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Review Article

The role of serotonin and possible interaction of serotonin-related genes with alcohol dehydrogenase and aldehyde dehydrogenase genes in alcohol dependence-a review

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Abstract: Alcohol dependence is believed to be a multifactorial, polygenic disorder involving complex gene-gene and gene-environment interactions and confounded by heterogeneity and sociocultural factors. Serotonin (5-Hydroxytryptamine, 5-HT) is thought to be involved in many aspects of alcohol consumption, abuse, and dependence. There was some evidence that serotonin-related genes might interact with the alcohol dehydrogenase (ADH) and the aldehyde dehydrogenase (ALDH) genes in the development of alcohol dependence. In the current review, we discuss the role of serotonin and possible interaction of serotonin-related genes with ADH and ALDH genes in alcohol dependence.

Keywords: Alcohol dependence, gene-gene interaction, 5-HT, serotonin-related genes, ADH, ALDH

Introduction

Alcohol dependence is believed to be a multifactorial, polygenic disorder involving complex gene-gene and gene-environment interactions and confounded by heterogeneity and sociocultural factors [1-3]. Family [4], twin [5], and adoption studies [6] have convincingly demonstrated that genes play an important role in the development of alcohol dependence, accounting for more than 50% of the population variance [7]. Additionally, patterns of alcohol use seem to be under genetic influence. Twin studies have demonstrated that dimensions of alcohol use, such as quantity of alcohol consumed on a typical drinking occasion, frequency of use, frequency of intoxication, and alcohol metabolism measures, such as time to peak blood alcohol concentration and rate of elimination, are under substantial genetic influence [8]. Furthermore, there is evidence of genetic effects on patterns of alcohol use as early as adolescence, and these effects seem to increase over time [9].

Many researchers have attempted to divide alcohol abuse and alcohol dependence into subtypes based primarily on elimination characteristics. In prospective adoption studies, Cloninger proposed a neurobiological learning model that distinguished alcohol use disorders into two genetic subtypes (type I and II) [1]. Type I alcohol use disorders included more psychological dependence, high harm avoidance, high reward dependence, and low novelty-seeking, whereas type II alcohol use disorders included early-onset drinking behavior, more behavioral disturbances, and low levels of brain serotonin. Other subtypes of alcohol use disorders have also been proposed [10-12]. For example, Lu proposed that there are at least three subtypes of alcohol dependence in Han Chinese population: alcoholic with more emotional disturbance (type I, anxiety/depressive type) [11]; late-onset and less severe alcoholics with more social drinking (type II, pure alcoholics type); earlier onset and severe alcoholics with more behavior disturbance (type III, antisocial type). It is suggested

that the anxiety/depressive type of alcoholism might correlate with serotonin system; antisocial type might correlate with dopamine system [11].

In the current review, we discuss the role of serotonin and possible interaction of serotonin-related genes with alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) genes in alcohol dependence. Specifically, the serotonin-related genes include genes encoding functional proteins in metabolic pathway of serotonin, serotonin receptors, and serotonin transporter [13,14].

Genetic studies of alcohol dependence

Despite strong evidence for genetic effects contributing to alcoholism susceptibility, detecting the specific genes that increase or decrease the risk of alcoholism has been proven to be difficult. Many factors lead to the slow progress in isolating the genes involved in drinking behavior. Many genes are thought to contribute to alcoholism susceptibility, and different genes are likely to cause alcohol dependence in different individuals [15,16]. Furthermore, there is substantial phenotypic heterogeneity in the manifestation of alcohol dependence, with alcoholics differing on dimensions such as age of onset of problems, alcohol symptoms, drinking history, and comorbid disorders. Some evidence suggests that heritability (or genetic risk) may be more important in certain subtypes of alcoholics [17]. Other investigators have studied endophenotypes as a means to deal with the substantial heterogeneity involved in alcohol dependence. It is possible that genes act more directly on an endophenotype, as compared with a diagnostic classification; therefore, the study of endophenotypes may more efficiently lead to the identification of genes [3]. All of these factors considerably complicate efforts to identify the genes involved in alcohol dependence and to understand the contribution of any specific gene that is identified.

