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Alcohol and Secobarbital Effects as a Function of Familial Alcoholism: Extended Intoxication and Increased Withdrawal Effects

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Response differences following administration of alcohol between adult males with a positive (FHP) versus negative (FHN) family history of alcoholism have been demonstrated in previous research and are thought to be related to risk for developing alcoholism. If this is so, the pharmacological breadth of addiction risk conferred by a positive family alcoholism history might be studied by determining whether FHP subjects show different responses than FHN to drug classes other than alcohol. We have previously reported on the acute effects of ethanol as compared with secobarbital in FHP and FHN subjects and found that FHP subjects showed greater sensitivity across a variety of subjective measures than FHN subjects for both drug classes. The data reported here are based on an extended data collection period of 3 to 18 hr postingestion, following completion of the acute laboratory portion of the study. Specifically, in the present study, dose-effect timecourse functions for a variety of physiological (heart rate, blood pressure, and breath alcohol level), subjective (analog mood, drug effect, and withdrawal, Subjective High Assessment Scale (SHAS)), and psychomotor measures (Digit Symbol Substitution Test and numeric recall) were examined in FHP and FHN college-aged males for secobarbital (0, 100, 200 mg daily) and ethanol (1 g/kg daily). FHP and FHN subjects were matched on light-to-moderate drinking patterns, anthropometric dimensions, age, years of schooling, and drug use. FHP subjects reported more extended intoxication and greater withdrawal effects following both ethanol and the high dose of secobarbital than did FHN subjects. In addition, these intoxication and withdrawal effects reported by FHP subjects persisted longer than effects reported by FHNs; this was true both for ethanol and the higher secobarbital dose. No differences in physiological responses emerged between the two groups in any drug condition. The present study is the first demonstration of extended intoxication and withdrawal differences between these groups and points to the need to further examine extended time periods following drug ingestion, as this may reveal additional parameters across which these family history groups differ.

Key Words: Alcohol, Familial, Barbiturate, Intoxication, Withdrawal.

CONVERGING LINES of evidence for a familial predisposition to alcohol dependence have led to the study of alcohol challenge doses in adult children of alcoholics who have not yet themselves developed the disorder. The goal of this area of research is identification of physiological, subjective and/or behavioral markers which may place FHP males at risk for development of alcohol dependence. Early reports were generally consistent in findings of decreased sensitivity to ethanol on a variety of measures in family history positive (FHP) subjects as compared with matched family history negative (FHN) subjects at equivalent blood alcohol levels.[1-5] More recently, with an increase in the number of laboratories engaged in this research, there has been increased diversity in findings. Some studies have found no difference or even increased sensitivity on a variety of measures for FHP as compared with FHN subjects.[6-10] For example, in a recent study in our own laboratory, FHP subjects reported greater analog high scores and greater Subjective High Assessment Scale scores as compared with FHN subjects at equivalent blood alcohol levels.[11]

The above studies have compared FHP and FHN groups on the acute effects of ethanol over a period of several hours following ethanol administration. Interestingly, there have been no laboratory studies of the extended psychophysiological effects of ethanol or of ethanol withdrawal symptoms following administration of a standardized ethanol dose in matched FHP and FHN subjects. Using retrospective questionnaire methodology, Newlin and Pretorius[12] found evidence of more frequent and intense hangover symptoms in the last year for sons of alcoholics than for sons of nonalcoholics, although the two groups did not differ in their reported quantity and frequency of drinking. These self-report data suggest possible elevations in sub-acute withdrawal symptoms in FHPs as compared with FHNs.

In an earlier report we have presented data comparing the acute pharmacological effects of ethanol and secobarbital as a function of family history status.[11] Data reported here were collected during the extended post-session observation period and were intended to assess and compare these same study drugs with respect to their postacute effects on withdrawal symptomatology in the two family history groups. Specifically, the time course of ethanol effects (1 g/kg) for a variety of physiological, subjective and psychomotor measures was assessed in FHP and FHN subjects from 3 to 8 hr following administration and also

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the next morning. Between-group differences in dose-effects and time course were also examined for the short-acting barbiturate, secobarbital (0, 100, and 200 mg). Fraser and colleagues[13] demonstrated the similarity in intoxicating effects and withdrawal symptoms between alcohol and barbiturates. Thus, secobarbital doses were included to explicitly examine the specificity to ethanol of any family history group differences in extended effects or withdrawal symptoms.

