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Alcohol Dehydrogenase Polymorphisms Influence Alcohol-Elimination Rates in a Male Jewish Population

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Background: Genetic variation in the alcohol dehydrogenase (ADH) enzyme is associated with an aversion to alcohol and a lower risk of alcoholism among Asians. There is growing evidence of a functional role of the *ADH2*2* allele in alcohol-drinking patterns among Jews, who have traditionally exhibited low rates of alcoholism and alcohol-related problems. The mechanism by which this allelic effect is mediated is not yet clearly understood. This study examined the effect of *ADH2*2* on alcohol-elimination rates (AER) under experimental conditions.

Methods: Young adult male Jews ($N = 109$) received an intravenous alcohol infusion; metabolism was measured by using standard breath alcohol concentration tests. A clamping technique was used to achieve and maintain a target breath alcohol concentration of 50 mg/100 ml for a defined time period. The AER at steady state was calculated. The alcohol disappearance rate was also calculated from the descending limb slope. Polymerase chain reaction was used for allelic determination of the *ADH2* and *ADH3* loci.

Results: The mean AER among *ADH2*2* carriers was significantly higher (8.09 ± 1.4 g/hr) than among *ADH2*1* homozygotes (7.14 ± 1.5 g/hr; $p = 0.003$). Significance was retained on adjustment for potential confounding covariates. The *ADH2* allele explains 8.5% of the AER variance in this population. Little AER difference was observed across *ADH3* genotype groups. The slope of the descending limb increased with increasing copies of the *ADH2*2* allele.

Conclusions: The rate of alcohol elimination is significantly associated with the *ADH2* genotype of Jewish males. Evidence for variation in alcohol metabolism across ADH genotypic groups provides support for the role of physiologic protective factors in alcohol drinking and suggests that reduced drinking among Jews may be genetically as well as environmentally determined. We believe that application of the novel "Indiana clamp" enhances AER measurement accuracy, allowing for detection of hitherto undetectable differences.

Key Words: Alcohol, Elimination, ADH, Genetics, Jews.

ALCOHOL DEHYDROGENASE (ADH) and aldehyde dehydrogenase (ALDH) are the two enzymes that dominate the metabolism of ethanol. Numerous studies, primarily among Asians (Chao et al., 1997; Chen et al., 1999; Maezawa et al., 1995; Osier et al., 1999; Shen et al., 1997; Thomasson et al., 1994), but also in Europeans (Borras et al., 2000; Whitfield et al., 1998), have demonstrated an association between the *ADH2*2* allele and reduced alcohol consumption and a decreased risk of alcoholism, even after accounting for the strong effect of *ALDH2*2*. Recent studies of Jewish populations show a similar protective effect of this allele: individuals who carry this allele tend to drink less and less often (Neumark et al., 1998; Shea et al., 2001) and to be less likely to meet DSM-IV criteria for alcohol dependence (Hasin et al., 2002).

Although carried by 60–80% of Asians, the *ADH2*2* allele is rare (<10%) in Caucasian populations. A higher-than-expected allele frequency (20–31%) of the allele has been noted in Jewish sample populations in Israel (Hasin et al., 2002; Neumark et al., 1998) and in the US (Shea et al., 2001).

Because ADH is the enzyme with rate-limiting activity in the pathway for metabolizing alcohol, we hypothesized that inheriting the protective effect of the *ADH2*2* allele would be correlated with a greater alcohol-elimination rate (AER; yielding lower and shorter brain exposures to alcohol and a less pleasant drinking experience because of greater concentrations of acetaldehyde, all else being equal). To test the hypothesis, we examined the influence of ADH2 (and ADH3) polymorphisms on the pharmaco-

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kinetics of ethanol metabolism in young adult Jewish males. Specifically, we predicted a higher mean AER (g/hr) among Jewish males carrying the *ADH2*2* allele compared with *ADH2*1* homozygotes. On the basis of our earlier findings, we did not anticipate any substantial AER differences across ADH3 genotypes.

