse strain differences in alcohol sensitivity do not appear to be attributable to pharmacokinetic factors but to a pharmacodynamic difference in neuronal sensitivity, as shown by studies of isolated neuronal tissue (Spuhler et al., 1982). Several lines of evidence suggest that GABAergic neurotransmission is one key factor in alcohol sensitivity. Brain GABA_A receptor binding and
GABA_A channel function are modulated by alcohol, and there is a difference in ligand affinity between LS mice and SS mice (Miller et al., 1988). To investigate the molecular basis of this difference in GABA_A channel function, Wafford et al. (1990) expressed brain mRNA from brains of LS and SS mice in Xenopus laevis oocytes. N-Methyl-D-aspartate responses were inhibited equally in oocytes injected with mRNA from the two mouse lines. However, alcohol facilitated GABA responses in oocytes injected with mRNA from LS mice but antagonized responses in oocytes injected with mRNA from SS animals. In addition, a specific difference in GABA_A receptor gamma subunit function was detected between the LS and SS lines, and was proposed to be a critical determinant of differences in ethanol sensitivity (Wafford et al., 1990).

The ANT rat line, developed by selective breeding for high sensitivity to alcohol-induced motor coordination, also exhibits an enhanced sensitivity to GABA agonists at GABA_A receptors such as diazepam (Hellevoet et al., 1989). Korpi et al. (1993) identified a missense Arg100Gln substitution in the α6-subunit gene of ANT rats. The α6-subunit is specifically expressed in cerebellar granule cells and forms a GABA_A receptor complex that is benzodiazepine-sensitive but selectively responsive to the benzodiazepine derivative Ro5-4513. Ro5-4513 antagonizes alcohol-induced motor incoordination (Luddens et al., 1990). The Arg100 residue had previously been implicated as a key determinant of the insensitivity of the GABA_A α6-subunit to benzodiazepines, since its replacement with a histidine (His100) resulted in high-affinity benzodiazepine binding (Wieland et al., 1992). Recombinant α6(Gln100)β2γ2 and α6(Arg100)β2γ2 GABA_A receptors were expressed in a mammalian cell line, and the Gln100 α6-receptor was indeed potentiated by benzodiazepines as well as by alcohol, and in contrast with the Arg100 α6-receptor (Korpi et al., 1993). These results suggest that the potentiation of GABA currents at receptors with the Gln100 allele is the underlying factor in the enhanced response of ANT rats to alcohol and benzodiazepines.

Human Alcohol Response. The detection of genetic influences in susceptibility to alcoholism has stimulated a search for intermediate phenotypes that can serve as indicators of vulnerability before the development of the disease. Detection of intermediate phenotypes may identify alcoholism subgroups and direct genetic analyses toward particular physiology. For example, relatively alcohol-naïve offspring of alcoholics tend to be less sensitive to the motor, endocrine, and subjective effects of alcohol, and a 10-year follow-up of 453 men revealed that low level of response to alcohol at age 20 was a powerful predictor of later alcoholism (Schuckit 1985, 1994). Low response to modest doses of alcohol predicted a 4-fold increase in subsequent development of alcoholism, irrespective of family history (Schuckit, 1994). Selective genotyping was performed in a portion of this sample for candidate genes for alcohol response, including the GABA_A α6-receptor (Schuckit et al., 1999). Two polymorphisms, a common functional polymorphism of the serotonin transporter promoter, and a GABA_A α6-amino acid substitution polymorphism Pro385Ser (Iwata et al., 1999), were associated with alcohol sensitivity (Schuckit et al., 1999). In a separate study, the GABA_A α6-polymorphism was also associated with benzodiazepine sensitivity (Iwata et al., 1999).

Alcohol-Related QTL Mapping in Rodents

Genes for complex genetically influenced traits may be detectable as quantitative trait loci. QTL mapping in rodents has identified candidate genes for alcohol-related behavior for further investigation in humans (e.g., Buck et al., 1997; Buck and Hood, 1998). Approximately 68% of the genetic variability influencing acute alcohol withdrawal severity may be attributable to QTLs on mouse chromosomes 1, 4, and 11.

The role of a GABA_A gene cluster in the chromosome 11 QTL accounting for 12% of the genetic variance in withdrawal has been further investigated (Buck et al., 1998). Genes in this cluster encode α1-, α6-, β2-, and γ2-GABA_A subunits. There is an Ala11Thr sequence difference in the γ2-GABA_A subunit gene between C57BL/6J (B6) mice, which has high acute withdrawal severity, and DBA/2J (D2) mice, which have low withdrawal severity. In recombinant inbred strains, the γ2-subunit polymorphism correlates with alcohol withdrawal severity. The mouse chromosome 11 GABA_A cluster is thus a potential example of a genetic pharmacodynamic difference in alcohol response.

