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Stress and consumption of alcohol in humans with a Type 1 family history of alcoholism in an experimental laboratory setting

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ABSTRACT

Background: This paper investigates how stress interacts with alcohol consumption in subjects with a family history of alcoholism. One mechanism for increases in alcohol intake may be that stress alters the subjective effects produced by the drug.
Methods: 58 healthy volunteers, divided into two groups of family history positive (FHP) and two groups of family history negative (FHN) participated in two laboratory sessions, in which they performed in one out of two sessions a stress task. Then subjects were allowed to choose up to six additional drinks of ethanol or placebo depending on which session they were randomly assigned to start with.
Results: It was found that FHP subjects increased their consumption of alcohol after stress.
Conclusions: It is possible that both stress and alcohol specifically exaggerate the feelings of the reward in the FHP individuals in such way that it may increase the likelihood of consuming more alcohol.

1. Introduction

Consumption of drugs results from a complex interaction of direct drug effects and mood/subjective state. One factor that makes both animals and humans vulnerable to drug taking behavior is stress. Several lines of evidence indicate that stress increases both craving and consumption of alcohol and also changes the subjective effects of alcohol and other drugs of abuse (O'Doherty, 1991; Sinha et al., 1999; Söderpalm and de Wit, 2002; de Wit et al., 2003). There is also a large body of literature that suggests that a family history of alcoholism influences drug seeking behavior in humans. The present study is one of a series designed to investigate how stress and family history of alcoholism alter one's response to drugs and how this affects the consumption of alcohol in normal healthy volunteers.

There is both preclinical and clinical evidence that a family history of alcoholism can alter the responses to alcohol. Selective breeding of rats has produced stable lines that reliably consume high or low quantities of alcohol (McBride and Li, 1998). These lines of alcohol preferring rats show increased sensitivity to the sedative–hypnotic effects of ethanol and they also develop tolerance to the high dose effects of ethanol (McClearn and Rodgers, 1959; McBride and Li, 1998; Crabbe, 2002). These studies also suggest that severe withdrawal symptoms are associated with a tendency to avoid self-administration of alcohol (Metten et al., 1998; Chester et al., 2002). Human research also suggests that genetic factors exert a strong influence for the development of alcoholism (Cloninger 1988, Merikangas, 1990; Kendler et al., 1992). These studies show a strong relationship between biological vulnerability and alcoholism. Furthermore, human studies have also identified differences in the subjective response to alcohol in subjects differentiated by family history of alcoholism (Newlin and Thomson, 1990; McCaul et al., 1991; Schuckit, 1994; Morzorati et al., 2002; Erblich et al., 2003; Conrod et al., 1997, Söderpalm Gordh and Söderpalm, 2011). There is also human research suggesting that there is no difference in the reinforcing effects of alcohol in alcoholic first degree relatives (de Wit and McCRacken, 1990). The research suggests that subjects with a family history positive (FHP) of alcoholism have different levels of sensitivity to the acute effects of alcohol compared to family history negative (FHN) individuals (Schuckit, 1981). The different levels of sensitivity can make FHP subjects more likely to consume more alcohol. Thus, the differences in subjective effects noted, and further described below, could also be related to a number of milieu-determining factors, rather than genes, related to the family history positivity, for example alcohol intoxication expectancies or common third factors, such as other psychopathology, and more.

Stress has regularly been cited as a factor contributing to increased drinking in humans. As mentioned, a number studies show that stress or negative mood states, such as anxiety, increase both craving for alcohol and alcohol consumption. Survey data indicate that people consume more alcohol during and after stressful life events such as a divorce, financial difficulties, or being victim of a crime (Jose et al.,

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2000). The relationship is supported indirectly by the observation that alcohol abusers report more stressful life events than non-abusers (O'Doherty, 1991). The effect of stress on alcohol craving and consumption has also been examined in the laboratory. In one study, acute stress (stressful imagery) increased craving for alcohol and cocaine in cocaine-dependent individuals (Sinha et al., 1999). In two other studies, stressful negative mood states or negative affect imagery increased urge to drink alcohol in alcoholics, either directly or after exposure to alcohol-related cues in alcoholics (Biondi and Picardi, 1999; Litt et al., 2000; Cooney et al., 1997). It is generally believed that ethanol intake in addicted individuals is driven by negative reinforcement, i.e. the by the ability of ethanol to relieve the negative state. However, early in an alcohol career also the positive reinforcing effects of stress, stress hormones and alcohol, and the combination of these, could be involved (Piazza and Le Moal, 1996). Indeed, stress has also a direct effect on the subjective effects of alcohol in normal healthy volunteers. Previous work of the author has showed that subjects who were exposed to the Trier Social Stress Test (TSST) showed increased sedative responses to alcohol compared to controls and that the stressed subjects also showed increased "liking" to alcohol after stress (Söderpalm and de Wit, 2002). In another study, we also found that when subjects were exposed to the TSST they drank more alcohol and they also drank more placebo suggesting a nonspecific beverage consumption after stress (de Wit et al., 2003). In a recent publication of Childs and de Wit 2010, it was tested if acute psychosocial stress (TSST) increased cigarette smoking in daily smokers. They found that stress significantly increased cigarette craving but it did not increase smoking. These effects are in line with previous studies investigating the effects of acute stress on alcohol (Söderpalm and de Wit, 2002; de Wit et al., 2003) and on food (Epel et al., 2001) but also previous research on the self medication hypothesis research, suggesting an increase in drug intake for relaxing purposes (Boys et al., 2001; Wanberg, 1969). These studies, using negative mood induction techniques, thus indicate that acute stress increases the urge to drink alcohol in individuals addicted to alcohol, and that stress affects both the subjective response to alcohol and alcohol consumption in normal healthy volunteers. However, these studies do not take family history of alcoholism in consideration.

