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Review Article

Genetic Basis of Idiosyncratic Responses to Alcoholism

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Abstract: Aim: The scientific viewpoint of genetic polymorphisms associated with risk of alcoholism and its adverse individual behavioural reactions is the main focus of this review. A complex syndrome like alcoholism and its idiosyncrasy may not be entirely understood on the basis of pathophysiological concept of neurotransmission alone. While neuropharmacology explains the mechanism behind molecular basis of alcoholism, the variation in alcohol induced abnormal neurotransmission due to presence or absence of different gene variants or isoenzymes of a particular gene on the other hand is a strong indication of genetic predisposition to alcoholism. In this article the term alcohol is used as a generic name for ethanol, which is the main subject of this discussion. Conclusion: The concomitant untoward intrinsic toxicity associated with alcoholism that makes it a potential trigger to a myriad of abnormal behavioural reactions in not only dose dependent pattern but with strong genetic disposition arises majorly due to different modes and levels of genetic variation in metabolic enzymes.

Keywords: Alcoholism, Genetic, Polymorphism Neurotransmission, Enzymes, ALDH, ADH, Cytochrome P_{450}

1. Introduction

Ethanol which is generically called alcohol has been a part of human culture with a universal history across almost all societies in which it is consumed, experiencing net health and social problems [1, 2]. Alcohol is one of the commonly available and widely abused substances and its beverages are one of the most widely consumed drinks [3]. It is the third-most popular drink overall, after water and tea [4] and viewed by some to be the oldest fermented beverage [5-8]. With the industrialization of alcohol production and the globalization of its marketing, alcohol consumption and its related problems have increased worldwide [9].

The volumes, patterns and concentrations of alcohol consumption are likely a risk factor to some chronic diseases and conditions. In some traditions, ethanol consumption is recommended as an antidote for people who have consumed ethylene glycol, as it inhibits its oxidation to the toxic ethanal (aldehyde) and subsequently to oxalate, allowing time for the glycol to be eliminated from the body unchanged [9]. Rather than having nutritional value, complications of alcohol nutritional implications abound. In small doses it stimulates appetite while larger amounts suppress hunger, which deprives the body of nutrients leading to malnutrition and anaemia. This is because it displaces nutritious foods like protein, carbohydrate, etc from the diet due to its high calorific value (but devoid of nutritional content) which can satisfy caloric requirements but easily leads to malnutrition.

The relatively high solubility of ethanol in water to its fat absorption tendency helps it to distribute itself mostly in tissues rich in water (muscle) than in those rich in fat [10]. This could also account for slight differences in alcoholism among people with different body mass indices (BMI). Alcohol is one of the most widely used groups of pharmacologic active agents that are of important medical uses with multiple psychoactive actions in varying doses in different individuals ranging from loss of integrative role by the cortex, resulting to confused and disorganized thinking to disruption of adequate motor control [11]. The effects of alcoholism in humans can be very devastating even to psychiatric disorders and increasing the risk of other diseases like hypertension, epilepsy, foetal alcohol syndrome, e. t. c., which mostly occur secondary to alcohol intoxication [12, 13]. Alcohol crosses the blood placental barrier to affect the foetus in the womb causing some negative effects on the cells. These effects lead to impairment of some structures responsible for spatial memory, cognitive and coordination function in the brain. It also diminishes thiamine absorption in the intestine

and depletes hepatic stores of this healthy vitamin. This leads to impairment of active thiamine in the body leading to thiamine deficiency in alcoholics [14, 10].

Alcohol idiosyncrasy may not be entirely understood on the basis of neurophysiological functioning alone but also from the genetic angle. The genetic polymorphisms associated with alcohol-induced flushing in alcoholism are through molecular mechanisms that include accumulation of acetaldehyde, release of histamine [15] and genetic influence of transmitter chemicals and their metabolic enzymes. These in turn influence alcohol consumption and have been viewed as high risk factors for developing alcohol abuse and dependence [16-18]. The drug-related mechanisms generating cumulative changes in neurotransmission are majorly genetic in nature since the presence of different gene variants can leads to diverse reactions to a particular chemical agent. While a drug may not really change a person's genes, it can stimulate some genes to amplify their production of proteins, causing alteration in cellular physiology and morphology [19].

