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ALCOHOLISM: CLINICAL AND EXPERIMENTAL RESEARCH

Biphasic Effects of Alcohol on Heart Rate Are Influenced by Alcoholic Family History and Rate of Alcohol Ingestion

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The present study investigated cardiac response to acute alcohol challenge along the blood alcohol concentration (BAC) curve in two groups of young adult nonalcoholic men with (MFH) and without (FH−) multigenerational family histories of alcoholism, matched for drinking history. BACs and resting heart rate measurements were recorded every 10 min for 3 hr after ingestion of a 1.0 ml/kg dose of 95% USP alcohol at two different rates: one of 20 min (slow drinking) and the other of 5 min (fast drinking). Several analyses of variance were performed for each of the dependent measures [BAC and heart rate change from baseline (HRCH)]. A significant risk × BAC phase interaction emerged from the HRCH analysis, indicating that the MFH group was characterized by a significantly greater increase in resting heart rate along the ascending limb of the BAC curve. A significant risk × BAC phase × rate interaction indicated that, when alcohol was consumed at a faster rate, men with multigenerational family histories of alcoholism demonstrated a greater HRCH, which persisted throughout the BAC curve.

Key Words: Heart Rate, BAC Phase, Drinking Rate, Sons of Alcoholics.

YOUNG MEN with multigenerational family histories of male alcoholism (MFH) in the paternal lineage are at ~4 to 9 times increased risk for alcoholism.[1] Twin, adoption, and family studies suggest that this elevated risk is due primarily to genetic factors.[2] Several potentially genetically influenced mechanisms apparently play a role in determining alcoholic behavior. Differential sensitivity to reinforcement—particularly positive reinforcement—seems particularly relevant.[3] Such reinforcement has been associated with activity in a dopaminergically mediated appetitive motivational system [the behavioral activation system (BAS)],[4] whose operations underlie approach and active avoidance. Under certain conditions, heart rate increase from resting baseline apparently reflects activity in the BAS[5]: heart rate varies, for example, with intensity of the appetitive motivational qualities of a given stimulus[6] and in a dose-dependent manner when the stimulus is of a pharmacological nature.[7,8] Accordingly, heart rate increase has been used directly in challenge studies as a psychophysiological indice of response to ethanol-induced reward.[9]

Pihl and Peterson[10] recently reviewed evidence suggesting that susceptibility to alcohol-related problems may be mediated by sensitivity to the psychostimulant effects of alcohol ingestion. Such sensitivity seems highly characteristic of alcoholics[11–14] and nonalcoholic offspring of MFH alcoholics[15–18]; furthermore, magnitude of such sensitivity predicts self-reported[19] and laboratory[20] nonalcoholic alcohol consumption patterns and alcoholic craving for alcohol.[11,21] Furthermore, the BAS seems highly susceptible to sensitization with repeated stimulus presentations or drug administrations.[22] Accordingly, the development of chronic sensitization to psychomotor stimulant effects has been implicated in the genetic predisposition to alcoholism. Newlin and Thomson[23] demonstrated, for example, that sons of alcoholics developed sensitization after repeated exposure to a moderate dose of alcohol on measures putatively reflecting psychomotor stimulation.

Vulnerability to the development of alcohol tolerance likewise seems associated, or even causally linked, to alcohol abuse and dependence. Tolerance refers to greater recovery of affect, performance or physiological or metabolic functioning during alcohol intoxication, and may therefore be considered an opposite process to sensitization. Schuckit[24–28] has hypothesized that the vulnerability mechanism in individuals genetically predisposed to alcoholism is heightened tolerance to the effects of alcohol on static ataxia, serum prolactin, and cortisol levels. Schuckit has suggested that some of these mechanisms are associated with dopaminergic function and that the need to consume larger amounts of alcohol over longer periods of time (to achieve the desired effects) precedes the development of alcoholism. A recent report indicates that the eventual development of alcohol dependence is significantly associated with measures of tolerance to the effects of alcohol, assessed 10 years earlier.[29] A paradox therefore confronts researchers in the alcoholism field: how can increased sensitization to putatively dopaminergic effects and increased tolerance to the same (or similar) effects both be invoked as causal agents in the developmental chain leading to alcoholism?

Resolution of this paradox seems to require consideration of the biphasic, dose-related effects of alcohol on the

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sensitization and tolerance processes. The psychomotor stimulant effects of alcohol (which are sensitized with repeated exposure to alcohol) are typically observed as blood alcohol concentrations (BACs) are rising (during the first 30 min after alcohol consumption).[30,31] The development of tolerance, by contrast, seems associated with the sedating/depressant effects of alcohol, observed at higher BACs, or as BACs are falling.[32,33] In the course of an extensive review of alcohol challenge studies, both Newlin and Thomson[34] and Sayette[35] suggested that confusion with respect to the sensitization/acute tolerance data can be resolved by specifying more precisely which point along the BAC curve reported findings occur. If this is done, the relevant conceptual conflicts disappear: family history of alcoholism seems associated with sensitivity to alcohol reinforcement *as BACs are rising* and exaggerated acute tolerance processes *as BACs fall*.