METHODS

Subjects and Recruitment

Male Jewish university students were recruited. Recruits who met preliminary screening criteria were invited for a medical examination, at which time they completed a detailed structured self-administered questionnaire. Information was collected regarding age, country of origin, religiosity, personal and family history of cardiovascular and other major diseases, and data on lifestyle exposures, including cigarette smoking and coffee consumption. Alcohol-drinking history (frequency and quantity in the past year and lifetime peak period) was obtained, and an abridged Michigan Alcohol Screening Test (Selzer, 1971) was administered. The medical examination included auscultation of the chest and heart, palpation of the abdominal region, and a general medical history. Standardized measurements of blood pressure, height, and weight were obtained. Body mass index (BMI) was calculated as weight/height^2.

Exclusion criteria comprised any of the following: abstinence from alcohol; a positive screen for alcoholism or excessive drinking; a familial history of alcoholism; a personal history of a DSM-III-R axis 1 psychiatric condition, including substance abuse; a history of seizures or loss of consciousness; recent hospitalization due to illness; current illness requiring medication; personal or familial history of early-onset heart disease or liver disorders, or obesity (>20% of ideal BMI); complications during phlebotomy; presence of other serious illness; or an inability to pass the project's medical examination. Eligible applicants were given a full description of the study protocol, and all subjects provided institutional review board–approved informed consent before the start of the experiment. A total of 109 individuals participated in the study.

Experimental Protocol

Subjects arrived at the hospital clinic after a 12-hr fast, having been asked to abstain from (nonritual) alcohol drinking for a minimum of 7 days. Breath alcohol tests at the start of the experimental session confirmed the absence of ethanol and allowed for low-end calibration of the breath alcohol concentration (BrAC) meters (Alco-Sensor IV, Intoximeters Inc., St. Louis, MO). An indwelling venous catheter was inserted into the antecubital fossa, and a baseline blood sample was drawn. To provide a direct measure of the AER (g/hr), a BrAC clamping technique (O'Connor et al., 1998) was used. In the Indiana BrAC clamp, the infusion rate of a 6% (v/v) ethanol in Ringer's lactate solution is adjusted so that the difference between online measurements of BrAC and the target concentration of ethanol is eliminated. In the steady state, after equilibration of ethanol in all body water compartments, the mass flow of infused ethanol precisely equals the AER if the BrAC is sustained at the target level. In addition, the infusion was managed so that the brain of each subject was exposed to the same time course of BrAC (Ramchandani et al., 1999). An infusion profile was precomputed by forcing a physiologically based pharmacokinetic model of an individual's alcohol distribution and elimination to follow the desired time course of BrAC (linear ascension to a target BrAC of 50 mg/100 ml at 20 min, followed by a steady BrAC maintained within 5 mg/100 ml of the target until a steady-state basis for calculating the AER was established). A plot of a typical clamp is displayed in Fig. 1. The target concentration is a reasonable approximation of the mean BrAC during moderate social drinking and is low enough that nausea would not pose a problem for most subjects. Three identically calibrated BrAC meters were alternated to avoid instrument fatigue. After steady-state levels of both BrAC and infusion rates were attained for a minimum of 45 min, the infusion was stopped, and BrAC was measured every 15 min for determination of the descending limb slope (DLS; mg/100 ml/hr). The DLS measures the disappearance rate of alcohol concentration calculated as the slope of the pseudolinear portion of the descending limb of BrAC by linear least-squares regression over at least five measurements. Subjects received a standard postchallenge meal and were released from the clinic only after their breath alcohol level fell to less than 10 mg/100 ml and a final blood sample was drawn.

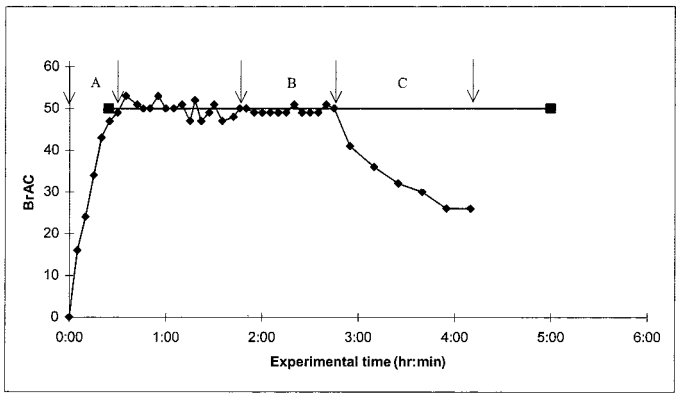

Fig. 1. Time course of a typical ethanol clamp showing the initial alcohol-push phase (A), the steady-state interval (B), and the postinfusion stage (C).