Mouse QTLs for other alcohol-associated behaviors, such as alcohol consumption and alcohol-associated hypothermia, have also been identified (Crabbe et al., 1994, 1996a). Chromosome 9 QTLs for alcohol-induced hypothermia, alcohol consumption, and certain responses to morphine and amphetamines coincide with each other and with the location of the serotonin 5-HT1B and DRD2 receptor genes (Crabbe et al., 1996a). The convergence in locations of genes influencing different alcohol-related traits and traits related to other drugs suggests that the same genes may influence these several behaviors. Such convergence was also observed in mice in which the 5-HT1B gene was knocked out. These gene knockout mice consume twice as much alcohol, are less intoxicated, and are more aggressive compared with parental stock (Crabbe et al., 1996b). The 5-HT1B knockout mice also work harder to self-administer cocaine and show an increased locomotor response, as if already sensitized to the drug (Rocha et al., 1998).

As a follow-up to the mouse 5-HT1B QTL and knockout findings, linkage studies were performed in several hundred human sibling pairs from each of two isolates, one from Finland and the other from an American-Indian community in the Southwestern United States (Lappalainen et al., 1998). The linkage phenotype was antisocial alcoholism (Alcohol Dependence plus either Antisocial Personality disorder or Intermittent Explosive disorder) so that affected individuals had both increased alcohol consumption and increased aggression. Linkage to the 5-HT1B gene was observed in both populations (Lappalainen et al., 1998). In addition, the DRD4 dopamine receptor, which is located at the site of one of the alcohol-related QTLs, has been knocked out in mice (Rubinstein et al., 1997). The DRD4 knockout mice are supersensitive to alcohol, cocaine, and amphetamines. In a whole-genome linkage scan performed in humans, suggestive evidence for linkage to alcohol dependence was detected (level of detection = 3.1; nominal p = 0.00007) near the chromosome 11p telomere, near the location of DRD4 (Long et al., 1998).

Neurocircuitry Targets for Alcohol Reinforcement and Dependence

The target of ethanol’s actions in the brain was once thought to be the cell membrane, but the focus of attention has now shifted to specific brain proteins (Hoffman and Tabakoff, 1996). These include neurotransmitter receptors including ligand-gated ion channels that show different sensitivities to alcohol and specific chain length cutoffs for action of alcohols (e.g., Weight et al., 1993; Wick et al., 1998). The genes encoding these proteins are a possible source of variation in susceptibility to alcoholism.

Dopamine System. The dopamine neuronal system that arises from the ventral tegmental area is the major neurobiological substrate for the mediation of the reinforcing actions of substances of abuse in the brain reward system, which includes the nucleus accumbens, the hippocampus, and part of the prefrontal cortex (for a review, see...
McBride et al., 1999). In reinforcement by alcohol, the ventral tegmental area has been the only region shown to support direct alcohol administration, and increased dopamine neuronal activity has been shown to be associated with the reinforcement processes involved in continued alcohol consumption (Wise, 1987).

Despite the importance of the dopamine pathways in alcohol reinforcement, and the presence of functionally significant polymorphisms in several dopamine receptor genes, no consistent demonstration of a role of such genes in alcoholism has been reported (Goldman et al., 1998). For example, association of a nonfunctional DRD2 dopamine receptor polymorphism with alcoholism was not supported by larger and more carefully controlled linkage and association studies, one of which analyzed the functional DRD2 Ser311Cys polymorphism (Goldman et al., 1998). Recently reported promoter polymorphisms at DRD2 (Ishiguro et al., 1998) and at dopamine transporter type 1 (Ueno et al., 1999) that seem to differ functionally by altering transcription levels seem to provide promising tools for understanding possible roles of these genes in alcoholism.

**Opioid Receptors.** Several lines of evidence converge on the idea that endogenous opioids, especially the delta and mu opioid receptor pathways, are involved in both the initial sensitivity and the reinforcing effects of alcohol (Nutt, 1996). It seems that via the stimulation of delta and mu opioid receptors, alcohol increases dopamine release in nucleus accumbens, thus reinforcing its intake (Benjamin et al., 1993). The opioid receptor antagonist naltrexone reduces alcohol intake in humans and other animals and reduces alcoholism relapse in humans (O’Malley et al., 1993; Volpicelli et al., 1993). Although no association has been found between mu opioid receptor type 1 variants including the functional Asn40Asp variant and alcohol dependence (Bergen et al., 1997; Sander et al., 1998), these variants provide an important opportunity for pharmacogenetic studies of naltrexone response.

