

Attenuated cortisol response to alcohol in heavy social drinkers[☆]

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Abstract

Individual differences in response to stress may play a role in the development and maintenance of addictive behaviors. While there is evidence that people with a biological family history for alcoholism have a blunted cortisol response to alcohol, data are lacking in other at-risk subgroups, such as heavy social drinkers. The present study examined salivary cortisol response to administration of 0.0, 0.4 (2 drink equivalent), and 0.8 g/kg (4 drink equivalent) alcohol in two groups of social drinkers: heavy drinkers ($n=32$) and light social drinkers ($n=23$). The study was conducted double-blind and drink-order was counterbalanced between groups. Salivary cortisol and subjective measures were obtained at predrink baseline, and 15, 45, 105, and 165 min after beverage consumption. Results showed a significant group \times dose \times time interaction ($p < 0.005$), with alcohol (0.8 g/kg) producing an attenuated cortisol response in heavy drinkers compared to the light drinkers during the declining phase of the BAC. This outcome remained even after controlling for the effects of smoking status, family history of alcoholism, sex, and negative affect ratings during the session. Neither placebo nor the lower dose of alcohol significantly increased cortisol levels. In sum, a relatively high dose of alcohol produced a smaller increase in cortisol in heavy drinkers compared to light drinkers. The reduced cortisol reactivity in the heavier drinkers is consistent with reports that individuals at risk for alcoholism are hyporesponsive to physical and psychological stress. Further research may help determine whether alteration in cortisol response to alcohol is a biological marker of the propensity to abuse alcohol.

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1. Introduction

Variations in responsivity to stress may play a role in the development and maintenance of alcohol use disorders. Heavy alcohol consumption and rapid increases in blood alcohol levels reliably increase cortisol or corticosterone in humans and nonhumans (Kalant, 1975; Mendelson and Stein, 1966; Merry and Marks, 1969; Valimaki et al., 1984). Both acute alcohol intoxication (Cobb and van Thiel, 1982; Elias et al., 1982; Rivier et al., 1984) and withdrawal (Adinoff et al., 1991; Iranmanesh et al., 1989; Risher-Flowers et al., 1988) increase levels of hypothalamic–pituitary–adrenal (HPA) axis derived stress hormones. Further, diurnal cortisol secretion is dysregu-

lated in alcoholics, although levels return to normal within approximately one week of abstinence (Adinoff et al., 1991). While alcohol-related effects on the HPA axis have been determined in persons with alcohol dependence, the role of stress hormones in the etiology, development, and maintenance of alcohol use disorders remains unclear.

Several lines of evidence suggest that the HPA axis may be important in the development of alcohol dependence. Individuals with a positive family history of alcoholism (FH+) have abnormal stress responses compared to those without family history of alcoholism (FH−). Early studies showed that compared to FH− males, FH+ males exhibited a reduced cortisol response after consuming a moderate to high dose of alcohol (Schuckit, 1984a; Schuckit et al., 1987). In addition to attenuated cortisol reactivity, FH+ individuals also experienced diminished subjective response including reduced sedative effects and less psychomotor impairment as measured by body sway (Schuckit, 1984b, 1985, Schuckit et al., 1996; Schuckit and Gold, 1988). Moreover, in other studies, prepubertal sons of alcoholics had attenuated salivary cortisol responses to antic-

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ipatory stress (Moss et al., 1995), and FH+ adults with antisocial tendencies had reduced cortisol responses to a speech stressor (Sorooco et al., *this issue*). Administration of opioid antagonists (which remove tonic opioid inhibition of the HPA axis) have also been shown to produce a differential pattern of results as a function of family history of alcoholism, with FH+ subjects exhibiting greater plasma cortisol and adrenocortical hormone (ACTH) response compared to their FH-counterparts (King et al., 2002a; Wand et al., 1999). Taken together, these data indicate that FH+ and FH- individuals differ in HPA stress responsivity to several psychological as well as pharmacological laboratory challenges.

