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Evaluation of the Influence of Alcohol Dehydrogenase Polymorphisms on Alcohol Elimination Rates in African Americans

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Abstract

Introduction—The relationship between alcohol dehydrogenase (ADH) polymorphisms and alcohol use disorders in populations of African descent has not been clearly established. This study examined the effect of ADH1B polymorphisms on alcohol metabolism and subjective response, following intravenous (IV) alcohol administration, and the influence of gender, recent drinking history, and family history of alcoholism (FHA), in nondependent African American drinkers.

Materials—The sample included eighty-seven 21- to 35-year-old, light social drinkers of African descent. Participants included 39 sib pairs, 2 sibships with 3 siblings each, and 3 individuals who were not part of a sibship. Participants received infusions via the use of the clamp method that refers to the goal of controlling breath alcohol concentration in 2 randomized sessions at 0.06 g% ethanol and 0 mg% (placebo), and a battery of subjective scales at predefined time points. Dependent measures included alcohol elimination rates (AERs), alcohol disappearance rates (ADRs), subjective measures peak scores, and area under the curve. General linear model and mixed models were performed to examine the relationship between ADH1B genotype, dependent measures, and influence of covariates.

Results—Participants with ADH1B1/1 genotypes showed higher number of drinks ($p = 0.023$) and drinks per drinking day ($p = 0.009$) compared with the persons with ADH1B1/3 genotype. AER (adjusted for body weight) was higher in ADH1B*1 homozygotes ($p = 0.045$) compared with ADH1B1/3 heterozygotes. ADR differed significantly between males and females ($p = 0.002$), regardless of body weight ($p = 0.004$) and lean body mass ($p < 0.001$) adjustments. Although a few subjective measures differed across genotype, all measures were higher in alcohol sessions compared with placebo sessions ($p < 0.001$). These observations were mediated by drinks per drinking day, gender, and FHA.

Conclusions—ADH1B polymorphism had a marginal effect on alcohol pharmacokinetics following IV alcohol administration in nondependent drinkers of African descent. Session (alcohol vs. placebo) and ADH1B genotype did, however, influence subjective response to alcohol with some variation by gender, FHA, and drinks per drinking day.

Keywords

Alcohol Dehydrogenase Polymorphisms; Breath Alcohol Clamping; Alcohol Elimination Rate; African Descent Population; Sib Pair Analysis

Alcohol use disorders are multifactorial diseases with genetic influences. Gene and environment interaction and risk of alcohol use disorders have been examined in Caucasian and Asian populations; however, limited studies of this relationship have been published in persons of African descent. The genes for the 2 main enzymes involved in alcohol metabolism, cytosolic alcohol dehydrogenase (ADH) and mitochondrial aldehyde dehydrogenase (ALDH2), demonstrate functional polymorphisms that result in isoforms which can vary significantly in expression and function across populations and likely contribute to variability in response to alcohol and susceptibility to alcohol use disorders (Bosron et al., 1993; Li et al., 2000; Luczak et al., 2006; Ramchandani et al., 2001). Previous studies have suggested correlations of the pharmacokinetics and pharmacodynamic consequences following ethanol (EtOH) ingestion (Chen et al., 2009); however, these studies were primarily conducted in persons of Asian descent.

While the functional significance of the ALDH2 polymorphism on metabolism, response, and risk of alcohol use disorders has been well characterized, the influence of ADH1B polymorphisms is less clear. There are 2 functional single nucleotide polymorphisms in the ADH1B gene: *ADH1B**2, seen in Asian and Jewish populations, and *ADH1B**3, seen in individuals of African descent and various Native American tribes (Bosron and Li, 1987; Ehlers 2007; Osier et al., 2002; Scott and Taylor, 2007; Thomasson et al., 1995; Wall et al., 1997). *ADH1B**3 allele has been associated with many characteristics including protection against development of alcoholism and birth defects for African Americans (Arfsten et al., 2004; Edenberg et al., 2006; Ehlers et al., 2001, 2003; McCarver et al., 1997; Scott and Taylor, 2007). Additionally, the *ADH1B**3 allele was associated with a negative family history of alcohol dependence (Ehlers et al., 2001), elevated alanine transaminase levels in alcohol dependent individuals (Ehlers et al., 2007), higher levels of sedation and a sharper increase in pulse rate immediately following alcohol consumption (McCarthy et al., 2010), higher risk of alcoholic liver cirrhosis (Khan et al., 2010), and some measures of acute sensitivity to alcohol (Cook et al., 2005; Duranxeaux et al., 2006; Scott and Taylor, 2007).