A family history of alcoholism is the most common risk factor for the development of alcohol problems and there is a large body of evidence to support this. Schuckit (1984) was first to suggest that FHP subjects subjective response to alcohol is associated with risk of future alcohol problems. He found that sons of alcoholic fathers reported less intense feelings of subjective intoxication and less body sway response after drinking 0.75 or 1.1 ml/kg of ethanol. A decade later Schuckit (1994) demonstrated that a low level of response to alcohol at a young age is associated with a fourfold greater likelihood of future alcoholism in the sons of alcoholic fathers. However, studies on actual consumption of alcohol in this specific group are lacking. In one study by Labrie et al. (2009) it was reported that FHP women over the course of five weeks consumed significantly more drinks, maximum drinks and heavy drinking than FHN peers did. Family history positive individuals with a FHP has also been found to report increased binge drinking (Turrisi and Wiersma, 1999), they have more alcohol and drug problems and they also have strong alcohol expectancies (Sher et al., 1991).

Previous literature has also suggested a link between genetic predisposition, stress and alcoholism. FHP subjects have consequently been found to differ in their psycho-physiological response to stress and alcohol suggesting that the HPA-axis may be involved in the development of alcoholism. For example, Zimmerman et al. (2004, 2009) suggested that alcohol specifically dampens a stress response in FHP compared to FHN subjects. In a placebo controlled study, they found that when FHP subjects were given 0.6 g/kg alcohol before a public speaking stress paradigm there was a significantly attenuated prolactin stress response in the FHP group compared to controls. In another placebo controlled study by Dai et al. (2007) they found that an acute dose of 0.5 g/kg of ethanol administered after a stress task, dampened activation of the HPA-axis in both subjects high and low risk for alcoholism. In other alcohol challenge studies differences were found in the peripheral levels of beta-endorphin response (Dai et al., 2005) and ACTH and cortisol responses (Dai et al., 2002) to stress in FHP subjects. Taken together, alterations in the HPA-axis in response to stress may contribute to both subjective changes and consumption of alcohol in FHP subjects.

The studies in this introduction have employed different definitions of family history positivity. Some of the studies use only sons of alcoholics and others use subjects with both first and/or second degree relatives. Less emphasis has been put on the type of alcoholism involved. There are a number of subtypes of alcoholism characterized by different groups of patients with different traits such as for example age of onset of heavy drinking (early or late), patterns of drinking (e.g. continuous or binge), rate of alcohol metabolism, sensitivity to intoxication, rapidity of progression to medical problems, and presence or absence of co-occurring psychiatric illness (Leggio et al., 2009).

In the present study we used only subjects with a Type 1 family history of alcoholism, which is the most common form of alcoholism. Type 1 alcoholism is characterized by a late onset of dependence in socially well-adjusted individuals, low prevalence of familial alcoholism and a milder course, in contrast to Type 2, which is characterized by early onset of dependence, high familial alcoholism in fathers, frequent antisocial personality, and severe intensity of alcohol-related problems (Cloninger 1987, Babor et al., 1992). Type 1 heredity is considered to be "milieu-limited", meaning that genetics interact with an unfavorable milieu to inflict increased risk of developing alcoholism, whereas Type 2 heredity appears milieu independent. The purpose of this study was to examine the role of a family history of alcoholism (Type 1) on consumption of ethanol and placebo in healthy social drinkers both in a non stressful situation and after stress. The development of Type 1 alcoholism seems to be related to adverse environmental conditions e.g. stress, therefore individuals with Type 1 history may be particularly susceptible to alcohol after stressful conditions. It was hypothesized, based on preclinical and clinical studies, that subjects with a Type 1 family history of alcoholism would increase their consumption of the ethanol beverage when stressed in comparison with FHN subjects. In addition a measure of how the alcohol was subjectively perceived after stress vs non-stress was included.

2. Materials and methods

2.1. Subject recruitment and screening

Fifty-eight healthy men and women, who were non-problem social drinkers between the ages of 19–35, participated (see Table 1). Twenty-seven men and women had a family history of Type 1 alcoholism (see Family history below). Subjects were accepted without regard to race or ethnicity. The volunteers were recruited from the university and surrounding community via posters. Initial eligibility was ascertained in a telephone interview. Candidates also completed a psychiatric symptom checklist (SCL-90; Derogatis, 1983), the Audit (Babor et al., 2001) and a health questionnaire with a detailed section on current and lifetime social–economic status and drug use. The subjects in this study were included if they drank between 4 and 8 alcoholic drinks per week. Subjects were excluded from the study if they had: any current medical condition requiring medication; prior corticosteroid treatment; any current Axis I psychiatric disorder (APA, 1994), or any history of psychosis; history of drug or alcohol abuse or dependence; less than a high school education; lack of fluency in Swedish and English, or night shift work. Before participation, subjects read and signed a consent form

Table 1
Demographic and drug use data of subjects participating in the family history positive groups and the family history negative groups.