Candidate genes of alcohol dependence

In general, the genes concerning biochemistry, physiology, pharmacology, and pathology that are related to alcohol could be the candidate genes of alcohol dependence. Enzymes that function in the metabolic breakdown of alcohol have been considered a major biological factor influencing drinking behavior and the development of alcohol dependence [18-20]. In vitro, most ethanol is first metabolized into acetaldehyde by ADH and then to acetate by ALDH [21,22]. Until today, the actual gene etiology is not yet assuredly identified because of the highly heterogeneous and complex genetic mechanisms of this mental disorder [7]. The genes that have been consistently replicated to contribute to alcoholism susceptibility (or protection effect) are polymorphisms in the alcohol-metabolizing enzymes: ADH and ALDH [24,25]. The other candidate genes that have been proposed include genes involved in GABAergic, dopaminergic, serotonergic function, and neuropeptide Y [3].

Alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) genes

There are seven human ADH genes (ADH1–ADH7) [25,26]. All seven genes have been mapped to an approximately 380-kilobase region of chromosome 4q21–23 (GenBank accession numbers AP002026, AP002027, AP002028, and AC097530). The functional polymorphism of the ADHIB gene (previously called ADH2) and the ADH1C gene (previously called ADH3) are produced by a single-nucleotide substitution in exon 3 of ADH1B*2, exon 9 of ADH1B*3, and exon 6 of ADH1C*2 [27,28].

There are sixteen ALDH genes [29]. The ALDH2 gene has been mapped to chromosome 12q24 [28]. This gene has a functional SNP in exon 12, resulting in a glutamic acid/lysine exchange at position 487 (ALDH2*2). This polymorphism causes a reduction in the enzyme's activity [28,30].

In vivo, the ADH1B, ADH1C, and ALDH2 gene products have a lower K_m and a higher catalytic efficiency (V_{max}/ K_m) than their other ADH or ALDH counterparts. These findings are consistent with a primary role of ADH1B, ADH1C, and ALDH2 in the metabolism of ethanol and acetaldehyde. Enzymatic studies have demonstrated that the ADH1B*2/*2-encoded enzymes exhibit a 30- to 40-fold greater V_{max} for ethanol oxidation than that for the ADH1B*1/*1-encoded enzymes [31,32]. Furthermore, the oxidation of ethanol by the ADH1C*1/*1-encoded enzyme occurs at twice the rate of that catalyzed by the ADH1C*2/*2-encoded enzyme [33,34]. The ALDH2*1/*1-encoded enzyme is an active

form, whereas the enzyme encoded by ALDH2*1/*2 or ALDH2*2/*2 is an inactive form [35].

Studies with East Asian subjects have indicated that this functional polymorphism of the ALDH2 gene can influence the blood level of acetaldehyde after alcohol ingestion [36-39]. Furthermore, the frequencies of the ADH1B*2 and ALDH2*2 allele have been found to be lower in alcohol-dependent subjects than in non–alcohol -dependent subjects among several East Asian populations, including Han Chinese [23,24,40], Koreans [41,42], and Japanese [43-45].

In contrast to the suspected role of ALDH2 in alcohol dependence, an ADH1C polymorphism may exert only a minimal or no effect on the development of alcohol dependence [24,46]. Linkage disequilibrium between the ADH1B and ADH1C loci [45] indicates that the observed differences in the frequency of the functional polymorphism at ADH1C between alcohol-dependent and control subjects are dependent on the polymorphism of ADH1B. Thus, the association between the risk of alcohol dependence and ADH1C cannot be inferred when ADH1C is considered singly [24].

Serotonin (5-Hydroxytryptamine; 5-HT)

5-HT is thought to be involved in many aspects of alcohol consumption, abuse, and dependence. Serotonin systems affect mood, consummatory behaviors, and the development of tolerance to alcohol [47]. Ethanol produces transient increases in serotonergic functioning that activate the mesolimbic dopaminergic reward system [48]. There was evidence that DRD2 gene might interact with the ADH and the ALDH genes in the development of anxiety-depressive alcohol dependence [49]. Besides, there is report concerning pharmacological agents that increase 5-HT may cause a reduction or increase in alcohol self-administration in both rats and humans [50].