Other factors such as gender have been shown to influence alcohol metabolism, which can impact the risk for alcohol use disorders. Factors such as body weight, body composition (total body water), gastric absorption, and genetics have been shown to underlie gender differences in alcohol metabolism (Duncan et al., 2009; Kwo et al., 1998; Thomasson et al., 1995). The effect of *ADH1B**3 polymorphism on alcohol metabolism and influence of factors such as gender have not been fully characterized. Thomasson and colleagues (1995) examined the effect of *ADH1B**3 on alcohol metabolism following oral alcohol administration in male and female African Americans and demonstrated that the alcohol disappearance rate (ADR) or beta-60 was approximately 25% higher in subjects of both genders who carried the *ADH1B**3 variant.

The level of alcohol response can be measured by oral challenges (Addicott et al., 2007; McCarthy et al., 2010; Taylor et al., 2008; Wilhelmsen et al., 2003) as well as the intravenous (IV) clamp technique (Neumark et al., 2004; O'Connor et al., 1998; Ramchandani and O'Connor, 2006; Ramchandani et al., 1999, 2009), using validated self-report instruments such as Subjective High Assessment Scale (SHAS; Schuckit, 1984), Bodily Sensation Scale (BSS; Maisto et al., 1980), and the Biphasic Alcohol Effects Scale (BAES; Martin et al., 1993). These scales measure the individual's own perception of the

intensity of their feelings of high, intoxication, stimulation, sedation, and bodily sensations induced by alcohol and have been used widely in alcohol challenge studies (Hendler et al., 2013; Morean and Corbin, 2010). Pederson and McCarthy (2013) examined differences in subjective measures in response to acute alcohol administration between African Americans and European Americans showing a stronger response to alcohol for African Americans. There is, however, limited data on the effect of ADH polymorphisms on subjective responses to alcohol, particularly in persons of African descent. Thus, the purpose of this study was to examine the effect of ADH1B polymorphisms on alcohol elimination rate (AER), ADR, and subjective response during the alcohol clamp in African American nondependent drinkers. The study also evaluated the influence of gender and family history of alcoholism (FHA) on alcohol metabolism and response. Given the previous findings of altered alcohol metabolism and responses following oral alcohol administration in individuals carrying the ADH1B*3 variant (McCarthy et al., 2010; Thomasson et al., 1995), this study hypothesized that the protective effect of *ADH1B**3 allele would be associated with a greater AER, ADR, and a greater subjective response to alcohol in persons of African descent.

MATERIALS AND METHODS

Participants

A total of 87 healthy nondependent alcohol drinkers of African descent (21 to 35 years old) are included in this analysis. The participants were recruited as sibling pairs from the Washington, DC Metropolitan area, and screened prior to enrollment into the study. Participants included 39 sib pairs, 2 sibships with 3 siblings, and 3 individuals who were not part of a sibship. Included were 36 men and 51 women with a mean age of 26.5 ± 5.0 years, mean weight (kg) of 81.8 kg, mean height (cm) of 169.5, and mean recent drinking history of 2 alcoholic drinks per drinking day. Participants from 21 sib pairs had a positive family history of alcohol dependence, defined as having at least 1 first- or second-degree biological relative with alcohol dependence, as described below. The initial eligibility of participants for enrollment in the study was determined by a phone screen. Individuals found eligible for enrollment were invited to return to undergo a second screening consisting of a history, physical examination, and general laboratory screen (including drug testing and, if female, pregnancy testing). Screening assessments also included the Semi-Structured Assessment of the Genetics of Alcohol (Bucholz et al., 1994) to assess for alcohol problems. Family history of alcohol problems was defined as having a first- or second-degree relative diagnosed as alcohol dependent and was assessed with the Family History Assessment Module (FHAM) and the Individual Assessment Module of the FHAM (Janca et al., 1997). These instruments measured family history of psychiatric disorders including alcohol dependence using relatives' self-reported information. Among siblings and offspring implicated of dependence, this instrument has a specificity of up to 97% (Rice et al., 1995). Participants also completed the Timeline Followback (TLFB) questionnaire (Sobell and Sobell, 1992) at the start of each study session. This questionnaire measures drinking history, by asking participants to self-report the number of standard drinks consumed each day over an interval of 28 days. The quantity of drinks, total number of drinks consumed in 28 days, and number of drinks per drinking days were obtained from the TLFB.