AER was calculated as the steady-state infusion pump rate (ml/hr) multiplied by the infusate ethanol concentration (0.048 g/ml). The AER was corrected for small nonzero values of the slope of the steady-state BrAC by using the measured DLS and an estimate of the subject's total body water (liters) as additional information. AER values were determined blind to genotype status. For some subjects, the exact start and end points for steady-state were discussed between investigators until a consensus was reached. In nearly all cases, the effect of these differences on the calculated AER was minor. Valid AER measurements were obtained for 100 of the 109 study participants—a stable steady-state period was not obtained for three subjects, and for six subjects the quality of the AER measurements was deemed to be questionable. No appreciable differences were noted when the analyses were rerun on exclusion of these six individuals.

Data on subjective responses to the ethanol exposure were collected but not analyzed in the context of this study. Subjects completed the Biphasic Alcohol Effects Scale (Martin et al., 1993), the Bodily Sensation Scale (Maisto et al., 1980), and a subset of the Subjective High Assessment Scale (Schuckit, 1984) at baseline and at 30-min intervals throughout the infusion. At these time points, the physician who was conducting the experimental session assigned a facial flushing score (not addressed in this report).

Laboratory Techniques

Blood samples were sent to the Alcohol Research Center at Indiana University School of Medicine, Indianapolis, IN, for genotyping. Genomic DNA was isolated from the white blood cells. All subjects were genotyped at the *ADH2* and *ADH3* loci by using enzymatic amplification of the DNA followed by hybridization of the polymerase chain reaction products with allele-specific oligonucleotides (Xu et al., 1988). Genotype results were available for 108 subjects.

Statistical Analyses

The null hypothesis of homogeneity in mean AER by *ADH2* genotype was tested by one-way analysis of variance. We applied linear regression to assess the association between *ADH2* genotype and AER while controlling for possible confounding factors such as BMI, smoking status, coffee drinking, *ADH3* genotype, and ethnicity. In addition, interactions between

Table 1. Selected Characteristics of the Study Population (n = 109)

Variable	Data
Age, years, mean ± SD (range)	26.0 ± 2.5 (19–33)
Origin (% Ashkenazic)	79
Religiosity (% secular)	82
Smoking (% current smokers)	31
Coffee (% regular drinkers)[a]	60
BMI (mean ± SD)	23.6 ±3.1
ADH2 genotype, % (count)[b]	
1*1	67.6 (73)
1*2	27.8 (30)
2*2	4.6 (5)
ADH3 genotype, % (count)[b]	
1*1	52.8 (57)
1*2	37.0 (40)
2*2	10.2 (11)

[a] Regular drinking was defined as one or more cups of coffee daily.
[b] Genotype information was missing for one subject.

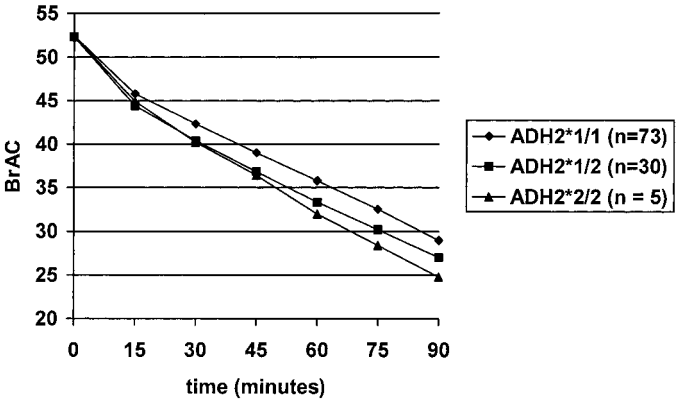

Fig. 2. Postinfusion elimination (measured by breath alcohol concentration) by *ADH2* genotype.