METHODS

Subjects

Thirty-two white males (18–25 years of age) enrolled in local colleges and universities completed the study. Advertisements for participation in the laboratory study were run regularly throughout the academic year in the newspapers of six college/university campuses. In addition, three local colleges provided mailing lists of male students. Questionnaire mailings which included a supportive cover letter from the school administration were sent out. The questionnaire was adapted from a screening instrument developed by Schuckit[14] and included information on demography, personal and familial alcohol and drug use patterns and associated problems, and a brief personal medical and mental health history. Alcohol and drug use characteristics of students responding to the questionnaire are reported elsewhere.[15] Students were pre-screened for research eligibility based on their responses to this screening questionnaire; persons were excluded during the pre-screening stage if they reported high levels of or problems associated with alcohol or other drug use. Potential subjects were invited for an in-person interview conducted by a clinical psychologist that included a brief medical screen, the Family History-Research Diagnostic Criteria (FH-RDC),[16] the Michigan Alcoholism Screening Test (MAST),[17] and the SCL-90R.[18] Personal alcohol and drug use data were also obtained during the interview and included typical monthly drinking patterns (quantity, frequency), lifetime maximum drinking for a duration of at least 1 week, and actual drinking levels during the week prior to the interview. Finally, based on interview findings, students were excluded from laboratory participation on the basis of: extensive drug use; any psychiatric diagnosis in the subject (FH-RDC); a score of five or greater on the MAST; a total score of 70 or above on the SCL-90R; reported maternal alcoholism based on FH-RDC; or reported regular use of prescription medications or continuing care for a chronic health problem.

A subject was classified as family history positive (FHP) if his biological father met FH-RDC criteria for Alcohol Abuse based on the subject's report; in all instances, subjects reported symptomatology for the fathers that also met DSM-IIIR criteria for Alcohol Dependence.[19] For nine of the 16 FHP subjects, the father was the only first- or second-degree relative who met FH-RDC criteria for alcoholism; for the remaining seven subjects, the father and at least one additional first- and/or second-degree relative met these criteria. A subject was classified as family history negative (FHN) if no first-degree relative met FH-RDC criteria for alcoholism; two out of 16 FHN subjects had a second-degree relative only who met criteria. FHP and FHN subjects were matched on the basis of height/weight ratio, age, years of school, typical and maximal alcohol use patterns, and recent (past 6 months) and lifetime drug use. Subject characteristics are summarized in Table 1; there were no significant differences on any subject variable for FHP and FHN groups. Subjects who were eligible for the study provided prior written, informed consent, and were paid approximately $400 for their participation. At the conclusion of participation, FHP subjects were counseled with regard to their increased risk for the development of Alcohol Abuse/Dependence and possibly other psychoactive substance use disorders and were encouraged to contact the investigators should they have questions or concerns in the future.

Table 1. Subject Characteristics as a Function of Family History Groups

	FHP	FHN
Age	20.9	21.1
Weight/height	2.4	2.4
Yrs school	14.0	14.4
Mean drinks/month	24.6	24.4
No. drinks last week	6.7	5.4
Max No. drinks any week	30.4	26.1
Marijuana (No. occasions/6 months)	1.7	2.6
Cocaine (No. occasions/lifetime)	0.8	1.1

Procedures

In separate sessions, subjects received two secobarbital doses (100 and 200 mg), ethanol (1.0 g/kg) and placebo in semirandom order; subjects could not receive the high dose of secobarbital as the first dose. Doses were administered using a double blind, double dummy procedure; that is, during each drug ingestion period, subjects first received an opaque orange capsule and then drank a 16-ounce beverage. Only one active drug was administered per dosing occasion. The beverage consisted of orange juice mixed with the appropriate dose of ethanol and was consumed using a pacing procedure. The total drink volume was divided into three glasses; subjects had 5 min to complete each glass. In order to conceal the alcohol content of the drink, a wrist band soaked in ethanol was placed around the top of the glass to deliver a strong odor of alcohol and 1 ml of ethanol was floated on top of each glass to deliver an initial taste of alcohol. The research assistant and subjects were blind to the dose protocol.

Experimental sessions were conducted on an outpatient basis with at least one nonstudy day separating sessions. On each study day, subjects participated in a 3-hr laboratory session during which they remained seated in a quiet room except when standing was required for a psychomotor task. During each laboratory session, a battery of subjective, physiological and psychomotor measures was repeated once prior to and four times following drug administration. Drug ingestion occurred during session min 40 to 55; total session duration was 200 min. These session data are reported separately.[11]

