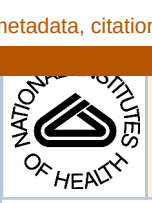

Published in final edited form as:
Alcohol. 2007 June ; 41(4): 263–270.

Rates of Ethanol Metabolism Decrease in Sons of Alcoholics Following a Priming Dose of Ethanol

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Abstract

Rapid changes in rates of ethanol metabolism in response to acute ethanol administration have been observed in animals and humans. To examine whether this phenomenon might vary by risk for alcoholism, 23 young men with a positive family history of alcoholism (FHP) were compared to 15 young men without a family history of alcoholism (FHN). Rates of ethanol metabolism were measured in all subjects first after an initial ethanol dose (0.85 g/kg) and then, several hours later, a second dose (0.3 g/kg), and the two rates were compared. The two groups of subjects were similar in their histories of ethanol consumption. FHP subjects demonstrated faster initial rates of ethanol metabolism, 148 ± 36 mg/kg/hr, compared to FHN subjects, 124 ± 18 mg/kg/hr, p=.01. However, FHN subjects increased their rate of metabolism by 10 ± 27 percent compared to a decrease of -15 ± 24 percent in FHP subjects, p =.007. Fifty-two percent of the FHP and none of the FHN subjects exhibited a decline in metabolic rate of 20% or more, p=.0008. Since a significant proportion of FHP subjects exhibited a decrease in the second rate of ethanol metabolism, these preliminary data might help to partly explain why FHP individuals differ in their sensitivity to ethanol and are more likely to develop alcohol dependence.

Keywords

alcohol metabolism; alcoholism; family history

INTRODUCTION

Alcoholism affects on the order of 12% of individuals in the United States over a lifetime (Hasin & Grant, 2004). Over the past 30 years evidence has accumulated to indicate that there is a strong genetic component underlying vulnerability to alcoholism (Cloninger, 1987;Kendler et al., 1992), though its phenotypic expression is incompletely defined. Convincing evidence has been presented for a number of biological differences between subjects considered at high (family history positive, FHP) or low (family history negative, FHN) risk for alcoholism

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because of family history. For example, FHP subjects have been shown to have a decreased amplitude of the P300 wave in the evoked cortical potential (Hesselbrock et al., 2001) and a decreased sensitivity to some effects of ethanol (Schuckit, 1994) compared to FHN subjects. It is of interest that ethanol metabolism was reported as similar between the FHP and FHN populations in the latter study. These observations suggest that biological differences exist between FHP and FHN individuals prior to the onset of overt alcoholism. Furthermore, such biological markers may represent phenotypic expression of risk for alcoholism.

It was observed a number of years ago that 2.5 hours after administration of a large dose of ethanol, a rapid increase in rates of oxygen uptake and ethanol metabolism occurred in the isolated perfused rat liver. This observation was defined as the Swift Increase in Alcohol Metabolism (SIAM) (Yuki & Thurman, 1980), and has subsequently been shown to have a heritable basis in rats *in vivo* (Thurman et al., 1980), to exist in inbred strains of mice (Thurman et al., 1983), deer mice (Glassman et al., 1989) and in man (Thurman et al., 1989). Thurman et al demonstrated that 20% of the FHN subjects studied exhibited an increase in their rate of ethanol elimination by at least 40% following an initial dose of ethanol. Under these conditions, SIAM was characterized by an increase in elimination (Widmark's β) without changes in the volume of distribution, indicating a true acceleration in the rate of ethanol elimination (Thurman et al., 1989). Subjects who exhibited the SIAM phenomenon reported few problems with alcohol. This latter observation led us to hypothesize that increased rates of ethanol metabolism in humans with the SIAM phenotype might lead to diminished intoxication time and thus, perhaps, a lower likelihood of developing dependence and associated psychosocial problems.

In a pilot study, nine FHP subjects were examined for the SIAM phenomenon. These subjects self-reported that their fathers had alcohol related problems. In this small group, rates of ethanol metabolism decreased significantly, an average of 21%, after rechallenge with ethanol following an initial dose (Handler et al., 1990). This suggested that individuals at risk for alcoholism might differ in their pattern of metabolism of ethanol after an initial priming dose of ethanol compared to individuals at low risk for alcoholism.

The purpose of the present study was to evaluate the effect of ethanol administration on ethanol metabolism in a population of FHP and FHN subjects carefully screened for verification of family history of alcoholism and with similar rates of reported ethanol consumption.