ADH2 and other covariates were examined through the introduction of multiplicative terms into the model. Finally, the putative association between *ADH2* genotype and decline in BrAC on cessation of alcohol infusion was explored by using a generalized linear model with repeated measures (SPSS Inc., Chicago, IL).

RESULTS

The *ADH2*2* allele was carried by 32% (n = 35) of subjects, including 4.6% (n = 5) who were homozygotes (Table 1). The *ADH3*2* allele was found in 47% (n = 51) of subjects, including 10% of the sample population who were homozygous (*ADH3*2/3*2*). Both of these genotype distributions were in accordance with Hardy-Weinberg equilibrium (*ADH2*: $\chi^2 = 0.68, p = 0.41$; *ADH3*: $\chi^2 = 0.98$, $p = 0.32$). Although most (79%) of our sample was Ashkenazic, we tested for ethnic heterogeneity with regard to *ADH2* and *ADH3* genotypes. No substantial difference between Ashkenazic and non-Ashkenazic subjects was noted with regard to *ADH2* ($p = 0.668$). A somewhat larger difference was found for *ADH3*: the frequency of the *ADH3*2* allele was higher among Ashkenazic subjects ($p = 0.098$).

The mean ± SD AER for the entire sample was 7.44 ± 1.5 g/hr and ranged from 3.9 to 11.6 g/hr. A significantly higher mean AER was observed among subjects who carried the *ADH2*2* allele (8.09 ± 1.4 g/hr; n = 34) compared with *ADH2*1* homozygotes (7.14 ± 1.5 g/hr; n = 71; p = 0.003). The mean AER increased monotonically with an increasing number of copies of the *ADH2*2* allele (Table 2). In regression analysis, the *ADH2* allele alone explained 8.5% of the variance in AER. A significant independent effect of BMI on AER was noted ($\beta = 0.254$; $p < 0.001$); however, the introduction of multiplicative interaction terms into the regression model revealed no significant interaction between *ADH2* genotype and BMI on AER. Similarly, no interaction was noted between *ADH2* and *ADH3* genotypes in their association with AER. The difference in AER across *ADH2* genotypes remained significant on regression adjustment for BMI, smoking status, coffee drinking, and *ADH3* genotype. These covariates accounted for 27.4% of the AER variance. Inclusion of *ADH2* into the regression model significantly improved the model fit ($p = 0.012$); *ADH2* contributed an additional 4.7% to the explained variance of AER. The regression coefficient for *ADH2* remained virtually unchanged on inclusion of ethnicity into the model. Differences in mean AER observed across *ADH3* genotype groups were not statistically significant. The AER-*ADH3* association remained nonsignificant after controlling for ethnicity and the other covariates.

Table 2. Mean (±SD) AER (g/hr) by ADH2 and ADH3 genotypes

Genotype	ADH2	ADH3
1*1	7.14 ± 1.5	7.63 ± 1.5
1*2	7.98 ± 1.3	7.30 ± 1.6
2*2	8.71 ± 2.0	7.02 ± 1.4
	$F = 5.3, p = 0.006$	$F = 1.2, p = 0.375$

The DLS ranged from 5.04 to 15.73 mg/100 ml/hr. The mean value of the slope was steepest among those who carried two copies of the *ADH2*2* allele (mean ± SD, 15.6 ± 4.9 mg/100 ml/hr), compared with 13.6 ± 3.6 mg/100 ml/hr among heterozygotes and 13.08 ± 4.2 mg/100 ml/hr among *ADH2*1* homozygotes (Fig. 2). A test of repeated measures showed these differences to be of borderline significance ($p = 0.048$). This difference achieved statistical significance ($p = 0.015$) when these three genotype groups were collapsed into two groups—individuals with and without the *ADH2*2* allele. Virtually no difference in the mean slope of the descending limb was noted across ADH3 genotypes.

DISCUSSION

This study provides evidence for the notion that expression of an *ADH2*2* genotype is associated with an increased rate of alcohol metabolism. The association of AER with ADH genotype provides support for the role of physiologic protective factors in alcohol drinking and for the observation that reduced dependent drinking among Jews may be determined by genetic as well as by environmental factors.