Immediately following each laboratory session, subjects were deinstrumented and escorted to the inpatient General Clinical Research Center (GCRC) on the hospital campus where extended monitoring of physiological, subjective and psychomotor measures continued at 1-hr intervals from 3 to 8 hr following drug administration and again the next morning (18 hr postingestion). Data were collected by nursing staff blind to drug dose and family history. Physiological measures included breath analysis of blood alcohol level (BAL) using a hand-held Intoximeter, manual auscultatory systolic and diastolic blood pressure, and heart rate by palpation. Subjective measures included four self-report analog questions (high, liking, desire to drink an alcohol beverage ("craving"), and sleepy). Analog items were displayed individually on a computer screen; subjects responded on an analog scale labeled at each end as "not at all" (scored as zero) and "most ever" (scored as 100) by using a joystick which advanced a cursor on the screen. In addition, subjects completed the Subjective High Assessment Scale,[20] and the short form of two subscales of the Addiction Research Center Inventory (Morphine/Benzedrine Group (MBG) and Pentobarbital/Chlorpromazine/Alcohol Group (PCAG) Scales.[21] Finally, data were collected on 10 alcohol withdrawal symptoms (sweaty, loss of appetite, shaky, trouble concentrating, racing heart, anxious, alcohol craving, tired, restless, and irritable). Each item was displayed separately on the computer and was rated on an analog scale labeled at each end as "not at all" (scored as zero) and "most ever" (scored as 9).

Psychomotor measures included a computerized version of the Digit-Symbol Substitution Test (DSST) designed to assess both reaction time

and associative memory. In this task, each of 10 symbols was paired with a digit from 0 to 9. As a digit appeared on the computer monitor, the subject was required to enter the associated appropriate pattern on the computer digit pad. Outcome measures included the number of attempted trials, correct trials and accuracy (% correct) during the 90-sec test period.[22] In addition, a computerized numeric recall task was used to assess short-term memory. A randomly generated seven digit number was displayed on the computer screen followed by a 0 to 30-sec random delay; subjects were required to reenter the digits in the correct order. Measures included the number of correctly recalled complete eight-digit sequences (number correct) and the number of individual digits entered in the wrong sequence (position errors).

Data Analysis

Physiological, subjective and psychomotor measures were analyzed using repeated measures analyses of variance. Factors included group (FHP vs. FHN), drug condition, and time (hr). All analyses of variance used Huynh-Feldt probability levels (BMDP) to correct for violations of sphericity with repeated and possibly interdependent measures. Only significant interaction effects are reported, with F values provided in the text. Post-hoc comparisons of means (Tukey) were conducted, and significance levels are provided in parentheses in the text. Results are organized by type of dependent measure, with subcategorizations of group, dose (condition), and timecourse effects within each section.

RESULTS

Subjective Effects Measures: Extended Intoxication

Ethanol Effects. In general, FHP subjects reported greater intensity of intoxication-related ethanol effects than did FHN subjects. FHP subjects scored significantly higher on the total SHAS instrument than FHN subjects ($p < 0.01$; Fig. 1, top row). Significant group differences were also obtained for the following individual SHAS items: uncomfortable, high, clumsy, slurred speech, floating (at $p < 0.01$) and confused and drug effect (at $p < 0.05$).

There were significant differences in subjective reports as a function of drug condition (Table 2). After ethanol administration, FHP subjects reported greater analog sleepy (Fig. 1, middle row) and high as compared with placebo, whereas FHN subjects showed no differences between alcohol and placebo. For both groups, total SHAS scores (Fig. 1, top row) were elevated after alcohol in comparison to placebo ($p < 0.01$). With the exception of the item "good effects," all individual SHAS items were significantly elevated in FHP subjects (all $p < 0.01$). In contrast, FHN subjects reported elevated scores only for nauseated, intoxicated (at $p < 0.01$), alcohol/drug effects and difficulty concentrating (at $p < 0.05$) after ethanol administration as compared with placebo. Neither MBG nor PCAG scales revealed any significant effects as a function of family history or dose conditions.

There were significant differences in timecourse of subjective effects across drug conditions (Table 2) which for some measures interacted with family alcoholism group. Generally, following ethanol administration FHP subjects began at an elevated level of subjective effect, and were slower to return to placebo levels as compared with FHN subjects. This tendency was significant for Total SHAS scores (Group × Time $F(5,150) = 4.25$; $p < 0.01$). By contrast, analog liking and sleepy scores for FHP subjects declined more rapidly after ethanol administration (liking Group × Times $F(5,150) = 4.34$, $p < 0.01$; sleepy Group × Time $F(5,150) = 3.12$, $p < 0.01$). Of particular note is the evident decline in liking effects in FHP subjects to below the level reported by FHN subjects at 4 to 18 hr after ethanol ingestion (Fig. 1, bottom row).

