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Blunted Stress Cortisol Response in Abstinent Alcoholic and Polysubstance-Abusing Men

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Background: This study tested cortisol responses to a psychological stressor in controls (CT) versus patients who were diagnosed as alcohol dependent (AD) or alcohol and stimulant dependent (ADSD) by DSM-IV criteria and who were abstinent for 3 to 4 weeks from alcohol and illicit drugs. Alcohol increases cortisol secretion acutely and during withdrawal. However, there is little information about abnormalities of hypothalamic-pituitary-adrenocortical (HPA) reactivity in recovering alcoholics.

Methods: Accordingly, we tested HPA function in the laboratory between 7:00 and 9:30 AM on control versus stress days. Stress consisted of a 20-min public speaking challenge with preparation and delivery of two short speeches, ostensibly evaluated for quality of delivery, whereas control involved relaxing for the same period. Cortisol was measured in saliva collected at baseline, stress or control, and recovery period, and also at home at 9:00 PM on one of the two days.

Results: The three groups did not differ in diurnal patterns of cortisol secretion on the rest day and 9:00 PM sample, which indicated that AD and ADSD patients had intact diurnal HPA regulation at rest. During speech stress, the CT subjects showed the expected cortisol increase ($p < 0.0001$), whereas neither AD nor ADSD patients responded significantly. Cortisol values were not accounted for by covariates such as depression, posttraumatic stress disorder, glucose metabolism, or anthropometric or demographic characteristics.

Conclusions: The apparent stress hyporesponsiveness of the AD and ADSD patients suggests a persistent disruption of HPA function, perhaps due to incomplete recovery from prior abuse, or to a preexisting alteration in neural systems that regulate HPA responses to stress.

Key Words: Alcoholism, Drug Abuse, Cortisol, Stress.

THE PRESENT STUDY examined adrenocortical responsiveness to acute psychological stress in patients that met DSM-IV criteria for alcohol dependence with or without concurrent dependence on cocaine or amphetamine. Cortisol secretion is regulated by the hypothalamic-pituitary-adrenocortical axis (HPA) in response to metabolic and diurnal signals and to stress, which includes psychological stress (Lovallo et al., 1990; Munck et al., 1984). The normal pattern of cortisol secretion is altered by alcohol. Acute ethanol administration increases cortisol secretion by direct stimulation of the hypothalamus and the adrenal cortex in rat models and in humans (Cobb and Van Thiel, 1982; Elias et al., 1982; Rivier et al., 1984). Alcoholics in withdrawal have a flattening of cortisol's circadian rhythm and an elevated daily secretion (Iranmanesh et al., 1989; Risher-Flowers et al., 1988). However, the diurnal rhythm appears to normalize by 1 week of abstinence (Adinoff et al., 1991).

Although the diurnal pattern is normalized with abstinence, other evidence suggests a more chronic disruption of HPA regulation in alcohol dependence. Recovering alcoholics have a blunted adrenocorticotropic hormone (ACTH) and cortisol response to exogenous corticotropin releasing factor (CRF) at 1 to 3 weeks of abstinence (Adinoff et al., 1990; Bardeleben et al., 1988, 1989), with some evidence of a blunting that persists up to 6 months (Adinoff et al., 1990). They also may have reduced cortisol responsiveness to physical and psychological stressors. Alcoholics abstinent 1 to 2 weeks showed a lack of cortisol response to the stress of insulin-induced hypoglycemia (Costa et al., 1996). We have observed a blunted-to-absent secretion of cortisol in 3 to 4 week abstinent alcoholics exposed to behavioral and mental stressors that include mental arithmetic plus a cold pressor test (Errico et al., 1993). Subsequent studies that used mental arithmetic plus isometric handgrip in males (Bernardy et al., 1996) and simulated public speaking followed by isometric handgrip in females (Bernardy, 1995) also found a blunted stress cortisol response. These findings led us to hypothesize that

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sober alcoholics may have a blunted stress cortisol reactivity.

Limitations of these earlier studies included infrequent sampling of cortisol and reliance on changes from baseline in a single session. The present study used more frequent cortisol sampling and included an unstressed control day to capture important phases of the diurnal cycle and provide clearer contrasts of stressed with unstressed states. In addition, due to increasing prevalence of polysubstance abuse among alcoholics, we also included patients with a history of alcohol dependence and cocaine or amphetamine dependence.