Various methodological problems further obscure the picture. Phenomena as central as sensitization and tolerance themselves tend to be differentially classified and measured; furthermore, alcohol dose, time of postalcohol consumption, definition of genetic vulnerability, and details of initial alcohol consumption patterns among subjects all vary substantially from study to study. Equally troublesome is the fact that subjective experience along the BAC curve is biphasic in nature: perception of stimulant and depressant effects seem associated with different points on the curve.[36,37] Classification of "at-risk" subjects also poses a problem. Pihl and Peterson[3] have argued that the study of genetic vulnerability through the examination of individuals simply "family history-positive" for alcohol abuse/dependence is unlikely to clarify the nature of the genetic contribution, given that ~30% of men meet DSM-III-R diagnostic criteria for these "disorders" at some point in their lives. More stringent subject inclusion criteria may therefore be required. In addition, because sensitization is a process that develops with repeated exposure to substances, it is essential to account for initial alcohol consumption patterns. This latter methodological issue is particularly relevant to alcohol challenge studies with MFH men, because these subjects have been shown to drink more alcohol,[15] initiate use at a younger age,[38] and develop more alcohol-related problems early in life.[39] It is also important to ensure that the total experimental sample contains a broad range of drinkers, to reduce the possibility of restriction of range and the problems thereof. The matter of the appropriate control might also be considered: should the ubiquitous (and abnormally healthy) college student be used, as is generally the case (often with probands, as well) or individuals drawn from a population or clinical sample?

Finally, *rate* of consumption is a potentially important variable that has remained largely unexamined or controlled for. Substance abusers frequently use extreme methods (such as injection) to ingest psychostimulants at faster rates. In consequence, theoretically, they experience an enhanced pharmacological effect. In alcohol challenge experiments, most subjects are given an equivalent amount of time to ingest a particular dose of alcohol (i.e., 20 min). However, the precise rate at which subjects choose to self-administer, during this time, is rarely measured; and there is indirect evidence that faster rates produce greater cognitive, affective, motoric, and physiological (including cardiac) effects.[40–43] These studies provide preliminary support for the notion that rate of consumption warrants further study.

The present investigation—focusing on psychomotor stimulant sensitivity, sensitization, and tolerance among MFH men and matched family history-negative (FH−) controls—was designed to address these methodological issues. Probands were selected for their high-density family pedigrees (detailed herein). Controls were matched with the MFH probands for drinking, and were drawn from a sample of community volunteers; furthermore, explicit care was taken to ensure that the total group of subjects were characterized by drinking behavior patterns that spanned the range from low to borderline alcohol abusing. All subjects were administered two (comparatively high) doses of alcohol, on different occasions, at markedly different and stringently controlled rates. Psychomotor stimulation was operationally defined as postalcohol heart rate acceleration. Finally, cardiac response to ethanol was assessed across the blood alcohol curve, to ensure differential measurement of ascending and descending limb changes. The study was essentially based on twin hypotheses: (1) that MFH probands would be characterized by increased resting baseline heart rate during the ascending limb of the BAC curve; and (2) that differential rates of alcohol ingestion might interact with this character, such that MFH subjects would experience more heart rate increase during the fast-drinking condition.

Heart rate change from postdrink baseline has been implicated as a potential explanation for the observed elevated stress-response dampening from alcohol in MFH sons of alcoholics.[35] In a critical review of heart rate as an index of stress response in alcohol challenges, Sayette[35] suggested that data illustrating the timeline of postalcohol consumption resting baseline heart rate for MFH and FH− subjects is necessary for the understanding the effects of familial history of alcoholism on stress-response dampening from alcohol. Although the present protocol does not include a stress induction procedure (other than alcohol consumption), data will have implications for the investigation of sensitivity to stress-response dampening from alcohol.

METHODS

Subjects

Fifty men between the ages of 18 and 25 were recruited from French and English arts and entertainment weeklies circulated free in the greater Montreal area. Ads were featured in the "Help Wanted" division of the

Classified Section and were run repeatedly throughout a 2-year period (1992 to 1993). Subjects were initially contacted by telephone and participated in a screening interview after a debriefing of the objectives and procedure of the study. Information detailing their medical history, psychiatric history, personal drinking history, and family history of alcoholism was obtained in a semistructured format. Subjects who did not report medical conditions for which alcohol consumption was contraindicated, a personal or family history of schizophrenia or bipolar disorder, or a personal history of substance use disorder were classified into two groups according to their family histories of alcoholism (as assessed by DSM-III-R criteria for alcohol abuse and the brief version of the Michigan Alcoholism Screening Test).[44,45] An individual with an MFH had an alcohol-abusing biological father, and additionally, two first- or second-degree male relatives who were alcohol-abusing (lifetime criteria). An individual with FH−, by contrast, had no identifiable alcoholic relatives in the previous two generations of the maternal and paternal lineage. Subjects were also matched for drinking practices based on the frequency at which they consume alcohol to the point of legal intoxication, or above. Two somewhat arbitrary ranges were set to facilitate the extensive screening process, ensure sampling across the span of drinking behavior, and select two samples that were matched for drinking behavior. Heavier drinking subjects (who comprised half the total sample) consumed enough alcohol to exceed the legal level of intoxication (BAC > 0.08) at least once per week. Lighter drinking subjects, by contrast, did not exceed legal intoxication more than once every 2 weeks. This method of assessing drinking behavior—detailed in a recent publication,[46] described herein—seems potentially more effective than traditional measures in the measurement of excessive drinking.