Secobarbital Effects. Similar to ethanol's effects, FHP subjects demonstrated greater sensitivity to the subjective effects of secobarbital (200 mg only) than did the FHN subjects. Total SHAS was elevated in FHP subjects after secobarbital 200 mg ingestion in comparison with FHN subjects ($p < 0.05$). Individual items that were particularly salient were drunk and sleepy (at $p < 0.01$) and high, slurred speech and worst ever felt (at $p < 0.05$). Neither group demonstrated significant subjective effects following secobarbital 100 mg.

Following secobarbital 200 mg administration total SHAS score was significantly elevated in comparison to placebo only in FHP subjects (Fig. 1, top row) as well as the individual items of high, drunk, sleepy, drug effects (at $p < 0.01$) and clumsy, confused, slurred speech, difficulty concentrating and floating (at $p < 0.05$). Analog high ($p < 0.05$) and sleepy ($p < 0.01$; Fig. 1, middle row) were similarly increased in FHP subjects following the high dose of secobarbital. There were no significant effects following the low dose of secobarbital.

Generally, and as found after ethanol ingestion, following secobarbital 200 mg administration FHP subjects began at an elevated level of subjective effect, and were slower to return to placebo levels as compared with FHN subjects (see overall significant Group × Time interactions as given in Ethanol Timecourse Effects). This effect is shown for total SHAS score in Fig. 1 (top row). In contrast, analog sleepy and liking levels for FHP subjects fell below levels reported by FHN (Fig. 1, middle and bottom rows).

Comparison of Ethanol and Secobarbital Effects. For FHP subjects, ethanol and secobarbital 200 mg produced comparable subjective effects for total SHAS Scale score, nearly all individual SHAS items and analog items. Exceptions were SHAS items of uncomfortable ($p < 0.01$) and nauseated ($p < 0.05$) which were more elevated after ethanol than after secobarbital. Also for FHN subjects, the SHAS item "nauseated" was higher following ethanol administration ($p < 0.05$). Secobarbital and ethanol produced comparable subjective reports in FHN subjects for all other measures.

Subjective Effects Measures: Hangover/Withdrawal

Ethanol Effects. FHP subjects attained a higher total Withdrawal Scale score than FHN subjects ($p < 0.01$); Fig. 2, 2nd column), contributed to particularly by the items of sweating, shaky, and racing heart ($p < 0.05$). There was also a tendency for FHP subjects to report a