2. Alcohol Consumption and Effects

Consumption and intoxication of alcohol can cause a serious damage to tissues in the brain and many organs in the body as it affects some important and vulnerable areas of the brain like the cerebral cortex, the hippocampus and the cerebellum. Alcoholism remains one the most rife and devastating form of substance abuse in the United States and the rest of world [20]. While a short term intoxicating alcohol consumption may be associated with decreased attention, alterations in memory and sedation, continued acute consumption may result in lethargy, confusion, amnesia, loss of sensation, difficulty in breathing, and even death. Alcohol's excitatory actions with behavioural manifestations of intoxication seem to be caused by suppression of inhibitory neurotransmitter systems [21].

The nervous system is one of the major means that coordinates the body physiology through high level processes controlled in the brain. It utilises the chemical transmission pathway between one nerve cell to another and to receptors in the effector cells. Alcohol is thought to produce its effect not only by binding to specific receptors but also by its lipophilicity which is believed to decrease transmitter release and post synaptic responsiveness by interacting with membrane lipids as well as membrane proteins. The chemical transmission takes place through the release of small amount of transmitter substances called neurotransmitters from the nerve terminals into the synaptic cleft to effect a post synaptic action by binding to specialised receptor molecules. Most of the neurotransmitters are destroyed by enzymes while some undergo "reuptake" in the sending neurone for re use. The genetic variation in the enzymes that destroys these neurotransmitters is of great importance in alcoholism. Ethanol like some other drugs of abuse mimics the natural transmitter substances to stimulate transmission of abnormal messages in the excitatory or inhibitory systems. Monoamineoxidase (MAO) is an important enzyme in the metabolism of most brain neurotransmitters that affect behaviour such as dopamine, norepinephrine, and serotonin. The genetic cum physiological variation of this enzyme and its likes in humans is key to alcoholism idiosyncrasy.

Alcohol is a known product of the addiction that alters brain function by interacting with multiple neurotransmitter systems and positively reinforces drinking through several neurochemical systems that lead to dependence, tolerance and withdrawal syndromes.

Alcohol's interaction with neurotransmitter produces neurochemical effects like magnifying the effect of gama amino butyric acid (GABA), glycine, serotonin and endorphins alongside antagonising effect on glutamate activities, increased turnover of norepinephrine and dopamine, decreased transmission in acetylcholine. This makes alcoholics to try drinking to achieve an ecstatic mood or to relieve a moody state like anxiety and in the process, increase the frequency and quantity of consumption to achieve the same effect which eventually culminates to unsuccessful attempts to stop consumption without experiencing negative physical symptoms (alcohol withdrawal syndrome). The decline in GABA function which usually results from a decrease in receptor levels or a change in the protein composition of the receptor in long term alcohol consumption leads to decreased sensitivity to neurotransmission. Similarly, glutamate receptors appear to adapt to the inhibitory effects of alcohol by increasing their excitatory activity [22, 23]. Additional studies show a compensatory decline in adenosine activity following continuing alcohol exposure [23]. It also directly or indirectly interact the brain's reward system by flooding the circuit with dopamine leading to their reinforcing characteristic. Dopamine is a neurotransmitter in the brain that is involved in regulation of emotion, motivation and pleasurable feelings that rewards our natural behaviours.