Another risk factor for alcoholism is heavy drinking at a young age (Hingson et al., 2000). Not only is early-onset heavy alcohol drinking in itself a potentially hazardous behavior, it is also a risk factor for lifetime alcohol problems (Chou and Pickering, 1992). While some college-aged binge drinkers may “mature out” of their problematic drinking habits, for others, alcohol misuse persists or progresses in severity over time (Gruenewald et al., 2002; Hasin et al., 1990; Schulenberg et al., 1996). Recent investigations by our group suggest physiological differences in response to alcohol at the level of the HPA axis in young adult heavy drinkers (defined as consuming 5+ drinks/occasion for males or 4 for females) versus light drinker controls (Holdstock et al., 2000; King et al., 2002b). While our first study with a small sample size did not show alterations in plasma ACTH after alcohol consumption as a function of habitual alcohol consumption (Holdstock et al., 2000), another study with a priori selection of subjects for heavy ($n=20$) and light drinkers ($n=14$) showed that heavy drinkers had lower salivary cortisol responses after drinking (King et al., 2002b). This finding in non-alcohol dependent young binge drinkers is consistent with the previously mentioned findings from Schuckit and colleagues in their high risk subjects, i.e., FH+ men.

The present study was designed to examine cortisol response to two doses of alcohol or placebo in light and heavy social drinkers. Salivary cortisol levels were obtained before beverage consumption, and during both the rising and falling portions of the blood alcohol curve. It was hypothesized that heavy drinkers, compared to lighter drinkers, would show a reduced cortisol response to alcohol, especially at the higher alcohol dose. Secondary analyses using multivariate models were used to assess the role of drinking history independently of family history of alcoholism, smoking status, sex, and negative affect. It was predicted that the effect of drinking status would remain after controlling for family history of alcoholism and other potential confounding factors.

2. Methods

Subjects ($n=55$) were recruited through newspaper and Internet advertisements, word-of-mouth referrals, and local flyers. Candidates were first interviewed over the phone and if eligible, they attended an in-person screening. Subjects were accepted if they were aged 21–35 years, had a body mass index between 18.5 and 30, and qualified as either light

drinkers (LD) or heavy drinkers (HD). To qualify for the LD group, subjects had to be lifetime social drinkers with typical alcohol consumption of 1–3 drinks up to several times weekly and with rare consumption of five or more drinks on one occasion (4 for females) totaling to less than 4 times a year. The HD group included regular heavy social drinkers (i.e., predominant pattern for at least the past two years) with a minimum of 10 or more alcoholic drinks per week, and regular weekly binge drinking (5 or more drinks for men and 4 or more drinks for women in one occasion) 1 to 4 times each week. Moderate drinkers with an intermediate amount of alcohol consumption or drinkers with an inconsistent pattern of drinking were not eligible. The drinking inclusion criteria were based on laboratory, epidemiological, and clinical studies of “binge” drinking as 5 or more drinks consumed in an occasion (4 for females) which departs from normative social drinking and may indicate aspects of loss of control (Dawson, 2000; Dufour, 1999). Such binge drinking is also frequently associated with adverse consequences (Dawson, 1999; Single, 1996).

2.1. In-person screening

At the in-person screening, participants were first required to read and sign the consent form, which stated that the purpose of the study was to assess responses to commonly used substances. To control for alcohol expectancies, participants were informed that they might be receiving a stimulant, sedative, alcohol, placebo or a combination of substances. The participants filled out several questionnaires including a demographic information form, the Beck depression inventory (BDI; Beck et al., 1961), the Spielberger Trait Anxiety Inventory (STAI; Spielberger et al., 1970), the Short Michigan Alcoholism Screening Test (SMAST; Selzer et al., 1975), the Alcohol Use Disorders Identification Test (AUDIT; Babor et al., 1992), and a quantity–frequency index scale (QFI; Cahalan et al., 1969).

After completing the questionnaires, the participants underwent a modified Structured Clinical Interview for DSM-IV (SCID-P; First et al., 1995) conducted by a trained Master’s level clinician. Selected SCID Modules for lifetime mood disorders, alcohol and substance use disorders, and nicotine dependence (where applicable) were also administered. On the questionnaires and interview, standard cut-off thresholds were used to exclude subjects with significant major current or past psychiatric symptomatology (i.e., lifetime history of psychotic disorder, alcohol and other substance dependence, or a past year history of other Axis I disorders). Subjects were not excluded if they met criteria for past or current Alcohol Abuse.

Participants also filled out a family history tree identifying both primary and secondary biological relatives with alcohol use disorders. Parental history of alcohol use disorders was coded positive only if either one or both parents were identified by the subject as having an alcohol use disorder. A less stringent family history criteria was also examined and coded positive if one or more primary relatives, or two or more secondary relatives, were identified with alcohol use disorders.