	FHP + Alcohol (n = 16)	FHP + Placebo (n = 11)	FHN + Alcohol (n = 18)	FHN + Placebo (n = 13)
Age (years)				
Range				
Mean ± SEM	25.8 ± 0.7	25.0 ± 1.0	23.8 ± 0.6	23.0 ± 0.4
Weight (kg, mean ± SEM)	76.5 ± 4.8	70.2 ± 3.0	66.3 ± 2.5	69.4 ± 2.3
Race/ethnicity (*n*)				
White	15	11	16	13
Hispanic	1	0	1	0
Gender (*n*)				
Male	10	5	8	6
Female	6	6	10	7
Education (*n*)				
High School	16	11	18	13
College degree	16	11	18	13
Advanced degree	15	10	17	13
Full time student				
Current drug use				
Alcohol (mean ± SEM, drinks/week)	5.1 ± 0.7	4.9 ± 1.1	4.4 ± 0.8	7.3 ± 1.1
Caffeine (mean ± SEM, drinks/week)	5.3 ± 1.5	4.5 ± 2.0	3.1 ± 0.7	6.0 ± 1.7
Cigarettes (number/week)	0 ± 0	1.3 ± 1.3	0.1 ± 0.1	0.7 ± 0.5
Lifetime drug use				
Stimulants (n, ever used)	0	1	2	2
Tranquilizers (n, ever used)	0	1	1	0
Hallucinogenes (n, ever used)	0	0	0	0
Opiates (n, ever used)	0	0	0	0
Marijuana (n, ever used)	8	2	9	5

informing them that the purpose of the study was to investigate the effects of drugs on mood and behavior. For blinding purposes subjects were told that they might receive alcohol or placebo. Subjects were told not to smoke, exercise or eat 4 h before they arrived to the laboratory. The experimental protocol was approved by Gothenburg regional ethical committee for the use of human subjects and that procedures are in compliance with the Declaration of Helsinki for human subjects.

2.2. Design

The study utilized a mixed within- and between-subjects design. Subjects that were family history positive (FHP) or family history negative (FHN) were randomly assigned either to a group receiving ethanol on two sessions or to a group receiving placebo on two sessions. Therefore, the between subject variables consisted of two groups FHP or FHN and alcohol vs placebo. We also used a within subjects design (one stress and one stress free session) because earlier studies have found a habituation effect on the cortisol response to the Trier Social Stress Test (TSST; Kirschbaum, 1993). On one session subjects were exposed to a modified version of the standardized TSST (Kirschbaum, 1993) immediately before consuming their beverage, and on the other session subjects was stress free, before consuming their beverage. Thus there were eight experimental conditions: FHP + stress + alcohol and FHP + no stress + alcohol, FHP + stress + placebo and FHP + no stress + placebo, FHN + stress + alcohol and FHN + no stress + alcohol, FHN + stress + placebo and FHN + no stress + placebo. Sessions were conducted in a randomized order with a minimum of 48 h between treatments. There was no maximum interval between sessions and the average interval between sessions was one week. The dependent measures were beverage consumption, the subjective drug effects, and physiological and subjective responses after stress.

2.3. Laboratory environment

The study was conducted in a laboratory environment at the Institute of Neuroscience and Physiology, Department of Psychiatry and Neurochemistry, Addiction Biology Unit (ABU), Sahlgrenska University Hospital, Gothenburg University, Sweden. This environment consists of one room furnished to resemble a living room. The room had incandescent lighting, a couch and two leather chairs, a table with magazines, paintings on the walls and curtains in the windows. When not completing questionnaires they were allowed to relax, but they were not allowed to work, watch videos or study.

2.4. Detailed procedure

On each session, subjects arrived at the ABU at 13.00 h, a time when cortisol levels are relatively stable (Weitzman et al., 1971). Upon arrival to the test room (−30 min), subjects were allowed to relax for 10 min. At −20 min they provided a saliva sample for baseline cortisol analysis, and completed baseline physiological (blood alcohol concentration), and subjective self-report of the drug effect measures. They were also informed whether they would be required to perform the "mental arithmetic" (stress) that day. At −15 min they were allowed to drink 0.5 dl of water to reduce the effects of thirst on the consumption of the ethanol or placebo drinks. Subjects were always run in a group of three or four and all of them always received either stress or no stress on the same session, so that the stress test could be administered with the whole group. At −10 min the stress task or the stress free period began. On sessions when stress was scheduled, one interviewer and one observer entered the room, sat down behind a desk and administered the stress protocol (see below). In the stress free condition, subjects were allowed to relax and converse with a technician for 10 min. Immediately after the stress test or stress free period, salivary cortisol was measured and subjects were asked to rate how distressed they felt on four visual analog questions. Then subjects consumed a beverage containing 0.3 g/kg ethanol or placebo during 10 min. During the next 30 min, subjects were offered up to six additional drinks of 0.1 g/kg of ethanol on the ethanol session or placebo on the placebo session. They could only have another drink if they had finished their previous drink. The six drinks were served at the same time on a tray and they were allowed to drink the beverages as fast or

as slow as they liked. The beverage consumed (expressed as the percentage of total volume available) during this free consumption period was the primary dependent measure. Half of the subjects in each group always received ethanol and the other received placebo on the same session. FHP and FHN subjects were randomly mixed in each group. Blood alcohol concentration (BAL) and the subjective drug effects were measured at baseline (−20), 15 and 75 min time point after ethanol or placebo ingestion. Subjects were allowed to leave the laboratory when they were completely sober with a BAL level 0.0 permillage. After completing both sessions they were debriefed by the experimenter and paid.