METHODS

Subjects

Subjects were 20 hospitalized male patients who included 10 alcoholics and 10 alcoholic stimulant abusers, and 10 community controls. All met the following criteria: age 22 to 55 years; normal nighttime sleep schedules with no reported sleep disorders; in good health by hospital chart and self-report; no present or past treatment for cardiovascular disorders, liver dysfunction, organic brain syndrome, chronic obstructive pulmonary disease, or diabetes mellitus; weight ±20% of normal by Metropolitan Life Insurance Company norms; education ≥ninth grade; and estimated verbal IQ above the low-normal adult range, based on a Shipley Institute of Living Scale verbal score ≥20 (Shipley, 1940). All volunteers signed a written informed consent form approved by the Institutional Review Board of the University of Oklahoma Health Sciences Center and the Veterans Affairs Medical Center and were paid for their participation.

Alcohol Dependence (AD). AD patients met the previously listed general inclusion criteria plus criteria for alcohol dependence by American Psychiatric Association DSM-IV (American Psychiatric Association, 1994). All AD patients had their last drink within 24 hr of admission, had no abstinence period >30 days during the past 12 months, had a quantity-frequency index of alcohol use >5.0 (Cahalan et al., 1969), and reported no prolonged use of any other drug during the past year.

Alcohol Dependence and Stimulant Dependence (ADSD). ADSD patients met the previously listed general inclusion criteria plus criteria for AD and criteria for cocaine and/or amphetamine dependence by DSM-IV. ADSD patients matched the alcohol use patterns of the AD group and also reported using any form of cocaine and/or amphetamine ≥3 times per week for at least the past year.

Controls (CT). CT met all general inclusion criteria, reported a current alcohol intake of <10 drinks per week, and had no reported history of DSM-IV Axis I disorders including any substance use disorder.

Procedures

Recruitment. Patients were identified by chart review during their first 2 weeks in treatment for alcoholism or polysubstance abuse at one of two local treatment facilities in the Oklahoma City area. The research staff contacted the patients while they were in treatment and explained the goals of the project. Those patients interested in participating were given an extensive battery of self-report instruments and a clinical interview for inclusion criteria. CT subjects were recruited by advertisement in local newspapers and flyers placed on the local campus. They initially were screened by telephone and then were invited to visit the laboratory for the same screening battery given to the patients. Prospective volunteers who met all inclusion criteria signed the consent forms and were scheduled for two visits, one rest day, and one stress day. Test sessions were held from 1 to 7 days apart depending on scheduling factors.

Test Protocol. Volunteers were given written instructions to get a normal night's sleep the night before testing and to abstain from food, caffeine, alcohol, nicotine, and nonprescription medications following dinner. Compliance was ascertained by signed statement on days of testing and Breathalyzer® test for alcohol. No other drug screening was employed.

The laboratory protocol included the following: reporting to the laboratory at 7:00 AM, Breathalyzer® test (5 min), self-report of compliance with dietary and substance restrictions (5 min), consumption of a canned milkshake breakfast (220 kcal, 20 g carbohydrate, 1 g fat) (5 min), instrumentation for cardiovascular measurement (to be reported elsewhere) (15 min), adaptation (30 min), orthostatic challenge or continued rest (15 min), recovery (10 min), public speaking challenge or continued rest (20 min), and recovery (24 min).

Rest Periods. During all rest periods, the subjects remained semirecumbent in a recliner chair.

Orthostatic Challenge. During orthostatic challenge, the subject moved the recliner to the sitting position, arose, and remained standing for the task duration. Orthostasis was included to examine cardiovascular function and was not expected to exert independent effects on cortisol. In fact, there were no cortisol responses to orthostasis, and so the postorthostasis measurement at 8:30 AM is considered an extension of the baseline.

Public Speaking. Public speaking consisted of a 3 min speech preparation period followed by a 3 min speech, repeated twice. Along with brief transitions, this took 20 min. Two speech scenarios were presented in counterbalanced orders: (1) whether homosexual couples should be allowed to adopt children, and (2) defending oneself following an accusation of shoplifting (al'Absi et al., 1997). The subject sat semirecumbent in front of a video camera, and a white-coated female experimenter with a clipboard remained in the testing room to observe the speeches. The subject was told that his speeches would be videotaped and judged by the research staff for clarity, accuracy, interest, content, poise, and style, and that he could earn a $10 bonus if they were judged as especially good. In fact, the speeches were not taped, and all subjects received the bonus.

Screening Instruments, Blood Glucose, and Cortisol Measurement

Interview Materials. Cortisol regulation may be affected by alcohol intake patterns and severity of withdrawal, and these variables were assessed by interview. At screening, during weeks 2 to 3 of treatment, a quantity-frequency index (QFI) of alcohol and other drug consumption was established for the previous 12 months by structured interview by using a calendar method that involved a time-line follow-back of daily drinking (Cahalan et al., 1969). QFI (typical ethanol intake, oz/day) was calculated based on frequency of wine, beer, and liquor consumption standardized for drink volume and alcohol content of each beverage type. This technique has good reliability and validity (Sobell and Sobell, 1978). Subjective withdrawal severity was determined by a modified Clinical Institute Withdrawal Assessment (Shaw et al., 1981). This instrument has good external validity against clinical observation (Hesselbrock et al., 1983).

