Alcohol and the Asian flush reaction

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A substantial proportion of Asian populations suffer from the 'Asian flush reaction', which is characterized by adverse reactions upon the consumption of alcohol. Common symptoms include heart facial flushing, heart palpitations, and nausea. These negative reactions are caused by a genetically polymorphic aldehyde dehydrogenase (ALDH) enzyme that is deficient and fails to break down acetaldehyde, causing an inability to metabolize standard alcohol. The accumulated acetaldehyde in the human body results in serious health consequences for Asian American populations. This targeted population faces an increased risk of developing disease including colorectal cancer, Alzheimer's disease, and markedly head and neck cancers. Western social and cultural trends in alcohol use among Asian American youths demonstrate a great influence by social pressures to consume alcohol. Due to severity of the public health implications, it is important to educate and raise awareness of this health risk and explore a harm reducing method in order to facilitate safe alcohol consumption for affected individuals.

Understanding the complex relationship between alcohol use and specific population groups is important from a public health perspective. Asian populations are an appealing ethnic target group in the study of alcohol due to the prevalence of the 'Asian flush reaction'. Approximately 30 to 50% of Asian individuals have a genetic mutation in their alcohol metabolizing enzymes found in the liver.^{1, 2} As a result, individuals carrying this genetic mutation will experience varying unpleasant reactions (e.g. facial flushing, palpitations, and nausea) immediately after consuming alcohol; these adverse effects are considered to be a natural protection from excessive drinking and alcoholism.^{1, 3, 4} Moreover, focus will be put on Asian Americans, as they are one of the fastest growing ethnic minority populations in the United States.⁵ Thus as the population grows, the importance of understanding the implications of these genetic differences increases.⁵

This paper argues that Asian individuals susceptible to the genetic flushing reaction are especially vulnerable to increased health risks, which is why public health interventions must take place to address this issue. A historical review of Western public perceptions and attitudes demonstrates how alcohol has become a widely accepted psychoactive substance in current society. The scientific review of alcohol metabolism facilitates the discussion of the specific aldehyde dehydrogenase genetic polymorphisms relevant to the Asian flushing reaction. Next, the examination of current social and cultural trends in alcohol use among Asian American youths, and discussion regarding recent scientific evidence of related pathology, demonstrates the need for change in the future. In an effort to increase

awareness and education about this genetic vulnerability, public health policy initiatives should be undertaken to target Asian ethnic minority populations. Ultimately, this proposal accepts alcohol as an inevitable component in the fabric of society, which means the best possible action is to create a strategy that reduces the harm by diminishing major health risks and allowing genetically susceptible individuals to consume alcohol more safely.

HISTORICAL AND SCIENTIFIC REVIEW

Changing Attitudes Towards Alcohol Use

In North America, social attitudes towards alcohol during the 19th and early 20th century promoted a strongly moralistic perspective against alcoholism.⁶ Society's persuasive attack on alcoholism eventually led to legislative policy action - complete prohibition. It was not until prohibition that alcoholics began to be regarded as individuals that required help and could be rehabilitated.⁶ E.D. Whitney describes how the concept of alcoholism as a moral issue during the 1920s was largely rejected by the public, and that alcoholism was then considered an individual weakness.⁶

Based on moral and religious views, alcoholic beverages were not always seen as deviant, but were considered a component of a regular diet.⁶ In North America, it was much easier to accept the ideas of alcoholism as an illness requiring treatment, than to let criticism fall on the practice of social drinking.⁶ After World War II, there was another shift in public opinion, where a greater emphasis on public health led to the establishment of public organizations specifically instituted for combating alcoholism and aiding alcoholics.⁶

The treatment of alcohol as a social problem emphasized the fact that only a small proportion of consumers were alcoholics, which meant that addressing alcoholism in this manner disregarded other social problems associated with alcohol.⁶

Alcohol Metabolism

Alcohol metabolism systems in the human body are important to discuss the relevant biological mechanisms for this paper's discussion. The pathways in the human body responsible for eliminating alcohol are found primarily in the liver with the following enzymes: alcohol dehydrogenase (ADH), aldehyde dehydrogenase (ALDH), cytochrome P450 (CYP2E1) and catalase.¹ The non-oxidative pathways involved include CYP2E1, considered an important enzyme for chronic alcohol metabolism, and catalase, which is considered a minor pathway. Thus, this paper will be focusing on oxidative pathways surrounding the isozymes of ALDH as well as some elements of ADH.^{1,3}