MATERIALS AND METHODS

Subject Selection

FHP and FHN subjects were identified using direct mail techniques targeted to students at North Carolina State University, Raleigh, N.C. Packets were sent to randomly selected Caucasian male students between the ages of 18 and 25 consisting of a cover letter, a Schuckit Questionnaire (to gather information on personal and familial history of alcohol and drug use and related problems as well as basic demographic data, (Schuckit, 1994)), a consent form, a receipt for a cash payment of $5.00 for returning the questionnaire, and a return envelope. Several FHP subjects were also recruited from contacts with alcoholic families.

The Schuckit Questionnaire was used to initially categorize subjects as FHP (father alcoholic as determined by drinking-related problems) or FHN (no 1st/2nd degree relative with alcohol-related problems). FHP and FHN subjects were selected from the database after eliminating subjects who indicated a maternal history of alcoholism, a personal history of heavy alcohol or drug use accompanied by problems, or significant personal medical or psychiatric problems. FHN subjects were selected to approximate the FHP population on the variables of age, body size, and use of alcohol. Confidentiality was maintained throughout the study.

Subjects selected for participation in the study were interviewed by a psychiatrist (JCG) and by a research assistant (LLP) with a focus on two major areas: 1) determining personal history of substance abuse problems, psychiatric problems, and medical problems, and documenting alcohol and drug use and 2) documenting family history of substance abuse and/or psychiatric problems. Research Diagnostic Criteria (Spitzer et al., 1978)) were employed for the diagnosis of substance use disorders and major mental illnesses in the subjects and Family History-RDC Criteria (Andreasen et al., 1977) were used to establish the presence of alcoholism in the father and other relatives and to screen for a family history of major mental illnesses.

Ethanol use was calculated based on subjects' self-report of average number of drinks/session and average number of sessions/month for the previous six months and the product of these numbers was used to establish a drinking index. Cigarette smoking was based on self-report of the average number of cigarettes smoked per month for the previous six months. Marijuana use was based on the estimate of lifetime number of times smoked. A height/weight ratio was calculated in cm/kg.

Twenty-three FHP subjects were selected for study and 15 FHN subjects were chosen based on their similarities to the FHP group on the variables described above. None of the subjects had a personal history of alcoholism, drug dependence or major mental illness. The characteristics of the FHP and FHN subjects are shown in Table 1. There were no significant mean differences between groups in age, body size, ethanol use, cigarette use or lifetime marijuana use. 8/23 FHP subjects reported using cigarettes, though only two reported an average consumption of more than five cigarettes/month; 0/15 FHN subjects smoked cigarettes. 15/23 FHP subjects reported having used marijuana compared to 9/15 FHN subjects.

Experimental Procedures

The study was approved by the Committee for the Protection of the Rights of Human Subjects at the University of North Carolina and a consent form was obtained from each subject. Prior to testing, all subjects were briefed on the experimental design and were instructed not to consume ethanol for three days before study. The experimental design used in this study was quite similar to that first described by Wilson and later utilized by Thurman (Wilson et al., 1984) (Thurman et al.,1989). Subjects arrived at the research unit at 0800 hours after consuming a light (low fat) breakfast. Starting at about 0830 subjects consumed ethanol (0.85 g/kg) as carbonated wine over 20 minutes. Following wine consumption, subjects were asked to rinse their mouths with water for 5 minutes to remove ethanol. Breath samples to measure breath ethanol concentrations [BAC] were then collected every 10 minutes using a Smith and Wesson 900A Breathalyzer to estimate blood ethanol levels until peak blood ethanol levels were attained (around 90 mg/dl) and subsequently at about 20 minute intervals until blood ethanol levels declined by 30%. Rates of ethanol metabolism were calculated based on the linear rate of decrease in breath ethanol concentrations as described previously (Widmark, 1932) A second dose of ethanol (0.3 g/kg) was consumed to elevate blood ethanol concentrations, again to around 90 mg/dl, and breath samples were collected as before. Breath ethanol levels were monitored until they declined below 20 mg/dl, then vital signs were monitored and the subject was released if stable. The first rate of ethanol elimination is identified as E_1 and the second rate as E_2. The change in rate between E_1 and E_2 is defined as $(E_2\text{-}E_1)/E_1$. "Area under the Curve" (AUC) of the estimated blood ethanol levels was mathematically calculated to estimate tissue exposure to ethanol from the peak following the second ingestion of ethanol to an estimate of a zero ethanol level.