Self-Report Instruments. Because cortisol secretion is perturbed by a variety of behavioral and emotional states, potential sources of confound were explored with self-report instruments.

We assessed depression at screening by using the Beck Depression Inventory (BDI) (Beck et al., 1961). Stressful life events may also affect cortisol secretion (DeBellis et al., 1994). The Scaling of Life Events (SLE) was used to quantify events experienced in the past year and their perceived impact. This scale has acceptable psychometric properties and is valid across age and socioeconomic status (Paykel et al., 1971).

Posttraumatic stress disorder (PTSD) was quantified using the Modified Posttraumatic Stress Disorder Symptom Scale (MPSS), a self-report scale that covers the frequency and severity of DSM-IIIR symptoms of PTSD experienced in the past 2 weeks. This scale has good internal reliability and validity against the structured clinical interview for DSM-IIIR for PTSD (Falsetti et al., 1993).

Sleep characteristics the night before each day of testing were determined by using the St. Mary's Sleep Questionnaire (Fujiwara et al. 1992).

Affective experience during exposure to a stressor may also affect cortisol secretion (al'Absi et al., 1997), and we assessed group differences

Table 1. Demographic Data

	CT	AD	ADSD	*p* and Contrasts
Demographics				
Age (yr)	40 (2.0)	40 (2.9)	38 (2.0)	
Height (inches)	70 (0.7)	69 (1.6)	70 (1.1)	
Weight (lb)	192 (7.5)	167 (10.7)	185 (9.4)	
Education (yr)	16.3 (0.8)	12.5 (0.5)	13.0 (0.7)	†CT > AD = ADSD
Verbal age (yr)	18.8 (0.5)	16.4 (0.5)	16.1 (0.4)	†CT > AD = ADSD
Substance use				
QFI-Alcohol (oz/day)	0.3 (0.1)	9.4 (0.4)	12.8 (2.3)	†AD = ADSD > CT
Alcohol withdrawal				
Severity	—	29 (3.6)	12 (3.2)	**AD > ADSD
Medical index	3.3 (0.8)	5.5 (0.4)	3.8 (0.6)	
Nicotine (cig/day)	0.0 (0.0)	22 (4.7)	14 (2.4)	†AD = ADSD > CT
Caffeine (mg/day)	189 (81)	610 (182)	1092 (444)	
Psychosocial characteristics				
Scaling of Life Events	41 (8)	111 (27)	144 (50)	
Beck Depression Inventory	0.8 (0.4)	12 (2.6)	14 (2.2)	†AD = ADSD > CT
Posttraumatic stress disorder Symptoms				
Frequency	1.5 (1.0)	15.9 (4.1)	11.6 (2.8)	*AD = ADSD > CT
Severity	1.3 (0.8)	14.1 (3.7)	10.6 (3.2)	

Values shown are mean (±SEM). CT, non-substance-abusing controls; AD, alcohol dependence; ADSD, alcohol dependence with stimulant dependence (cocaine and/or amphetamine). Verbal age estimated by Shipley Institute of Living Verbal Scale. Withdrawal severity derived from the Clinical Institute Withdrawal Assessment. Medical index is a total of reported history of medical disorders. Contrasts are pairwise group contrasts using Tukey's multiple comparison test after analysis of variance comparing three groups.

* $p \leq 0.05$, ** $p \leq 0.01$, † $p \leq 0.001$.

in emotional state before and after the stressor by using the Profile of Mood States (POMS) (McNair et al., 1992).

Saliva Cortisol and Blood Glucose. Saliva was collected in the laboratory at 8:00, 8:30, 9:00, and 9:30 AM, which corresponded respectively to the end of baseline, orthostasis recovery, public speaking, and final recovery. Control day specimens were collected at these same times. After the first laboratory day, subjects were told to collect a saliva sample at 9:00 PM the evening before their second test day. To control home food intake for this sample, subjects ate their evening meal before 7:00 PM and consumed a prepared milkshake at 8:30 PM.

Specimens were collected with a commercially available device that consisted of an absorbent cellulose collector and storage tube (Salivette®, Sarstedt, Germany). The collector was placed in the mouth for 2 to 3 min until saturated with saliva, replaced in the tube, and capped. After each test session, the tubes were centrifuged and the saliva pipetted into a storage tube (Cryotubes®, Nunc, Copenhagen, Denmark) and stored at −70°C until assay.