Six subjects who could not be classified on family history were excluded from these analyses.

The participants also underwent blood chemistry/hepatic function tests as well as a routine physical examination by a resident physician to rule out any liver problems and or other medical disorders. A urine toxicology test was used to identify and exclude regular or heavy use of other drugs (cocaine, opiates, benzodiazepines, amphetamines, barbiturates, and PCP). Occasional social use of marijuana was accepted if the participant agreed to refrain from marijuana use for a minimum of 48 h prior to each session.

2.2. Procedure

This study is part of the Chicago Social Drinking Project, an ongoing investigation of social drinkers' responses to alcohol in various domains of functioning. Participants were tested individually in three experimental sessions and received a low dose of ethanol (0.4 g/kg), a high dose of ethanol (0.8 g/kg) and a placebo beverage. The order of dose conditions was randomized and counterbalanced within each group, and doses were administered double-blind. The low-dose ethanol beverage consisted of 8% volume 190-proof alcohol (0.4 g/kg) while the heavy dose had 16% volume alcohol (0.8 g/kg). The placebo beverage contained 1% ethanol as a taste mask in order to reduce alcohol expectancy effects. Across the three doses, in addition to alcohol, the beverage contained Grape flavored Kool-Aid® and artificial sweetener to add flavor and mask the taste of alcohol. Beverages were administered in opaque cups and consumed through a straw. Sessions were conducted in a comfortable living room-like laboratory environment, with at least 48 h separating each session. Sessions began between 3:00 and 5:00 PM and lasted for 4–5 h.

Participants were instructed to abstain from any alcohol, drugs or medication for 48 h before each session, and to refrain from eating, smoking and drinking caffeinated beverages 3 h prior to each testing session. Upon arrival, the subject completed an arrival questionnaire providing information on recent drug and alcohol use. To confirm compliance with drug and smoking instructions, respectively, subjects were given urine toxicology and expired air carbon monoxide (CO) tests (Bedfont EC50 Microsmokerlyzer II, Medford, NJ). Women were given a pregnancy test. The subject then consumed a light snack (a noncaffeine, low-fat meal with 10% protein, 55% carbohydrate, 35% fat, with calories calculated based on body weight) to avoid hunger effects on mood state and to help reduce the potential for alcohol-induced nausea.

At 30 min postarrival, baseline objective [saliva samples and blood alcohol concentration (BAC) levels] and subjective [the Positive Affect/Negative Affect Schedule (PANAS); see below] measures were obtained. Thirty minutes later, the subject consumed the first half of the beverage within 5 min, followed by a 5-min break and then consumed the second half of the beverage over the next 5 min. Beverages were consumed in the presence of a research assistant. BAC levels and salivary cortisol were measured post-beverage consumption, at the ascending (15 and 45 min) and descending (105 and 165 min)

limbs of the BAC. To reduce fatigue and complacency with other subjective and performance measures that were administered as part of the larger study, the PANAS was obtained at 15 and 105 min post beverage consumption. The three experimental sessions were identical except for the contents of the beverages (placebo, low and high dose alcohol). At session end, the subject was driven home and instructed not to drive or operate heavy machinery for at least 12 h after the session. After completing the study, each subject was debriefed and paid (US \$150+\$50 bonus).

2.2.1. Dependent measures

2.2.1.1. Cortisol. Saliva samples were collected using plain cotton Salivettes (Sarstedt) and stored in a -20°C freezer until assayed using a high sensitivity salivary cortisol enzyme immunoassay kit (Salimetrics®, State College, PA; cat # 1-0102/1-0112). The salivary immunoassay is designed using a matrix that matches saliva against standards and captures the full range of salivary cortisol levels while using only 25 μL of saliva. The minimal concentration of cortisol that can be distinguished from 0 is $<.007\text{ }\mu\text{g/dL}$. Frozen samples were thawed and centrifuged at $1500\times g$ (@ 3000 rpm), and assayed in duplicate along with standard. The assay method is standardized and validated in the University of Chicago Clinical Research Center core laboratory. The inter- and intra-assay coefficients of variation were 6.88% and 7.12%, respectively. Cortisol units are represented as $\mu\text{g/dL}$ ($\mu\text{g/dL} \times 27.59 = \text{nmol/L}$).