Statistical Methods

All values are given as the mean ± standard deviation. Analyses were carried out using Statistical Analysis System (SAS) software. For statistical comparisons between different time

points within groups the Student's t-test was used where significance was set at $p<0.01$. For comparisons between two groups, Fisher's test was used with dichotomous variables, otherwise Satterthwaite's unequal-variance t-test was used. Three-group comparisons were based on one-way analysis of variance; and adjustment for covariables was carried out using the standard analysis of covariance. Results of these parametric procedures were confirmed by nonparametric analyses (details not reported).

RESULTS

Figure 1 depicts a typical experiment for a subject. Following ingestion of ethanol, breath samples were taken at 20 to 30 minute intervals. Rates of elimination were calculated using the decrease in BAC per unit time extrapolated from the linear portion of the elimination curve as described in Methods. In this example, the first rate of ethanol metabolism, E_1 was 141 mg/kg/hr and the second rate, E_2, was 94 mg/kg/hr with a decrease in rate of -33% in this subject.

Peak BAC_1 and BAC_2 were similar for FHN and FHP subjects (Table 1). E_1 was lower in FHN subjects compared to FHP subjects, t=-2.67, p=.01, (Table 1 and Figure 2), whereas E_2 was not different between FHN and FHP subjects. The change in rate between E_1 and E_2 was not significant for the FHN group, (t=1.42, p=.18) but there was a significant decrease in the FHP group (t=-3.03, p=.006). Furthermore, the mean change in rate was +10 ± 27 percent in FHN subjects and a decrease of -15 ± 24 percent in the FHP group, between group difference, t= 2.91, p=.007.

A dot plot of the individual changes in rate of ethanol metabolism for FHP and FHN subjects is shown in Figure 3. These data cluster into two distinct groups. Two cutoff points are shown on this figure; one for an increase in rate of 40% or greater (SIAM) and the other for a decrease in rate of 20% or more (which we have defined as Decrease In Ethanol Metabolism, DIEM). Our previous work in humans demonstrated that the prevalence of SIAM, a rate increase of 40% or more, occurred in 20% of the FHN subjects studied (Thurman et al., 1989). In the present study, as shown on Figure 3, SIAM was observed in 4 of 15 subjects or 27% of the FHN sample examined, numbers which are comparable to our earlier observation. However, in the FHP subjects, only one (4%), demonstrated SIAM (FHP vs. FHN, Fisher's exact test, p=.07). Conversely, DIEM, or a decrease in rate of ethanol metabolism of more than 20% was observed in 0% of FHN subjects and in 52% of FHP subjects (Fisher's exact test, p=. 0008).

Reported ethanol consumption, E_1 and rate change were examined as factors contributing to peak BAC_1, E_1, and rate change. There was no evidence that reported ethanol consumption was associated with either E_1 (r=.15, p=.37) or rate change (r=-.03, p=.85). E_1 was, however, significantly correlated with rate change, r= -.56, p=.0003. In other words, the higher a subject's initial rate of ethanol metabolism the more likely he was to have a decrease in rate. Because E_1 differed between FHP and FHN subjects we conducted an analysis of covariance controlling for E_1 and examining for group status and rate change. Using this analysis, group status continued to show evidence as a factor in predicting rate change, p=.06.

Examination of peak BAC_1 and E_1 revealed no correlation between these two in either FHN (r=-.34, p=.21) or FHP (r=.14, p=.54) subjects. To examine whether differences in peak BAC_1 affected group differences in rate change an analysis of covariance was conducted. After matching on peak BAC_1 significant group differences were still present in rate change, p=.03.

Estimated area under the curve (AUC) was calculated from peak BAC_2 to time of estimated zero BAC in FHP and FHN subjects. This was used as an additional way in which to validate the rate of metabolism E_1 and E_2 in the event that the linearity of the ethanol decline did not follow a perfect zero order kinetic. The mean AUC_2 was 14,676 ± 5344 mg/dl min for FHN

subjects and 16,628 ± 5993 mg/dl min for FHP subjects, t=-1.05, p=.30. FHP subjects were subdivided into groups defined as those that exhibited the DIEM phenomenon (FHP-DIEM) and those that did not (FHP-Non DIEM) and the AUC was compared (Figure 4). FHP-DIEM subjects exhibited increased AUC, 19,792 ± 6003 mg/dl min, compared to FHP-Non-DIEM subjects, 13,177 ± 3778 mg/dl min, (t=3.19, p=.005) or to FHN subjects, 14,676 ± 5344 mg/dl min (t=2.31, p=.03). The characteristics of FHP-DIEM, FHP-Non-DIEM and FHN subjects are shown in Table 2. FHP-DIEM subjects were similar to the other groups in body size and in self-reported ethanol consumption. FHP-DIEM subjects exhibited higher peak BAC_1 and peak BAC_2, faster initial rates of ethanol metabolism, and slower second rates of ethanol metabolism.