Eligibility requirements for this study included self-reported African American/Black race of African descent; adult men and women aged 21 through and including 35; low-to-moderate social alcohol consumption (<7 drinks per week for females, <14 drinks per week for males per National Institute on Alcohol Abuse and Alcoholism [NIAAA], 2003 guidelines); negative history of alcohol dependence; physically healthy as determined by medical history, physical examination; absence of clinically significant abnormalities on

clinical laboratory screen, negative urine drug screen, negative serum pregnancy test for females; no medication except for multivitamins or oral contraceptives within 30 days of study enrollment; ability to speak and read the English language; and read and understand the informed consent and health insurance portability and accountability act (HIPAA) documents. This study protocol was approved by the Howard University Institutional Review Board and General Clinical Research Center (GCRC) advisory committee.

This study excluded participants (i) with no alcohol consumptions (abstainers) and (ii) with heavy or dependent patterns of drinking that might demonstrate metabolic or behavioral tolerance to alcohol, to ameliorate these confounds in the evaluation of genetic (i.e., *ADH1B*3*) influences on the metabolism and response to alcohol that are the foci of this study. Following screening and genotyping, participants were stratified into 2 groups: those that were homozygous for the *ADH1B*1* allele and those that were either heterozygous or homozygous for the *ADH1B*3* allele.

Study Design and Procedures

Each participant completed 2 randomized sessions: an alcohol session at a target breath alcohol concentration (BrAC) of 60 mg% and a placebo session, on separate days. At the start of the first session, a blood sample was obtained from each subject by finger puncture and blotted on filter paper. Samples were genotyped for *ADH1B*3* polymorphism at the Indiana University Alcohol Research Center Indianapolis, Indiana. The deoxyribonucleic acid (DNA) was isolated for genotyping. Polymerase chain reaction was used to amplify the significant portions of the ADH and ALDH2 loci, followed by hybridization with allele-specific radiolabeled oligonucleotides (Xu et al., 1988).

At the start of each session, each study participant provided a urine sample for drug testing and pregnancy test for females. Following a standardized breakfast including cereal, milk, and juice, participants completed a baseline BrAC and an IV catheter was placed in the antecubital area of arm for infusion. Participants were then fitted with an electroencephalogram (EEG) cap and leads for electrophysiological measurements. Each participant was familiarized with the study tasks, including the self-report instruments. Following a light snack, participants completed the baseline sequence of the study tasks and the baseline EEG.

After completion of the baseline tasks, participants had a 10-minute break during which time they were asked to go to the bathroom to empty their bladders. Following this, subjects received infusions of EtOH (6% v/v EtOH in Ringer's Lactate solution) or placebo (Ringer's Lactate solution) in counter-balanced order. During the alcohol session, subjects received an individualized infusion profile, based on their individual measures including height, weight, age, and sex to achieve a target BrAC of 0.06 g% in 10 minutes and maintain or clamp this level for 2.5 hours. The infusion rate profile was computed based on a physiologically based pharmacokinetic model for EtOH implemented in Matlab version 6.5 (Mathworks Inc., 2002; O'Connor et al., 1998; Ramchandani and O'Connor, 2006; Ramchandani et al., 1999). BrACs were obtained frequently, and minor adjustments made to the profile to ensure that target levels were maintained within 0.005 g% of target. Following the end of the infusion, BrAC levels were tracked at regular intervals. Measurements were taken every 10 to 15 minutes of the descending phase, with at least 4 measurements taken for each participant. Participants were not allowed to leave the GCRC until their BrAC level decreased to below 0.015 g%.

Participants completed several self-report scales to assess their subjective perceptions of alcohol effects after each task within each block during the infusion and at 2 time points following the end of the infusion at BrAC levels of 0.04 and 0.02 g%. These scales included

(i) *BAES*, which measures both sedative and stimulant effects of alcohol (Martin et al., 1993); (ii) *BSS*, which measure the subjective experience of physiological changes following alcohol consumption (Maisto et al., 1980); and (iii) *SHAS*, which assesses perceptions about a variety of sensations that are often associated with alcohol but not specifically attributed to alcohol (Schuckit, 1984). In addition, participants performed tasks designed to determine motor and cognitive effects of alcohol in attempts to assess reaction and neurosensory responses to EtOH. These included resting EEG, startle task, and eye tracking. These results will be published separately.