In the US, Jews exhibit lower rates of alcohol dependence compared with other religious groups (Yeung and

Greenwald, 1992), and Israel has one of the lowest per capita alcohol consumption levels (World Health Organization, 1997). It has been suggested that, alongside cultural influences, a heightened sensitivity to the effects of ethanol among Jews might account for these reduced levels of alcohol consumption (Monteiro et al., 1991).

In this article, we have shown that inheritance of the *ADH2*2* allele, which is prevalent in the Jewish population and is associated with reduced frequency and quantity of alcohol intake (Neumark et al., 1998), also contributes to an increased rate of elimination of alcohol. Such an increase would decrease the brain's exposure to alcohol for a given dose. This interpretation is consistent with our further observation that the presence of the *ADH2*2* allele is associated with an increased slope of the descending limb after equilibration of alcohol in the total body water. Another possibility is that the faster alcohol elimination attending the *ADH2*2* status may increase the exposure of the genotype to relatively larger concentrations of acetaldehyde: this is known to be associated with aversive experiences, at least when it is achieved by slowing ALDH activity (Thomasson et al., 1991). Both factors may be at work, but it is clear that the influence of the *ADH2*2* allele on reduced drinking patterns is mediated, at least in part, via its effect on AER in this sample population.

Although there is fairly consistent evidence supporting an independent protective effect of the *ADH2*2* allele among Asians, a study among Japanese men failed to note a significant difference in alcohol metabolism rates between individuals who did and did not carry the *ADH2*2* allele (Mizoi et al., 1994). This seemed to suggest that the protective effect of this allele is not mediated via acetaldehyde accumulation (Chen et al., 1999). Studies to date, including that of Mizoi et al. (1994), have relied on indirect estimation of alcohol metabolism—the ethanol disappearance rate or the DLS—after oral ingestion. This measure requires conversion of the DLS (mg/100 ml/hr) to an elimination rate by multiplying the DLS by a calculated volume of distribution and by a scaling constant.

$$(\text{mg/100 ml/hr}) \times \text{volume [dl]} \times 0.001\ \text{g/mg} = \text{g/hr}.$$

The volume of distribution may vary substantially across subjects for reasons that have no association with ADH status and can only be approximated in any case. Application of the "Indiana clamp" allows for direct measurement of the AER on the basis of a steady infusion achieving a steady BrAC, thereby avoiding much of the background noise that may have been preventing detection of the ADH signal. We believe that this novel technique enhances the accuracy of measurement of the AER and may explain our detection of an *ADH2* effect on metabolism, whereas earlier studies were unable to do so.

The prevalence of the *ADH2*2* allele may be underestimated because individuals who carry this allele, especially in homozygous form, tend to avoid alcohol and thus may have been less likely to participate in the study. This possible bias was minimized because recruitment posters specifically mentioned that the study was appropriate for alcohol-nonpreferring persons. Indeed, the observed *ADH2*2* prevalence in this sample is identical to that found in an earlier study of Israeli Jews (Neumark et al., 1998), although it was lower than that observed in a sample of US Jews (Shea et al., 2001).

In this study, AER was evaluated at a BrAC of 50 mg/100 ml. The AER increases with the target concentration as the Michaelis-Menten kinetics of hepatic elimination are pushed closer to saturation. Because higher concentrations of alcohol would compound the higher concentrations of acetaldehyde expected in people with greater AER, per se, an expansion of this avenue of research would be of interest. Such a study might investigate the *ADH2* allelic effect at higher ethanol concentrations and the association of that effect with blood acetaldehyde concentrations, subjective responses to alcohol, and drinking patterns. Because gender differences in alcohol metabolism are known to exist and because our results may not be generalizable to women, we look forward to investigating these issues in a sample of women.

This study adds to the literature about genetic influences on alcohol metabolism and their association with drinking patterns in different human population groups. Male Jewish university students comprise a useful sample population because both alleles of *ADH2* and *ADH3* genes are represented with reasonable frequency and because the university setting provides a fairly uniform social drinking environment. Application of the direct method of measuring the AER provided by the Indiana clamp may also advance this important area of research.

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