DISCUSSION

The present study demonstrates that individuals at high risk for the development of alcoholism, based on family history, are more likely to exhibit a decrease in their ability to metabolize ethanol following an initial priming dose of ethanol than individuals at low risk for alcoholism. The decrease in rate of alcohol metabolism or DIEM is tentatively defined as a decrease of at least 20% in the rate of ethanol metabolism between an initial rate and a second rate. The finding that DIEM is much more prevalent in FHP subjects than FHN subjects is of interest and may have clinical relevance. Perhaps most intriguing is the possibility that when some FHP subjects exhibit a slow rate of ethanol metabolism this would lead to longer tissue exposure to ethanol compared to FHN subjects-- even when both groups have similar consumption patterns (Table 2). Assuming that increased tissue exposure is a factor in the development of pharmacodynamic tolerance, DIEM could represent a new mechanism to explain why some FHP individuals exhibit higher CNS tolerance or develop CNS tolerance faster than FHN individuals.

This study and a previous paper from our group (Thurman et al., 1989) described two phenomena, in humans, after administration of ethanol: a SIAM phenomenon, more commonly found in the FHN population, a metabolic tolerance, that potentially could have a protective effect against alcohol dependence; and a DIEM phenomenon, more commonly found in the FHP population, that might be associated with increased vulnerability to alcoholism.

Differences in initial rate of metabolism

It is important to note that we found a difference in the initial rate of ethanol metabolism between FHP and FHN subjects, with FHP subjects having a faster rate. In contradiction to our findings, Schuckit reported that FHP and FHN subjects had similar rates of ethanol disappearance using the same dose as the present study resulting in similar peak alcohol concentrations in FHN and FHP subjects (Schuckit, 1984). Lower peak values and rate differences in the present study may be the result of experimental design. It is important to note that our experiment and Schuckit's differed in that our subjects ate a light breakfast prior to drinking alcohol whereas Schuckit's subjects consumed alcohol on an empty stomach (10 hour fast). More recently, Schuckit demonstrated that when FHP and FHN subjects were fed a light standardized breakfast the slope of the decline in ethanol concentration was about 33% faster in FHP vs FHN subjects (Schuckit et al., 1996). These data were not discussed per se in this paper but the differences are consistent with the present study and suggest that food consumption prior to alcohol can affect the absorption and metabolism of alcohol.

It is long known from work in the rat that rates of alcohol metabolism cannot be accelerated after fasting (Yuki & Thurman, 1980); however, Wilson elegantly demonstrated that in human subjects, acute metabolic tolerance to ethanol or AMTE can occur after fasting (Wilson et al., 1984). These data evaluated the role of ethnicity in metabolic tolerance with fasted subjects using very similar experimental protocols as the current study. SIAM occurred in 11 subjects

out of 46 in all subjects. Those subjects of Polynesian and Oriental descent exhibited a greater average increase in rate than Caucasian subjects. Additionally, DIEM was observed in 8% of subjects in Wilson's study; however, the ethnicity of the subjects was unclear from the published data.

Why differences were found in initial metabolic rate between FHP and FHN subjects in the present study remains an unanswered question. Some possible reasons that the FHP subjects had a faster initial metabolic rate of alcohol than the FHN subjects include: 1) differences existed between FHP and FHN subjects in prior ethanol use such that FHP subjects had developed a metabolic tolerance; 2) differences in biochemistry between FHP and FHN subjects in their ability to metabolize alcohol. One could speculate that differences in ethanol consumption between FHP and FHN subjects were not reported. It is possible that the FHP subjects were more likely to underreport their alcohol consumption and that they, in fact, consumed more alcohol than FHN subjects; however, we have no way to assess this factor.

Induction of ADH has been reported in the rat using continuous infusion of an alcohol containing diet in a chronic model (Badger et al., 2000). In humans, hepatic ADH II has been reported to contribute from 15% at 5 mM to 40% at 60 mM ethanol to total alcohol metabolism in humans (Li et al., 1977). These data suggest that this enzyme pathway does not require induction and makes a significant contribution to alcohol metabolism. Accelerated metabolism via ADH II may result in the higher initial rates in FHP than FHN individuals. This explanation would be plausible if there was evidence that this form of ADH was correlated with FHP individuals. Choi et al has demonstrated differences in gene expression of ADH 2 and ALDH 2 in FHP alcoholics, FHN alcoholics and normal subjects of Korean dissent. (Choi et al., 2006). These findings are encouraging suggesting that a genetic link providing differential expression of ADH in FHP and FHN subjects exists.