2.5. Family history

To confirm a family history of alcoholism the subjects answered yes or no on the following questions regarding their relative(s), covering in essence the diagnostic criteria of alcohol dependence according to the DSM IV (APA, 1994): 1) Has any biological relative of yours have what you would call problems with alcohol/drugs? If yes, who? 2) Has this biological relative of yours had problems with alcohol/drugs before 21 years of age? 3) Has this biological relative of yours been in contact with the police/state before 21 years of age? 4) Has this biological relative of yours had repeated use of alcohol that leads to inability to take care of for example work or house holding? 5) Has this biological relative of yours had repeated use of alcohol in situations where that person is in physical risk, for example driving or at work? 6) Has this biological relative of yours had repeated contacts with police/state as a consequence of misuse of alcohol or drugs? 7) Has this biological relative of yours had continued use despite recurrent problems? Subjects answering yes on questions 1, 4 and 7 but no on 2, 3, 5 and 6 were included in the study and considered family history positive, whereas subjects answering no on the first question did not answer any further questions and were considered family history negative. By including only subjects answering no in questions 2, 3, 5 and 6, Type 2 alcoholism, according to Cloninger et al. (1981), was most likely largely excluded and the group selected thus probably mainly comprise subjects family history positive for Type 1 alcoholism. Fifteen percent of the subjects had multigenerational family histories (parent and grandparent) of male and female alcoholism, 74% of the subjects had multigenerational family histories (parent and grandparent) of male and female alcoholism, 18.5% had a father or mother with a history of alcoholism, 55.5% had a male or female grandparent with a history of alcoholism, 22.2% had an uncle (brother of their father or mother) with a history of alcoholism. 0.03% had a sister or brother with history of alcoholism. By contrast, the control subjects had no identifiable alcoholic relative in the previous two generations.

2.6. Ethanol consumption

Ethanol (Absolut Vodka 40%) was mixed with Tropicana orange juice (pulp free) to a concentration of 16% ethanol. The priming dose of 0.3 g/kg was adjusted for body weight, to be consumed during a 10-minute period. The 30 min consumption phase began 5 min after finishing consuming the required priming dose. Subjects were allowed to consume up to six beverages each. The additional six doses of ethanol consisted of 0.1 g/kg each. Subjects could choose to accept the drinks or not. The placebo beverage consisted of orange juice mixed with 1 ml vodka and was administered at the same volume as the alcoholic drinks. The beverages were served cold in white colored glasses. The total volume of beverages consumed per session was recorded and a percent of maximum available beverage evaluated (de Wit et al., 2003).

2.7. The modified version Trier Social Stress Test

The stressor in this study was a modified version of the Trier Social Stress Test, a social stress procedure that reliably induces an increase of cortisol (Kirschbaum et al., 1993). In this procedure subjects were required to perform a timed arithmetic task in front of an interviewer and an observer who monitored their performance. Subjects were told that they were being tape-recorded and that their presentation would be analyzed for accuracy. The four subjects stood in a row in front of the "judges", and were randomly asked individually to subtract numbers aloud. They were required to count backwards, out loud, from 1754 in intervals of 13 to 17, for 10 min. If they stopped they were instructed to continue by the interviewer. Subjects were tested in the group to increase the social pressure to perform well, and thus enhance the effectiveness of the stressor.

2.8. Cortisol levels

Free cortisol is the protein-unbound, biological active fraction of total cortisol. Saliva flow rate does not influence salivary cortisol levels and it has been demonstrated that there is a very high correlation between serum free and saliva cortisol levels (Riad-Fahmy et al., 1982). Salivary cortisol measurement is a common method of choice in human psychoneuroendocrinology stress research (Bassett et al., 1987; Kirschbaum et al., 1993).

2.9. Dependent measures

Dependent measures included assessment of subjective and physiological effects as described below. The primary dependent measure was consumption of alcohol, secondary measure was the Drug Effects Questionnaire (DEQ). Physiological measures were blood alcohol concentration and salivary cortisol.

2.10. Subjective effects

The subjective effects were measured using The Drug Effects Questionnaire (DEQ). DEQ consists of four questions concerning current drug effects (Fischman and Foltin, 1991). Subjects indicate on 100-mm lines whether they are currently "feeling any drug effects" (from "none" to "a lot"), if they "like the effects they feel" (from "dislike" to "like very much"), if they "are high" (from "not at all" to "very much"), and if they "want more of the drug" (from "not at all" to "very much").

Four visual analog questions (FVAS). Subjects indicate on 100-mm lines whether they are currently feeling "uneasy", "anxious", "nervous" or "calm".

2.11. Objective measures

The objective measures were breath alcohol and salivary cortisol. Blood alcohol concentrations were estimated from breath alcohol level using Alco-Sensor III breathalyzers Alcometer (Alert J5, Alcohol Countermeasure Systems Corp, 2006). One breathalyzer was used for each subject throughout the sessions. Saliva samples for the cortisol assays were collected using a salivette (Sarstedt, Newton, N.C., USA), which contains a piece of cotton that the subject gently chews on for approximately 30 s. No additional saliva flow stimulant was used. All the objective measures were taken while subjects were seated. The saliva samples were frozen and assayed by the Department of Clinical Chemistry, Sahlgrenska University Hospital, Gothenburg using a Coat-A-Count cortisol radioimmunoassay kits (Orion Diagnostica).