Saliva free cortisol concentrations were quantified with a commercial radioimmunoassay kit (Orion Diagnostica, Espoo, Finland) adapted to measure low cortisol concentrations (Copinschi and Van Cauter, 1996). Saliva samples were mixed with a fixed amount of ^{125}I-labeled cortisol derivative and cortisol antiserum. The labeled and unlabeled antigens were then allowed to compete for the high-affinity binding sites of the antibody during an incubation period. Bound and unbound antigens were separated with polyethylene glycol. The actual concentrations in the unknown samples were obtained by means of a standard curve based on known concentrations of unlabeled antigen analyzed in parallel with the unknown. Intra- and interassay coefficients of variations were 8.51% and 11%, respectively.

Blood Glucose. Blood glucose was measured as an additional control for potential confounds in cortisol secretion because cortisol is elevated by low blood glucose levels. A rapid, painless finger stick was made using an automated safety lancet (Microtainer®, Becton Dickenson, Franklin Lakes, NJ) at 7:00, 7:30, 8:00, 8:30, and 9:30 AM. Glucose was quantified using a One Touch® Basic glucose meter with commercial test strips (Lifescan, Milpitas, CA).

Data Analyses

We compared subject demographics, anthropometric characteristics, and psychosocial data by using between-subjects univariate analyses of variance (ANOVAs) with three groups (CT, AD, ADSD). We further explored significant differences by using Tukey's multiple comparison test. Blood glucose was tested by univariate repeated-measures ANOVA with 3 groups × 2 days (rest, stress) × 5 periods (7:00, 7:30, 8:00, 8:30, and 9:30 AM). To examine possible demographic and psychosocial confounders, laboratory cortisol and POMS values were subjected to Pearson *r* correlations with demographic, drinking, and psychosocial variables. Background variables that showed significant correlations with primary dependent variables were used as covariates in testing the latter.

Cortisol values on the rest day were tested for diurnal pattern using a 3 groups × 5 periods (8:00, 8:30, 9:00, and 9:30 AM, and 9:00 PM) repeated-measure ANOVA. The prediction of similar diurnal and metabolic cortisol secretion for the three groups calls for a nonsignificant groups × periods interaction for these rest day values. Specimens from the laboratory were tested using a 3 groups × 2 days (rest, stress) × 4 periods (8:00, 8:30, 9:00, and 9:30 AM) repeated-measures ANOVA. To test the hypothesis of differential reactivity to the speech stressor between controls and patients, this larger ANOVA design was subjected to the following simple effects tests. First, we tested the simple day × periods interaction for each group. A significant simple interaction was considered to indicate differential reactivity in the lab from day to day. Second, we carried out a simple effects test on the cortisol value at end of orthostasis versus the end of public speaking, by using the appropriate error term from the main ANOVA. Finally, we contrasted the cortisol at the end of the speech on the stress day with the corresponding value on the rest day. This contrast allowed a time of day control for the stress sample taken at that time. All tests that involved multiple levels of the periods factor were tested using Greenhouse and Geisser's correction for repeated measures.

All analyses were carried out using PC-SAS® or SPSS® for Windows.

RESULTS

Group Demographics, Alcohol Use, and Psychosocial Characteristics

Group comparisons are shown in Table 1. As expected, the patient groups reported greater use of alcohol than controls. AD subjects reported having more severe alcohol withdrawal symptoms than ADSD subjects. The AD and ADSD groups were more likely than controls to smoke