All subjects were asked to refrain from consuming alcohol for 72 hr before the study, and to avoid consuming breakfast on the day of the study. Subjects participated in two separate alcohol challenge sessions, counterbalanced for order, at 9:00 AM. When subjects arrived in the laboratory for the first session, they were asked to complete a number of questionnaires detailing their drinking history and personality characteristics (see next section).* Subjects were then seated in a comfortable chair and attached to the polygraph. After a 5-min resting baseline recording session for heart rate, alcohol was administered, in the form of 5 "shots" of 40% vodka (equivalent to 1.0 ml/kg body weight of 95% USP alcohol in total), and frozen to reduce taste intensity. In the "fast-drinking" condition, subjects received a shot at 0, 1, 2, 3, and 4 min; in the "slow-drinking" conditions, subjects received a shot at 0, 5, 10, 15, and 20 min. Shots were consumed in one swallow. This dose of alcohol was chosen based on the results from placebo-controlled studies, indicating that the effects of alcohol on resting heart rate are dose-dependent and that the familial history effect on heart rate response to alcohol is most evident at high doses (1.0 ml/kg to 1.32 ml/kg).[8,47,48] Resting heart rate and BAC measures were recorded every 10 min for 3 hr after consumption of alcohol. When their BACs reduced to a 0.06 level, subjects were disconnected from the polygraph, fed, and presented a movie until their BACs further reduced to a 0.04 level. Subjects were paid $5.00 per hour. One FH− subject vomited during the procedure; his results were eliminated from all analysis.

Measures and Apparatus

Drinking Behavior: Six alcohol consumption measures were used to assess drinking behavior patterns: (1) self-report number of alcoholic beverages consumed per month; (2) self-report alcohol consumption on special occasions; (3) self-report estimates of the number of occassions per year alcohol is consumed such that one feels drunk (drunk/year); (4) number of occasions per year alcohol is consumed such that one cannot drive a vehicle (drive/year); (5) frequency per year that legal intoxication is reached (BAL > 0.08); and (6) presence of problem-drinking symptoms as measured by the Michigan Alcoholism Screening Test (brief version). These measures were collected based on a semistructured interview detailing an individual's estimate of average number of drinking occasions per week and the quantity of alcohol consumed on such habitual occasions. The special drinking occasions item was also included in the interview, which concerned the number of occasions per year alcohol is consumed in quantities that deviate from the average estimate. Subjects were then asked to estimate the number of occasions per year they felt that they met the criteria for intoxication specified by variables (3) and (4) presented herein. The number of occasions per year that an individual indirectly reported reaching a BAC of at least 0.08% (variable 5) was calculated based on his habitual and special occasions estimates, and his weight.[46] Subjects were also asked to provide information regarding their involvement with cigarettes and illicit drugs.

Personality Questionnaires: Sensation-seeking, psychoticism, extraversion, neuroticism and symptoms of depression were assessed using Zuckerman's Sensation-Seeking Scale,[50] the Eysenck Personality Questionnaire,[51,52] and the Beck Depression Inventory.[53]

Heart Rate: A Grass model 7d polygraph with a model 7P4 EKG tachograph preamplifier was used attached to Medi-Trace pellet electrodes placed bilaterally on the lower chest of the subject for the measurement of heart rate. Within the 5-min resting baseline period, the most artifact-free, 60-sec period was selected, and heart rate samples were scored every 2.5 sec for the entire minute. An average heart rate was then obtained to reflect sober resting heart rate. Resting heart rate was measured in a similar manner every 10 min after alcohol consumption: one sober and, on average, 15 postalcohol resting heart rate averages were thus obtained.

BACs were determined using an Alco-Sensor III (Thomas Instruments, Montreal) and were recorded only if the subject had not consumed alcohol within the previous 10 min. Subjects were asked to provide a strong breath that remained at a consistent intensity for 6 sec. The Alco-Sensor III provides BAC estimates with an error of measurement of ±0.003.

RESULTS

Demographic, Drinking, and Personality Variables

One-way analyses of variance (ANOVAs) were performed on all continuous variables representing subject demographic information, involvement with alcohol and illicit drugs, and personality characteristics. The three variables assessing frequency of assessing drinking (drunk/year, drive/year, and BAC > 0.08%) were not normally distributed, and required log transformation before ANOVA. Variables representing daily smoking, illicit drug consumption, and problem drinking symptoms were severely skewed toward a lower limit of zero. Transformation did not result in normalization; such variables were therefore converted to categories and analyzed using χ^2. Analysis presented in Table 1, including Cohen's[54] effect sizes, indicated that MFH and FH− men were adequately matched with respect to age and drinking-related variables. Differences emerged on measures of academic achievement, duration of cigarette smoking (MFH men had been smoking 2.6 times longer than the FH− men), presence of daily smoking (MFH > FH), and sensation-seeking (FH− > MFH).