Alcohol (ethanol) enters the body and is chiefly absorbed by the small intestine and transported from the portal vein into the liver where ethanol is exposed to enzymes and subsequently metabolized.¹ The ADH enzyme catalyzes the conversion of ethanol into acetaldehyde, a highly volatile and toxic byproduct that can be damaging to cells and tissues.^{1,7} More than 95% of the acetaldehyde is further metabolized in the liver, but a small quantity does escape metabolism and enters the blood.^{8,9} Furthermore, the ALDH enzyme catalyzes the conversion of acetaldehyde into acetate and NADH,⁷ where it is oxidized in the liver. Meanwhile acetate escapes into the blood, reaching the heart, skeletal muscle and brain cells, where it will ultimately be oxidized into carbon dioxide.¹

The byproducts acetaldehyde and acetate acutely affect cell function by interacting with certain proteins and cell membranes, both contributing to cell and tissue damage in various ways, which increases the risk of various diseases.^{1,3} Potential negative consequence of alcohol metabolism are seen through oxygen deficits in the liver (hypoxia), including formation of harmful compounds adducts, formation of highly reactive oxygen-containing molecules (ROS), changes to reactive-oxidation states, fetal damage, impairment of metabolic processes, cancer and medical interactions.^{1,3,4} When large amounts of alcohol are consumed, metabolism of other nutrients is disrupted as the oxidation of alcohol becomes a major energy source.⁴ Chronic alcohol consumption is strongly linked to tissue damage and pathological consequences.¹

The effects of alcohol consumption vary among individuals, as blood alcohol concentration (BAC) is dependent on environmental and biological genetic factors.¹ The environmental factors influencing BAC include the rate of drinking, presence of food in the stomach and type of alcoholic beverages.¹ Other essential factors include chronic alcohol consumption, diet, weight, age, and smoking.¹ Asian individuals experience differences in alcohol metabolism

since the genetic factors influencing BAC include allelic variations in the major alcohol metabolizing enzymes, ADH and ALDH.¹

Genetic Aspects of Alcohol Metabolism

The flushing reaction to alcohol consumption has been noticed in Asian populations in the past, but it was not until the discovery of the disulfiram-alcohol reaction that closer examination of ALDH enzymatic mechanisms began.⁷ Discovered in 1948, the disulfiram-alcohol reaction demonstrated striking similarities to the symptoms of the flushing reaction.⁷ The connection between ALDH inhibition and the unpleasant reactions were associated with high blood acetaldehyde levels.⁷

The isozymes of ALDH identified to be responsible for acetaldehyde metabolism are cytosolic ALDH1 and mitochondrial ALDH2. The most significant genetic polymorphism is in the ALDH2 gene, which results in the allelic variants: ALDH2*1, the normal allele, and ALDH2*2, which are virtually inactive.^{1,3,4} As previously noted, Asian populations are strongly associated with this genetic variation, with scholars estimating that up to 50% of specifically Taiwanese, Han Chinese and Japanese populations have the ALDH2*2 allelic variant and demonstrate no acetaldehyde metabolizing activity.¹ The point mutation of ALDH2 causes the glutamic acid protein subunit to be substituted with a lysine.³ Without this acetaldehyde metabolism, acetaldehyde interacts with body cells and tissues through the bloodstream and saliva.⁴ Inherited autosomal co-dominant individuals with heterozygous or homozygous copies of the ALDH2*2 allele show significant increases in blood acetaldehyde levels after alcohol consumption, resulting in severely unpleasant physiological responses.^{1,7}

As it is commonly referred as the 'flush reaction', the symptoms characteristic of high levels of blood acetaldehyde include: rapid onset skin vaso-dilation in the face, neck and chest region (facial flushing), tachycardia (palpitations), headache, nausea, hypotension, pruritus (itchiness), alcohol-induced asthma and extreme drowsiness.^{1,3,4} The intensity and effect of the symptoms are variable among individuals with the ALDH2*2 allele. The flushing reaction is experienced in other ethnic populations including some Caucasians and American Indians, but these effects are less readily understood in scientific literature.³

This knowledge of ALDH inhibition to induce adverse effects was immediately applied to alcoholism treatment studies as a potential therapeutic agent, commonly known as Antabuse.⁷ In theory, through psychological and physical experience, the aversive effects following alcohol consumption would discourage further consumption.⁷ During the early 1970s, a great deal of research focused on the ethnic differences in alcohol metabolism.⁷ The understanding of the polymorphic mechanisms and the role of acetaldehyde progressed significantly during the early 1980s due to improved methods of measuring blood acetaldehyde levels.⁷