2.12. Data analysis

Data were analyzed using SPSS 18.0. The data for alcohol consumption was analyzed with a one way ANOVA comparing the

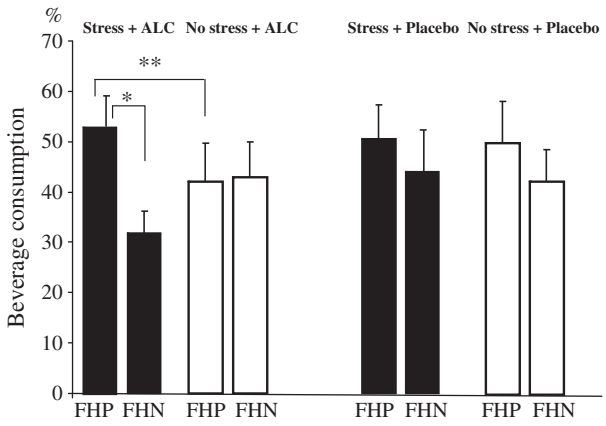

Fig. 1. Mean (±SEM) percent alcohol and placebo consumed during the 30 min session for the family history positive groups (FHP) and the family history negative groups (FHN) under stress vs no stress. The open bars symbolize the no stress sessions and the closed bars the stress sessions. The asterisks denote significant differences between the stress and the no stress sessions $^{*}p<0.05$, $^{**}p<0.01$.

groups after the stress and no stress session. Each of the dependent measures (DEQ), (FVAS) and cortisol levels were analyzed with a two-way mixed between and within-subject analysis repeated measure of variance (ANOVA). The between-subject factor was drug (ethanol or placebo), and history of alcoholism (FHP or FHN) and the within-subject factors were stress (stress or no stress) and time. Measures were obtained before stress, (baseline time point −20), immediately after the stress (or control) and before the beverage (time point 0; only for certain measures), and at varying times after alcohol (time points +30, +45, +60, +75). The DEQ was analyzed by adding the four questions and then analyze it as one measure. The FVAS questions were answered before the stress situation (baseline time point −20) and directly after the stress situation i.e. before any alcohol or placebo intake. They were analyzed as the other dependent measures as described above. The significance level for all statistical tests was set at $p<0.05$.

3. Results

3.1. Subject demographics

Table 1 shows the demographic characteristics of the subjects in the four assigned groups (two FHP n=27 and two FHN groups n=31). Fifty-eight subjects (29 men and 29 women) completed the study and provided usable data. The mean age in the FHP group was 25.4±0.8 year and in the FHN 23.4±0.5 year. The mean weight in the FHP group was 73.3±3.9 kg and in the FHN group 67.8±2.4 kg. Fifty six subjects were Caucasian (not Hispanic), and two were Hispanic. Together both groups reported a mean weekly consumption of 5.4±0.9 alcoholic drinks, 4.7±1.4 caffeinated drinks, and 0.5±0.4 nicotinic cigarettes. The subjects assigned to the FHP or the FHN group did not differ on any of the demographic or drug use variables obtained.

3.2. Consumption of alcohol in the FHP and FHN groups

When the FHP group was compared to the FHN group after stress, a one way ANOVA showed that the FHP group drank significantly more alcohol compared to the FHN group when stressed $F(1.33)=5.26$, $p<0.02$. There was no difference found when the no stress session was analyzed. A paired sample *t*-test also showed that the FHP group, when stressed, drank significantly more alcohol compared to the no stress session, $p<0.007$. There were no other differences in consumption between the four groups (Fig. 1).

3.3. Blood alcohol levels in the FHP and FHN groups

To verify the increased consumption of alcohol in the FHP group after stress, Fig. 2 shows that when the four groups where compared a significant difference in BAL $F(3.52)=2.83$, $p<0.000$, was found. A significant difference was found between the stress and the no stress session in the FHP+ALK group $F(1.14)=4.7$, $p<0.04$. This effect was expected since the FHP group consumed more alcohol when stressed compared to the no stress session. This difference was not seen in the FHN+ALK group $F(1.16)=0.002$, ns.

3.4. Physiological and subjective effects of stress

Cortisol: Fig. 3 shows that including all groups, a two way repeated measure ANOVA revealed that there was a significant effect of stress on cortisol between the four groups $F(1.53)=9.24$, $p<0.004$. The FHP+ALK group showed a significant increase in cortisol levels between the stress and the no stress condition $F(1.15)=7.0$ $p<0.01$ and over the course of the session $F(4.60)=6.54$, $p<0.000$. The FHN+ALK, showed a significant increase over time after stress $F(4.64)=3.98$, $p<0.006$, the FHP+PL group showed a cortisol increase after stress $F(1.10)=11.8$, $p<0.007$ and over time $F(4.40)=9.29$, $p<0.000$ but the FHN+PL did not show a significant increase of cortisol after stress $F(1.11)=2.41$, ns. There were no differences in cortisol levels at baseline, neither between the four groups nor between the stress and the stress-free