*This allowed the subject to become familiar with the laboratory on the first day in order to reduce the potential effects of novelty on session order (prior exposure to the laboratory has been shown to influence the effect of alcohol).[49] The duration of this questionnaire session was ~1 hr. Therefore, subjects consumed alcohol between ~10:00 and 11:00 AM for both drinking sessions.

Table 1. Risk Group Means and Standard Deviations for Demographic, Personality, Alcohol, and Drug-Related Variables

Variable	FH- Mean	FH- SD	MFH Mean	MFH SD	F-ratio	Effect size†
Age	20.96	2.18	22.36	2.92	3.49	0.51
Years of education	13.91	1.57	12.65	1.84	6.45*	0.69
Personality variables						
Depression	4.43	4.01	4.88	4.03	0.10	0.11
Extraversion	14.81	5.29	14.00	4.91	0.29	0.16
Psychoticism	4.62	2.49	4.30	2.49	0.17	0.15
Neuroticism	8.81	5.80	8.33	4.87	0.25	0.16
Sensation-seeking	26.49	6.08	23.5	3.92	4.08*	0.56
Alcohol and drug variables						
No. of drinks/month	35.49	37.57	35.36	33.99	0.00	0.00
Occasions/month	6.89	5.27	7.28	7.19	0.06	0.06
No. of drinks/occasion	4.96	2.19	4.74	2.38	0.09	0.10
Special drinking occasions/month	2.23	2.08	1.90	1.82	0.25	0.17
No. of drinks/special occasion	7.56	4.22	7.42	4.06	0.02	0.03
Excessive drinking (BAL > 0.08)	60.74	68.91	62.96	75.10	0.01‡	0.03
Excessive drinking (drunk/yr)	31.59	39.63	25.65	33.86	0.30‡	0.16
Excessive drinking (drive/yr)	45.45	64.83	23.96	34.67	1.95‡	0.39
% Group members MAST > 2	21.7		32.0		0.64§	
% Group members reporting monthly cannibis or cocaine use	34.8		40.0		0.14§	
% Group members who smoke every day	26.1		60.0		5.60*,§	
No. of years smoking	1.52	2.87	4.42	3.77	8.78**	0.87
n	24		25		49	

BAL, blood alcohol level; MAST, Michigan Alcoholism Screening Test.
p values are as follows: *$p < 0.05$; **$p < 0.01$.
† Effect sizes >0.20 = small; >0.50 = moderate; >0.80 = large.
‡ Means calculated from nontransformed data. ANOVA performed on log-transformed data.
§ χ^2 analysis performed on categorical data.

Postalcohol Consumption Onset Measures

Methodological Note: We used initiation of alcohol consumption as the zero point, instead of the more conventional end-of-drinking-session zero, because of the difference in the duration of our two drinking sessions (5 vs. 20 min). BAC curves for the two sessions had to be calculated from onset of drinking to line up meaningfully, because BAC starts rising from the first moment of drinking, and not from offset of drinking. BAC measures are also "missing" for the 10- and 20-min points in the slow drinking condition, as a consequence of this choice of zero, because subjects were still actually drinking at these points and could not therefore be assessed by breathalyzer. Furthermore, all missing heart rate data points were replaced with cell means. All missing BAC data points were handled similarly, with one exception. When subjects had decreased to below a 0.06 level; BACs were no longer recorded. A regression analysis was performed with BACs from the previous three time points as independent variables to predict these missing data points. The rationale for such a procedure was that cell means for such subjects necessarily overestimated their BACs, because data were based on means from subjects who had not reached a 0.06 BAC. Each prediction yielded R^2's ranging from 0.70 to 0.90.

As a preliminary analysis to determine the configuration of the BAC curve (to determine the location of the ascending and descending limbs), a two-way (Rate × Time) ANOVA was performed on BACs. The interaction between rate and time was not significant, indicating that the configuration of the BAC curves after fast and slow drinking did not differ over time. However, a significant main effect for rate [$F(1,1081) = 5.88, p < 0.02$] showed that the slow drinking condition resulted in higher BACs overall. Analysis of the means indicated that BACs rose from 30 min until 50 min postinitiation of consumption, and began falling for both fast and slow drinking conditions, thereafter. The peak of the BAC curve was therefore determined to be 50-min postinitiation of each alcohol consumption period. [BACs were defined as rising until 50 min after initiation of the consumption period (ascending limb) and as falling thereafter (descending limb).] These results are consistent with other reports detailing the timeline of the BAC curve.[55]

BACs. A three-way ANOVA (Risk × Rate × Time) was performed on the BACs to determine whether the risk groups differed with respect to the configuration of the BAC curve. A significant three-way interaction [$F(12,536) = 1.87, p < 0.04$] indicated that the groups did demonstrate different BAC curves after fast and slow drinking. However, when corrected for sphericity (Huynh-Feldt $\epsilon = 0.15$), this interaction was no longer significant. The BAC curve was then divided in two (ascending/descending), and two separate three-way analyses were performed to investigate potential effects of familial risk and rate of consumption on the rate of metabolism of alcohol without violating the sphericity assumption for repeated-measures ANOVA. A

