ALCOHOLISM CLINICAL & EXPERIMENTAL RESEARCH

Physiological and Endocrine Reactions to Psychosocial Stress in Alcohol Use Disorders: Duration of Abstinence Matters

Katrin Starcke, Ruth J. van Holst, Wim van den Brink, Dick J. Veltman, and Anna E. Goudriaan

Background: Recent research findings suggest that heavy alcohol use is associated with alterations of the hypothalamic–pituitary–adrenal axis and autonomic nervous system function and that early abstinence is associated with blunted stress responsiveness.

Methods: This study investigated abstinent alcohol-dependent participants (AADs; $n = 31$), who had a drinking history of levels about 97 drinks per week (abstinence range: 2 weeks to 24 months), actively drinking problem drinkers (PRDs; $n = 23$), who reported drinking levels about 47 drinks per week and who were abstinent for at least 24 hours, and healthy control (HC) participants ($n = 20$). It was investigated how participants responded to a psychosocial stress task. All of them were exposed to a modified Trier Social Stress Test. Salivary cortisol, heart rate, skin conductance levels, and negative affect were assessed as stress indicators.

Results: AADs showed stress reactions comparable to HC participants, whereas active PRDs showed increased heart rate and cortisol stress responses. In the AAD group, duration of abstinence was positively related to cortisol stress responses.

Conclusions: Active PRDs showed increased responses to psychosocial stress. Results indicate that duration of abstinence is a key factor when analyzing and interpreting stress responses in alcohol abuse and dependence.

Key Words: Alcohol Dependence, Problem Drinking, Stress, Cortisol, Heart Rate.

ALCOHOL ABUSE AND alcohol dependence (alcohol use disorders [AUDs]) are associated with a strong increase in morbidity and mortality in developed countries (Rehm et al., 2009) and are characterized by high rates of relapse after initial abstinence (73 to 82%; see Lowman et al., 1996). Recent studies suggest that (abnormal) stress reactivity is an important contributing factor to the onset of heavy drinking and the development of AUDs (reviews in Koob, 2008; Sinha, 2001; Uhart and Wand, 2009). Conversely, heavy alcohol use and AUDs appear to affect the regulation of the stress systems: alcohol use stimulates the hypothalamic–pituitary–adrenal (HPA) axis resulting in elevated baseline cortisol levels in actively drinking participants (e.g., Boschloo et al., 2011; Gianoulakis et al., 2003) and a blunted cortisol awakening response in the early stage of abstinence (Junghanns et al., 2003). Markers of the sympathoadrenal system, such as heart rate, have also been shown to be elevated in actively heavy drinking persons (Boschloo et al., 2011).

In addition to these baseline differences in the physiological stress systems between (heavy) drinking and nondrinking samples, studies have investigated acute stress reactions in response to laboratory stressors in alcohol-dependent subjects. Several studies in abstinent alcohol-dependent patients (AADs) have shown a blunted cortisol response to acute laboratory stressors (Bernardy et al., 1996; Ehrenreich et al., 1997; Fox et al., 2007, 2012; Junghanns et al., 2003; Lovallo et al., 2000; Sinha et al., 2009, 2011). A blunted stress response has also been reported for other markers of the HPA axis, such as adrenocorticotropic hormone (Adinoff et al., 1990; Brady et al., 2006). Stress indices other than those of the HPA axis, namely those of the sympathoadrenal system, such as heart rate or blood pressure, were mostly found to be in the normal range (e.g., Junghanns et al., 2003), although Sinha and colleagues (2009) reported that AADs had a higher baseline heart rate compared to healthy controls (HCs). Furthermore, prospective studies have shown that laboratory stress reactions may predict relapse. Junghanns and colleagues (2003) found that a blunted cortisol response in reaction to a psychosocial stressor was associated with early relapse. Higley and colleagues (2011)

From the Department of Psychiatry (KS, RJH, WB, DJV, AEG), Amsterdam Institute for Addiction Research, Academic Medical Center University of Amsterdam, Amsterdam, the Netherlands; Department of General Psychology: Cognition (KS), University of Duisburg-Essen, Duisburg, Germany; Department of Psychiatry (DJV), VU University Medical Center, Amsterdam, the Netherlands; and Arkin Mental Health Institute (AEG), Amsterdam, the Netherlands.