Data Analysis

All analyses were conducted in SAS version 9.2 (SAS Institute, Inc., 2002) and SPSS version 17.0 (SPSS, Inc., 2009). Significance was established at $p < 0.05$. Independent *t*-test and chi-square tests, as appropriate, were used to analyze continuous and categorical demographic data for differences across genotypes (*ADH1B**1 and *ADH1B**3 or *ADH1B**3). The primary pharmacokinetic measure was the AER (g/h), which was measured as the steady-state infusion rate (ml/h of infusate multiplied by 0.048 g/ml or concentration of EtOH in the infusate; Kwo et al., 1998; O'Connor et al., 1998; Ramchandani and O'Connor, 2006; Ramchandani et al., 2001). For the purpose of this estimation, steady state was defined as a period of at least 30 minutes with BrAC maintained within a range of ± 0.005 g% of the average. To account for variation of BrACs during this interval, the AER was adjusted for nonzero values of the slope of the steady-state BrACs using the ADR and the subject's estimated total body water, as previously described (Neumark et al., 2004). The ADR (mg%/min) was measured as a slope of the linear descending phase of the BrAC–time curve.

Pharmacokinetic Analysis

To examine the effect of demographics on pharmacokinetic measures, a general linear mixed effect model was used. Each pharmacokinetic measure (AER; AER adjusted for body weight [AER-BW]; AER adjusted for lean body mass [AER-LBM]; ADR; ADR adjusted for body weight [ADR-BW]; and ADR adjusted for lean body mass [ADR-LBM]) was analyzed separately as a dependent variable giving 6 individual models of dependent variables and demographic contributing factors. The *ADH1B* genotype, FHA, and gender were added as factors, while weight was added as a covariate for all dependent variables except AER-BW, AER-LBM, ADR-BW, and ADR-LBM because they were adjusted for body weight. Each model was also adjusted for sibship to account for multiple participants from the same family.

Pharmacodynamics Analysis

The area under the curve (AUC) is estimated by trapezoidal method for the following subjective measures: *SHAS* to reflect intoxication, *BAES* sedation, and *BSS* to reflect the bodily sensation. Peak scores and change in peak scores from baseline of these measures were obtained for each session and participant. Mixed model analysis was performed for each dependent measure (*SHAS*, *BAES*, and *BSS*), with treatment (alcohol or placebo), FHA, gender, and genotype added as fixed factors in the model, while sibship was added as a random factor, and drinks per drinking day added as a covariate. To examine the effect of demographics on pharmacodynamics measures, a general linear model was used. The effect of sibship on pharmacodynamic outcomes yielded no significant results ($p > 0.05$).

RESULTS

Table 1 depicts demographic characteristics stratified by *ADH1B* genotype. Most demographic variables such as gender and family history positive for alcoholism were

similar regardless of genotype. There were no significant differences in gender distribution by genotype (Pearson's $\chi^2 = 1.70$, $p = 0.19$). However, drinks per drinking day were higher in *ADH1B1*1* compared with *ADH1B1*3* ($p = 0.009$). Similarly, those with the genotype *ADH1B1*1* consumed almost twice the quantity of drinks *ADH1B1*3/ADH1B3*3* consumed ($p = 0.023$). The differences in drinking history by genotypic group remained significant even after controlling for gender, suggesting no gender by genotype effect on drinking measures.

Pharmacokinetics

Table 2 shows pharmacokinetic measures and how genotype in addition to weight, FHA, and gender influence these measures. AER differed as a function of body weight ($p = 0.008$). ADR and adjusted ADR variables (ADR-BW and ADR-LBM) were significantly associated with gender. Females were more likely to have higher ADR ($p = 0.002$) compared with males. After adjusting for body weight and lean body mass, females continued to show higher ADR although not to the magnitude of ADR before adjustment (ADR-BW $p < 0.001$ and ADR-LBM $p < 0.001$). *ADH1B* genotype and FHA did not influence AER or ADR, although a trend for higher AER-BW and ADR-BW was observed for *ADH1B1*1* compared with *ADH1B*3* carriers ($p = 0.087$ and $p = 0.071$). Running sibship as a covariate revealed that sibship was significantly related to all pharmacokinetic outcomes, with effect sizes ranging from 6 to 25%, and sibship accounted for greater variability in pharmacokinetic outcome measures such as AER-LBM compared with other pharmacokinetic outcomes such as ADR.