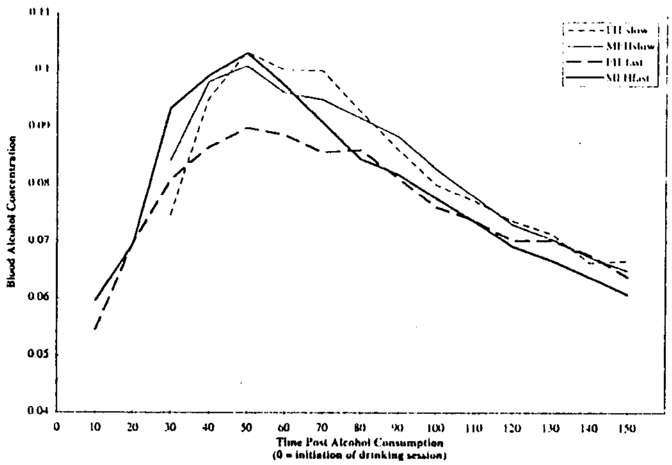

Fig. 1. Mean BACs for MFH men and FH− men after fast and slow drinking.

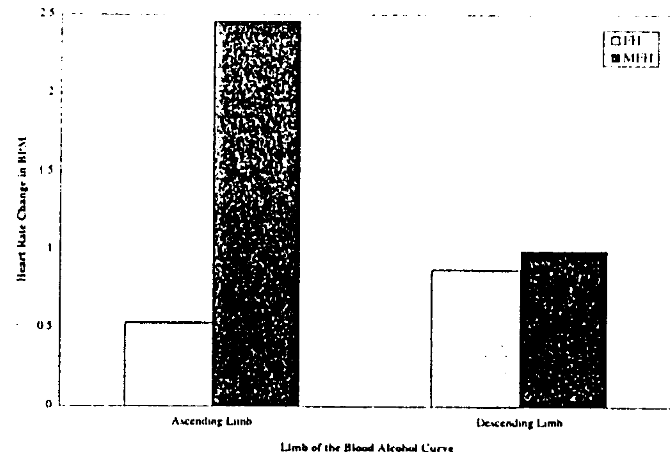

Fig. 2. Mean alcohol-induced heart rate change (in bpm) from resting baseline as BACs are ascending and descending for MFH men and FH− men. Illustration of a significant two-way (Risk × BAC phase) interaction ($p < 0.05$).

significant Rate × Time interaction was yielded for the analysis of the ascending limb of the BAC curve [$F(2,92) = 8.71, p < 0.001$, with Huynh-Feldt correction for sphericity ($\epsilon = 0.86$)]. The Risk × Rate × Time interaction for the ascending limb was not significant, yet was significant along the descending limb [$F(9,414) = 3.49$, $p < 0.05$, with Huynh-Feldt correction for sphericity ($\epsilon = 0.26$)]. Analysis of simple main effects demonstrated that, at 50 min post-alcohol consumption onset, the FH− group demonstrated a trend to achieve lower BACs for the fast drinking condition [$F(1,45) = 3.78, p < 0.06$], which became significant at 60 min [$F(1,45) = 4.33, p < 0.05$] and persisted until 70 min postinitiation of alcohol consumption [$F(1,45) = 4.68, p < 0.05$]. A significant effect for rate was yielded at each time point from 80 to 150 min postinitiation of alcohol consumption. The overall rate effect for this portion of the BAC curve was $F(11,45) = 11.77$, $p < 0.0001$. Analysis of the means revealed that fast drinking resulted in a low BAC throughout the descending limb of the BAC curve. The three-way interaction is illustrated in Fig. 1.

Resting Heart Rate Change from Baseline (HRCH). A Risk × Rate × BAC phase ANOVA was performed first, to test our primary hypothesis—that MFH subjects would show increased baseline heart rate during the ascending BAC limb. The analysis yielded a significant Risk × BAC phase interaction [$F(1,46) = 7.37, p < 0.01$], indicating that, regardless of rate of consumption, the MFH group demonstrated heightened HRCH along the ascending limb that was no longer evident along the descending limb. The size of this effect was 0.36, according to Cohen's calculation.[54] An effect of 0.50 (half a standard deviation) is considered moderate. According to this analysis, the FH− group did not evidence HRCH along either limb of the BAC curve. Figure 2 portrays the interaction.

A three-way ANOVA (Risk × Rate × Time) was performed on heart rate change from sober resting baseline levels (HRCH) to determine precisely where risk and rate effects manifested themselves over time. The analysis indicated a significant Risk × Rate × Time interaction [$F(14,644) = 1.84$, $p < 0.03$], which remains significant when corrected for sphericity with Huynh-Feldt's ϵ (0.85, $p < 0.04$). This interaction is illustrated in Fig. 3.†