Received for publication July 23, 2012; accepted January 5, 2013.

Reprint requests: Katrin Starcke, PhD, Department of General Psychology: Cognition, University of Duisburg-Essen, Forsthausweg 2, 47057 Duisburg, Germany; Tel.: +49 203 3792251; Fax: +49 203 3791846; E-mail: katrin.starcke@uni-due.de

DOI: 10.1111/acer.12103

similarly found that a low cortisol response toward a psychosocial stressor was associated with high craving reactions and that high craving reactions were associated with a shorter time to relapse.

Finally, studies in actively drinking subjects have investigated whether acute stress induction affects subsequent drinking behavior in the laboratory. Stress induction has been reported to increase the amount of drinking in the laboratory independent of individual stress reactions (Miller et al., 1974; Thomas et al., 2011). Another study found that a blunted cortisol response to the stressor was associated with the amount of alcohol that was consumed in the laboratory (Pratt and Davidson, 2009).

In summary, there is evidence that active drinking is associated with increased baseline activity of the stress systems and that AADs show blunted HPA axis responses to laboratory stress, and both are associated with craving and relapse. Thus, heavy drinkers and AADs may differ in baseline levels of the physiological and endocrine stress system and in stress reactivity in response to psychosocial stressors, suggesting a role for abstinence duration. Studies addressing the question whether HPA axis reactivity in alcohol-dependent participants is related to abstinence duration have used *physiological* challenges, such as the corticotropin-releasing hormone test (Adinoff et al., 1990; Ehrenreich et al., 1997), physical exercise (Coiro et al., 2007), or a multifaceted stress test including cold stress, noise, and arithmetic (Ehrenreich et al., 1997). Results of these studies demonstrated that at short durations of abstinence (1 to 8 weeks) stress responses are blunted, but that these responses normalize with the duration of abstinence.

This study aims to add to this literature by investigating physiological and endocrine reactions to a *psychosocial* stressor in 3 groups of participants: nontreatment-seeking heavy drinkers (PRDs), AADs, and HCs. We hypothesize that AADs will show stress reactions similar to HCs, because reactions to physiological challenge normalize with the duration of abstinence (Adinoff et al., 1990; Coiro et al., 2007). In contrast, sober but actively drinking heavy drinkers will demonstrate abnormal stress reactions, that is, increased cortisol responses and probably increased heart rate responses. Furthermore, we expect a positive association between cortisol responses and duration of abstinence, and a negative association between cortisol responses and relapse in the group of AADs. For exploratory reasons, we also measured skin conductance level (SCL) as a further indicator of sympathoadrenal stress response and affective reactions toward the psychosocial stress test.

MATERIALS AND METHODS

Participants

Seventy-four men, aged 21 to 61 years, participated in the study. Of these, 31 were AADs, 23 were PRDs, and 20 were HC. AADs were recruited from Dutch addiction treatment centers, whereas PRDs and the HCs were recruited through advertisements in local newspapers. The study was approved by the ethical review board of the Academic Medical Centre, and all participants gave written informed consent.

AADs were diagnosed according to DSM-IV alcohol dependence criteria with section J of the Dutch version of the Clinical International Diagnostic Inventory (CIDI; World-Health-Organization, 1997). To ensure that all participants were detoxified from alcohol, AADs had to be abstinent for at least 2 weeks to be included in the study, which was verified by treatment status and self-report. In addition, recent alcohol use was excluded by screening for alcohol with a urine test. A measure of severity of alcohol-related problems was obtained by administering the Alcohol Use Disorder Identification Test (AUDIT; Bush et al., 1998). This test was also administered in the PRD group and in the HC group. For the PRD group, only PRDs who scored higher than 8 on the AUDIT and who were not in treatment or looking for treatment were included in the study. Participants of the PRD group did not meet alcohol dependence according to DSM-IV criteria, but 10 of them fulfilled some criteria (0 to 2) for alcohol dependence and 16 of them fulfilled criteria for last year alcohol abuse, with 9 of them fulfilling these criteria in the last month, and 7 fulfilling criteria with a recency of 1 month to 1 year. None of the participants in the PRD group met criteria for alcohol withdrawal, based on the CIDI interview.