The liver is the primary site of alcohol metabolism [24] where several biochemical agents called enzymes help to convert it to other compounds (or metabolites), which can be easily processed by the body. Alcohol is also metabolized in non liver (extrahepatic) tissues [25] that do not contain alcohol dehydrogenase (ADH) enzyme, such as the brain, by other enzymes like cytochrome P_{450} and catalase. Alcohol metabolism can be categorised into two pathways viz; oxidative and nonoxidative pathways. ADH, present in the cytosol, converts alcohol to acetaldehyde (CH_3CHO). The acetaldehyde is generally short-lived as it is quickly metabolised to a less toxic acetate (CH_3COO^-) by another enzyme called aldehyde dehydrogenase (ALDH) [26]. The activities of these enzymes may lead to variation in alcohol elimination rates among individuals [27]. The amount of alcohol metabolised in the body varies widely among individuals and depends on a range of factors including liver size, body mass, learned behaviours [28], age of onset in consumption of alcohol, environment [29] and most importantly genetic factor. Reports of some analytical studies such as genome-wide association studies (GWAS), Collaborative Studies of Genetics of Alcoholism (COGA), Single nucleotide polymorphism (SNP) etc, have suggested

the occurrence of novel micro loci implicated in alcohol consumption and dependence [30]. Research has shown that different people carry different forms of ADH and ALDH enzymes. These different versions can be traced to variations in the same gene [31] as subtypes of the same receptor may respond differently among individuals depending on the location and genetic mediated structure activity relationship of neurotransmitters with the effector cells [32].

3. Alcoholism and Genetics

Although alcohol intoxication is largely dose dependent, but not all individuals who consume alcohol become alcoholics even at a given dose. Vulnerability to intoxication, addiction and tolerance has been largely linked to some genetic factors. Research findings aggregately indicate that genetic factors have a lot of influence in development of alcoholism with increase in risk for close relatives of alcoholics developing alcohol dependency among the general population [33-36]. Goodwin and colleagues suggest a stronger genetic influence than environmental influence on alcohol dependence [37]. Sensitivity to alcohol intoxication is a potent factor suggesting that both sensitivity and dependency are genetically influenced [38]. This predisposition to alcoholism is somewhat in traced to a gene in chromosome 11 that controls a type of dopamine receptor. The risk of alcohol abuse is seven times greater among the first-degree relatives of alcoholics than among first-degree relatives of non problem drinkers [33]. Other major genetic causes are mostly neurotransmitter based which is highly linked to genetic variation in most neurotransmitters involve in alcohol interaction especially dopamine receptors mediated [39] metabolism rate of alcohol in the brain. According to Yingmei Zhang and Jun Ren (2012) [20], twin case studies projects a strong genetic predisposition for alcoholism and female twin studies demonstrate that females have much lower concordance rates than males [40] for gender differences [41] which may be probably due to difference in water- fat-concentrations and BMI. Some individual genes in neurotransmitter signalling pathways linked with the ventral tegmental area (VTA) and nucleus accumbens in human studies have been identified with alcohol addiction. They include cholinergic (muscarinic and nicotinic) receptor genes [42, 43], GABA A receptor, [44], glutamate receptor [45], serotonin (5-HTT) [46], [47], dopamine [48], opoid receptors [49], etc. The effect of genetics on the degree of alcohol intoxication lies more in the basis of alcohol enzymatic metabolism in the body. The genetic variation of ADH, ALDH, cytochrome P450 (CYP2E1), and catalase in humans is a major genetic influence in alcohol consumption, intoxication, dependence and even alcohol-related tissue damage. Seven different ADH genes and nine different ALDH genes exist in humans and they have varying effects on alcohol metabolism [50]. Out of the seven forms of ADH protein, the ADH2 also known as ADH1B form is expressed in three polymorphic versions and accounts for most of the alcohol metabolism [51]. One of ADH2 polymorphism is linked with a high susceptibility to alcohol intoxication. This could account for high alcohol elimination rates seen in African Americans [52] and Native Americans[53] with the ADH1B*3 allele who metabolize alcohol at a faster rate than those with ADH1B*1. Also people of Jewish origin carrying the ADH1B*2 allele show an elevated alcohol elimination rates compared with people with ADH1B*1 [54]. On the other hand, the ADH7 gene is monomorphic in the human population and is highly expressed in the stomach and metabolizes about 30% of the alcohol before it is absorbed into the blood [50]. The ADH7 gene in females is not transcribed and translated to protein hence it is silent and this actually why females are generally more sensitive than males in response to alcohol intoxication