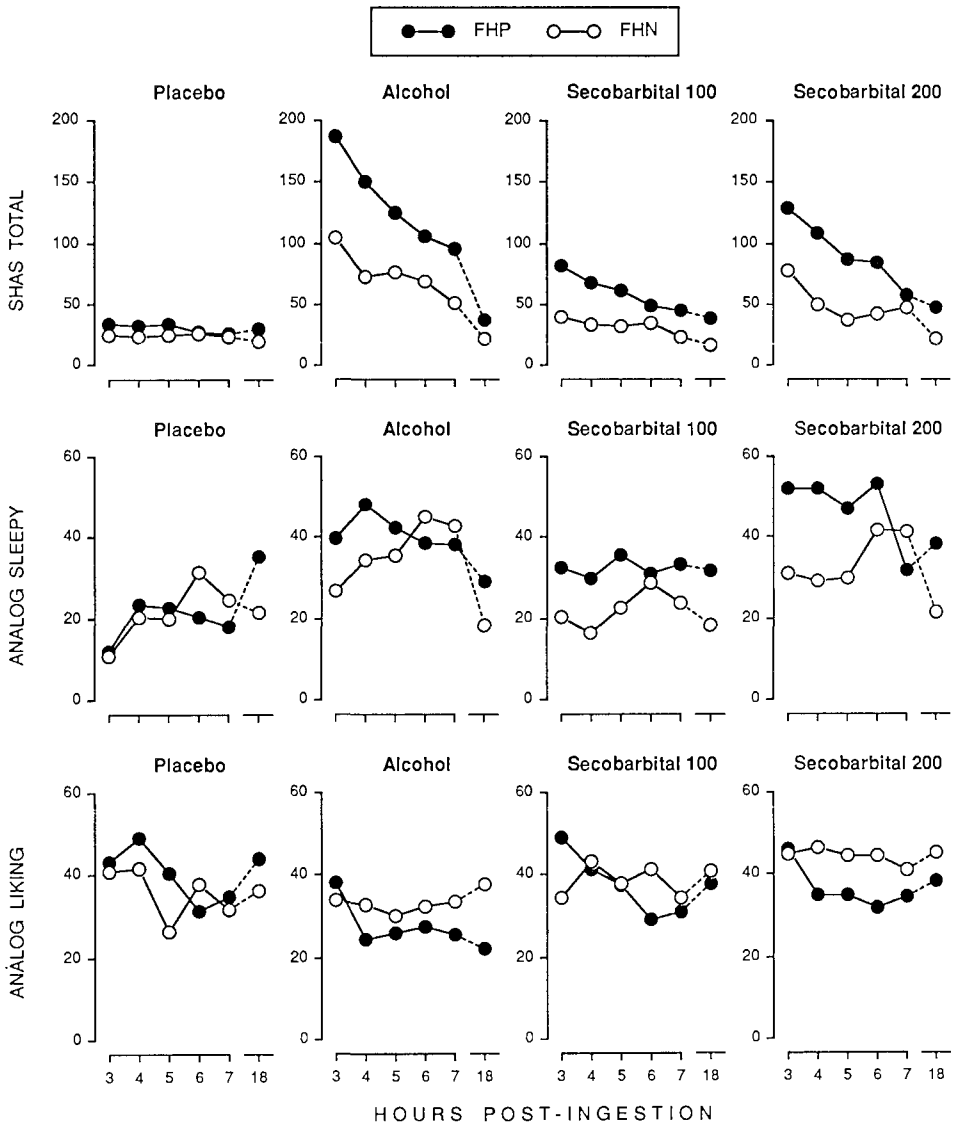

Fig. 1. Subjective reports of intoxication effects as a function of family history of alcoholism. Shown are mean responses on the total SHAS (top row) and the analog items "sleepy" (middle row) and "liking" (bottom row). Shown in separate panels are response to placebo, alcohol, and two doses of secobarbital for six time periods, encompassing 3–18 hr postingestion. Each data point is an average of 16 subjects. Total SHAS Scale scores could range between 0–540; analog "sleepy" and "liking" scores could range between 0–100.

more intense desire to drink an alcoholic beverage ("craving") after ethanol administration than FHN ($0.05 < p < 0.10$).

A comparison of the dose effects for ethanol vs. placebo showed that total Withdrawal Scale score (Fig. 2, top row) was significantly elevated following ethanol administration as compared to placebo only in FHP subjects ($p < 0.01$). There were significant differences in timecourse of subjective effects across drug conditions (Table 2) which for some measures interacted with family alcoholism group. Generally, following ethanol administration FHP subjects began at an elevated level of subjective effect, and were slower to return to placebo levels as compared with FHN subjects. This tendency was evident for total Withdrawal Scale score (Group × Time $F(5, 150) = 2.18$; $p < 0.10$).

Secobarbital Effects. Similar to ethanol's effects, FHP subjects demonstrated greater sensitivity to the subjective effects of secobarbital (200 mg only) than did the FHN subjects. These effects were evident for total Withdrawal scores ($p < 0.01$), and are illustrated for the individual withdrawal item "tired" ($p < 0.05$) (Fig. 2, 4th column).

Following secobarbital 200 mg administration, total Withdrawal Scale score (and in particular the individual item "tired"; $p < 0.01$) was significantly elevated in comparison with placebo only in FHP subjects ($p < 0.05$; Fig. 2). Generally, and as found after ethanol ingestion, following secobarbital 200 mg administration FHP subjects began at an elevated level of withdrawal (Fig. 2, top row), and were slower to return to placebo levels as compared with FHN subjects (see overall significant Group × Time interactions as given in Ethanol Timecourse Effects).

Comparison of Ethanol and Secobarbital Effects. FHP subjects reported comparable withdrawal effects following both ethanol and secobarbital 200 mg. For FHN subjects, total Withdrawal Scale score was greater following ethanol than following secobarbital 200 mg ($p < 0.01$).

Psychomotor Measures

Ethanol Effects. FHP subjects attempted fewer items ($p < 0.01$; Fig. 3, top row) and scored fewer correct ($p <$

Table 2. *F* Values and Probability Levels for Analyses of Variance

	Group	Condition	Timecourse
Subjective			
High	4.62*	9.94***	36.06***
Sleepy	2.19	11.41***	2.52*
Craving	1.79	0.73	3.84**
Liking	0.73	3.09*	7.15***
Total SHAS	4.66*	24.43***	38.14***
MBG	2.14	0.93	3.86**
PCAG	1.52	1.94	1.64
Total withdrawal	1.62	5.33**	23.71***
Psychomotor			
DSST			
No. Attempted	7.56**	5.10**	2.20
No. Correct	7.19**	8.00***	6.59***
Numeric recall			
No. Correct	1.20	1.30	7.16***
No. Position errors	0.79	4.38**	5.67***
Physiological			
Heart rate	0.54	21.67***	17.35***
Systolic BP	0.84	6.21***	1.24
Diastolic BP	0.29	0.62	3.53**
BAL	0.03	116.62***	44.90***

Probability Levels: · $0.10 > p > .05$ *$p < 0.05$ **$p < 0.01$ ***$p < 0.001$.

