Alcohol Dependence in Taiwan: From Epidemiology to Biomedicine

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1. Introduction

Alcohol dependence (AD) is a global issue. According to the Global Status Report on Alcohol by the World Health Organization (WHO) in 2007, 1 the prevalence of AD among adult populations of European and American countries are significantly high, ranging from 7.0% to 12.2%. Although not as high as seen in Western countries, the prevalence of AD is also high in Asian countries, ranging from 4.1% to 7.3%. The causes of alcohol-related problems are complicated, and associated with a combination of genetic, physical, psychological, social, and environmental factors. In addition, alcohol policy, availability of alcohol, as well as cultural background and financial conditions of individual countries, also contribute to the variations of prevalence. For example, the prevalence of alcohol dependence among aboriginal people in Taiwan is 10 folds higher than that of Han people.1,4

Taiwanese people, with a low prevalence of AD, have long been thought to be the ethnicity immune to AD.4 However evidence revealed that the alcohol problem is severe in Taiwan. For example, the total consumption of pure alcohol in Taiwan, is as high as that in many Asian countries.5 Therefore, the problem of alcohol is of a greater concern nowadays in Taiwan. In this article, we will review alcohol research in Taiwan, focusing on its psychiatric epidemiology and biomedicine.

2. Epidemiology of AD in Taiwan

Three nationwide psychiatric epidemiological studies in Taiwan were conducted from the end of World War II to the 1980s.6,7 The first survey, which was conducted between 1946 and 1948, found only two cases of AD (0.01%) among Taiwanese communities. From 1949 to 1953, a survey was conducted in 11,442 individuals from four Taiwanese aboriginal tribes (Atayal, Paiwan, Saisiat, and Ami). In this study, only 13 cases (0.11%) were found to have AD. Among these, 8 drank actively during the survey period, while 5 were abstinent. Later in the 1980s, Hwu et al reported a 100-fold increase in prevalence (of 1.5% AD in the Taiwanese community, and 10% in Aboriginal tribes).8 The findings of the drastic increase in AD prevalence, caused academic debate concerning the issue of methodology, like interviewers’ reliability and Chinese version’s validity. A further hospital-based survey by psychiatrists, showed that the prevalence of AD was 6.6%, 5 times higher among inpatient s than community samples.9 In 1995, Cheng and Chen further showed that the prevalence of AD is 17%−32% among various aboriginal tribes.3 A more recent survey, conducted in a medical center, revealed that 12.6% inpatients have AD.10 Although so far there is a lack of nationwide prevalence of AD among Taiwanese Han populations, 3% is a reasonable prevalence estimate based on the data of the inpatient survey.

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3. Are Han Taiwanese immune to AD?

Despite the dramatic increase of prevalence of AD in Taiwan, the AD prevalence of the Taiwanese is significantly lower than that of Caucasian counterparts and neighboring countries, as well as the Formosan aborigines. Hence, Han Taiwanese are speculated to be immune to AD. Several socio-cultural factors have been proposed to account for the low AD incidence among the Taiwanese society. For example, alcohol is only consumed during ceremonial occasions, or primarily at meals and drunkenness is viewed as bad manners. In the 1970s, it was first reported the alcohol sensitivity may exist among different ethnicities, which implied that the low AD prevalence among the Taiwanese may be linked to the biological mechanism. In the 1980s, it was further revealed that the lack of the alcohol metabolizing enzyme, aldehyde dehydrogenase (ALDH) in particular, may cause aversive reactions to alcohol drinking. A series of phenotypic studies, conducted in Taiwan and Japan, confirmed that ALDH deficiency and a flush response after drinking, are significantly correlated with AD prevalence among different ethnic groups in Asia.

4. AD and alcohol-metabolizing enzymes genes

4.1. Genetic factors of AD

That AD runs in families is well-recognized. Family, twin, and adoption studies indicate that susceptibility to AD is more likely caused by genetic factors, which carries 50%–60% of the liability of risk. Therefore, genetic factors are considered to be essential for the development of AD. However, AD is not a Mendelian trait with both genetic and environmental factors affecting the risk. Numerous functional and positional candidate genes have been postulated with notable successes.