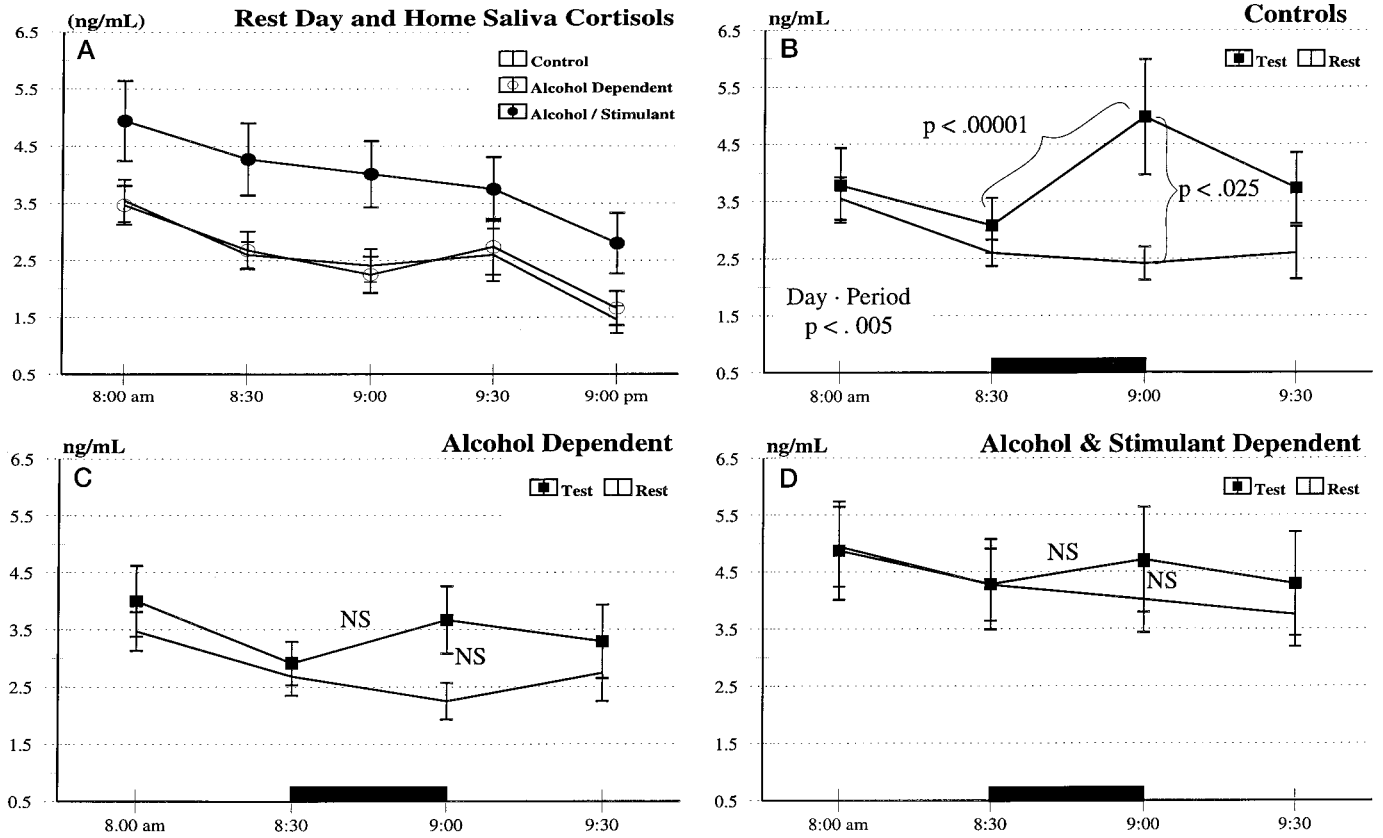

Fig. 1. Saliva free cortisol values during rest and in response to public speaking stress. CT = healthy controls, AD = alcohol dependent, ADSD = alcohol and stimulant dependent; $n = 10$ per group. Stress day includes rest, orthostatic challenge, and public speaking stress. Rest day includes quiet rest in the laboratory and one evening sample in the home or treatment unit. (A) Cortisol levels on rest days in the lab and at home. (B) Cortisol levels for CT on rest versus stress day. (C) Cortisol levels for AD on rest versus stress day. (D) Cortisol levels for ADSD on rest versus stress day.

cigarettes. On the psychosocial measures, patients scored higher than controls on the Beck Depression Inventory, although all subjects scored in the normal range. Patients also reported a greater frequency of symptoms of posttraumatic stress disorder.

Evening and Resting Cortisol Values

The rest day cortisol data indicate that all groups had similar diurnal cortisol changes over the times tested, although the ADSD group had consistently higher levels relative to the other groups (Fig. 1A). The ANOVA showed a significant effect of groups [$F(2,27) = 4.66$, $p < 0.02$], with ADSD values being higher than CT and AD ($p < 0.05$). There was a significant effect of periods [$F(4,108) = 22.82$, $p < 0.0001$], which indicated the expected diurnal decline across the waking hours, and the groups × periods interaction was nonsignificant ($F < 1$), which suggested that the diurnal pattern was the same for all groups over the range of times tested.

Stress Cortisol

The main groups × days × periods ANOVA yielded a significant days × periods interaction [$F(3,81) = 7.95$, $p < 0.0001$]. As a result, we examined this interaction separately for each of the three groups. These analysis are summarized in Table 2, and the cortisol values are shown in Fig. 1B, 1C, and 1D.