Contributions by gastric ADH for first-pass elimination of alcohol metabolism is an alternative explanation; however, Levitt reports that the contribution of gastric ADH to total alcohol metabolism in humans is inconsequential (Levitt et al., 1997) More recently, a new study carefully evaluated age, gender and alcohol concentration in human gastric mucosa in over 120 patients and concluded that gastric ADH and ALDH are not likely to participate in changes of first pass metabolism (Lai et al., 2000).

ADH activity is cofactor dependent and mitochondrial activation is key in regulation of the NAD^+/NADH redox state. Yuki observed a peak of hepatic respiration, only when glycogen reserves were high within a few hours after acute ethanol and a return to baseline rates of respiration by about 5-6 hours in the isolated perfused liver (Yuki and Thurman, 1980), supporting the theory that mitochondrial activation and return to normal levels could cause temporal changes in cofactor supply. Additionally, mitochondrial activation can be partially mimicked by adrenergic hormones. Alcohol has been shown to cause an increase in adrenaline and noradrenaline in rodent models (Yuki et al., 1980). Interestingly, noradrenaline levels are reported to be low in abstaining alcoholics as compared to controls and noradrenaline levels did not change when subjects were given stress tests (Ratsma et al, 2002). These data suggest that some of the FHP sons in this study may have inherited an altered or insufficient adrenergic response resulting in poor mitochondrial activation and this link could play a role in the varying cofactor supply to ADH and altering alcohol metabolism.

Chlorzoxazone was used as a marker of cytochrome P450 2E1 activity in non-alcoholic human subjects who were self reported drinkers or non-drinkers. Metabolism of chlorzoxazone was observed to be less in drinkers (Liangpunsakul S, et al., 2005). While it is well known that cytochrome P450 2E1 is one of the 3 primary pathways of alcohol metabolism, and that induction of this pathway occurs after chronic alcohol drinking, or induction can occur by use

of other drugs (Takahashi et al., 1993). It is important to note that in the current study, all subjects were matched based on the fact they reported similar drinking patterns prior to the study (Table 1) and were given the same dose of ethanol. These facts support the theory that cytochrome P450 2E1 might not be induced in the current experiment or be involved in alteration of rates of alcohol metabolism. However, as noted earlier, one cannot rule out that FHP subjects under-reported their drinking compared to FHN subjects and the current data does not rule out genetic variation in expression of CYP 2E1 in FHP or FHN subjects.

One recent interesting report demonstrated that blood catalase levels are higher in FHP than in FHN individuals (Koechling et al., 1995). These findings were independent of alcohol use suggesting that in addition to the other biochemical pathways for elimination of ethanol, catalase may contribute to decrease the blood levels to a greater extent during an initial challenge in FHP than FHN subjects. A required substrate for catalase dependent alcohol metabolism, hydrogen peroxide, is derived from fatty acid oxidation. The addition of oleate either in vivo or to the perfused liver can significantly stimulate catalase dependent alcohol metabolism by increasing hydrogen peroxide production (Bradford et al., 1999) (Handler & Thurman, 1997). Kaphailia demonstrated that fatty acid ethyl esters (FAEE) were elevated significantly after an acute exposure to ethanol as compared to a control group in which no FAEEs were detected (Kaphalia et al., 2004) . Furthermore, the appearance of 16:0, 18:0 and 18:1 fatty acids in plasma support the hypothesis that an increase in plasma fatty acid supply is present in human subjects after acute ethanol. Rates of production of malondialdehyde (MDA), a product of lipid peroxidation, in erthryocytes of male patients who were either FHN or FHP for alcoholism were examined (Bidder & Jaeger, 1982). This study assessed patients 10 days after admission to a treatment center and thus the subjects were not intoxicated. The results from this study indicate that subjects who are FHP have twice the level of MDA produced by erthyrocytes when exposed to hydrogen peroxide. Thus, the findings from these two studies suggest that those subjects who are FHP may be more likely to have elevated hydrogen peroxide levels after an acute dose of alcohol than FHN subjects and would have elevated rates of catalase dependent alcohol metabolism. While it is not possible at this time to evaluate catalase, peroxide or fatty acid levels in the present study, there is significant evidence from work in rodents to suggest that rates of metabolism are regulated by these key components and more than one pathway of metabolism (Bradford et al., 1999;Bradford et al., 1993).