The Alco-Sensor III (Intoximeter Inc., St. Louis, MO), which provides real-time display of the actual BAC reading, was used to take the BAC reading upon the participant's arrival. However, to maintain the double blind, the Alco-Sensor IV, which displays 0.000 for all readings masking actual BAC levels, was used in the testing sessions. The actual BAC levels were later downloaded to a computer.

2.2.1.2. Subjective. The PANAS is a 20-item questionnaire with items measured on a Likert Scale from 1 (Very Slightly) to 5 (Extremely; Watson et al., 1988). The PANAS has two subscales: Positive Affect, which reflects the extent to which the individual feels alert or enthusiastic, and Negative Affect, which reflects general subjective distress that is accompanied by various negative mood states. The PANAS has shown established reliability and validity with alphas of 0.84–0.90 (Watson et al., 1988).

2.2.2. Data analysis

Salivary cortisol data were analyzed using repeated measures analysis of variance (ANOVA), with group (HD, LD) as the between subjects factor, and dose (placebo, 0.4 and 0.8 g/kg) and time (baseline, 15, 45, 105, 165 min) as the within-subjects factors. Significant interactions were further examined to determine the group effect at different dose levels and time points, using two sample *t*-tests, with degrees of freedom adjusted for unequal variances when assumption of equal variance was not met. As a dose manipulation check, BAC data

Table 1
Demographics and drinking characteristics by group

| | Light drinkers (<i>n</i> = 23) | Heavy drinkers (<i>n</i> = 32) |
|-----------------------------------------------------------|------------------------------------|------------------------------------|
| <i>Demographics</i> | | |
| Age (yr) | 26.0 (0.7) | 24.8 (0.6) |
| Education (yr) | 16.5 (0.3) | 15.7 (0.2)* |
| BMI (kg/m ²) | 24.4 (0.6) | 24.9 (0.6) |
| Parental history of alcohol use disorders ^a | 6 (26%) | 8 (25%) |
| Family history of alcohol use disorders ^a | 14 (61%) | 22 (69%) |
| <i>Sex</i> | | |
| Male | 10 (43%) | 15 (47%) |
| Female | 13 (51%) | 17 (53%) |
| <i>Race</i> | | |
| White | 13 (56%) | 28 (88%)** |
| Black/African American | 5 (22%) | 3 (9%) |
| Asian | 3 (13%) | 0 |
| Hispanic/Latino | 0 (0%) | 1 (3%) |
| Other | 2 (9%) | 0 |
| <i>Drinking behavior^b</i> | | |
| Drinks per occasion | 2.1 (0.2) | 6.4 (0.9)*** |
| Drinking occasions/week | 1.4 (0.2) | 3.7 (0.2)*** |
| Drinks per week | 2.8 (0.4) | 21.6 (1.8)*** |
| Estimated # binges ^c (last 6 months) | 0.7 (0.2) | 55.4 (5.4)*** |
| Lifetime alcohol abuse ^d | 1 (4%) | 13 (41%) |
| <i>Smoking behavior</i> | | |
| Current smoker ^e | 6 (26%) | 20 (63%)** |
| Cigarettes/day | 2.0 (0.3) | 7.2 (1.3)* |

Note. Data presented are mean (SEM) or *N* (%). Data were compared by *t*-test or Chi-Square tests, where appropriate. **p* < .05; ***p* < .001, ****p* < .0001.

^a Parental history = one or both parents with alcohol use disorders, Family history = a minimum of two or more secondary relatives with alcohol use disorders; ^b Drinking Behavior derived from 6 month Quantity Frequency Index; ^c Binge defined as 5 or more drinks consumed in an occasion for men, four or more drinks for women; ^d SCID Module for substance use disorders was used to assess lifetime alcohol abuse; ^e Current Smoker defined as smoking one or more cigarettes per week.

was analyzed using a repeated measures ANOVA with group (HD, LD) as a between subjects factor and time (baseline, 15, 45, 105, 165 min) and dose (low, high) as a within subjects factors. Greenhouse–Geisser adjustments were used when the required covariance matrix compound symmetry assumption was not met (Greenhouse and Geisser, 1959). Multiple linear regression models were used to test the differential effect of group (HD vs. LD) to cortisol response, controlling for other variables such as sex, family and parental history of alcoholism, smoking status and negative affect during testing. All tests of hypotheses were conducted as two-tailed tests and at 0.05 alpha level.