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

In contrast to the complex effects of alcohol in the central nervous system (CNS), the hepatic metabolism of alcohol by ADH and ALDH is well-understood. Functional effects of the related genes on the activity of the enzymes have been reported. Alcohol is metabolized by ADH to acetaldehyde, which is further metabolized primarily by ALDH. Acetaldehyde produces a “flushing reaction” characterized by a set of uncomfortable symptoms. Genetic variants which impede ALDH function and increased ADH function, are thought to be protective against the development of AD.

For ADH, three different alleles, ADH1B*2, ADH1B*3 and ADH1*C, have been shown to alter the enzymatic activity of ADH, with ADH1B*2 and ADH1B*3 altering the activity more than 30-fold. Hence, individuals carrying these alleles presumably have higher levels of acetaldehyde, and therefore are at lower risk of AD development. However, the frequencies of the three alleles vary extremely between different ethnic populations. Specifically, ADH1B*2 is commonly found in Asians but rare in other ethnic populations, and ADH1*C is also higher in Han Chinese (90%) than Europeans (55%–90%). A meta-analysis revealed that ADH1B*2 has protective properties decreasing the risk of AD by a factor of 3, compared to the ADH1B*1 allele.

Work with ALDH2 provides an instructive insight into searching the candidate genes for AD. Among the nine gene families encoding for human ALDH, only ADH1 and ALDH2 play a major role in the acetaldehyde oxidation. The ALDH2*2 allele is particularly associated with enzyme inactivity resulting in symptoms of acetaldehyde syndrome. Although the allele is rare in Caucasian and African populations, it is commonly found in Asian populations. Studies examining the association between ALDH2*2 and alcoholism show that ALDH2*2 can reduce the risk of AD by a factor of 10. An effect greater than that from ADH1B and ADH1*C. ALDH2*2 allele carriers have only a 25% risk of developing AD compared with ALDH2*2 non-carriers.

Recently, researchers attempted to focus on candidate genes which map within linkage peaks. Two different regions of chromosome 4 are best characterized in the AD risk loci map: an ADH gene cluster in the long arm and a GABA_A receptor subunit gene cluster in the short arm. Using a range of methods, including Hardy-Weinberg disequilibrium analysis, structured association, and family based association, ADH4 has been shown to have a significant association with AD risk in the gene cluster.

4.3. Dopamine (DA) receptor gene

Dopamine (DA) is the neurotransmitter which has been classically associated with the reinforcing effects of drugs of abuse, and may have a key role in triggering neurobiological changes in the reward system. Alcohol can stimulate DA release in the nucleus accumbens through the mesolimbic dopaminergic pathway, to increase self-rewarding. Previous studies indicate that the DRD2 receptor is involved in DA-mediated reinforcing effects of alcohol. Therefore, the DA receptor gene (DRD2) has been considered a candidate gene to be implicated in AD. However, the results of the association between DRD2 gene variants and AD are indeed mixed across studies. Several possible explanations might account for these conflicting results; one of these may be that haplotypes, rather than single nucleotide polymorphisms (SNPs) of the DRD2 gene, play a more important role in the association with AD. For instance, in Mexican Americans, the exon 8 genotype in combination with five other SNP genotypes, Taq 1A, promoter gene, Taq 1B, intron 6, and exon 7 are associated with AD.

The distribution of allele frequencies of various DRD2 genotypes differs between populations to a noteworthy extent. In the Han Chinese population, the genetic variants of DRD2 are found to have equivocal associations with AD risks. It has been widely accepted that some disease-relevant genes may affect a range of genetically influenced intermediate characteristics (also called “endophenotypes”) which subsequently affect the risk for alcohol-related problems. As such, DRD2 genotypes are reported to be associated with anxiety/depression in alcoholism and alcoholism with conduct disorder. In a case-control study in an independent Han Taiwanese population (number of AD subjects: 320; number of non-AD individuals = 314), we did not find any genotypic or haplotypic association with AD (MC Huang and C.C. Chen, unpublished data).