Degrees of freedom: Group (1,30); Condition (3,90); Timecourse (5,150).

0.05) on the DSST than did FHN subjects. There were no group differences in numeric recall for total correct or position errors following ethanol administration.

For both groups, no differences were found between ethanol versus placebo administration on DSST. During the numeric recall task, only FHP subjects had a greater number of position errors following ethanol administration as compared with placebo ($p < 0.05$; Fig. 3, bottom row). There were no differences between groups in timecourse of effects; both groups improved their scores over the extended data collection period.

Secobarbital Effects. For both secobarbital doses, FHP subjects attempted fewer items and had fewer correct (all $p < 0.05$; Fig. 3, top). There were no group differences in numeric recall either for total correct or position errors following either dose of secobarbital.

For FHP subjects only, performance on the DSST (no. correct, $p < 0.01$, Fig. 3, top; no. attempted, $p < 0.05$) was significantly decreased following the high dose of secobarbital as compared with placebo. Effects following the low dose of secobarbital did not differ from placebo for either group. There were no differences in numeric recall after secobarbital in comparison to placebo for either group.

Both groups showed a gradual improvement on DSST across the extended observation period and tended to return to placebo levels by the last evening observation point (7 hr postingestion). By contrast, performance on the numeric recall task remained impaired throughout the evening (3–7 hr postingestion) but returned to placebo levels by the following morning (18 hr postingestion).

Comparison of Ethanol and Secobarbital Effects. Ethanol and secobarbital produced comparable impairments in performance on both psychomotor tasks in both groups.

Physiological Measures

Ethanol Effects. There were no overall significant group, dose, or timecourse differences in heart rate, blood pressure or blood alcohol level following ethanol administra-

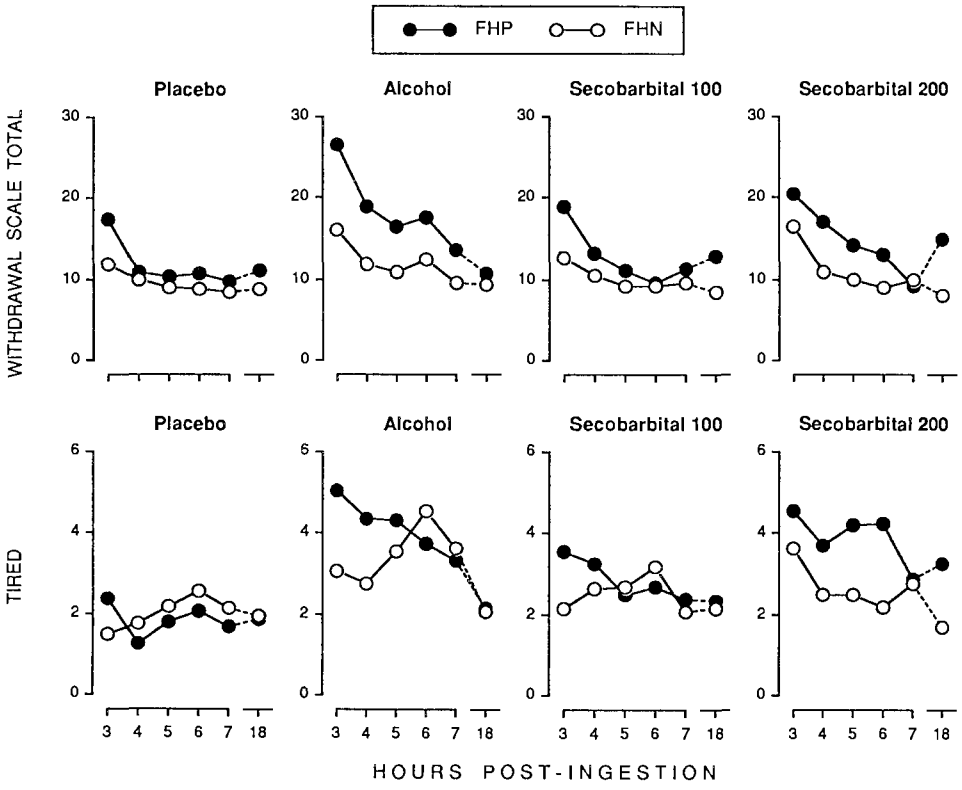

Fig. 2. Subjective reports of withdrawal symptoms as a function of family history of alcoholism. Shown are mean responses to the total Withdrawal Scale (top row) and the item "tired" from the Withdrawal Scale (bottom row). Shown in separate panels are response to placebo, alcohol, and two doses of secobarbital for six time periods, encompassing 3–18 hr postingestion. Each data point is an average of 16 subjects. Total Withdrawal Scale scores could range between 0–100; "tired" scores could range between 0–9.