Participants of the PRD group had to be abstinent for 24 hours prior to the study which was confirmed by a breathing test and a urine test. Urine was analyzed for all participants at a clinical toxicology laboratory (ATAL Medical Diagnostics, Amsterdam, The Netherlands), in mg/ml. None of the tests were found to be positive. All participants were asked how many days per week they drank in nonabstinent phases and how many drinks they drank per drinking day to estimate number of drinks they consumed per week.

Exclusion criteria for all groups were as follows: lifetime diagnosis of schizophrenia or psychotic episodes; 12-month diagnosis of manic disorder (CIDI, section F); obsessive compulsive disorder (CIDI, section E); posttraumatic stress disorder (CIDI, section K); and other substance use disorders than alcohol except for nicotine (CIDI, section L). Smoking was coded as either "yes" or "no"; treatment for mental disorders other than alcohol in the past 12 months; use of psychotropic medication; difficulty reading Dutch; age under 18 years; IQ below 80 (measured by the Dutch Adult Reading Test; Schmand et al., 1991); positive urine screen for amphetamines, benzodiazepines, opioids, or cocaine; and history or current treatment for major internal disorders, neurological disorders, brain trauma, or exposure to neurotoxic factors.

Stress Induction

A modified Trier Social Stress Test (TSST; Kirschbaum et al., 1993) was used as psychosocial stressor. In the TSST, participants have to perform 2 tasks in front of a selection committee and a video camera. The committee consists of 3 experimenters introduced as being trained in "behavioral observation." Participants are told that their performance is recorded on video to later analyze voice pitch and nonverbal behavior. Participants have a preparation time of 10 minutes. After that, they have to deliver a speech without using notes for 5 minutes. During the speech, participants have to convince the committee that he or she is the perfect applicant for a vacant position. Then the participant has to serially subtract the number 13 from 1022 as fast and accurately as possible within 5 minutes. On every failure, the committee asks the participant to start again at 1022. The committee does not provide any further feedback but acts in a very cold and reserved manner. The TSST has been shown to lead to a robust increase in cortisol through the activation of the HPA axis (for reviews, see Dickerson and Kemeny, 2004; Kirschbaum and Hellhammer, 1994) and also through activation of the sympathoadrenal system (e.g., Het et al., 2009; Kirschbaum et al., 1993). Two modifications of the standard TSST were made in this study: the committee (1 person) was placed behind a

1-way screen, and the arithmetic task was simplified (subjects were asked to make subtractions of 7 from 1029, and in case no errors were made during the first 5 subtractions, a switch was made to subtractions of 13). The latter modification was needed because subtractions of 13 were too difficult and resulted in participants not performing any subtractions in a pilot study.

Measurements of Stress Response

Endocrine, physiological, and subjective measures were obtained as indicators of stress reactivity. Cortisol levels were assessed using Salivette collection devices (Sarstedt, Nümbrecht, Germany) at 6 time points: twice before the stressor, twice during the stressor, and twice after cessation of the stressor (see Table 1). Participants had to chew on each salivette for 1 minute. Saliva samples were sent to the laboratory of the University of Dresden (Germany; laboratory of prof. Kirschbaum) to determine cortisol levels. Free cortisol levels were measured using a commercial chemiluminescence immunoassay (IBL International, Hamburg, Germany).

Heart rate and SCL were recorded continuously and are reported for 2-minute periods: (i) during baseline (ii) during the stress test, and (iii) during the poststress period (see Table 1 for timing of these periods within the procedure). The Vrije Universiteit Ambulatory Monitoring System-5 fs was used to measure heart rate and SCL (Klaver et al., 1994).

Heart rate was measured via 2 active electrodes and 1 ground electrode. Ag/AgCl electrodes were used (10 mm; Ultratrace ConMed Electrodes, Utica, NY). One active electrode was placed at the jugular notch of the sternum, between the collar bones. The other active electrode was placed below the left breast, 4 cm beneath the nipple. The ground electrode was placed at the right side of the chest, between the lower 2 ribs. The signal was led into a differential amplifier, with an input impedance higher than 1 M Ω. The amplified signal was passed through a band-pass filter at 17 Hz, and the filtered signal was used for *R*-peak triggering. At each *R*-peak, a millisecond counter was read and reset, yielding interbeat interval series. The interbeat intervals were transformed into heart rate in beats per minute (bpm).