Two-way repeated-measures ANOVAs performed separately for each drinking condition yielded a significant Risk × Time interaction for the slow drinking condition [$F(14,644) = 3.29, p < 0.001$, with Huynh-Feldt's correction for sphericity ($\epsilon = 0.73$)] and a trend toward a main effect for risk for the fast drinking condition [$F(1,46) = 3.55, p < 0.07$]. Analysis of simple main effects for the slow drinking condition indicated that the two-way interaction could be accounted for by the fact that a significant effect of time emerged for the MFH group after slow drinking only, indicating that HRCH was evident at earlier points along the BAC curve and then disappeared at later points [$F(14,336) = 2.50, p < 0.01$, with Huynh-Feldt's correction for sphericity ($\epsilon = 0.80$)]. The FH− group also showed significant changes in heart rate across time after slow drinking [$F(14,308) = 2.68$, $p < 0.01$, with Huynd-Feldt's correction ($\epsilon = 0.55$)]. However, in contrast to the MFH group, this group went from having no HRCH along the ascending limb of the curve to the highest HRCH at 130, 140, and 150 min postalcohol consumption onset. The overall three-way interaction could thus be accounted by the fact that the MFH group was characterized by significantly elevated heart rate increase as blood alcohol concentrations rose within the 40 min after onset of both drinking conditions. However, rate of consumption seemed to influence differentially the HRCH at later points along the BAC curve; in that HRCH disappeared after slow drinking, yet persisted throughout the BAC curve after fast drinking. This interaction and results from simple main effects analysis are portrayed in Fig. 4.

There is a large body of evidence indicating that the

† *It should be noted at this point that HRCH data from the 40-min point during the slow drinking condition for 11 MFH and 13 FH− subjects were previously reported in the context of a cumulative analysis by Peterson et al.*[18]

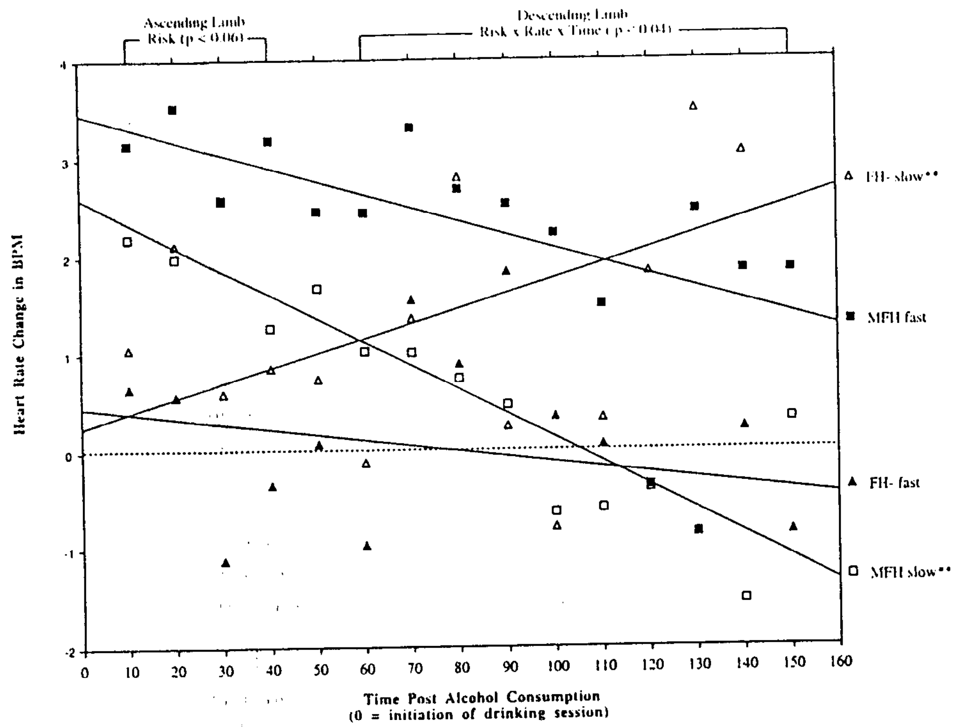

Fig. 3. Regression lines and results from simple main effects ANOVA on alcohol-induced HRCH (in bpm) at 10-min intervals along the BAC curve for MFH men and FH− men after fast and slow drinking. **Significant results from analysis of simple main effect for time ($p < 0.01$).

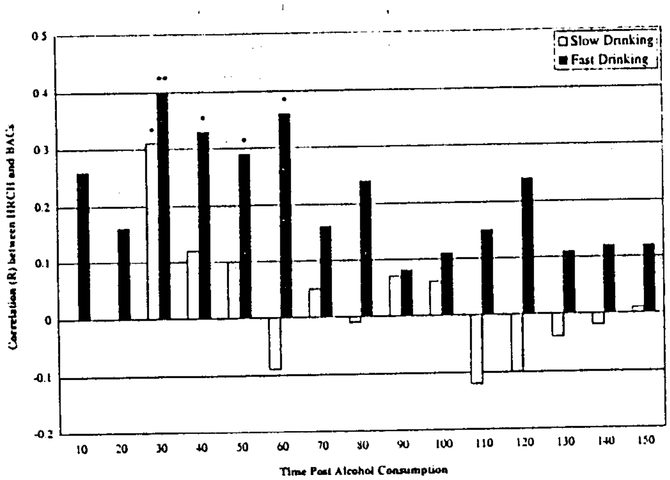

Fig. 4. Correlations between BACs and alcohol-induced HRCH at 10-min intervals along the BAC curve. *$p < 0.05$; **$p < 0.01$.