Pharmacodynamics

Table 3 shows the factors contributing to the total subjective scales score (AUC), peak subjective scale score, and peak score changes from baseline. Generally, differences were seen across the *ADH1B* genotype, session type (alcohol vs. placebo), or an interaction of both. These differences showed influences of FHA, gender, or drinks per drinking day that varied for each subjective scale measure.

Subjective High—For SHAS high, AUC differed by *ADH1B* genotype. Additionally, higher drinks per drinking day were associated with lower total score ($p = 0.013$). SHAS high peak score and change in peak score from baseline were also influenced by genotype but not by the interaction genotype with session type. Similar to AUC, higher drinks per drinking day were associated with lower peak score and peak from baseline score ($p = 0.002$ and $p = 0.003$).

Subjective Intoxication—SHAS intoxication followed the same pattern as SHAS high with a significant interaction of genotype and session ($p = 0.011$). Similarly, alcohol sessions showed higher AUC, peak scores, and peak from baseline scores than placebo sessions. Unlike SHAS high, only AUC had scores that were higher in *ADH1B1*3* compared to *ADH1B1*1*. Again, drinks per drinking day were inversely related to AUC ($p = 0.027$), peak score ($p = 0.004$), and peak score from baseline ($p = 0.007$).

Sensation—For sensation scores, there was a genotype–session interaction with *ADH1B1*3* genotype in the alcohol session having lower AUC, and peak score from baseline ($p < 0.05$). FHA influenced this relationship with family history positive more likely to have higher AUC than family history negative ($p = 0.033$). This indicates that while family history positive had lower total subjective scores (AUC) and lower peak scores, the difference between the peak score and baseline scores was equivalent for both family history positive and negative participants. The influence of alcohol on the peak score was moderated by FHA and gender with higher peak scores more likely among family history

positive ($p = 0.033$) and males ($p = 0.012$). Higher sensation peak score from baseline was mostly among males ($p = 0.003$).

Sedation—Sedation scores also differed by genotype. Sedation AUC ($p = 0.038$) and peak scores ($p = 0.011$) were influenced by gender with males more likely to have higher scores compared with females. Sedation peak score from baseline was however not influenced by gender, FHA, or drinks per drinking day.

Stimulation—Family history positive participants showed higher AUC ($p = 0.036$) and peak scores ($p = 0.040$), but FHA had no influence on peak scores from baseline. This suggests that while family history positive had higher total subjective scores (AUC) and peak scores, they also had higher baseline scores for this measure, which may have resulted in equivalent change in AUC and peak scores for both family history positive and negative participants. The reason for this baseline difference in stimulation scores by family history is unknown. Gender and drinks per drinking day had no influence on all stimulation measures.

From these results, it appears that performance under alcohol conditions or ADH1B*3 genotype yields higher scores for SHAS high, SHAS intoxication, and sedation, while sensation and stimulation only differed by alcohol versus placebo conditions and not by genotype. Higher scores were more prevalent among those with a positive family history, males, and those that had fewer drinks per drinking day. In all mixed models, sibship did not account for any significant increase in degree of heterogeneity on the pharmacodynamic effect of alcohol on outcome measures.