The gene encoding the 5-HT transporter (HTT) has been mapped to human chromosome 17q11.2 [51]. It exhibits functional polymorphism, with the shorter allele demonstrating lower transcriptional efficiency. An association between the short allele of HTT and anxiety-related personality traits has been reported [52], supporting the idea that HTT may play a role in alcohol use via its involvement in harm avoidance [1].

A number of studies have investigated the role of HTT, with contradictory results. In a case-control study of German alcohol-dependent subjects with a history of withdrawal seizure or delirium, the frequency of the short allele was found to be increased among alcoholic subjects [53]. A subsequent study comparing alcohol-dependent patients and controls also suggested a higher frequency of the short allele of HTT among patients [54]. Another study revealed an increased frequency of the short allele among habitually violent type 2 alcoholics, as compared with type 1 alcoholics and normal controls [55]. A family-based association study also found support for an association between the short allele of HTT and alcohol dependence [56]. However, a number of studies have suggested positive results supporting the role of the long allele of HTT in alcohol use. A small, preliminary study of the level of response to alcohol revealed that individuals homozygous for the long HTT allele had lower levels of response to alcohol and the sample had a higher proportion of alcoholics [57]. A case-control study of alcoholics also found a higher frequency of the long allele among alcoholics as compared with controls; this association became more significant when limited to type II alcoholics [58]. Nevertheless, no associations remained significant after correcting for multiple testing. A study of children of alcoholics uncovered that children homozygous for the long allele had higher levels of behavioral disinhibition, negative affect and an earlier age of onset of alcohol use [59]. Finally, a case-control study of Japanese alcoholics revealed that alcoholics with the long allele had a significantly earlier onset of alcohol dependence than individuals who were homozygous for the short allele [60]; no association was found between the short allele and a diagnosis of alcoholism or antisocial alcoholism.

Other studies have suggested no evidence of association with HTT. With a family-based design in the genome-wide screen of alcoholism in the Collaborative Study of the Genetics of Alcoholism (COGA) project, no support was found for either linkage or association between the HTT gene and alcohol dependence, defined by using a variety of diagnostic systems [61]. In a large case-control study of Japanese alcoholics, no differences in the frequencies of the long or

short alleles were found between alcoholic and control subjects; however, alcoholic binge drinkers had a significantly higher frequency of homozygous short alleles than alcoholics who did not binge drink [62].

A very limited number of studies have also tested polymorphisms in other serotonin-related genes. A sample of alcoholics and normal controls was tested for differences in polymorphisms in a variety of the other genes involved in the serotonergic pathway, specifically, variations in tryptophan hydroxylase, the 5-HT receptors 5-HT2A and 5-HT2C, and monoamine oxidase A (MAOA) genes [58]. The allele frequencies of 5-HT2A differed between alcoholics and normal controls, and a MAOA gene polymorphism differed between type II alcoholics and controls; however, no association was significant after correcting for multiple testing [58]. The Schuckit study, previously mentioned in relation to HTT [56], suggested no evidence of association with the 5-HT2A and 5-HT2C receptor genes with a low level of response to alcohol or a diagnosis of alcoholism. Two recent case-control studies have also investigated the role of the 5-HT1B receptor gene and failed to show an association with 5-HT1B and alcohol dependence [63,64], even when limited to alcoholism comorbid with antisociality [64]. However, linkage has been reported to mouse chromosome 9 with a variety of alcohol-related phenotypes, such as alcohol consumption and alcohol-induced hypothermia, in a region containing the 5-HT1B receptor gene [65].

Thus, the role of the serotonin-related genes in alcohol use and dependence remains unclear. The role of the HTT gene is controversial, with studies reporting association to alcohol dependence and drinking behavior with each of the two alleles. There is currently little support for the role of the 5-HT receptor genes and additional genes involved in the serotonergic pathway.