DIEM occurs in a subset of FHP subjects

Despite the differences in E_1 between FHP and FHN subjects, when statistically controlled for, FHP subjects were still more likely than FHN subjects to slow their rate of ethanol elimination. The observation that ethanol metabolism slows down in a significant portion of subjects at high-risk for alcoholism and is more likely to speed up in subjects at low-risk for alcoholism may have relevance for the development of tolerance to ethanol and, hence, to the risk of developing dependence. In animals, it has been shown that the duration of exposure to ethanol as well as the ascending rate of blood ethanol levels are associated with greater severity of physical dependence (Le Bourhis & Aufrere, 1983). We did not observe a difference between FHP and FHN subjects in time to peak ethanol level however, the extent of exposure to ethanol, as measured by area under the curve after Peak 2, was significantly greater in the subset of FHP-DIEM subjects (Table 2).

The increase in ethanol exposure observed in FHP-DIEM subjects is a function of two factors--higher peak BAC_2 and slower E_2. The reason for the higher peak BAC_2 in FHP-DIEM subjects is not clear. However, it is noteworthy that FHP-DIEM subjects also had higher peak BAC_1 levels. Factors that increase peak ethanol levels after oral consumption include greater ethanol use, female gender, and an empty stomach. Our subjects were all male and had reported eating

a light breakfast prior to the start of the experiment to minimize variation in initial gastric absorption. At the time of the second alcohol ingestion, all subjects had not eaten for about two hours, so food consumption should not have been a factor; however, cofactor supply for ADH-dependent or catalase dependent metabolism may have been limited. It is possible that FHP-DIEM subjects were heavier drinkers than FHN or FHP-NonDIEM subjects, despite similar self-reports of ethanol consumption, and that this explains their higher peak ethanol levels and their higher initial metabolic rate. It still does not account for their reduction in rate after the second alcohol consumption.

In humans, it has been a long-standing observation that rapid development of tolerance to ethanol is likely one factor in the development of alcohol dependence (Jellinek, 1960). Furthermore, the work of Schuckit (Schuckit, 1994) indicates that evidence of behavioral tolerance to ethanol early in life and prior to heavy drinking is a predictor of alcohol dependence later in life. Most likely, the major reason why some individuals develop tolerance to ethanol more rapidly than others is because of a differential neurobiologic response to ethanol. However, the duration and magnitude of exposure to ethanol is another factor that would be predicted to interact with neurobiologic adaptive systems to either hasten or slow the development of tolerance. Thus, one could hypothesize that FHP subjects with the DIEM phenomenon would be more likely to show behavioral tolerance to ethanol, in part, because of greater exposure to ethanol compared to FHN or other FHP subjects-- even when alcohol consumption is similar. The DIEM phenomenon would then represent another factor affecting the metabolism of ethanol with implications for risk of developing alcoholism--in addition to the evidence that genetic heterogeneity of alcohol dehydrogenase and aldehyde dehydrogenase affects risk for alcoholism (Higuchi et al., 1995).

Conclusions

Before the DIEM phenomenon can be accepted as a possible factor contributing to risk for alcoholism it will be necessary to replicate the core finding in high-risk and low-risk subjects with very careful assessment of prior consumption of ethanol. It will also be of interest to genotype subjects to examine for relationships between alcohol metabolizing pathways and the DIEM phenomenon. Examination of alcohol metabolism over the course of a continuous drinking period in DIEM vs. Non-DIEM subjects will also be of interest to more closely model what the effects of DIEM might be during more natural drinking behavior. Testing the hypothesis that DIEM is indeed associated with greater behavioral tolerance to ethanol will be necessary to determine if DIEM affects the behavioral response to ethanol.

In summary, we have described a phenomenon of a decrease in rate of ethanol metabolism following a priming dose of ethanol that is more prevalent in young men with an alcoholic father compared to young men without a family history of alcoholism. Though the reason for the DIEM phenomenon is unknown, DIEM could have implications for understanding the differential development of tolerance in high-risk vs. low-risk subjects and, thus, represent another factor in the complex path leading to alcoholism.

Acknowledgements

This work was completed with the assistance of grant MH33127 from the National Institute of Mental Health, Rockville, Md. and a grant from the North Carolina Alcoholism Research Authority. The authors would like to acknowledge and thank Dr. Dana Quade of the Biostatistics Department at the University of North Carolina, Chapel Hill for his excellent guidance on statistical evaluation of our data and the support of the nursing staff of the Clinical Research Unit, Dorothea Dix Hospital. The authors would like to dedicate this paper to the memory of the late Dr. Ronald G. Thurman, Ph.D, Professor of Pharmacology and Director of the Laboratory of Hepatobiology and Toxicology at the University of North Carolina, Chapel Hill.