**5-HT3 Receptors.** Alcohol modulates 5-HT3 serotonin receptor ion channel function (Lovingier, 1991; Weight et al., 1993). Neurochemical and neuropharmacological studies in rodents have revealed that alcohol increases extracellular concentrations of both dopamine and 5-HT in nucleus accumbens and that the dopamine release can be blocked with a 5-HT3 antagonist (Campbell and McBride, 1995). In humans, there is also evidence that some of the pleasurable effects of alcohol are mediated by binding to 5-HT3 receptors, as was shown when alcohol and the 5-HT3 antagonist ondansetron were coadministered to normal volunteers (Johnson et al., 1993). Two 5-HT3 receptor genes (i.e., HTR3A and HTR3B) have been identified (Davies et al., 1999), but no sequence variants have been reported at this juncture.

**Neuronal Nicotinic Acetylcholine Receptors.** Nicotine addiction and alcoholism share common genetic determinants (Wise, 1996). This contrasts with the largely independent inheritance of alcoholism and other substances (Goldman and Bergen, 1998). These ligand-gated ion channels are modulated by alcohol at concentrations associated with moderate alcohol consumption (Weight et al., 1993).

It has been suggested that ethanol exerts part of its mesolimbic dopamine activating and reinforcing effects via interaction with central nicotinic acetylcholine receptors, thus providing a basis for the comorbidity and coinheritance of alcoholism and nicotine addiction. The central nicotinic acetylcholine receptor antagonist mecamylamine totally counteracted the ethanol-induced elevation of extracellular dopamine in nucleus accumbens, while the quaternary nicotinic receptor antagonist hexamethonium did not (Blomqvist et al., 1986). Furthermore, the increase in accumbal dopamine overflow after systemic ethanol was counteracted by local perfusion of mecamylamine in the ipsilateral ventral tegmental area, but not by mecamylamine perfusion in nucleus accumbens (Blomqvist et al., 1997; Ericson et al., 1998). These results provide further evidence that ethanol-induced activation of the mesolimbic dopamine system is mediated via stimulation of central nicotinic acetylcholine receptors, and that the receptor population within the ventral tegmental area may be the most important. Two classes of neuronal nicotinic acetylcholine receptor subunits (eight α and three β) form the presumed heteropentameric ligand-gated ion channel (Boyd, 1997). Genetic variation in neuronal nicotine receptors may be critical for understanding the pharmacodynamics of alcohol.

**GABA_A Receptors.** Many of the behavioral effects (anxiolytic, ataxic, sedative/hypnotic) of alcohol and clinically important central nervous system depressants (e.g., benzodiazepines and barbiturates) are similar and show cross-tolerance (Hoffman and Tabakoff, 1996). Benzodiazepines and barbiturates allosterically modulate the action of GABA at GABA_A receptors, leading to the investigation of the effects of alcohol on these receptors (Hoffman and Tabakoff, 1996). Alcohol increases GABA_A receptor-mediated chloride influx in brain tissue (Allan and Harris, 1986; Suzzak et al., 1986) and in X. laevis oocytes (Wafford et al., 1990). The sensitivity of the GABA_A receptor to alcohol might depend on eight amino acids contained in the long-spliced version of the γ2-subunit (Wafford et al., 1991; Harris et al., 1995).

Agents that act as GABA positive modulators at GABA_A receptors, such as benzodiazepines, barbiturates, and neurosteroids, enhance acute sensitivity to alcohol and maintain alcohol preference. However, antagonists such as picrotoxin and bicuculline decrease many acute actions of alcohol and reduce alcohol preference (Boyle et al., 1993). Nowak and collaborators (1998) investigated the effect of GABA_A blockade in alcohol reward by injecting picrotoxin directly into the ventral tegmental area of alcohol-prefering (P) rats. Picrotoxin decreased alcohol consumption, whereas the intake of control saccharin solution was not significantly altered. These results suggest that anterior ventral tegmental area mechanisms regulating alcohol-drinking behavior are under tonic GABA_A inhibition. In addition, alcohol withdrawal is diminished by GABA agonists at GABA_A receptors, whereas antagonists increase withdrawal severity (Buck and Harris, 1990). Thus, in addition to the genetic evidence discussed earlier, there are convergent pharmacologic findings that modulation of GABA neurotransmission via GABA_A receptors is important in genetic pharmacodynamic differences associated with alcohol consumption and alcoholism.

**References**


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