5. Oxidative stress associated with the metabolism of alcohol

The multi-organ toxicity caused by alcohol is related to its metabolism by forming free radicals or interacted compounds. In addition to ADH and ALDH, a minor pathway for alcohol metabolism is ethanol-inducible cytochrome P450 2E1 (CYP2E1). However this pathway may play an important role in the range of high alcohol levels, as well as in chronic alcoholics. CYP2E1-mediated metabolism induced by alcohol generates more toxic metabolites, including reactive oxygen species (ROS, containing superoxide anion and hydrogen peroxide) as well as ethanol-derived (hydroxyethyl) free radicals. These products cause DNA
damage, generate protein adducts, and initiate lipid peroxidation. Among them, malondialdehyde (MDA) is a reliable marker of oxidative damage, and reflects the extent of interaction between oxygen molecules and polyunsaturated fatty acids. However, several antioxidant defense mechanisms exist, which are involved in the elimination of ROS, including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPX). SODs catalyze superoxide radicals to hydrogen peroxide and thus are critical for prevention from further toxic oxidative radicals. CAT and GPX are responsible for further metabolizing hydrogen peroxide to water and oxygen.

5.1. Elevated lipid peroxidation and weakened antioxidant defenses in AD patients

A host of studies have investigated the effect of alcohol on oxidative stress in humans. In comparison to controls, MDA levels are increased significantly in alcoholic.36,37 Antioxidant activities are generally decreased in chronic alcoholics. After withdrawal, SOD and GPX activities are reduced, while CAT activity is unchanged from the baseline levels.38,39 Our data have also shown that MDA levels and activities of SOD and GPX in the blood in alcoholic patients are significantly different from those in healthy controls.40–42 In AD individuals, MDA levels are found to be significantly higher than those in controls; they gradually normalize after 2 weeks of detoxification. Meanwhile, a remarkable and persistent lowering of SOD and GPX activities is found throughout the 2-week withdrawal period. CAT activity is no higher than that in controls at baseline, but is decreased markedly afterwards, and even levels lower than those in controls after 2 weeks of detoxification. We suggest that alcoholic patients have enhanced lipid peroxidation and depressed antioxidative mechanisms.

5.2. Enhanced oxidative DNA damage following chronic alcohol consumption

As mentioned before, radical-driven products through alcohol metabolism can induce oxidation of various cellular biomolecules, including lipids, proteins, and DNA, and cause oxidative damage. Among ROS, the highly active hydroxyl radical can cause strand breaks in DNA and base modifications, by reacting with the C-8 position of the guanine base on DNA through hydroxylation, and generating 8-hydroxy-2'-deoxyguanosine (8-OHdG).43 In addition, nitrous oxide (NO) can also react with superoxide to form peroxynitrite, to produce 8-OHdG by a “hydroxy radical like” mechanism.44 8-OHdG is considered to be a sensitive biomarker to estimate the ROS-induced DNA damage in vivo45 and has gained much attention because of its mutagenic potential as well as its relevance to cancer, aging, and neurodegeneration. Of note, we found that a significant increase of serum 8-OHdG levels exists in AD patients compared with normal controls. While serum MDA levels are normalized after alcohol detoxification treatment, serum 8-OHdG levels remain elevated in the same period. This finding suggests that a heightened oxidative DNA damage would not recover during early alcohol withdrawal.46

5.3. Oxidative stress contributes to alcohol withdrawal and addiction

During prolonged exposure to alcohol, individuals with AD will experience the alcohol withdrawal syndrome (AWS) when they abruptly reduce or discontinue alcohol consumption. The overexcitation of N-methyl-D-aspartate (NMDA) glutamate receptors has long been implicated in the mechanisms underlying AWS. Due to the characteristics of high oxygen consumption, rich polysaturated fatty acids, and poor SOD and CAT activity, the brain is highly susceptible to alcohol-induced ROS generation which promotes neuronal damage. Therefore, oxidative stress plays an important role in the manifestations of AWS by interacting with glutamate overactivation.47

Consistently, our clinical study has also shown that the AWS may be a possible reflection of excessive oxidative damage in the CNS.40 We found that AWS severity is correlated more robustly with 8-OHdG and MDA levels.46 The phenomenon suggests that AWS, a manifestation of central glutamate overexcitation, is interwoven with oxidative damage which presumably contributes to mechanisms of addiction.