SCLs was recorded through 1-cm^2 AgAg/Cl electrodes attached with Velcro straps to the medial phalanx surfaces of the middle and index fingers of the nondominant hand. A 0.5 V constant voltage procedure was used with a sample rate of 100 ms. Electrolyte gel (0.05 M NaCl) was applied to the 2 electrodes (Fowles et al., 1981).

At the same time points of cortisol assessment and at 1 additional time point directly after the debriefing, participants filled out the von Zerssen Scale (1986) measuring current negative affect (NA). The scale was used to obtain a subjective indicator of affective changes during the stress test. Participants had to mark on a 3-point scale how they currently felt on a list of 9 positive and NA labels, such as "good," "bad," or "none of those." The positive affect label was scored as "0," the indecisive label was scored as "1," and the NA label was scored as "2." Thus, total scores could range from 0 to 18 with high values representing high negative effect.

Measurement of Abstinence Self-Efficacy

Abstinence self-efficacy was measured with the alcohol abstinence self-efficacy scale (AASES; DiClemente et al., 1994). The scale measures the temptation to drink in 20 high-risk situations and contains 20 items. Each item has to be answered on a 5-point Likert scale that ranges from 1 ("not at all") to 5 ("very much"). Thus, a total score of 20 represents very low temptation to drink, and a total score of 100 represents the maximum temptation to drink.

Measurement of Duration of Abstinence and Relapse

The duration of abstinence was assessed in the AAD group prior to the experiment. The CIDI was used to determine the duration of abstinence in which a score of "1" represented 2 weeks, "2" represented 3 to 4 weeks, "3" represented 1 to 6 months, "4" represented 6 to 12 months, "5" represented 12 to 24 months, and "6" represented more than 24 months of abstinence. To determine whether patients relapsed after participation in the study, they were contacted by telephone 4 and 8 months after the study. Relapse was coded as either "yes" or "no," according to any self-reported drinking. Additionally, AUDIT data were collected again during the telephonic follow-up 8 months after research participation.

Procedure

The diagnostic procedures, briefing, and obtaining written informed consent took place on a separate day. On the testing day, the electrodes for measuring heart rate and SCL were attached first. Then, participants filled out questionnaires prior to the modified TSST. These initial procedures took approximately 90 minutes. The timeline of the modified TSST is shown in Table 1. All testing sessions took place between 1 and 4 PM to ensure that there were no large variations in cortisol secretion due to circadian rhythm (Kudielka et al., 2004).

Statistical Analysis

All analyses were carried out with SPSS 20.0 (IBM Corporation, New York, NY). Analyses of variance (ANOVAs) were used to analyze between-group differences in age, intelligence, AASES scores, AUDIT scores, and level of drinking. Smoking status was compared between groups with Pearson's chi-square test. ANOVAs with repeated measurements were used to compare stress reactions with "group" as the between factor and "time" as the within factor. Greenhouse-Geisser-corrected *p*-values were used when appropriate. Partial eta-squared (η_p^2) was used as a measure of effect size. The relationship between individual stress responses with relapse and smoking status was calculated with point–biserial correlations; the relationship between individual stress responses and duration of abstinence was calculated with Spearman's correlation; the relationship between individual stress responses, AUDIT scores, and level of

Table 1. Procedure of the Modified Trier Social Stress Test

	Baseline 2 minutes	Preparation 10 minutes	Talking 5 minutes	Math test 5 minutes	Poststress 2 minutes	Debriefing
−20 minutes S 1 NA	−1 minutes S 2 NA	+10 minutes S 3 NA		+20 minutes S 4 NA		+40 minutes S 5 + 60 minutes S 6 NA

S, saliva sample; NA, measurement of negative effect.

Minutes relative to the beginning of the stress induction, that is, minute 0 represents the starting point. The stress induction period is highlighted in gray. Heart rate and skin conductance level were recorded continuously and analyzed from baseline to poststress period for the minutes displayed.

drinking was calculated with Pearson correlation. Two-tailed tests were performed for all analyses, and p was set at 0.05.