Table 2. Statistical Tests of Cortisol Response to Stress

	CT	AD	ADSD
Day × period interaction *df* = 3,81	7.38	1.77	0.97
	(0.005)	(NS)	(NS)
Variation across stress day *df* = 3,81	6.99	2.31	0.91
	(0.005)	(NS)	(NS)
Pre- to poststress change *df* = 1,81	18.64	0.986	0.973
	(0.0001)	(NS)	(NS)
Rest vs. stress day at poststress *df* = 1,108	22.62	1.38	1.71
	(0.025)	(NS)	(NS)

CT, controls; AD, alcohol dependence; ADSD, alcohol and stimulant dependence. See text for further explanation of diagnostic categories. Entries show *F* ratios and *p* values. NS indicates $p > 0.1$.

Controls. Figure 1B indicates that the controls had a large cortisol increase in response to the public speaking task. Their cortisol values showed a highly significant day × period interaction, and their cortisol levels varied significantly across periods on the stress day. This rise to public speaking was significant relative to the prestress baseline on the speech day and in relation to the comparable time period on the rest day.

Alcoholics. The day × period interaction for the alcoholics (Fig. 1C) was nonsignificant. Their cortisol levels on the stress day did not vary significantly across periods, and the contrasts between pre- versus postspeech samples and rest versus stress day postspeech samples were similarly nonsignificant.

Alcohol and Stimulant Dependents. These same tests on the results for the ADSD group were all nonsignificant (Fig. 1D), and the cortisol response to the speech stressor was numerically smaller than in the AD group. Because the ADSD group had elevated cortisol levels relative to the other groups, we examined the relationship between levels and stress reactivity for the data set as a whole. The Pearson correlation between the mean value across the rest day and the change from pre- to poststress on the stress day was nonsignificant ($r = 0.159$, $p > 0.40$), which indicated that the elevated levels for the ADSD group were not responsible for their stress hyporeactivity.

Moderator Variables in Relation to Cortisol Response

Blood Glucose Values. As expected, glucose levels (not shown) were all in the normal range, and they rose in all groups after the morning milkshake [$F(4,17) = 26.40$, $p < 0.0001$], which suggested that the patients' cortisol hyporesponsiveness was not a consequence of abnormal glucose levels or metabolism.

Smoking and Caffeine Intake. The AD and ADSD subjects reported substantially more cigarette use and caffeine intake than CT subjects, who reported little of either behavior (Table 1). To assess potential influences of nicotine and caffeine use on cortisol responses of the patients, we formed a combined AD+ADSD group from all 20 patients and compared those patients with low versus high cigarette and caffeine intake in cortisol response to stress. Using 10 cigarettes per day as a natural break point between lighter versus heavier consumption, we found that seven AD+ADSD subjects were low in nicotine intake (6.4 ± 1.6 cigarettes per day, range = 0.5–10) with the other 13 considered higher in intake (24 ± 2.8 cigarettes per day, range = 15–50). Student's t test revealed no nicotine group difference in cortisol change from baseline ($t = 0.158$, $p = 0.88$). Pearson correlations for all 20 AD+ADSD subjects on baseline cortisol, poststress cortisol, and cortisol change in relation to cigarettes per day were also nonsignificant (rs = −0.129, −0.214, and −0.209, respectively, ps > 0.36). Analyses using total lifetime nicotine exposure estimated by pack years of intake (cigarettes per day/20 × years of smoking) were similarly nonsignificantly related to cortisol levels or responses.

When we divided patients into light versus heavy caffeine intake at a natural break point of three cups per day (approximately 300 mg/day), we found that seven patients had relatively lower intake (98 ± 42 mg/day, equivalent to one to two cups of coffee per day, range = 0–280) and 13 had relatively higher intake (1256 ± 317 mg/day, equivalent to 12–15 cups per day, range = 440-4500). High caffeine intake led to a marginally smaller cortisol response ($t = -1.87$, $p = 0.084$). Pearson correlations across the 20 AD+ADSD patients for baseline, poststress, and change in cortisol were in the direction of higher levels and smaller responses among heavy users of caffeine (rs = 0.37, 0.12, and −0.21, respectively, ps = 0.045, 0.536, and 0.263).

Depression, PTSD, and Demographic Variables. Depression and PTSD scores and demographic characteristics were examined for their relationship to cortisol levels. There was an inverse relationship between years of education and test day cortisol levels in controls (rs > −0.64, ps < 0.04), which perhaps suggested greater discomfort with the test situation in the less well educated subgroup. No other correlation achieved significance (all rs < 0.25, NS), which suggested that the cortisol values were not systematically affected by the key psychiatric variables, depression and PTSD. Subjects reported greater levels of POMS tension/anxiety in response to the speech stressor, as indicated by a significant day × period interaction [$F(3,25) = 4.71$, $p < 0.01$], with nonsignificant interactions involving the groups variable. However, the ADSD group reported globally more negative affect (tension/anxiety, anger/hostility, depression/dejection) on both days than the other groups [groups main effects Fs (2,27) > 5.10, ps < 0.01].