The strength and validity of experimental data prior to 1978 varied due to problems measuring acetaldehyde levels without compromising the data.⁷

Next, ADH is polymorphic at two gene loci with allele variants that demonstrate different kinetic properties.^{3, 4, 7} High activity ADH variants increase the rate of acetaldehyde production.⁷ Thus genetic polymorphic variants of ADH and ALDH2 play important roles in determining blood acetaldehyde levels and consequently influences alcohol intake as the aversive reaction may deter further consumption.¹ Initially, the fast rate of alcohol oxidation leads to increased amounts of acetaldehyde, however, studies show that increased blood acetaldehyde levels are more strongly affected by ALDH2*2 than ADH variants.⁷ A fast ADH or a slow ALDH are expected to elevate acetaldehyde levels and thus reduce alcohol consumption due to fear of the unpleasant aversive effects.¹

The severe dysphoric effects of the ALDH and ADH polymorphisms are considered a genetic protection from alcoholism because many studies have found a correlation with lower incidences of alcoholism.^{3, 7} Individuals homozygous for ALDH2*2 experience the most severe dysphoric symptoms while Asian individuals with ALDH2*1 variants have reported experiences of flushing, but are unlikely to be deterred from alcohol consumption due to the milder symptoms.³

CURRENT STATUS

Societal and Cultural Factors

Despite the generally accepted notion that the genetic Asian flush reaction acts as a natural protection to chronic alcohol consumption and alcoholism, research also shows that alcohol consumption of Asian American college students is not significantly lower when compared to the alcohol consumption of other ethnic groupings.¹⁰ Aside from genetic variation, Hendershot et al. identifies some of the major environmental and cultural factors that correlate with alcohol use among Asian Americans.⁵ Parental alcohol use, gender, and acculturation were found to be significant predictors of alcohol drinking behaviour.⁵ Other factors include employment, years spent in the United States, birthplace (outside of U.S.) and preference for Western television and movies.¹⁰ Adolescents of Asian and other ethnic backgrounds share common correlates of alcohol use, including psychosocial factors in perceived adult and peer alcohol use, however, these were strongly influenced by Western cultural norms.^{5, 10} Thus, many Asian individuals are susceptible to adverse flushing reactions to alcohol, however, this does not mean they are immune to the social pressures and Western cultural norms surrounding alcohol consumption.^{5, 10, 11}

Articles in the media have described how college students struggle with their flushing reactions to alcohol due to social pressures to drink alcohol.^{12, 13} The anecdotal evidence shows how the adverse reactions bring negative social consequences: "embarrassment, unwanted attention

and physical discomfort".¹³ Millikan reaffirms the claims that the genetic deficiency helps lower alcoholism, but also describes how many suffering students choose to ignore their biological reactions and continue consuming alcohol, building tolerance of alcohol.¹³ Furthermore, the social influence in the college-university setting places significant pressure to participate in social drinking, as evidenced in the valuation of superior drinking abilities.¹³

Millikan also raises the topic of methods used to alleviate the flush reaction symptoms to facilitate social drinking.¹³ Ingesting famotidine or similar products (e.g. product commonly known is Pepcid AC), traditionally used for alleviating heartburn, prior to alcohol consumption is reported to be a popular partial remedy as it masks external symptoms of facial flushing.^{13, 14} Famotidine is a histamine H2-receptor antagonist that works to block acid secretion in the stomach to alleviate heartburn and acid indigestion.¹⁴ There is some research demonstrating how histamine H2-receptor antagonists have the ability to activate ALDH isozymes, but the causation mechanisms are not well understood.¹⁴ The pursuit for remedies to prevent facial flushing demonstrates the affected individual's desire to consume alcohol in a manner similar to their peers; without the adverse reactions. For example, Millikan reports many Facebook networking groups devoted to this topic, and comprehensive discussions take place on internet message board communities where susceptible individuals can share knowledge and experiences.¹⁵

Recent Health Research Developments

In the study of alcohol related pathology, it is well understood that alcohol itself is not a carcinogen; rather it is the metabolic byproduct acetaldehyde that has proven to have mutagenic and carcinogenic effects in animals.^{16, 17} More recent scientific research in this field has revealed further evidence supporting the harmful effects of acetaldehyde and clarifying the increased risk of disease. Therefore, Asian individuals with the ALDH2 allelic variants face an even higher risk of disease due to their elevated levels of un-metabolized acetaldehyde. For example, correlations have been established between ALDH2 allelic variant individuals and increased risk of developing colorectal cancer, Alzheimer's disease and markedly head and neck cancers.^{17, 18, 19, 20}