3. Results

3.1. Background characteristics

Table 1 includes background and drinking characteristics of the participants. The HD (*n* = 32; 15 males) and LD (*n* = 23; 10

males) group did not differ in age, gender, body mass index or percentage of positive family (or parental) history for alcohol use disorders. However, HD subjects were more likely to be smokers, Caucasian, and have less education than LD subjects (see Table 1). As expected, the groups differed in alcohol consumption: HDs consumed more drinks per occasion, drank more frequently, consumed more drinks per week, and reported more binge episodes.

3.2. BAC

As expected, in both the LD and HD groups, alcohol increased BAC levels in a dose dependent manner [Dose: $F(1, 52) = 810.13$, $p < .0001$; Dose \times Time: $F(4, 208) = 9.67$, $p < .0001$]. BACs peaked to 0.098 for the high dose and 0.044 for the low dose within 45 min after alcohol consumption and declined steadily thereafter [Time: $F's(4, 212) \geq 100.06$, $p's < .0001$]. At the low dose, HDs exhibited greater initial rise 15 min after consumption of alcohol [Group \times Time: $F(4, 212) = 10.22$, $p < .001$; simple effects at 15 min: $p < 0.05$]. However, the LD and HD groups did not differ on BAC over time at the high dose [Group \times Time: $F(4, 212) = 2.09$, $p = .08$].

3.3. Cortisol

Repeated measures ANOVA revealed a significant three-way Group by Dose by Time interaction [$F(8, 424) = 5.10$, $p < .005$]. After consumption of the high alcohol dose, the HD group exhibited lower cortisol response relative to the LDs during the later portion of the BAC curve, at 105 min [$t(22.9) = 2.21$, $p = 0.04$] and 165 min [$t(23) = 2.02$, $p = 0.05$]. The groups did not differ on cortisol levels during the rising portion of the BAC (see Fig. 1). In contrast to the findings with the high alcohol dose, cortisol levels during both placebo and low alcohol dose sessions did not increase for both groups.

Analyses were also conducted to compare the groups on peak cortisol response (see Fig. 2). Peak cortisol response will henceforth refer to each participant's highest cortisol level across the four time points (15, 45, 105 and 165 min) excluding baseline. The results confirmed that the HDs exhibited lower peak cortisol at the high dose compared to LDs [$t(23.6) = 2.10$, $p < 0.05$]. There were no group differences in peak cortisol secretion during the placebo or the low alcohol dose sessions. Finally, analyses comparing cortisol response as measured by area under the curve (AUC) confirmed that HDs showed reduced cortisol secretion to the high dose as compared to LDs [$t(27.4) = 2.20$, $p < .05$]. Since group differences were only evident at the high alcohol dose, all remaining analyses specifically refer to high dose session data, unless otherwise specified.

In terms of other factors that may relate to cortisol, peak cortisol responses did not differ for men and women [$t(53) = 1.68$, $p = ns$], as well as in subjects with or without parental [$t(53) = -0.52$, $p = ns$] or family history of alcoholism [$t(47) = 0.36$, $p = ns$]. Peak cortisol also did not differ based on individual differences in BAC levels at all time points ($p's > ns$). However, peak cortisol was greater in non-smokers