The ALDH that detoxifies the toxic acetaldehyde by breaking it down to acetic acid has a variant form, (ALDH2) which allele carries a single base mutation that renders it non-functional [50]. Among the 18 genes encoding members of the ALDH enzyme family, only ALDH2 plays a major role in oxidizing acetaldehyde in the liver [55]. Individuals expressing this non-functional variant form of ALDH2 have elevated levels of acetaldehyde upon consumption of alcohol which produces unpleasant feeling of intoxication like flushed face, headache, nausea, and a rapid heart rate. This makes alcohol consumption either repulsive to people with ALDH2 or highly intoxicated with very little quantity. [50]. Rivera-Meza e*t al*., (2012) [56]. showed that gene carriers of fast ADH or slow ALDH, which delay the processing of acetaldehyde in the body, tend to be non alcoholics and while carriers of slow ADH or fast ALDH that favours accumulation of acetaldehyde in the system are not only alcoholics but are also at very high risk of other concomitant intrinsic health consequences of alcoholism. Thus ALDH2 is the single genetic factor that most strongly correlates with the incidence of alcoholism in humans. Genetic differences in these enzymes may help to explain why some ethnic groups have higher or lower rates of alcohol-related problems [57-61]. For example, one version of the ADH enzyme, called ADHI*2, is common in people of Chinese, Japanese, Korean descent but are in people. These enzymes protect against alcoholism [62] by metabolizing alcohol to acetaldehyde very efficiently, leading to elevated acetaldehyde levels that make drinking unpleasant [63]. Also genetic variation in CYP2E1has been identified to affect alcohol metabolism. Enhanced alcohol metabolism by CYP2E1 contributes to alcoholics' metabolic tolerance for ethanol, thereby promoting further alcohol consumption. Genes coding for GABA receptors or associated proteins may also be critical determinants of individual differences in ethanol sensitivity [64]. Functional polymorphism in some important neurotransmitters and metabolic enzymes involve in alcohol neurotransmission processes such as serotonin transporter gene, gene encoding for the enzyme monoamine oxidase (MAO), gene encoding for the enzyme catechol-O-methyltransferase (COMT), [65] is clearly implicated in genetic basis of alcohol idiosyncrasy. MAO is an important enzyme in the metabolism of most brain neurotransmitters that affect behaviour such as dopamine, norepinephrine, and serotonin. Roland D. Ciaranello, Richard

E. Boehme 1982 [66] also reported genetic control of dopamine receptors in the nigrostriatal and mesolimbic pathways in inbred mice. COMT is involved in catabolizing catecholamines such as dopamine which is the major neurotransmitter implicated in alcohol induced rewarding process [67]. It also catalyzes the O-methylation metabolism of S-adenosylmethionine to catecholamines, including the neurotransmitters dopamine, epinephrine, and norepinephrine which results in one of the major degradative pathways of the catecholamine transmitters [68]. The biochemical mechanism of these gene regulatory actions on the enzymes is on proteolysis rather than synthesis [66]. Non alcoholics have been found to have low platelet MAO activity levels than alcoholics [69-71]. Hence, genetic differences in the alcohol metabolic enzymes like mono amine oxidase and receptor genes helps to explain why some people have higher or lower rates of alcohol-related problems.

4. Conclusion

Idiosyncratic alcohol-induced responses arise majorly due to different modes and levels of genetic variation leading to functional polymorphism in some important neurotransmitters and metabolic enzymes involve in alcohol neurotransmission pathways. It is however not without untoward intrinsic toxicity which makes alcoholism a potential trigger to a myriad of abnormal reactions in not only dose dependent pattern but with strong genetic disposition.

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