Studies show that alcohol consumption along with environmental factors contribute significantly to the risk for colorectal cancer.^{18, 19} The health risk is further enhanced in the gene-gene and gene-environment interactions found among ALDH2 polymorphic individuals consuming alcohol.¹⁹ In addition, Wang et al. conducted a study to observe the role of acetaldehyde accumulating in relation to the risk of late-onset Alzheimer's disease within Chinese populations.²⁰ His results demonstrate a strong correlation, claiming that ALDH2 polymorphisms are found to interact synergistically with 'apolipoprotein E allele 4' a confirmed factor of Alzheimer's disease.²⁰

Asian populations with the ALDH2 allelic variant are also at a higher risk of developing head and neck cancer since current literature demonstrates the strongest pathological ALDH2 gene correlation is found with this disease grouping. The grouping of head and neck cancers includes the oral cavity, pharynx, larynx and esophagus.¹⁷ In Western countries, consumption of alcohol and tobacco smoking are identified as the main risk factors for head and neck cancer, as these factors account for 75 to 90% of the disease.¹⁷ Brennan et al. suggests that genetics are a significant factor,¹⁷ as incidence of head and neck cancer demonstrates that the majority of chronic alcohol consumers and smokers do not develop the disease. Although it is well established that alcohol consumption is a major risk factor for head and neck cancer, the specific mechanisms and causation for the disease is not well understood.¹⁷

In 2004, Brennan et al. undertook a Human Genome Epidemiology review and compiled a volume of published studies to further understanding of the effects of ADH and ALDH allelic variants in connection with risk for head and neck cancer.¹⁷ The results demonstrate that of the 4 genotypes of ADH studied, the possession of one of the fast metabolizing ADH alleles paired with the ALDH2*2 variant results in significant increases of acetaldehyde levels in the blood and thus increased risk of head and neck cancer.¹⁷ Research has also demonstrated that the acetaldehyde level in the saliva contributes to the likelihood of developing upper aero digestive tract cancer.²¹ Salivary acetaldehyde concentrations were impacted by the type of alcoholic beverage consumed, but Yokoyama et al. confirmed that inactive ALDH2 significantly increased concentrations of acetaldehyde in the saliva, thus increasing the risk for disease.²¹

PROPOSAL FOR THE FUTURE

Given all this information, the fundamental issue that arises is how Western society's perception of alcohol has a commanding influence on the perceptions of ethnic minorities. In altering this perception, the negative consequences of alcohol can be diminished. Thus, abstinence from alcohol consumption among inflicted Asian individuals would be the ideal solution, but it is evident that many indulge in social drinking despite the adverse reactions.^{10, 11, 12, 13} Therefore, a realistic proposal for the future includes a comprehensive plan to educate Asian populations about how alcohol consumption can increase the risk for disease due to their genetic predisposition. In addition to this, forming a strategy that allows individuals to consume alcohol safely can be achieved by investigating a scientific means to alleviate the adverse reactions caused by the deficient or inactive ALDH enzyme.

Targeted Education and Awareness

In order to increase awareness and education about this Asian genetic vulnerability, public health policy initiatives

should be undertaken to target Asian ethnic minority populations.

The increased risk of disease is a significant issue that greater populations should be made aware of. This issue may apply to a smaller portion of the population, but remains a pertinent issue that can be incorporated into existing alcohol education programs. In a multicultural society, Huerta & Macario consider improper risk communication to be an important factor in the disproportionate incidence and mortality rate of associated diseases in ethnic groups.²²

Increased awareness and education about the serious consequences of alcohol may contribute to preventative alcohol consumption, safer behavior, and possibly catalyze a change in the psychological perceptions of alcohol.²² It is evident that a proportion of Asian populations choose to ignore their body's natural reaction to alcohol, thus as they succumb to social pressures to consume alcohol, they are putting their health at risk. Brooks et al. encourages the important role that physicians play in making patients aware of this genetic vulnerability.² For example, Brooks et al. offers two different methods of recognizing an affected individual, including answering the two-question 'Flushing Questionnaire' about tendencies of facial flushing and 'The Ethanol Patch Test', which measures erythema.²

Moreover, Asian populations require targeted education about the unique and specific vulnerabilities due to their genetic predispositions. Through thoughtful media campaigns, Asian individuals can be made aware of the health risks. For example, incorporating the health risks into alcohol education programs in schools would be helpful, but also communicating and targeting information to known Asian communities would overcome significant barriers.²²