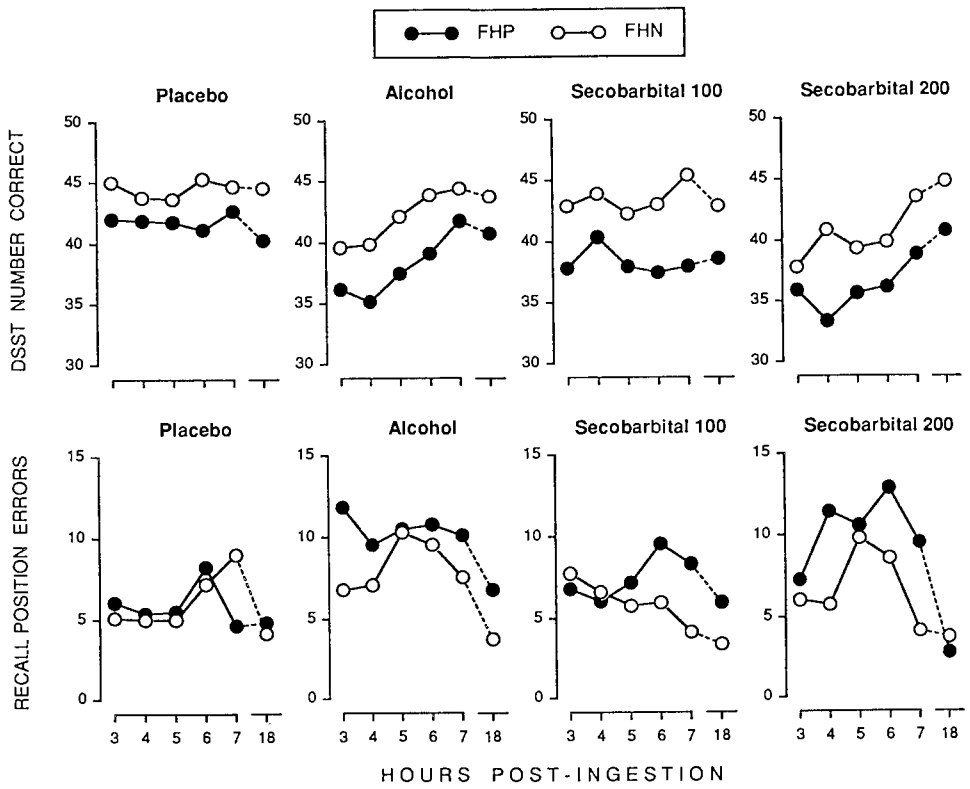

Fig. 3. Psychomotor responses as a function of family history of alcoholism. Other details as in Fig. 1. DSST = digit symbol substitution task; numeric recall position errors (see text).

tion. Both groups showed increases in heart rate after alcohol administration in comparison to placebo ($p < 0.01$).

Secobarbital Effects. There were no overall significant group, dose, or timecourse differences in heart rate or blood pressure following secobarbital administration. Further, there were no differences in physiological measures following either secobarbital dose in comparison with placebo.

Comparison of Ethanol and Secobarbital Effects. Heart rate was significantly elevated following ethanol administration as compared with secobarbital administration. The FHN subjects demonstrated this effect after both secobarbital doses ($p < 0.01$), whereas the FHP subjects showed this effect only following the high dose of secobarbital ($p < 0.05$).

DISCUSSION

Subjects with a family history of alcoholism reported greater intoxication and withdrawal effects following both ethanol and the high dose of secobarbital than subjects without a family history of alcoholism. Indeed, only in FHP subjects were withdrawal symptoms elevated after ethanol and after the high dose of secobarbital as compared with placebo. FHN subjects showed no differences in reported symptoms between placebo and either ethanol or high dose secobarbital. Moreover, the subjective effects reported by FHP subjects persisted longer than effects reported by FHN subjects; this was true both for ethanol and the higher secobarbital dose.

FHP subjects also demonstrated greater impairment in psychomotor performance than FHN subjects following both ethanol and secobarbital. The differences between family history groups seen in subjective and psychomotor effects were not mirrored, however, in physiological responses. No physiological differences emerged between the two groups in any drug condition.