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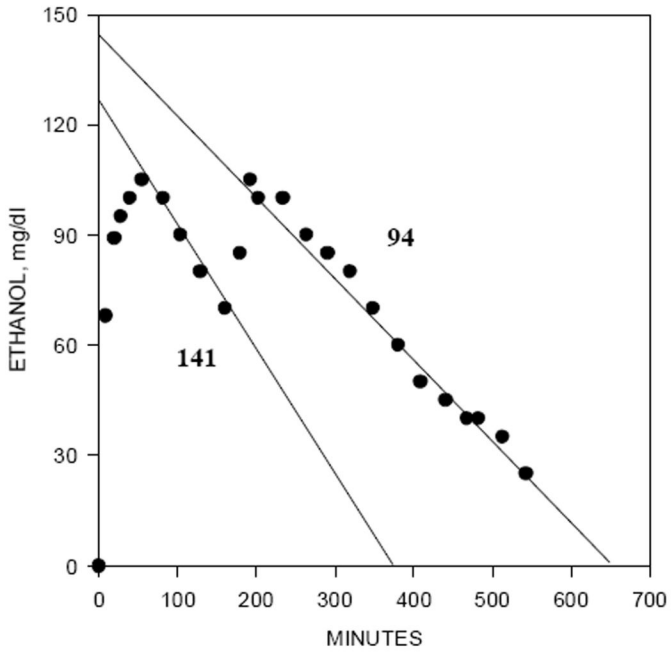

Figure 1.
Typical experiment in a Family History Positive Subject showing the two ascending ethanol phases, the two peak BAC levels and the two descending ethanol phases. The first rate of ethanol metabolism is calculated at 141 mg/kg/hr and the second rate at 94 mg/kg/hr with the change in rate being a reduction of 33%.

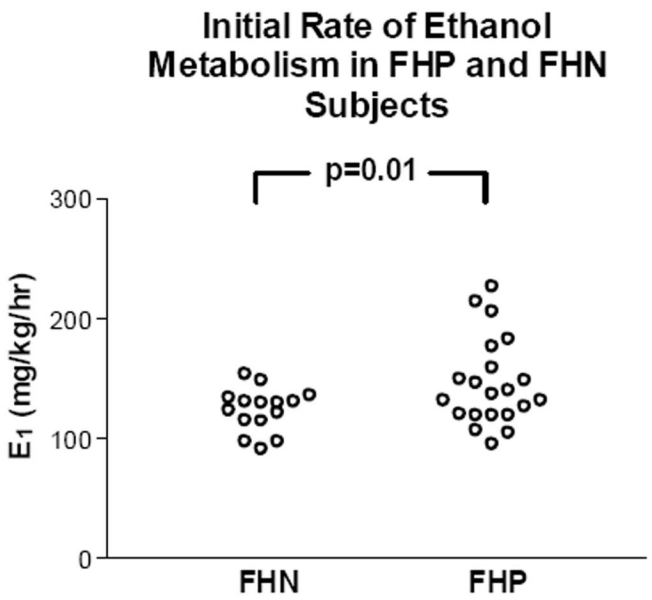

Figure 2.
Dot Plot of Initial Rate of Ethanol Metabolism, E_1, in FHN (n=15) and FHP (n=23) Subjects.

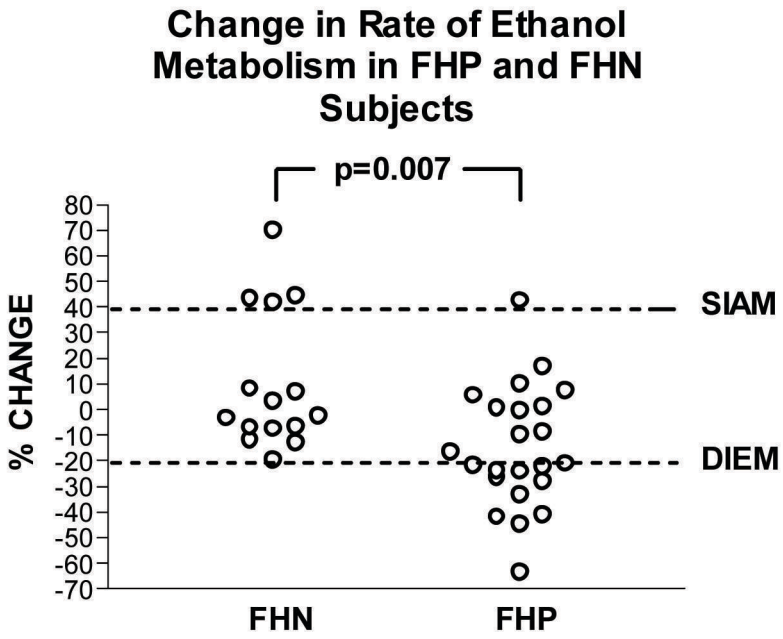

Figure 3.
Dot Plot of Change in Rate of Ethanol Metabolism in FHN (n=15) and FHP (n=23) Subjects.