RESULTS

Sample Characteristics

As shown in Table 2, groups did not differ in age or intelligence. As expected, groups differed on AUDIT scores, with Scheffé's post hoc tests revealing that all 3 groups differed significantly from each other (all ps < 0.001) with scores of the PRD group falling in between AAD and HC scores. Groups also differed in the reported temptation to drink, which was significantly higher in the AAD and the PRD groups compared to the HC group (ps < 0.001), whereas the AAD and PRD groups did not differ from each other ($p = 0.83$). Groups differed in their reported number of drinks per week (ps < 0.05), with the PRD group falling in between the AAD and HC groups. From the reported drinking habits (2 to 5 active drinking days per week), it can be concluded that members of the PRD group had their last drink(s) between 24 hours and 5 days prior to the study. Smoking status also differed between groups; 5.9% of the HC group, 34.8% of the PRD group, and 77.4% of the AAD group reported smoking, $\chi^2(2) = 24.46$, $p < 0.001$.

The AAD group had a median abstinence score of "3" which represents 1 to 6 months of abstinence. Abstinence ranged from 2 weeks to more than 2 years (2 weeks: $n = 4$; 3 to 4 weeks: $n = 8$; 1 to 6 months: $n = 12$; 6 to 12 months: $n = 5$; 12 to 24 months: $n = 0$; more than 24 months: $n = 1$). Eight of the 30 AAD patients who were reached for follow-up remained completely abstinent after 8 months. Those AAD patients who remained abstinent after 8 months had significantly lower AUDIT scores ($M = 0.0$, SD = 0.0) compared to those who relapsed after 8 months ($M = 13.9$, SD = 8.75), $t(28) = 4.98$, $p < 0.001$.

Stress Reactivity

Repeated measures ANOVAs revealed that the stress induction procedure using the modified TSST resulted in significant ($p < 0.001$) increases in cortisol, heart rate, SCL, and negative effect in all groups. Results furthermore indicated that groups did not differ before the start of the modified TSST on any of the psychophysiological and subjective measures, but that there was an interaction between group and stress reactivity for cortisol and heart rate, which remained significant after Bonferroni–Holm correction (see Table 3; for means and standard errors see Fig. 1*A,B*). Additionally, the participants of the PRD group showed a higher peak cortisol secretion than those participants in the HC group, $t(31.11) = 2.69$, $p < 0.01$, and than those participants in the AAD group, $t(50) = 2.16$, $p < 0.05$, while the peak heart rate did not differ significantly between groups (all ps > 0.05). No interactions between group and stress reactivity were found for SCL. For negative effect, a trend was present for the interaction between group and stress reactivity, with a higher peak NA in the AAD group compared to the HC group, $t(47.99) = -3.99$, $p < 0.001$ (for means and standard errors, see Fig. 1*C,D*).

Relationship Between the Individual Stress Response, Smoking Status and Drinking-Related Variables

We subtracted the scores of baseline measures (before stress induction) from the peak stress response (maximum cortisol, heart rate, SCL, or NA level) to obtain an indicator of individual stress response. With these scores, correlations were performed with smoking status and drinking-related variables within each group.

Smoking status was unrelated to individual stress responses with 1 exception: In the PRD group, cortisol increase and smoking status were negatively related ($r = -0.50$, $p < 0.05$) indicating that smoking was associated with lower cortisol increases in this group. Drinking-related problems as measured by the AUDIT were negatively related to heart rate increases in the AAD group ($r = -0.42$, $p < 0.05$). The estimated number of drinks per week was related to heart rate increase in the HC group ($r = 0.47$, $p < 0.05$) and to SCL increase in the PRD group ($r = 0.51$, $p < 0.05$).

In the AAD group, correlations between individual stress responses and the duration of abstinence at testing and relapse status 8 months after research participation were additionally performed. Time of abstinence was clearly related to cortisol responses during the TSST ($\rho = 0.51$, $p < 0.01$), indicating that longer duration of abstinence was

Table 2. Demographical Data

	HC mean (SD)	PRD mean (SD)	AAD mean (SD)	*F*	df	*p*
N	20	23	31			
Age	39.40 (10.88)	42.13 (13.71)	44.39 (8.79)	1.24	2, 71	0.30
IQ	106.20 (15.89)	106.65 (14.28)	104.37 (16.54)	0.16	2, 70	0.85
AUDIT	5.41 (4.54)	18.52 (5.32)	26.33 (7.14)	65.53	2, 67	<0.001
AASES	40.90 (14.85)	64.41 (13.85)	62.00 (13.89)	17.91	2, 70	<0.001
Drinks per week[a]	7.31 (7.19)	46.67 (31.51)	96.71 (61.21)	24.13	2, 64	<0.001

HC, healthy controls; AAD, abstinent alcohol dependents; PRD, problem drinkers; AUDIT, Alcohol Use Disorders Identification Test; AASES, alcohol abstinence self-efficacy scale.