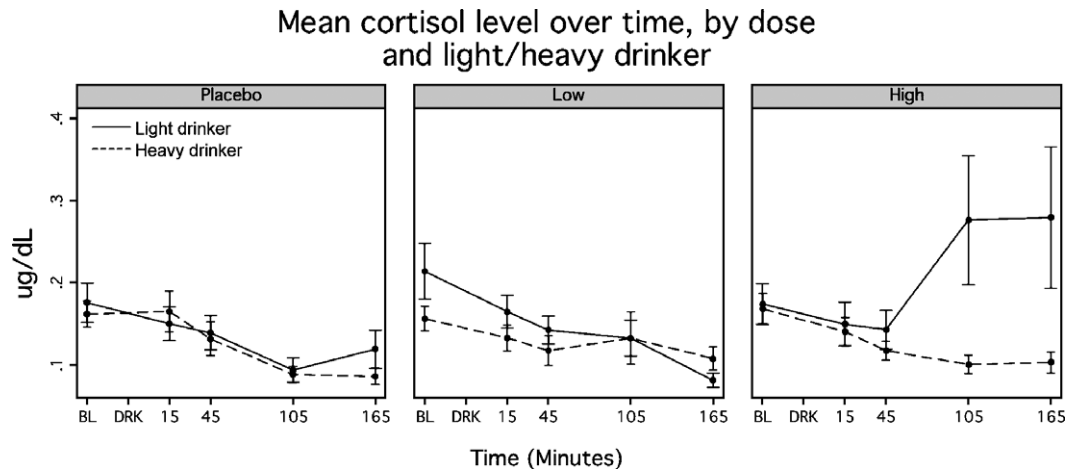


Fig. 1. Salivary cortisol levels in heavy and light drinker groups across the three doses (placebo 0.0 g/kg, low 0.4 g/kg, high 0.8 g/kg). Time points include baseline measure (30 min pre-drink=BL), when drink was administered (DRK), and 15, 45, 105 and 165 min after beverage completion. ANOVA revealed a significant Group by Dose by Time, $p < .005$. Post hoc tests showed significant differences between groups at the high alcohol dose at time points 105 and 165 min.

than smokers [$t(32.4)=2.28, p < .05$]. Cortisol levels of females using birth control pills ($n=16$) did not differ from other females not taking birth control pills ($n=14$) [$t(14.4)=0.80, p = ns$]. The latter analysis was conducted to control for any possibility of birth control pills affecting cortisol binding (van der Vange et al., 1990) or salivary cortisol response to laboratory stressors (Kirschbaum et al., 1995).

3.4. Negative affect

Alcohol did not change PANAS Negative Affect scores for either the LD or HD group (i.e., there was no main effect of group or time, or significant interaction effects). Further, negative affect did not relate to peak cortisol responses ($r = -0.14, p = ns$).

3.5. Controlling for potential confounds

Sex, parental and family history of alcoholism, negative affect and smoking status were controlled for as confounding

variables that could have accounted for the differential cortisol results between the LD and HD groups. Despite controlling for these potential confounding variables in a multiple regression, the HD group continued to show significantly lower cortisol response to alcohol than LDs [$t(43)=2.02, p < .05$].

4. Discussion

The results support the hypothesis that compared to the light social drinker group, the habitual heavy drinkers showed an attenuated HPA axis response to alcohol challenge. Specifically, this lower cortisol response was apparent after ingestion of a relatively high alcohol dose (i.e., 4–5 drink equivalent) rather than to a moderate-to-low alcohol dose or a placebo beverage. Lower cortisol secretion in the HD group was confirmed by both peak cortisol response and area under the curve analyses. The lower cortisol response in HDs was not due to differences in reported negative affect during the sessions. Moreover, the group differences in cortisol response to alcohol challenge remained even after controlling for

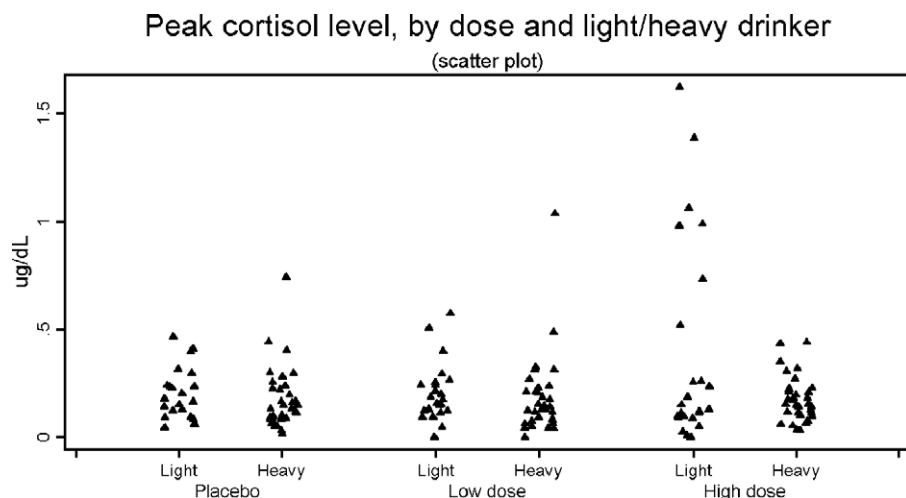


Fig. 2. Peak salivary cortisol level by alcohol dose and light/heavy drinker groups. Heavy drinkers exhibited reduced peak cortisol at the high dose compared to the light drinkers ($p < 0.05$). There were no differences during the placebo or low alcohol dose sessions.