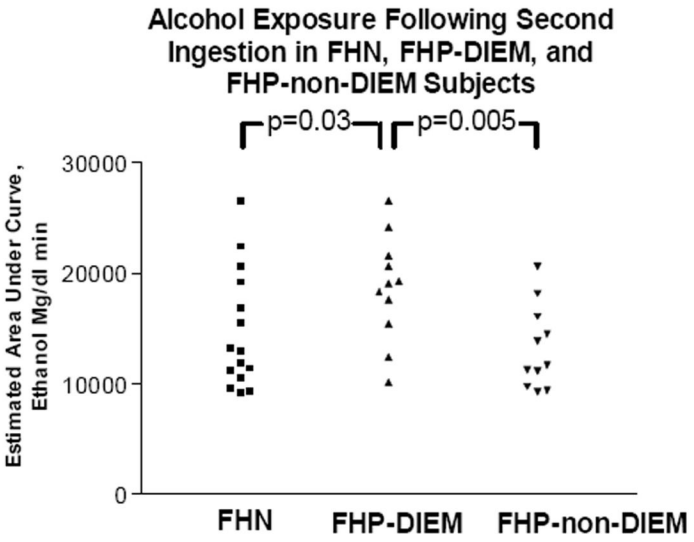

Figure 4.
Dot Plot of Area Under Curve following Second Peak Ethanol as an Estimate of Ethanol Exposure in FHP-DIEM (n=12), FHP-Non DIEM (n=11), and FHN (n=15) Subjects.

Table 1

Comparison of FHN and FHP Subjects on Demographic and Ethanol Metabolism Measures

Measure	FHN (n=15) Mean ± S.D.	FHN (n=23) Mean ± S.D.	t-test p-value
Age (yrs.)	22 ± 1	23 ± 3	.19
Height/Weight Ratio (cm/kg)	1.9 ± 0.1	1.9 ± 0.2	.74
Alcohol Use (Drinks/30 d)	38 ± 21	33 ± 23	.50
Nicotine Use (Cigarettes/30 d)	0 ± 0	7 ± 25	.18
Lifetime Marijuana Use	82 ± 258	60 ± 135	.76
Peak BAC_1 (mg/dl)	82 ± 13	91 ± 16	.06
E_1 (mg/kg/hr)	124 ± 18	148 ± 36	.01
Peak BAC_2 (mg/dl)	88 ± 15	97 ± 19	.13
E_2 (mg/kg/hr)	134 ± 30	121 ± 29	.19
Percent Rate Change	+10 ± 27	-15 ± 24	.007
AUC (mg/dl min)	14,676 ± 5344	16,628 ± 5993	.30

Table 2

Comparison of FHN, FHP-DIEM and FHP-NonDIEM Subjects on Demographic and Ethanol Metabolism Measures

Measure	FHN(n=15) Mean ± S.D.	FHP-DIEM(n=12) Mean ± S.D.	FHP-NonDIEM (n=11) Mean ± S.D.	F-test p-value
Age (yrs.)	22 ± 1	24 ± 4	21 ± 2	.02
Ht/Wt Ratio (cm/kg)	1.9 ± 0.1	1.9 ± 0.2	1.9 ± 0.1	.72
Alcohol Use (Drinks/30 d)	38 ± 21	34 ± 21	32 ± 27	.80
Peak BAC_1 (mg/dl)	82 ± 13	99 ± 14	83 ± 13	.005
E_1 (mg/kg/hr)	124 ± 18	161 ± 41	133 ± 25	.008
Peak BAC_2 (mg/dl)	88 ± 15	105 ± 18	89 ± 16	.03
E_2 (mg/kg/hr)	134 ± 30	107 ± 31	137 ± 18	.02
Percent Rate Change	10 ± 27	-33 ± 13	4 ± 16	.0001
AUC (mg/dl min)	14,676 ± 5344	19,792 ± 6003	13,177 ± 3778	.01