DISCUSSION

The objective of this study was to examine the effect of ADH1B polymorphisms on AERs and ADRs, and the influence of gender and FHA, using the IV alcohol clamp technique in a sample of social drinkers of African descent. The ADH1B*3 allele has been previously shown to have a protective effect on risk of alcoholism (Edenberg et al., 2006; Ehlers et al., 2007; Scott and Taylor, 2007), and this study hypothesized that this protective effect would translate into higher AER for African Americans carrying this allele. Results of this study revealed that ADH1B polymorphism (ADH1B*1 vs. ADH1B*3) was not associated with AERs or ADRs, measured using the alcohol clamp technique. These results differ from the study by Thomasson and colleagues (1995) that found significantly higher ADRs in African American participants with ADH1B*3 allele compared with those with the ADH1B*1 allele with EtOH administered orally. This may be partly due to differences in participant samples as well as the route of administration used in the 2 studies. Other oral alcohol challenge studies also suggest that individuals with ADH1B*3 and ADH1B*1 alleles show similar trajectories of the mean BrAC following administration of standardized doses of oral alcohol (McCarthy et al., 2010; Taylor et al., 2008). Following oral consumption of alcohol, absorption occurs from the stomach and small intestine, while IV alcohol directly enters the bloodstream avoiding gastrointestinal absorption. Determinants such as food, body weight, gender, route of administration, and type and quantity of alcohol beverages may determine the blood alcohol concentration and rate of elimination of alcohol in the body, and genetic polymorphisms may only explain a small proportion of the variation in AERs across individuals. The interpretation of our findings is also limited by the very small number of studies examining the effect of this genotype on alcohol metabolism. On the other hand, several studies have examined the effect of the ADH1B*2 polymorphism on alcohol metabolism in Jewish individuals (Luczak et al., 2002; Neumark et al., 2004) and Asians (Mizoi et al., 1994). Neumark and colleagues (2004) used the IV alcohol clamp technique to demonstrate a small but significantly higher AER in individuals carrying the variant ADH1B*2 allele and have also demonstrated a lower risk of alcoholism among Jewish

males carrying the variant ADH1B*2 allele. This suggests that ADH1B polymorphism may be protective. Our study did not show any significant protective factor effects for the ADH1B*3 polymorphism, but results from this study demonstrated lower alcohol drinks per drinking day in ADH1B1*3 compared with ADH1B1*1 individuals ($p = 0.011$). This is consistent with previous studies that have seen a similar pattern of lower alcohol consumption and lower prevalence of alcohol dependence in individuals from Trinidad and Tobago, who were of African or East Indian descent (Ehlers et al., 2007). Body weight was also significantly associated with AER and ADR and explained some of the gender differences in alcohol metabolism in this study. This is consistent with literature indicating that body weight may affect drinking behavior in gender and by race (Duncan et al., 2009; Thomasson et al., 1995). Body weight and lean body mass have been previously shown to be significantly associated with AERs measured using the alcohol clamp and may explain perceived gender and ethnic differences in alcohol metabolism (Kwo et al., 1998; Li et al., 2000).

Analysis of the subjective response measures indicated a complex, but consistent pattern of effects. Overall there was a significant effect of alcohol on the subjective measures, as expected, along with main and interaction effects of the ADH1B*3 polymorphism on most of the measures. The SHAS high and intoxication measures, and BAES sedation measures, all showed higher responses in ADH1B*3 carriers under alcohol compared with ADH1B*1 individuals, suggesting a greater sensitivity to alcohol in these individuals. Other studies have also reported higher sensitivity to alcohol in ADH1B*3 carriers of African descent (McCarthy et al., 2010). This higher sensitivity may be associated with lower alcohol consumption patterns and lower prevalence of alcohol use problems in individuals carrying the ADH1B*3 allele. Drinking history, particularly drinks per drinking day, was a significant predictor of the subjective response. This pattern of higher drinking associated with lower response to alcohol in this African American samples confirms previous findings in other social and nondependent drinking samples (Ramchandani et al., 2002) and may reflect the development of chronic tolerance to the effects of alcohol seen following heavy drinking (Gilman et al., 2012; Hendler et al., 2013).

Analysis of the effects of FHA on the pharmacodynamic responses indicated significant influences of family history on measures of stimulation and alcohol sensations, although peak change from baseline scores did not show family history differences, suggesting that these measures showed baseline differences between family history groups. The reason for this is unclear. Studies examining influences of FHA on subjective response have yielded differences with some studies showing higher responses in family history positive individuals (Morzorati et al., 2002) and some showing lower responses in family history positive individuals (Schuckit, 1984). These differences may be related to the route and rate of administration as well as the subjective measures used. One additional conundrum in studies examining family history effects in studies that include low-to-moderate drinkers is the potential bias for including participants who may be survivors of the risk that having an FHA, per se, connotes. In other words, the familial risk may drive these individuals to drink more heavily, and excluding heavy drinkers might result in samples that do not manifest the familial risk, resulting in fewer significant family history-related effects on the pharmacodynamic response. Comparison of light and heavy drinkers in FHP and FHN groups in future studies would help clarify the main and interactive effects of family history and drinking history on the response to alcohol.