DISCUSSION

The present findings suggest three points of interest: (1) The rest day data indicate that diurnal cortisol regulation in the patient groups did not differ from normal for the hours 7:00 AM to 9:30 PM; (2) the patient groups had blunted cortisol responses to the stress of public speaking relative to controls; and (3) these blunted responses of the patient groups apparently were not secondary to altered glucose regulation, clinical depression, PTSD, or demographic or anthropometric characteristics. The altered cortisol responsiveness in the patient groups may reflect changes due to excessive drinking and other drug abuse, or it may reflect preexisting differences in brain regions responsible for forming the psychological stress response.

Regulation of Cortisol Secretion

Cortisol has dual modes of regulation. Its diurnal pattern shows a morning peak and a nighttime nadir. The pattern results from activation of the paraventricular nucleus of the hypothalamus and negative feedback of peripheral cortisol to the pituitary, hypothalamus, and hippocampus (Jacobson and Sapolsky, 1991; Kovacs et al., 1987; Munck et al., 1984; Van Cauter, 1989). Acute stress elevates cortisol secretion relative to the diurnal curve. In this case, the paraventricular nucleus receives added stimulation by CRF-containing neurons from the basal forebrain and amygdala (Petrusz and Merchenthaler, 1992). A cortisol response can be produced by stimulation of the amygdala

(Allen and Allen, 1974; Gallagher et al. 1987), and stress activation of cortisol is blocked by amygdaloid lesions (Blanchard and Blanchard, 1972). The amygdala, and apparently its outputs to the hypothalamus, are particularly responsive to novelty, fear, or threat (Breiter et al. 1996; Lovallo, 1997; McEwen and Sapolsky, 1995). For example, noninvasive imaging reveals increased activity in the region of the amygdala during presentation of fearful faces (Breiter et al., 1996). Exposure to novelty or fear-producing situations can also lead to a stress cortisol response (al'Absi et al., 1997; Lovallo et al., 1990).

We chose public speaking as a stressor because it is widely experienced as threatening and anxiety provoking, and it robustly elevates cortisol secretion (al'Absi et al., 1997). Psychological stressors, such as public speaking, are effective because they are perceived as threats to well-being (Allen and Allen, 1974; Lovallo et al., 1990). The rise in cortisol to psychologically distressing manipulations requires intact relationships among cortex, basal forebrain, amygdala, and hypothalamus. By extension, disruptions in basal forebrain systems would result in a dissociation between otherwise distressing events and amygdaloid stimulation of the cortisol response.

Cortisol Secretion in Alcoholism

Alcohol increases cortisol secretion acutely (Rivier et al., 1984), and chronic abuse leads to long-term cortisol elevations, although some tolerance occurs (Rivier, 1996; Spencer and McEwen, 1990). The present study suggests that the unperturbed secretion of cortisol on the rest day was normal in our patients, similar to the control pattern. Other studies also suggest that alcoholics' basal secretion pattern is normal starting at 1 week of abstinence (Adinoff et al., 1990, 1991). The occurrence of a normal diurnal pattern suggests that the HPA in recovering alcoholics is normally regulated by the primary diurnal cues and negative feedback.

However, CRF challenge studies suggest a longer term and more subtle alteration of HPA function in alcoholics. Systemic CRF administration leads to stress CRF concentrations in the cerebrospinal fluid of the ventricles, which elevates secretion of ACTH and cortisol (Chrousos et al. 1984; Rivier and Vale, 1985). Recovering alcoholics have a blunted ACTH and cortisol response to exogenous CRF (Adinoff et al., 1990; Bardeleben et al., 1989) that persists for up to 6 months of abstinence (Adinoff et al., 1990) and suggests a long-term deficit in the HPA response to stress levels of CRF (Krystal et al., 1996). Because the system of CRF-containing neurons partly involves structures above the hypothalamus, the hyporesponsiveness of the HPA to CRF challenge in alcoholics could be due to a defect at some level from the forebrain and amygdala down to the pituitary and adrenal cortex.

In the present data, the intact diurnal cortisol curve of the patients suggests normal regulation of the hypothalamus, pituitary, and adrenal cortex. In contrast, the lack of response to the psychological stressor is compatible with a defect above the hypothalamus. The public speaking stressor used here was chosen because it reliably activates the HPA in controls (al'Absi et al., 1997; Buchanan et al., 1999). The hyporesponsiveness of the AD and ADSD groups to public speaking may involve altered activity of these higher structures.