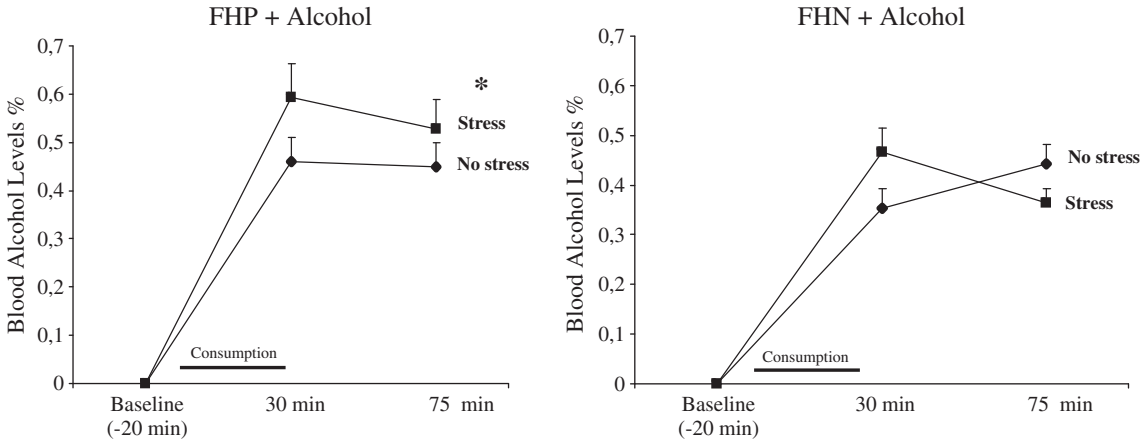

Fig. 2. Mean (±SEM) breath alcohol levels after the priming dose of 0.3 g/kg ethanol and the following 30 min ethanol consumption period. Breath alcohol levels differed in the stress vs the no stress condition in the family history positive group (FHP) but not in the family history negative group (FHN). The squares symbolize the stress session and the diamonds the no stress session. The asterisk denotes significant differences between the stress and the no stress sessions $^{*}p<0.05$.

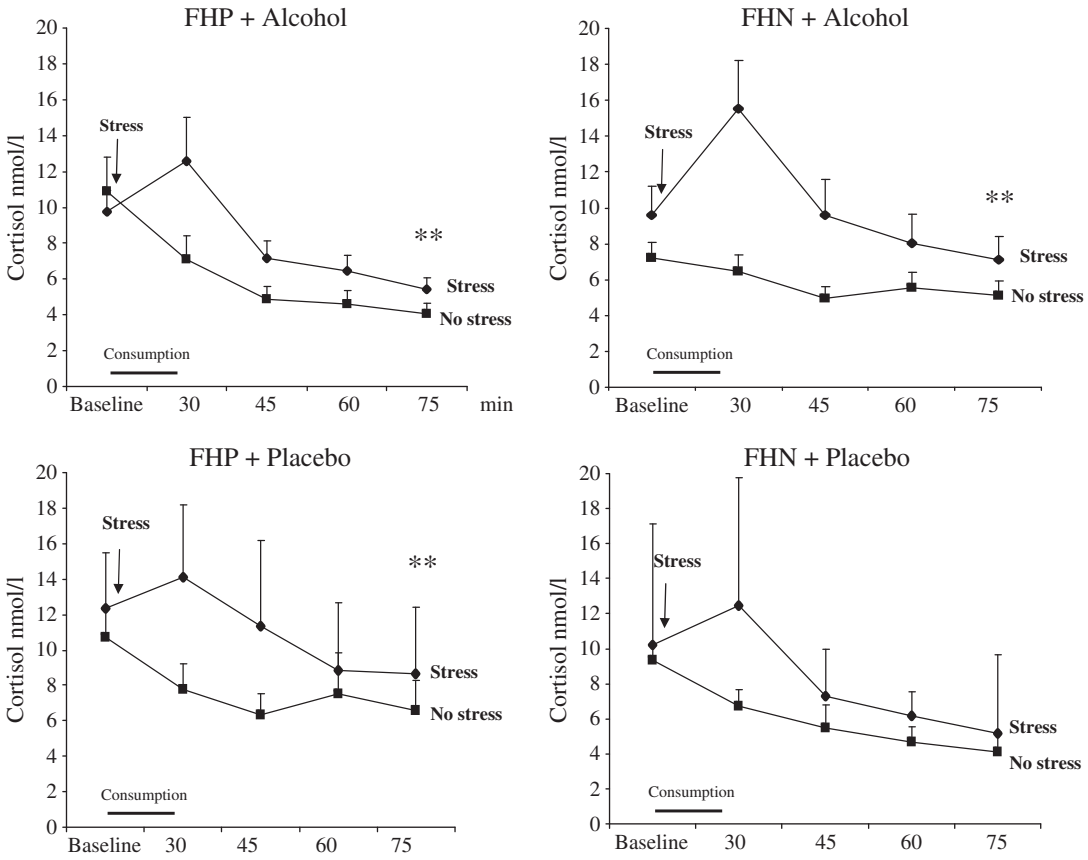

Fig. 3. Cortisol levels (nmol/ml) after stress and the no stress condition for the family history positive groups (FHP) and the family history negative groups (FHN). The squares symbolize the no stress session and the diamonds the stress session. The asterisks denote significant differences between the alcohol and the placebo condition. *$p<0.05$, **$p<0.01$.