The biological consequences of the gene polymorphism

The biological consequences of the gene polymorphism concerning alcoholism have been shown in some studies; for example, the role of acetaldehyde in the saliva and in the large intestine with respect to its role in the pathogenesis of alcohol-associated cancer [66]. Data identified individuals carrying homozygous ADH1C&1 allele as high on risk for alcohol-associated upper aero-digestive tract cancer. Although the role of the hepatic microsomal ethanol oxidizing system in the metabolism of alcohol in alcoholic disease is not clear, oxidation of ethanol via alcohol dehydrogenase may explains various metabolic effects of ethanol but does not account for the tolerance.

Also some article describing the differences between the ADH polymorphism in different ethnicity [67]. The role of polymorphism in the view that acetaldehyde (the metabolite produced from ethanol by either ADH or MEOS) impairs hepatic oxygen utilization and forms protein adducts, resulting in antibody production, enzyme inactivation, and decreased DNA repair has been debated.

Possible ADH and ALDH interactions on the metabolic pathways of serotonin and ethanol

Although serotonin appears to have a role in alcohol drinking, it is still not so clear that ADH or ALDH allelic variants interact with serotonin levels. There was observation that ethanol intake significantly alters serotonin metabolism [68]. Ethanol and biogenic amines share some catabolic enzymes, and during ethanol oxidation the conversion of serotonin shifts away from oxidation of the intermediate 5-hydroxyindole-3-acetaldehyde (5-HIAL), producing 5-hydroxyindole-3-acetic acid (5-HIAA) toward the reductive pathway forming 5-hydroxytryptophol (5-HTOL) [68,69]. This has been attributed to competitive inhibition of ALDH by ethanol-derived acetaldehyde, and an increased rate of reduction of 5-HIAL by ADH as a result of the raised NADH/NAD^+ ratio [70,71]. In addition, the ADH catalyzed re-oxidation of 5-HTOL is inhibited by ethanol, and this may also contribute to the shift in serotonin metabolism [72]. Although it is not yet clear that differences in the ratio of 5-HTOL/5-HIAA have any bearing on CNS 5-HT levels, the urinary 5-HTOL/5-HIAA ratio remains increased for several hours after blood and urine ethanol concentrations have declined to endogenous levels in humans [73]. A shift in serotonin metabolism could also be demonstrated in rats administered an oral dose of ethanol, although the increase in the urinary 5-HTOL/5-HIAA ratio was much less dramatic (~two fold) [72] compared with that found in man (>100 fold) [73] after a corresponding ethanol dose. Moreover, in rat, significantly in-

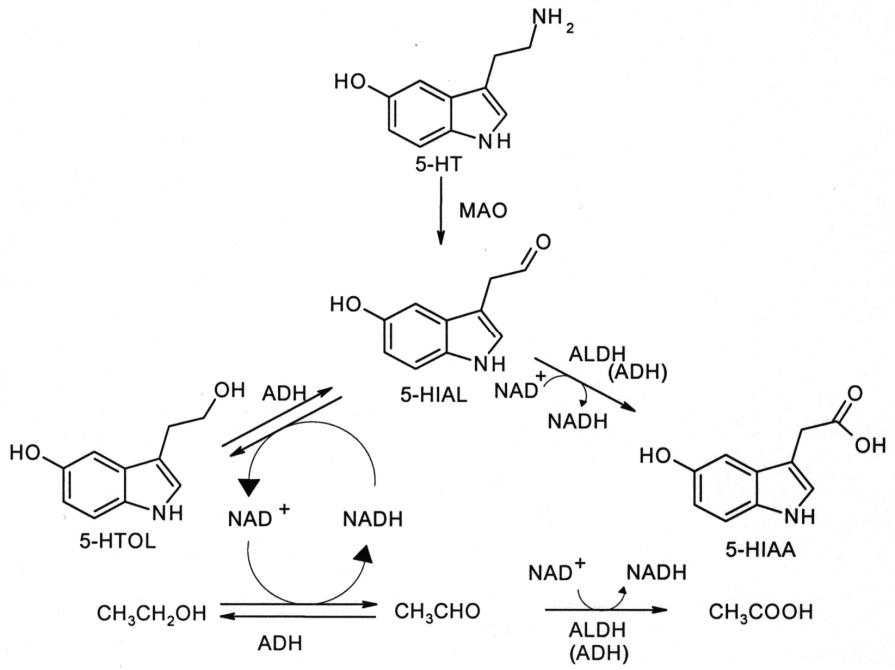

Figure 1. The possible ADH interactions on the metabolic pathways of serotonin and ethanol. (Adapted from Svensson et al. 1999 [71], with reprint permission).