Such evidence raises two possibilities about the nature of this alteration in alcoholics. First, the hyporesponsiveness of the AD and ADSD groups could be secondary to prolonged abuse, with the consequent long-term alteration of central dopaminergic systems (Koob and Bloom, 1988; Koob and Moal, 1997). Second, the stress hyporesponsiveness could reflect a preexisting alteration in forebrain and limbic functions related to processing of stressful and emotionally relevant stimuli (Robledo and Koob, 1993).

In the present sample, the ADSD group had the lowest HPA responsiveness. They consumed somewhat more alcohol than the AD group as well as stimulants. Therefore, their substantial hyporeactivity to the psychological stress of public speaking may have derived from greater drug-induced alteration of the relevant forebrain and limbic structures or to a more severe pattern of preexisting, perhaps etiological, alterations in these areas. It is noteworthy that the cortisol response to CRF challenge has been shown to be blunted in nonabusing young adults with a family history of alcoholism (Waltman et al., 1994).

Further Considerations

The present study was intended to examine cortisol reactivity in alcoholics while providing for more thorough information about basal cortisol activity during a resting control day and in response to an acute stressor. The presence of a normal diurnal pattern over the hours of observation lends confidence to the presence of intact HPA regulation at the level of the hypothalamus and pituitary. The patient groups' reduced response to a psychologically meaningful challenge to the HPA suggests that either the patients did not formulate a typical appraisal of the task as stressful or a perception of threat was not translated into appropriate descending activity that would activate HPA function via the hypothalamus.

The potential for a reduced communication of stress-related activation to the hypothalamus must be weighed against the relatively limited observations that have been made to date. Further studies of this sort with recovering patients should include measures of ACTH along with cortisol to assess pituitary response to the stressors in question. In addition, similar assessments are needed after longer periods of abstinence, preferably 6 months to 1 year, to help separate long-term recovery from persistent deficits. Further research should concentrate on whether the stress hyporesponsiveness in alcoholics and polysubstance

abusers is secondary to toxicity to relevant brain systems or reflects a preexisting alteration.

Of relevance to the question of a preexisting difference in cortisol reactivity are studies of preadolescent boys with substance-abusing fathers (Moss et al., 1995, 1999). Relative to family history-negative controls, these boys lacked a cortisol response in anticipation of an impending stressful procedure (Moss et al., 1995, 1999). Regardless of family history, boys who lacked a stress response were more likely than responders to smoke or use marijuana regularly at age 15. The authors concluded that a stress cortisol hyporeactivity may be "salient to the intergenerational transmission of substance abuse liability" (Moss et al., 1999). It is apparent that a blunted cortisol response to psychological stress may occur in the absence of prior substance abuse and that such blunting may predict future substance use.

The AD and ADSD groups differed from CT subjects in smoking and caffeine intake. Smokers also are less cortisol reactive than are nonsmokers to public speaking and mental arithmetic stress but not to exercise or corticotropin-releasing factor challenges (Kirschbaum et al., 1993). Our 20 combined AD+ADSD patients did not appear to show significant cortisol response variations across a wide range of nicotine intake. Similarly, habitual caffeine intake showed at best a modest relationship with cortisol responses to stress. Because of the small sample size in this study, the power is limited to detect relationships between potential confounders and cortisol stress hyporeactivity. Future studies should examine larger samples to rule out potential sources of bias.

Saliva as a specimen source for cortisol is reliable and valid compared with blood (Kirschbaum et al., 1989). Saliva free cortisol correlates particularly well with the unbound fraction in blood (Aardal and Holm, 1995; Riad-Fahmy et al., 1982). Unbound cortisol passes rapidly from the bloodstream through the parotid glands via passive intracellular diffusion, reaching equilibrium with blood levels of free cortisol within 5 min (Aardal and Holm, 1995), and its concentration is not influenced by saliva flow rate (Aardal and Holm, 1995; Riad-Fahmy et al. 1982). Its ease of collection makes it useful in behavioral studies, and it provides information about the unbound, biologically active fraction.

SUMMARY

The present study indicates that patients in treatment for alcohol dependence and alcohol and stimulant dependence have normal diurnal secretion of cortisol during the daytime to evening hours, but that their response to an acute psychological stressor is blunted-to-absent relative to community controls. This lack of response to a psychological stressor suggests a potentially important abnormality in the responsiveness of the HPA to psychologically relevant events. Relatively little is known about the potential recovery of this function with prolonged abstinence, and further study is needed to determine its likelihood. It is possible that cortisol stress hyporesponsiveness may be an important characteristic of persons prone to alcohol dependence.

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