[a]In nonabstinent phase.

Table 3. Results of the Repeated Measures ANOVAs for the Stress Reactivity Measures

Stress indicator	*F*	df	MSE	*p*	η_p^2
Cortisol: time	27.49	1.73, 110.44	63.93	<0.001	0.30
Cortisol: group	1.98	2, 64	237.13	0.15	0.06
Cortisol: time × group	3.38	3.45, 110.44	63.93	<0.05	0.10
Heart rate: time	83.85	2.49, 159.65	90.11	<0.001	0.57
Heart rate: group	0.83	2, 64	910.55	0.44	0.03
Heart rate: time × group	2.34	4.99, 159.65	90.11	<0.05	0.07
SCL: point in time	33.45	2.39, 148.42	3.61	<0.001	0.35
SCL: group	0.23	2, 64	64.53	0.79	0.01
SCL: time × group	0.73	4.79, 148.42	3.61	0.60	0.02
NA: time	16.67	3.34, 190.12	13.66	<0.001	0.23
NA: group	3.07	2, 57	52.22	0.05	0.10
NA: time × group	1.82	6.67, 190.12	13.66	0.09	0.06

SCL, skin conductance level; NA, negative effect.
"Time" represents the within-subject factor, "group" represents the between-subjects factor.

associated with higher cortisol stress responses. However, individual cortisol reactions were not related to relapse after 8 months ($r = -0.18$, $p = 0.41$). Correlations between the other stress reactivity measures and duration of abstinence and relapse were nonsignificant. AUDIT scores that were collected again after 8 months were not related to any of the stress responses either.

DISCUSSION

This study investigated physiological and endocrine stress reactions to a psychosocial stressor in 3 groups of participants: AADs, sober active PRDs, and HCs. We expected that the AAD group would show stress reactions similar to the HCs, whereas the active PRDs would show abnormal stress reactions. Results confirmed the main hypothesis, that is, AADs showed similar stress reactions to healthy participants, whereas active PRDs showed increased heart rate and cortisol reactions toward the psychosocial stressor. As a necessary precondition for interpreting the results, the psychosocial stressor elicited robust stress reactions in all groups of participants as shown by robust increases in heart rate, cortisol secretion, electrodermal activity, and self-reported negative effect.

Although comparable stress reactions were present in alcohol-dependent participants and HCs, individual cortisol reactions in the AAD group were related to the duration of abstinence. The overall normal stress reactions in the AAD group may at least partly be explained by the long duration of abstinence, with a median CIDI score of "3" representing 1 to 6 months of abstinence. Therefore, the current results are consistent with studies indicating a normalization of stress responses to physiological stressors with duration of abstinence (Adinoff et al., 1990; Coiro et al., 2007; Ehrenreich et al., 1997). Studies that reported a blunted cortisol response to laboratory stressors have investigated AADs with a shorter duration of abstinence, such as 3 to 4 weeks in the study by Junghanns and colleagues (2003). Thus, the normal stress reactions in the current study and the positive relationship between duration of abstinence and stress reactions imply that with longer duration of abstinence a normaliza-