creased 5-HTOL/5-HIAA ratios were seen in liver, ileum, and spleen, indicating that the interaction between ethanol and serotonin metabolism may also take place outside the liver [74].

Figure 1 illustrates the possible ADH interactions on the metabolic pathways of serotonin and ethanol [75]. Serotonin (5-HT) is metabolized in a first step by monoamine oxidase (MAO) to 5-HIAL. Normally, 5-HIAL is mainly oxidized to 5-HIAA by ALDH and the reduction to 5-HTOL catalyzed by ADH, and to some extent also NADP-dependent aldehyde reductase, constitutes a minor route. Ethanol metabolism increases the NADH/NAD^+ ratio on ADH and thereby makes ADH reduction of 5-HIAL more favorable. In addition to reduction, ADH has the capability to oxidize aldehyde.

Possible interaction of serotonin-related genes with ADH and ALDH genes in alcohol dependence

Serotonin system is well-known for modulating depression and anxiety. Alcohol dependence frequently coexists with anxiety disorder or mood disorder, which often are difficult to distinguish from each other [76-78]. Different subtypes of alcohol dependence have been reported, in particular the type I condition, which is associated with more emotional dependence, a more anxious/depressed personality, high harm avoidance, high reward dependence, and low novelty-seeking [1,79]. In contrary, type II is associated with early age of onset, impulsive, antisocial, and with low levels of brain serotonin. The high comorbidity between alcohol dependence and anxiety/depressive disorders, possibly at the genetic level, makes it vitally important to differentiate their categorical diagnoses in the association study. The foregoing observations, as well as the possible ADH and ALDH interactions on the metabolic pathways of serotonin and ethanol, let us hypothesize that the serotonin-related genes might interact with the ADH and ALDH genes to influence alcohol-drinking behavior.

Figure 2 depicts a schematic summary of the potential interactions among serotonin-related genes and ADH/ALDH genes. Genes encoding functional proteins in metabolic pathway of serotonin, such as tryptophan hydroxylase gene and monoamine oxidase A (MAOA) gene, might interact with ADH and ALDH genes to influence the vulnerability of alcohol dependence via al-

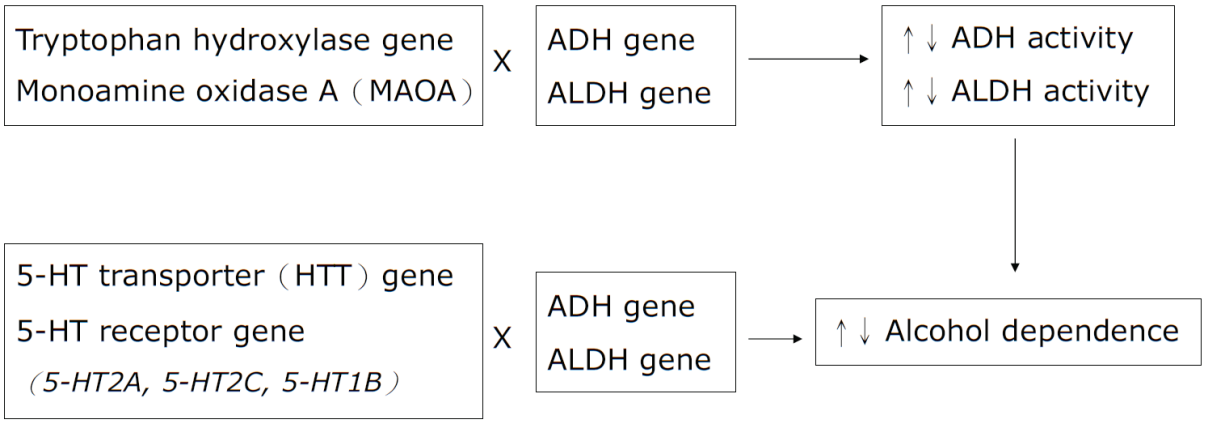

Figure 2. The potential interactions among serotonin-related genes and ADH/ALDH genes.