In conclusion, genetic variation in alleles for alcohol metabolizing enzymes is associated with differential subjective responses to alcohol in social drinkers of African descent. This variation can have a wide range of physical and psychosocial impact. This study demonstrated that (i) the protective effect of ADH1B allele did not correlate with a greater

AER in persons of African descent and (ii) ADH1B polymorphisms (ADH1B*1 vs. ADH1B*3) were not associated with AER and ADR, measured using the alcohol clamp technique. This study serves as a preliminary investigation of the influence of ADH polymorphisms on AERs and ADRs in African American social drinkers. It also contributes to the growing body of literature on evaluating subjective and physiological response to alcohol, and the role of genetic variation, in minority populations. Further research is needed to investigate the influence of route of administration, that is, IV and oral, on alcohol metabolic rates, as well as to examine these effects in light and heavy drinkers in other racial/ethnic groups. As there is a dearth of research that has examined the relationship between routes of alcohol administration, the role of ADH polymorphisms, and the risk of alcohol dependence persons of African descent, this study has important findings and supports the need for future prospective studies focusing racial/ethnic minority populations.

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Table 1Participant Demographics Across Genotype and Gender ($n = 85$)^a

	<i>ADH1B1*1</i>		<i>ADH1B1*3</i> or <i>ADH1B3*3</i>	
	Male ($n = 27$)	Female ($n = 34$)	Male ($n = 8$)	Female ($n = 16$)
Age (years)	26.0 ± 4.3	26.2 ± 4.3	24.8 ± 3.6	26.6 ± 4.7
Weight (kg) ^{c**}	85.96 ± 14.8	75.02 ± 19.4	97.46 ± 13.2	77.99 ± 19.4
Height (cm) ^{c**}	176.5 ± 11.8	165.1 ± 7.7	181.4 ± 5.2	164.4 ± 4.1
Total number of drinks ^{b,c**,d*}	15.6 ± 13.4	7.58 ± 6.6	10.4 ± 12.7	4.4 ± 4.0
Drinks per drinking day ^{c*,d**}	2.8 ± 1.2	2.0 ± 1.2	1.7 ± 0.7	1.5 ± 0.7
Family history of alcoholism				
Positive	12 (40.0)	18 (60.0)	2 (20.0)	8 (80.0)
Negative	15 (48.4)	16 (51.6)	6 (42.9)	8 (57.1)

ADH, alcohol dehydrogenase; SD, standard deviation.

Data are represented as mean ± SD or n (%).^aTwo participants, 1 male and 1 female, did not provide samples for genotyping.^bNumber of standard drinks (12 fl oz beer, 5 fl oz wine, and 1.5 fl oz 80 proof spirit; NIAAA, 2003).^cSignificant differences across gender.^dSignificant differences across genotype.*
 $p < 0.05$.**
 $p < 0.001$.

Table 2

Factors Contributing to Differences in Pharmacokinetics

	<u><i>ADH1B1*1</i> (mean ± SEM)</u>		<u><i>ADH1B1*3</i> or <i>ADH1B3*3</i> (mean ± SEM)</u>		<u>Effect estimate</u>				
	Male	Female	Male	Female	Weight	Genotype ^a	Gender ^b	Family history of alcoholism ^c	Genotype × Gender
AER	6.98 ± 0.32	6.86 ± 0.47	5.99 ± 0.66	6.03 ± 0.41	0.06 ^{**}	0.83	−0.05	0.66	0.83
AER-BW	0.09 ± .004	0.09 ± 0.01	0.07 ± 0.01	0.07 ± 0.01	n/a	0.01	<0.01	<0.01	<0.01
AER-LBM	0.11 ± 0.01	0.12 ± 0.01	0.10 ± .010	0.10 ± 0.01	n/a	0.01	<0.01	0.01	<0.01
ADR	13.01 ± 0.33	15.08 ± 0.39	12.79 ± 0.71	15.22 ± 0.45	0.03 [*]	−0.14	−2.42 [*]	−0.81	0.36
ADR-BW	0.15 ± 0.01	0.21 ± 0.01	0.14 ± 0.01	0.19 ± 0.01	n/a	0.02 [*]	−0.06 ^{**}	−0.01	<0.01
ADR-LBM	0.21 ± 0.01	0.28 ± 0.01	0.19 ± 0.02	0.26 ± 0.01	n/a	0.02	−0.07 ^{**}	−0.02 [*]	−0.01

ADH, alcohol dehydrogenase; AER, alcohol elimination rate (g/h); ADR, alcohol disappearance rate (mg%/min); AER-BW, AER adjusted for body weight (g/h/kg); ADR-BW, ADR adjusted for body weight (mg%/min/kg); AER-LBM, AER adjusted for lean body mass (g/h/kg); ADR-LBM, ADR adjusted for lean body mass (mg%/min/kg); SEM, standard error of the mean.