6. Neuroadaptation for alcohol dependence

The neuroadaptation theory has long been implicated in the mechanisms underlying addiction. Brain-derived neurotrophic factor (BDNF) is the most abundant member of the nerve growth factors in the brain. It promotes neuronal survival and differentiation, modulates the activity of neurotransmitters, and participates in plasticity mechanisms. Activity dependent activation of BDNF is associated with the neuroadaptation of neurons in brain reward circuitry and takes part in addiction.48,49

6.1. Brain-derived neurotrophic factor (BDNF) and AD

The acute effect of alcohol produces changes in signaling pathways altering gene expression, such as BDNF.49 BDNF expression is increased both in vitro and in vivo following acute alcohol exposure. The BDNF elevation is postulated to be an endogenous neuroprotective response against alcohol-induced disequilibrium to maintain the “homeostatic pathway” or to counteract the rewarding effects of alcohol.49 However, the opposing adaptation (i.e., neuroadaptation) accompanied by chronic alcohol exposure, causes a reduction in BDNF expression. Additionally, alcohol directly dampens BDNF expression and signaling.50 Therefore, the role of BDNF in counteracting addiction is attenuated after long-term alcohol consumption,49 causing an increase in drinking behavior. In animal studies, chronic alcohol exposure is shown to decrease BDNF and NGF expression.51 Consistently, our human studies also found that individuals with AD have lower BDNF levels in the blood.52,53

6.2. BDNF and alcohol withdrawal syndrome

The disinhibition of BDNF during alcohol withdrawal, is suggested to exert a protective function against neuronal damage through stimulation of sprouting and synaptic reorganization.51 Brain insults such as sustained stress, epileptic, hypoglycemic, ischemic, and traumatic events can trigger BDNF expression. It is postulated that increased glutamate release and calcium influx are responsible for increasing BDNF during the insults. In accordance, overexcitation of glutamate NMDA receptors, implicated in AWS-related neurotoxicity,54 would be expected to promote BDNF elevation to cope with the aggressive NMDA overactivation of AWS. Based on those clinical study observations, we suggest that the BDNF levels are increased after alcohol withdrawal in AD patients.52,53 and that BDNF elevation plays an important role in enhancing the resilience of neuronal cells during withdrawal, which would further contribute to the progressive nature of AD.

6.3. BDNF may be involved in modifying the phenotypes of AD

The spectrum of AWS ranges from mild symptoms to severe complications, such as withdrawal seizures and delirium tremens.
AD is a debilitating psychiatric disorder worldwide which is characterized by persistent, compulsive and uncontrolled drinking. A recent study has shown that, among drug-related harm, alcohol is listed as the most harmful drug. An earlier report also revealed in Taiwan that AD patients are associated with a higher mortality. In addition, according to the report of the Department of Health in Taiwan, more than 40% of domestic violence is associated with alcohol use. AD is also a potent risk factor for suicide, and is associated with a higher risk of depressive and anxiety disorders. Given the multiple harmful effects associated with AD, we believe that pertinent research can provide a key to a more detailed understanding and develop feasible approaches to deal with the challenging disease.

In this review, we have addressed the long-known relationship of the alcohol-metabolizing enzymes to AD risk in Asian populations, including Taiwanese, who are considered to be immune to the development of AD. ADH and ALDH findings have been replicated across many genes and populations beyond the initial work, although there still exist conflicting results in the association of genes in neurotransmitter systems such as DRD2 with AD risk. In recent years, a technological revolution has occurred to produce a shift from single-locus studies to genome-wide research and to promote our understanding of the mechanisms by which genetic variations alter molecular function and predispose individuals to AD.

We also have discussed the biomedicine issue associated with the process of AD. In addition to the notion that chronic alcohol consumption leads to excessive oxidative stress, we also propose that the oxidative stress may be closely linked with alcohol withdrawal severity in clinical samples and contribute to the pathophysiology of AD. On the other hand, prolonged alcohol drinking also dampens the neuroprotective mechanisms which counteract the development of AD. The long-term neuroadaptation following chronic drinking worsens the vicious cycle of addiction, favoring a process of more severe AD. We suggest that BDNF may be involved in modifying the severe phenotype of AD. However, knowledge about the underlying molecular mechanisms is just one part of the complex clinical architecture of AD. Looking ahead, our ability to better map the interactions between genes, biomedicines, and the environment offers strategies for more effective clinical management of AD, by focusing on preventative measures for vulnerable individuals.

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