ternating ADH or ALDH activity. Besides, other serotonergic genes including 5-HT transporter (HTT) gene and 5-HT receptors genes might interact with ADH and ALDH genes to increase or decrease drinking behavior.

Perspectives for future study

The conflicting findings about the role of serotonin genes in alcohol dependence have generated controversy. There are several possible explanations for these conflicting results. First, these studies did not subtype alcohol dependence, even though alcohol dependence is a complex phenotype with a heterogeneous etiology. Study of the various alcohol dependence subtypes could reduce contradictory factors of this heterogeneous affliction and thus uncover the association between serotonin-related genes and specific subtypes of alcohol dependence. Second, definitions of control groups in the various studies have been inconsistent. Some studies, for example, have used a “super” control, whereas other studies have not. In genetic association studies, the use of suitable controls is very important [80]. The serotonin-related genes might be associated with other substance use disorders and other mental disorders. Lack of a carefully matched control group may cause spurious positive or negative results. Thus, the control group should exclude substance use disorders and other major or minor mental disorders. Third, the conflicting results might be due to a racially or ethnically mixed study population, because the frequency of serotonin-related genes is quite different among different racial or ethnic groups [81,82]. The results of association studies of serotonin genes and alcohol dependence might be influenced by population admixture if subjects are recruited from different population groups. Fourth, the haplotype may be more powerful in an association study than any single nucleotide polymorphisms (SNPs) [83]. Thus, the haplotype of the serotonin-related genes locus could provide more information and a more compelling test in an association study of the serotonin-related genes and alcohol dependence.

Conclusion

Genetic variants for the principal enzymes of alcohol metabolism influence drinking behavior and protect against alcoholism. Vulnerability to alcoholism is likely to be due to multiple interacting genetic loci of small to modest effects. First-line therapeutic targets for alcoholism are neurotransmitter pathway genes implicated in alcohol use. Of particular interest are the 'reward pathway' (serotonin, dopamine, GABA, glutamate, and beta endorphin) and the behavioral stress response system (corticotrophin-releasing factor and neuropeptide Y) [84]. Common functional polymorphisms in these genes are likely to be predictive (although each with small effect) of individualized pharmacological responses. Genetic studies, including case-control association studies and genome wide linkage studies, have identified associations between alcoholism and common functional polymorphisms in several candidate genes. However, to date, the only genes that are known unequivocally to affect drinking habits are those that code for proteins involved in alcohol me-

tabolism. Despites the controversy concerning the role of serotonin genes in alcohol dependence exists, searching the interaction of ADH and ALDH genes with serotonin-related genes in alcohol dependence still plausible.

Further study should be designed to test whether there is an interaction (or epistasis) between serotonin-related genes and alcohol-metabolizing genes in certain subtypes of alcohol dependence. If epistasis between the serotonin-related genes and alcohol-metabolizing genes dose exist, association studies with the serotonin genes alone may not be sufficient to detect a true relationship between alcohol dependence and the serotonin-related genes [85]. Recruitment of "super-control" individuals with solely anxiety-depression, individuals with both alcohol dependence and anxiety-depression, and individuals with pure alcohol dependence may be one solution to overcoming the possible confounding effects, to reducing false-positive or false-negative results, and to re-evaluating the association between the serotonin-related genes and alcohol dependence.

Geneticists hope that before long, alcoholism will yield up more of its genetic secrets. This should lead to new therapies that target specific genes or their products, and possibly treatments tailored to individual genetic backgrounds, i.e. the pharmacogenomics of alcohol response.

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