stimulant properties of alcohol may be specific to the ascending limb, and the relationship between the variables under study may depend on the limb of the BAC curve.[30,31] In consequence, there was reason to perform the same analysis, but separately, for each limb of the BAC curve to understand better the time effects. Two separate three-way ANOVAs were therefore performed on HRCH and the analyses indicated: (1) a trend toward a risk effect [$F(1,46) = 3.86$, $p < 0.06$], with the MFH group demonstrating greater heart rate increases on the ascending limb of the curve and (2) a significant three-way Risk × Rate × Time interaction along the descending limb of the BAC curve [$F(9,405) = 2.06$, $p < 0.04$]. According to the latter analysis, the MFH group demonstrated a relatively elevated heart rate throughout the descending limb of the curve after fast alcohol consumption. Analysis of simple main effects indicated that the three-way interaction was largely accounted for by significant Risk × Rate interactions at 130, 140, and 150 min postalcohol consumption [$F(1,45) = 10.06$, $p < 0.01$; $F(1,45) = 10.44$, $p < 0.01$; and $F(1,45) = 15.59$, $p < 0.001$, respectively]. At these time points, the FH− group demonstrated a significantly elevated HRCH, compared with the MFH group for the for the slow drinking condition only [$F(1,45) = 5.32$, $p < 0.05$; $F(1,45) = 10.06$, $p < 0.01$; $F(1,45) = 10.70$, $p < 0.01$, respectively]. The interaction was explained by the fact that the FH− group after slow drinking and the MFH group after fast drinking were not distinguishable with respect to HRCH at the tail end of the BAC curve. Figure 4 also portrays the results from the these analyses.

These same three-way ANOVAs (Risk × Rate × Time) were performed on residual scores from the prediction of HRCH using BACs. The results remained unchanged when group differences in BAC were considered.

Correspondence Between HRCH and BACs

Figure 4 illustrates correlations between HRCH and BACs along the entire BAC curve. As indicated, HRCH corresponded to rising BACs only. In the fast drinking condition, correlations between BACs and HRCH were significant only at 10, 30, 40, 50, and 60 min postconsumption, with correlation coefficients ranging from 0.18 to 0.47. In the slow drinking condition, BACs were only available at 30 min postinitiation of the consumption period (i.e., 10 min after completion of the drinking session). At this time period, BACs and HRCH correlated significantly (r =

0.30); however, after 30 min, correlations were reduced to nonsignificant levels.

DISCUSSION

MFH subjects seem to be characterized by significantly increased alcohol-induced heart rate, during the ascending limb of the blood alcohol curve. In the slow drinking condition, which might be regarded as comparable with other (relatively high-dose) alcohol-challenge studies,[8,15–19,24–29,34,49] this effect only manifests itself until ~40 min postalcohol consumption onset. In the fast drinking condition, however, these effects seem to persist long into the descending limb. This indicates, perhaps, that the theoretically desirable stimulating ascending limb effects of alcohol might be prolonged, merely by increasing the rate of consumption, at least among those prone to such effects. The overall difference in heart rate change could not be attributed to the fact that the high-risk group absorbed alcohol more rapidly at certain points along the ascending limb of the BAC curve, because the results remained unchanged when BACs were covaried from HRCH scores.

Gianoulakis et al.[56] have recently shown that MFH subjects, essentially identical to those described in the present study, are characterized by increased levels of plasma β-endorphin postethanol consumption. Peterson et al.[18] demonstrated that these subjects were also characterized by accelerated postethanol heart rate—as in the present report—and that the magnitude of this response was highly and positively correlated with plasma β-endorphin change. We know from our other investigations that ethanol-induced heart rate change is positively associated with enhanced mood, level of self-report, and laboratory alcohol consumption.[20] All of these studies examined heart rate response to ethanol: (1) using a stringently defined high-risk population, (2) using a relatively high alcohol dose (typically 1.0 ml/kg 95% USP alcohol), and (3) during the ascending limb of the BAC curve. In the current study, had heart rate response to ethanol during the slow-drinking condition not been assessed before 40 min postalcohol consumption *onset* (equivalent to 20 min postalcohol consumption offset), *no effect of family history on response to alcohol would have been evident.* The BAC curve is sharp and nonsymmetrical (strongly skewed to the left). Failure to assess response during the short-lived ascending period (much of which might occur while subjects are actually drinking) means certainty of missing measurement of short-lived, but potentially critical sensitivity to reinforcing properties of alcohol. Furthermore, we know that doses below 0.75 ml/kg in a 20-min drinking period do not elicit significant alcohol effects on heart rate, among MFH subjects, in small sample studies.[8]

As noted in the introduction, heart rate acceleration is frequently considered a valid indice of stimulus-induced "reward"—most specifically, incentive reward, which is the positive affect/approach tendency generated in the presence of cues of consummatory reward.[5,9,57,58] Incentive reward seems dopaminergically mediated,[59] a consequence of activity in the mesolimbic dopamine system, or BAS.[4] It has recently been demonstrated that alcohol might produce these effects indirectly as a consequence of more direct influences on opiate mechanisms.[60–62] MFH subjects are characterized by heightened β-endorphin response to acute ethanol (manifested, in part, in heightened plasma levels); it is possible that this response, in turn, produces a brief dopaminergically mediated psychomotor-stimulant effect. Various recent studies indicate that this chain of events is plausible[60–63]—assuming that high plasma levels of β-endorphin are indicative of, or co-occur with, high central levels, or that plasma β-endorphin peptides cross the blood-brain barrier in sufficient quantity to produce central effects.