The present data were collected following a laboratory component of data collection in which the acute effects of alcohol and secobarbital were compared between these family history groups.[11] During the acute period, we found that FHP subjects reported greater subjective effects than FHN subjects following ethanol administration. These family history differences were observed to a lesser extent following the high dose of secobarbital, which in general produced subjective effects of smaller magnitude and on fewer measures than ethanol. In contrast with the subjective effects, FHP subjects were less impaired on a hand tremor task than FHN subjects following the high dose of secobarbital. Group differences were not found on other psychomotor tasks or physiological measures after either drug.

One approach to characterizing differences in responses to drugs between family history groups might be to examine differences in both the magnitude and the duration of drug effects. Across the acute and extended components of the study, after ethanol ingestion we found that the family history groups differed in their subjective responses both in magnitude and duration of effect. By contrast, after secobarbital ingestion, family history groups differed

primarily in terms of duration of subjective drug effect. An additional analysis of maximal change also revealed no differences between family history groups in the magnitude of secobarbital subjective effects. Some potential physiological underpinnings that may be the source of these observed differences between family history groups have been studied. In general, studies of the pituitary adrenocortical axis as well as blood alcohol clearance studies[7,20] have failed to detect reliable metabolic and other physiological differences between these groups. For example, while Schuckit et al.[5] have reported lower prolactin responses after ethanol ingestion in family history positive males, Moss et al.[7] have failed to replicate these findings. However, studies of brain monoamine oxidase levels have reported promising differences such that family history positive males display lower MAO levels.[23,24] Further, lower MAO levels have also been found in alcoholics.[25]

Another set of variables that may account for the relatively elevated subjective response of the family history positive males may be experiential and learning/expectancy-based. For example, Newlin[26] studied responses to a placebo challenge in family history positive and negative males and found that family history positive males tended to report greater intoxication and displayed greater heart rate decrement after non-alcoholic beer than did family history negative subjects. These augmented subjective responses to alcohol-related cues in the environment may predispose offspring of alcoholics to increased risk for drinking by additively combining with the pharmacological effects of alcohol ingestion in producing a greater total subjective effect. The failure to find a greater magnitude subjective effect after secobarbital administration may also be attributable to learning/expectancy factors. Because offspring of alcoholic fathers in this study reported no previous experience with secobarbital, there were no expectancies about its subjective effects. Therefore, conditioning history did not further enhance the direct intoxicating effects of secobarbital.

It has been generally confirmed that male offspring of alcoholics are at increased risk for the development of alcohol dependence.[27–30] Physical dependence has traditionally been studied by terminating drug administration in chronic users, then monitoring the withdrawal symptoms that ensue.[31,32] The increased severity of hangover/withdrawal symptoms seen in FHP subjects in the present study may therefore suggest that despite modest and comparable histories of alcohol exposure with FHN subjects, the FHPs may be at an increased risk of developing physical dependence. A model of acute precipitated withdrawal has allowed the study of physical dependence following acute administrations of opiate drugs,[33,34] rather than the more chronic administration model typically used. This model is being used to explore differential development of physical dependence on opiate drugs in FHP versus FHN subjects in our laboratory; the opiate antagonist naloxone is administered several hours following a single administration of the agonist hydromorphone.

There are a number of methodological dilemmas in the conduct of this type of research. Subjects are selected who have not yet developed symptoms of alcohol dependence; this may possibly exclude those FHP males who may be most genetically at risk for developing alcoholism,[35] thus potentially decreasing the likelihood of finding differences between the family history groups. Were this research area to include individuals who had already developed alcoholism, the predictive goal of identifying risk factors would be lost. In our own study we have minimized this potential recruitment bias by studying young men who have not yet passed beyond the age of risk for developing alcoholism. Another methodological issue centers on basing group assignment on proband self-report of family drinking status. While confirmatory interviews ideally can be conducted with family members to verify further the accuracy of family drinking patterns, the current study employed an extensive personal interview with a standard diagnostic system (FH-RDC) to minimize the potential for subject misclassification.

The present study is the first to examine the extended effects of alcohol and sedatives in family alcoholism history groups as this procedure may reveal differences in the prolonged time course of intoxicating effects and potentially drug withdrawal. Family history positive subjects displayed enhanced intensity of withdrawal as well as extended duration of withdrawal symptoms following ethanol and the high dose of secobarbital. This is the first laboratory demonstration of withdrawal differences as a function of family history following administration of equal doses of ethanol or sedatives to both family groups. Our findings confirm and extend a retrospective questionnaire study of FHP versus FHN college-aged males which found that FHP respondents reported more severe withdrawal symptoms than FHN respondents despite equivalent levels of reported ethanol use.[12] Results from the current study suggest the importance of examining not only acute differences in response to drug administration in laboratory studies of family alcoholism history groups,[11] but also point to the importance of extended measurement as potentially unmasking differences in the drug responses of these groups.

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