Sibship did not account for any significant degree of variability in the mixed models. Analysis included only the alcohol intravenous sessions as AERs and ADRs were not obtained in the placebo session (absence of alcohol).

^aReference group is *ADH1B1/3* or *ADH1B3/3*. There were no significant differences across genotype.

^bReference group is female.

^cReference group is family history of alcoholism positive.

* $p < 0.05$.

** $p < 0.001$.

Table 3

Factors Contributing to Differences in Subjective Scale Measures

Subjective scales measures	Model estimates from mixed effects model ^d							
	ADH1B1*1 (mean ± SEM)			ADH1B1*3 or ADH1B3*3 (mean ± SEM)				
	Placebo session	Alcohol session	Session	Genotype	Session × Genotype	FHA	Gender	Drinks per drinking day
SHAS High								
AUC	16947.1 ± 321.1	22558.6 ± 327.6	-7375.0**	-2093.8*	1763.4*	932.0	-866.6	-576.9*
Peak score	103.1 ± 2.2	149.0 ± 2.2	-52.7**	-9.8*	6.8	4.6	-3.9	-4.6*
Peak score from baseline	2.2 ± 2.2	47.1 ± 2.2	-52.7**	-10.0*	7.9	4.6	-4.8	-4.6*
SHAS Intoxication								
AUC	16938.9 ± 326.5	22621.7 ± 333.1	-7836.2**	2434.5*	2153.5*	734.1	-810.7	-518.9*
Peak score	102.9 ± 2.2	150.8 ± 2.2	-52.9**	-7.7	5.0	3.2	-3.4	-4.4*
Peak score from baseline	1.7 ± 2.2	49.1 ± 2.2	-52.8**	-7.8	5.4	3.0	-4.4	-4.1*
Sensation								
AUC	823.2 ± 408.5	4816.6 ± 416.7	-6169.9**	-2351.7*	2176.6*	1673.6*	-1252.2	-301.9
Peak score	7.8 ± 3.4	43.0 ± 3.5	-51.5**	-16.6	16.2	13.9*	14.8*	-1.7
Peak score from baseline	3.2 ± 3.1	35.7 ± 3.2	-48.5**	-15.9	16.1*	10.2	15.3*	-1.0
Sedation								
AUC	391.6 ± 197.1	2353.1 ± 201.0	-2776.1**	-1005.1*	814.6	645.8	-753.7*	-125.6
Peak score	5.8 ± 1.6	21.9 ± 1.6	-21.8**	-6.3	5.8	4.9	7.0*	-0.4
Peak score from baseline	2.8 ± 1.3	16.5 ± 1.3	-19.2**	-5.5	5.5	3.6	-3.9	-0.6
Stimulation								
AUC	1756.2 ± 334.1	3346.5 ± 340.8	-982.5**	96.8	-607.9	1370.8*	797.7	-515.5
Peak score	16.0 ± 2.2	29.4 ± 2.2	-8.3**	0.2	-5.1	8.8*	4.7	-3.2
Peak score from baseline	3.3 ± 1.1	7.6 ± 1.1	-8.1*	-3.1	3.8	-0.4	-1.0	1.0

ADH, alcohol dehydrogenase; SHAS, Subjective High Assessment Scale; AUC, area under the curve; FHA, family history of alcoholism; SEM, standard error of the mean.

Sibship did not account for any significant degree of variability in the mixed models. Model estimates are presented with reference to alcohol session for session, ADH1B1*3/ADH1B3*3 for genotype, family history of alcoholism positive, and females for gender.

^aModel 1 included session, genotype, and interaction of session with genotype; Model 2 included FHA, gender, and drinks per drinking day.

* Significant differences across genotype ($p < 0.05$).

** Significant differences across session ($p < 0.001$).