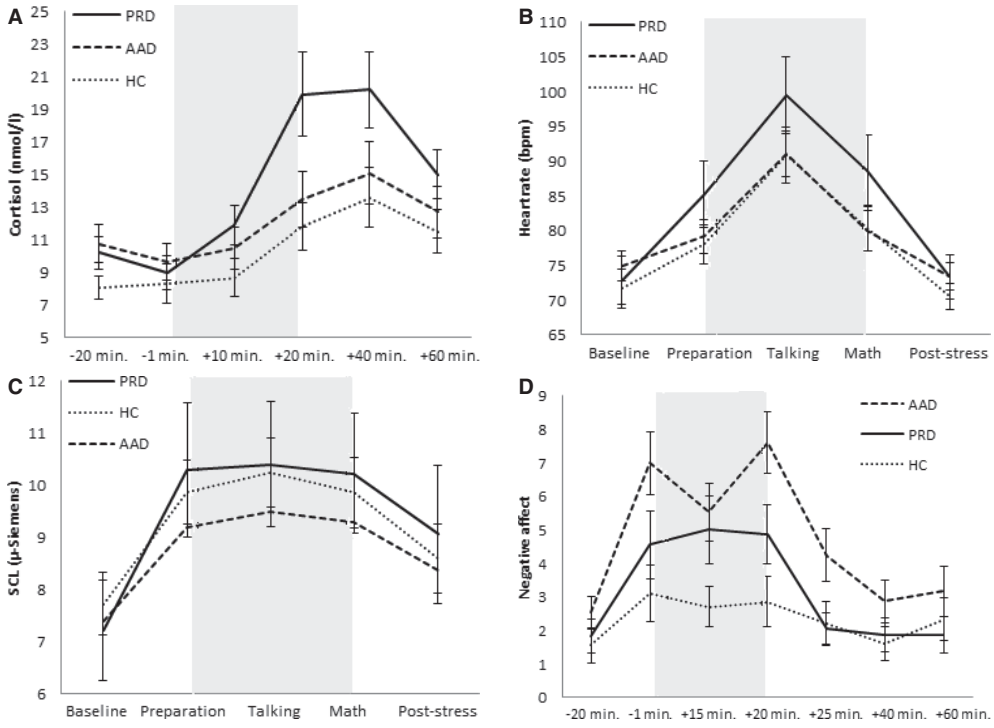

Fig. 1. (**A**–**D**) Stress levels at baseline, during stress induction, and after cessation of the stressor in the 3 groups. Error bars represent standard errors. The stress induction period is highlighted in gray. Minutes in Fig. 1*A,D* represent the time relative to the beginning of the stress induction. HC, healthy controls; AAD, abstinent alcohol dependents; PRD, problem drinkers; bpm, beats per minute; μ, micro; nmol, nanomole; l, liter.

tion of stress reactivity takes place. Results replicate findings from previous studies indicating normalization of responses to *physiological* stressors or combined *physiological* and *mental* stressors in alcohol dependence (Adinoff et al., 1990; Coiro et al., 2007; Ehrenreich et al., 1997), which can be generalized to pure *psychosocial* stressors now. Results are also in line with the finding that a blunted cortisol awakening response in the early stage of abstinence normalizes with duration of abstinence (Junghanns et al., 2007). Previous studies found a relationship between individual stress response and relapse (e.g., Higley et al., 2011; Junghanns et al., 2003), but this was not observed in the current study. Again, this may be explained by the relatively long abstinence duration in the AAD sample with most patients showing normalized stress responses. Furthermore, a follow-up 8 months after the study covers a very long time period in which many factors besides stress reactivity may influence return to drinking.