condition. Fig. 4 shows the means ± SEM cortsiol nmol/l (area under the curve) for FHP + ALC, FHP + PL, FHN + ALC and FHN + PL. *Stress*: Subjects rated their levels of distress immediately after the stressor, and before consuming the beverage, on four questions on the FVAS (Table 2). A two way General Linear Model (GLM) showed that after stress, subjects reported feeling more uneasy $F(1.3)=4.56$, $p<0.006$, nervous $F(1.3)=3.78$, $p<0.01$, and anxious $F(1.3)=5.90$, $p<0.001$ compared to the non-stressful condition. In an additional analysis examining the differences in the FVAS questions in the placebo stress session and no stress sessions between the FHP and the FHN groups it was found in a GLM between subjects design that there were a main effect of group on "uneasy" $F(3.54)=4.56$, $p<0.006$, "anxious" $F(3.54)=5.91$, $p<0.01$ and "nervous" $F(3.54)=3.78$, $p<0.04$. In a Tukey post hoc test it was found that the FHP + PL + stress significantly reported increased "unease" $p<0.006$, increased "anxiousness" $p<0.01$ and increased "nervousness" $p<0.04$ compared to the FHN + PL + stress. These differences was not seen in the no stress comparisons.

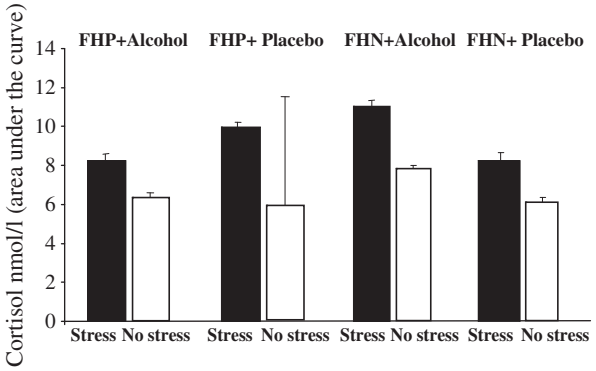

Fig. 4. Mean (±SEM) cortisol nmol/l over the timecourse in the stress vs no stress condition the family history positive groups (FHP) and the family history negative groups (FHN) receiving alcohol or placebo.

3.5. Subjective effects of alcohol

A two way repeated measure ANOVA revealed that there was a significant main effect between the four groups $(F3.54)=18.49$, $p<0.000$ on the DEQ scale. Fig. 5 shows that subjects in the FHP group after stress reported increased effects of alcohol on the DEQ scale than FHN did $F(1.32)=7.42$, $p<0.01$. This effect was not seen when placebo beverage was served. This result is in concordance with the BAL for the FHP group after stress $F(1.14)=4.70$, $p<0.04$ compared to the FHN group.

4. Discussion

The findings of this study investigating the effects of family history of alcoholism and stress on the consumption of ethanol were as follows: First, under stress, subjects with a family history of Type 1 alcoholism consumed more alcohol when compared to the FHN group. Second, the FHP group that consumed 53% alcohol after the stressful condition in comparison with 43% under the non stressful condition concomitantly reported increased subjective responses on the DEQ scale compared to the FHN group did under stress.

In the present study, the FHP subjects consumed 10% more alcohol under stress compared to the non stressful session. We believe that this effect was due to the stress. Our hypothesis that FHP subjects consume more alcohol after stress was tested in a study with an experimental design that measure real alcohol consumption including

Table 2
Mean (±SEM) FVAS answers after stress and no stress condition between the FHP and the FHN subjects receiving alcohol or placebo. FHP, family history positive; FHN, family history negative; VAS, Visual Analog Scale. ***$p<0.001$.

Dependent measure	Stress	No stress	Stress	No stress	Stress	No stress	Stress	No stress	Main effects (F1, 3)
VAS	FHP + Alcohol	FHP + Alcohol	FHP + Placebo	FHP + Placebo	FHN + Alcohol	FHN + Alcohol	FHN + Placebo	FHN + Placebo	
Uneasy	41.5 ± 6.0	13.0 ± 4.0	65.4 ± 7.2	20.6 ± 4.8	38.0 ± 5.6	14.6 ± 3.7	31.7 ± 6.6	10.2 ± 4.4	Stress***
Anxious	39.6 ± 5.5	8.2 ± 3.4	58.1 ± 6.6	23.6 ± 4.1	26.1 ± 5.1	12.7 ± 3.2	29.2 ± 6.1	11.4 ± 3.8	Stress***
Nervous	42.5 ± 5.9	11.8 ± 4.1	67.8 ± 7.2	25.4 ± 5.0	40.8 ± 5.6	17.1 ± 3.9	41.3 ± 6.6	13.4 ± 4.6	Stress***
Calm	39.0 ± 6.2	67.9 ± 4.8	40.6 ± 7.4	45.9 ± 5.8	34.9 ± 5.8	74.8 ± 4.5	40.8 ± 6.8	72.9 ± 5.3	Stress

a placebo beverage condition, such as ours (Higgins and Marlatt, 1975; Hull and Young, 1983, de Wit et al., 2003). The finding that stress both increase the consumption of alcohol and that this effect is accompanied with altered subjective responses is supported by a couple of earlier studies by the author. First, in a submitted study by Söderpalm Gordh et al. we noticed that when individuals with a family history of alcoholism are not exposed to stress and have the opportunity to consume alcohol over a 30 min period they do not drink more alcohol than the FHN group does. However, when they are exposed to a stressful situation and have the opportunity to consume alcohol over a 30 min period the "liking" and the "high" of alcohol are increased. Stress seems to be a psychological state that can trigger an alcohol drinking behavior.