The results of the present study are consistent with other reports from animal and human studies indicating that genetic factors influence sensitivity to the short-term activating effects of moderate alcohol doses[34,64–66]—effects that seem qualitatively separable from the sedating effects that emerge at higher doses, or farther along in time[67]—and with the review of Newlin and Thomson,[34] which concluded that genetic predisposition to alcoholism may be mediated by sensitivity to alcohol effects along the ascending limb of the BAC curve, but by acute tolerance along the descending limb of the curve. The persistent discrepancy between our findings and those reported by researchers, such as Mark Schuckit, can be most easily explained in these terms: MFH men manifest increased sensitivity (to psychomotor stimulant effects, for example) during the ascending BAC curve, and decreased sensitivity while blood alcohol levels are falling—at least under normal drinking conditions. When various contextual or pharmacological factors, such as rate, are varied, acute tolerance during the falling limb appears reduced or eliminated.

It is also of interest to consider the potential reasons for the effects of increased rate of consumption on HRCH, at least among the MFH group. Perhaps the higher BAC curve slope associated with heightened consumption rate is associated, directly or indirectly, with dopamine release of such magnitude that standard reuptake mechanisms[68] are overwhelmed. Alternatively, perhaps the fast drinking session is so novel that acute tolerance, learned under more standard conditions, does not manifest itself. Cardiac responses have been shown to habituate to certain facets of a drinking experience.[69–71] The findings suggest that individuals characterized by sensitivity to alcohol-induced changes in heart rate, may be particularly susceptible in drinking environments or situations that are relatively novel.

The overall size of the alcohol-induced heart-rate change, after consumption of a 1.0 ml/kg dose of alcohol, seemed lower in this study than in our previous reports,[15,16,17,20] although group differences in HRCH remained significant. Generally, MFH men are characterized by an increase of ~10.5 bpm under similar conditions; their

FH− counterparts show an increase of ~5.5 bpm.[18] In the present study, these numbers fell to 2.45 and 0.43, respectively. The current study differed primarily from our previous work with alcohol challenge in many ways. We selected higher drinkers, brought subjects in for two drinking sessions, and kept them attached to a polygraph for a much longer time, for example. Most importantly, however, we did not subject our participants to an aversive or otherwise stimulating stressor before consuming alcohol. In previous investigations, subjects were administered at least three signaled shocks, once while sober and again while intoxicated (after baseline heart rate measures were taken, in both conditions). The phenomenon of mesolimbic dopamine cross-sensitization between stress responding and psychostimulant administration is well documented.[72–75] Perhaps engagement in a stressful test sober, before consuming alcohol, increases the effect of alcohol on resting heart rate and, theoretically, its incentive reward effects. This type of effect might be expected, if heart rate response to alcohol is influenced by mesolimbic dopamine mechanisms.[71] The possibility seems worth investigating, in the attempt to specify contextual factors heightening sensitivity to alcohol reinforcement.

Finally, the results from the present study have implications for the understanding of the contribution of familial history of alcoholism on sensitivity to the stress-response dampening effects of alcohol. It has been suggested that elevated stress-response dampening in MFH men may be an artifact of elevated postalcohol consumption resting baseline levels.[35] According to the present analysis, there is no time effect on resting heart rate levels, if heart rate is measured along the ascending limb of the BAC curve (before 50 min postinitiation of alcohol consumption). Therefore, if one considers the slow drinking condition to be most similar to the alcohol challenge procedures of previous reports,[15–17] elevated stress-response dampening in MFH males might be accounted for by the fact that elevated postalcohol consumption baseline heart rate levels had disappeared by the time stress-response dampening was measured (55 min postinitiation of drinking or 35 min postoffset of drinking). In fact, there are no group differences with respect to postalcohol heart rate stimulation at 50 min postinitiation of drinking. Nevertheless, it is important to mention that previous reports have indicated that postalcohol heart rate dampening and postalcohol heart rate stimulation are only moderately correlated ($r = 0.39$), whereas sober reactivity and postalcohol dampening are highly correlated ($r = 0.87$)[19] and that MFH versus FH− group differences in stress-response dampening persist when postalcohol stimulation is considered as a covariate in the analysis.[76]

In conclusion, it seems (1) that MFH males are more sensitive to alcohol-induced cardiac effects on the ascending limb of the BAC curve and (2) that these effects might be enhanced or extended by the accelerating rate of alcohol ingestion. These cardiac effects appear *biphasic* (as well as dose-related)[8] and plausibly linked to incentive reward; it therefore seems that investigators conducting alcohol challenges should use sufficient doses and pay particular attention to the first 30 min after initiation of drinking. With respect to implication for treatment, finally it seems that counselors using controlled-drinking strategies might well be advised to concentrate both on reducing clients' dose *and rate* of ingestion during single drinking occasions to assist susceptible individuals in reducing their sensitivity to alcohol reinforcement.

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