Therefore, developing this culturally tailored curriculum will encourage youth to develop skills that will help them make educated decisions and be resistant to external peer and media-related influences.²³ For example, Ferketich et al. evaluated the delivery of "tobacco prevention curriculum" that was developed specifically for Chinese youths in New York City.²³ The report suggests that the consideration of cultural views of immigrant students aided in the success of the campaign.²³ In order to achieve the desired outcome, where education and awareness can act as a catalyst for behavioural change, it is crucial that the unique qualities of certain cultural groups are taken into account.²³

Harm Reduction Strategy

When accepting the concept and perception that alcohol is an inevitable element of society, the best possible action for the future is to work towards developing means for safer alcohol practices. By applying principles of the harm reduction model to this issue, public health can be improved. More specifically for susceptible Asian individuals, the harms of alcohol consumption can be successfully eliminated with abstinence. But in this case, by acknowledging the significant number of individuals choosing not to abstain

despite their genetic vulnerability, a harm reduction strategy is formed.

The best course of action is to further develop scientific mechanisms to prevent the flushing reaction in affected Asian populations. This course of action will allow these individuals to safely consume alcohol and successfully reduce the health risks. As previously mentioned, histamine H2-receptor antagonist have demonstrated ability to successfully eliminate facial flushing symptoms, but these results are reported to be varied among individuals and the scientific mechanisms involved are not clearly defined.^{14, 15} In view of the existing research in this area, different ways to manipulate acetaldehyde levels in the body have been studied with varying results.⁷ Limited research has been done in this area due to lack of clinical significance since blood concentration of acetaldehyde during ethanol inebriation is normally low.⁷ Potentially useful compounds acting to 'trap' acetaldehyde include sodium metabisulfite, and the therapeutically used copper chelating agent penicillamine.⁷ The latter compound, as well as cysteine and N-acetylcysteine, also show potential to reduce acetaldehyde levels.⁷ However, penicillamine has been found to be ineffective in reducing flushing in some experimental results conducted on Japanese individuals.⁷ Crow & Batt observe that these compounds act by trapping acetaldehyde, but need to be added in large quantities since acetaldehyde is continuously formed during alcohol consumption.⁷

Thus, for clinical purposes, developing a method that will permanently reduce the rate of production of acetaldehyde may be more effective.⁷ For example, the administration of the ADH inhibitor 4-methylpyrazole has been found not only to remove or drastically reduce acetaldehyde, but also alleviate associated cardiovascular stress responses.⁷ Therefore, the scientific means of achieving safer and healthier alcohol consumption for genetically polymorphic individuals has yet to be clearly defined, but it is evidently an important subject for future research.

Furthermore, traditional criticism for harm reduction models states that this approach will promote substance use rather than encourage individuals to abstain from substance use and abuse.²⁴ In this case, alcohol consumption is a legal practice where individuals of adequate age acting responsibly are not legally condemned for participating in social drinking. This strategy does not promote alcoholism as a separate group of risk factors, which includes biological variables, personality and environmental variables – all of which are associated with the development of alcoholism and alcohol abuse.²⁵ Presently, media reports and scholarly research indicate that inflicted individuals are continuing to consume alcohol, which means that facilitating healthier and safer ways of doing so would be beneficial.^{10, 11, 12, 13}

CONCLUSION

A significant proportion of Asian populations have a genetically polymorphic aldehyde dehydrogenase (ALDH) enzyme that is deficient and fails to break down acetaldehyde, resulting in incomplete regular alcohol metabolism. The adverse reaction to high acetaldehyde levels in the blood is commonly known as the Asian flush reaction, characterized by facial flushing, palpitations, nausea and various other unpleasant symptoms. High levels of acetaldehyde in the cells and tissues of the body lead to increased risk of developing disease, including head and neck cancer, colorectal cancer, and Alzheimer's disease. Western social and cultural norms encourage alcohol consumption and Asian American youths appear to be greatly influenced by social pressures to consume alcohol. Therefore, there is a great need to address the issue of continued use of psychoactive substances despite serious adverse effects. In a proposal for the future, it would be effective to incorporate targeted educational curriculum and raise awareness about the genetic vulnerability of Asian individuals. In addition, establishing a harm reduction strategy that allows Asian individuals to continue their consumption of alcohol in a safe and healthier manner would be ideal. Although scientific means to do so have yet to be solidified, scholars have nevertheless identified this area of research to be important.

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