Second, acute stress has been found to increase the consumption of alcohol and dampen the stimulant-like responses to alcohol in social drinkers (de Wit et al., 2003). In the de Wit et al. (2003) study we found that stress by the use of TSST boosts both ethanol consumption and the intake of the placebo beverage in a consumption paradigm like the ones used in the present study. This nonspecific pharmacological effect of stress could simply be because stress may increase thirst (Espiner, 1987) which we did not control for in the study by de Wit et al. (2003). In the present study we have found that FHP individuals consume about 10% more alcohol after the TSST compared to the no stressful condition report increased rewarding subjective effects on the DEQ scale compared to the FHN group did. In the present study all of the subjects drank 0.5 dl of water before the intake of alcohol to reduce the "thirst factor" after stress (Espiner, 1987). The increased subjective effects seen in the FHP group provides important information about the increased consumed ethanol. The FHP group may drink more alcohol under stress because alcohol has a greater effect for that group of subjects in that particular situation. Stress may increase the positive effects of alcohol and by that stimulate people to drink more alcohol in this situation. It was also noticed in this study that there was no difference in consumption between the alcoholic beverage and placebo beverage after stress in the FHP group. This result may be due to a nonspecific pharmacological effect of alcohol.

It is interesting that there was no difference in consumption between the FHN alcohol and placebo beverage consumption i.e. they consume approximately 40–45%of the available beverage regardless of content. Again, this result is probably due to a nonspecific pharmacological effect of alcohol. The FHN subjects may not psychologically experience stress in the same way as the FHP group and therefore drink the same amount regardless of stress or no stress, alcohol or placebo. At a closer look at the subjective ratings on the VAS scale on Table 2 it was found that the FHN group reported after the stress situation when drinking placebo, significantly lower rating on Uneasy, Anxious and Nervous compared to the FHP group. This supports the idea that the FHN group are not as sensitive to stress as the FHP group are and therefore we see no changes in consumption regardless of beverage.

The underpinnings of alcohol intake seem to be sustained by both stress and family history of alcoholism. Naturally, one possibility is that the subjective effects of alcohol depends and vary on the receptor systems where alcohol has its effects in the brain. If individuals with a family history of alcohol are more sensitive for stress and unease compared to controls, and therefore they increase their drinking in those situations. In this study we find support for this. The FHP subjects reported increased feelings of both unease and anxiousness after stress compared to the FHN subjects before they received any drug. Therefore we believe that this is true for these individuals in this study. Preclinically, rats with high endogenous corticosterone secretion and an enhanced corticosterone response to stress typically consume more ethanol (Prasad and Prasad, 1995). If stress is one candidate that makes FHP subjects more vulnerable and sensitive to the reinforcing effects of alcohol, stress could lead to an increased drug intake. Therefore it may be that an impaired functioning of the HPA-axis could prevent FHP individuals not to consume alcohol. Future pharmacological studies with for example dexamethasone will help us understand if a blockade of the HPA axis also blocks the rewarding subjective effects of alcohol after stress and consequently also the motivation to consume alcohol in humans. Studies such as described above may perhaps clarify the neurochemical mechanisms associated with the stimulant-like and positive reinforcing effects of alcohol.

In conclusion, the evidence discussed here indicated that stress alters the consumption of alcohol in subjects with a family history of

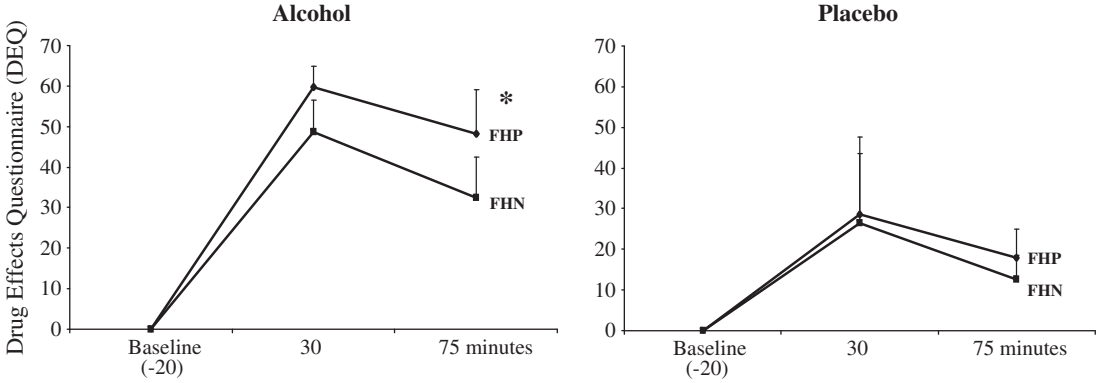

Fig. 5. Mean (±SEM) DEQ answers between the FHP and the FHN group after stress and placebo consumption. The asterisks denote significant differences between the stress and the no stress session. ***$p<0.000$.

alcoholism perhaps by activating the hypothalamic–pituitary–adrenal axis or through the release of neurosteroids. Although the results are modest they suggest that the effects may depend on family history and current neuroendocrine function. The altered subjective effects reported here may be related to both clinical reports that humans consume more alcohol after both acute and chronic stress and the fact that alcoholism is hereditary by about 50–60%. This study also emphasizes the need for early interventions targeted towards this at risk group. Future studies that include measures of stress, consumption, dose responses and gender are needed to understand the associations between stress, family history and alcohol in humans.

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