potential covariates such as parental or family history of alcohol use disorders, smoking status, and sex. The only individual factor that related to peak cortisol response was smoking status, with smokers showing lower reactivity than nonsmokers. This observation is consistent with previous reports that smokers exhibit a lesser cortisol response to a pharmacological (naloxone) challenge (Krishnan-Sarin et al., 1999). However, controlling for smoking status did not alter the main finding of heavy drinkers' reduced cortisol response to alcohol challenge. Taken together, the finding of a lower cortisol response after alcohol consumption in heavy binge social drinkers appears robust, and replicates prior work by our group in a smaller sample (King et al., 2002b). The results also extend prior findings to show that reduced cortisol response in heavy drinkers is not altered by factors that have been previously shown to relate to HPA axis regulation.

As mentioned earlier, both the HD and LD groups showed similar cortisol responses during the placebo beverage session, which can be interpreted as a general indication of normal diurnal patterns in the late afternoon and early evening. Moreover, during the early portion of the high-dose session, as well as the entire low-dose and placebo sessions, there was a general slight downward trend in cortisol secretion, which is also reflective of normal patterns at this time of day when cortisol usually reaches the nadir. These data in heavy and light drinkers are similar to prior findings showing normal circadian rhythmicity of cortisol in recovering alcoholics (Adinoff et al., 1991; Lovallo et al., 2002) and at-risk subjects by virtue of FH+ (Sorocco et al., *this issue*).

The cortisol elevations after alcohol consumption in LDs were not ubiquitous (see Fig. 2) and occurred in about one-third of that subgroup. A similar proportion of LDs had elevated cortisol response to high dose alcohol challenge in our prior study (King et al., 2002b). It is not clear why some and not other subjects exhibited a larger response to alcohol. Given that the sample size within the LD group is small, it is difficult to investigate the source of these individual differences. An initial examination of background characteristics showed that the high responders were largely male nonsmokers, but were similar to nonresponders on age, race, BMI, and negative affect. While the LD group was comprised of individuals who were phenotypically at lower risk for future alcohol disorders, the variability in their cortisol responsivity to alcohol challenge suggests that this group may be heterogeneous, and thus vary in risk for future alcohol abuse. It is important to note that in contrast to the light drinkers, none of the 32 heavy drinkers showed any cortisol increases throughout the alcohol challenge sessions. So, it may be speculated that increases in cortisol could buffer some lower risk subjects from continued alcohol consumption, although more direct tests of that theory need to be conducted.

Cortisol hypo-responsiveness in heavy drinkers was apparent during the declining limb of the BAC, approximately 2–3 h after alcohol drinking, which is similar to the time course of reduced cortisol response to alcohol observed in FH+ (Schuckit, 1984a; Schuckit et al., 1987). However, in contrast to Schuckit's results, secondary analyses in the present study

revealed that parental or family history did not relate to cortisol response to alcohol challenge. It has been theorized that reduced cortisol responses in at-risk subjects by virtue of FH+ may be indicative of greater inherent tolerance to alcohol (Schuckit et al., 1987, 1996; Schuckit and Gold, 1988; Schuckit, 1994). In terms of binge drinkers, reduced cortisol response to alcohol may be due either to premorbid differences in alcohol-induced activation of the HPA axis, or to acquired tolerance that develops after repeated exposures to alcohol. We may speculate that the less intense response to alcohol via lower activation of the HPA axis observed in all of the heavy drinkers and some of the light drinkers may represent a biomarker of propensity to alcohol misuse, although direct evidence for this theory is needed. This risk propensity, along with acquired tolerance from repeated exposure to binge drinking episodes, may render some young adult drinkers at heightened risk for continued alcohol abuse or progression to dependence.

In sum, the current paper provides additional support for a physiological difference in alcohol response at the level of the HPA axis in male and female heavy drinkers versus light social drinkers. This finding may be related to other findings of hypo-responsiveness to physical and psychological stress in persons at risk for alcoholism (Sorocco et al., *this issue*). Longitudinal studies currently underway by our group may help determine whether alteration in cortisol response to alcohol represents an important biological marker of propensity to future alcohol use disorders.

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