Results on psychosocial stress reactivity in the PRDs add new information to the existing literature. Problem drinkers showed baseline stress levels that were similar to those of HCs and AADs, but increased reactions to the psychosocial stress induction. The lack of baseline differences contradicts previous studies that found higher baseline cortisol in active heavy drinkers compared to nondrinkers and a higher heart rate in active heavy drinkers compared to moderate drinkers (Boschloo et al., 2011). However, the study by Boschloo and colleagues (2011) used the cortisol awakening response and evening cortisol levels as opposed to baseline cortisol samples that were taken between 1 and 4 PM in the current study. In the current study, the lack of baseline differences between actively drinking PRDs and HCs makes the interpretation of abnormal stress reactions in the active drinking group more straightforward: high baseline cortisol levels may result in blunted reactions to stressors due to ceiling effects, but this possibility can be ruled out in the current study. However, reasons for the high cortisol response in active heavy drinkers have to be elucidated. One possibility is that active drinking is associated with increased stress reactivity and that cessation of drinking is associated with an immediate blunted stress response due to the sudden changes in the stress reactivity systems (as reported in previous studies in AAD populations with a short abstinence duration of 1 to 4 weeks; Bernardy et al., 1996; Ehrenreich et al., 1997; Fox et al., 2007, 2012; Junghanns et al., 2003, 2007; Lovallo et al., 2000; Sinha et al., 2009, 2011). Thus, prolonged stimulation of the HPA axis during active drinking may result in a reduced stress tolerance that causes overactive stress reactions in acute stress situations. When alcohol use is suddenly stopped however, this may result in an acute—but temporary—blunted stress response due to a sudden drop in the chronic overstimulation of the HPA axis which was present during prolonged heavy drinking. In animal studies, it was also shown that rodents who were acutely exposed to alcohol displayed an increased corticosterone level, while rodents that were alcohol dependent but whose consumption was stopped showed a decreased corticosterone level (e.g., Richardson et al., 2008), which is consistent with our current findings of enhanced cortisol responses in the actively drinking PRDs versus the AADs. Whether the observed stress hyperreactivity in PRDs is a direct effect of recent alcohol intake or mainly associated with prolonged abuse cannot be concluded from the current data. The previously mentioned animal studies (Richardson et al., 2008) suggest that recent intake promotes cortisol hyperreactivity. However, in the current study, no relationship between the level of drinking and individual cortisol responses was present in the group of PRDs, probably because this group overall, drank considerably, and all PRDs drank recently. Although PRDs did not show abnormal increases in SCL (which was assessed for exploratory reasons), level of drinking was related to SCL increase indicating a potential relationship between sympathoadrenal stress responses and level of drinking. Another possibility is that heightened stress responses are associated with level of alcohol-related problems, but no relation between the AUDIT, a measure for alcohol-related problems, and stress responsivity was found within any of the groups.

This study has both strengths and limitations. An important strength of this study is that it compares 3 groups of participants on different endocrine and sympaticoadrenergic stress responses and therefore allows a simultaneous comparison between AADs and active PRDs on different indicators of stress response. The study also has some limitations. First, only male participants were included leaving the possibility that in female participants with AUDs, stress reactivity is differently affected, which should be examined in future studies. Second, the stress reactions are compared to a baseline phase, but not to a neutral stress condition, such as control groups that undergo the placebo version of the TSST (Het et al., 2009). Future studies should include such a nonstress control condition as well. Finally, for some of the variables, more sensitive or more fine-grained measurement instruments should have been used. Most importantly, a more precise assessment of alcohol-related parameters would clarify data interpretation. In the AAD group, there was a high variance in duration of abstinence, ranging from 2 weeks to 24 months. This variance allowed calculating relationships between duration of abstinence and stress reactivity. However, it is probably also responsible for differences in stress reactivity within the group, making the interpretation of group differences more difficult. Another limitation is that abstinence duration
was assessed for certain time ranges, for example, 6 to 12 months, which means that within a certain range patients differed in the duration of abstinence. Future studies should include exact duration of abstinence. This would also be an advantage for interpreting data of the PRD group: Data concerning the exact number of days since PRDs had their last drink could provide insight into whether the reported findings are a direct effect of recent alcohol intake or whether they are mainly associated with prolonged abuse. Further-

more, a more sensitive assessment of smoking status such as the Fagerström interview (Heatherton et al., 1991) would be helpful to investigate the association between the level of smoking and stress reactivity in AUDs. And a more sensitive measure of affective changes would be helpful to detect more fine-grained changes in negative effect. It would be interesting if a more sensitive measure could detect heightened affective stress responses despite normal endocrine and physiological responses in AADs.

This study provides evidence for increased physiological and endocrine stress reactivity to psychosocial stress in active PRDs. These findings indicate that both stress systems, the HPA axis and sympathoadrenal system, are hyperreactive to psychosocial stress in this group of active heavy alcohol users with alcohol-related problems, whereas this hyperreactivity disappears with prolonged abstinence. Recent literature and correlational data in this study suggest that early abstinence is associated with a blunted stress response and that a normalization takes place after prolonged abstinence. Taken together, these data suggest that cortisol response is not a trait but a state marker of alcohol effects on the regulation of the HPA axis. Based on the results of this study, it would be recommended to continue with stress control interventions in treatment for AUDs, until stress reactivity normalizes.

ACKNOWLEDGMENTS

We wish to thank Gerd Krönke for the help with the analysis of the skin conductance data and Prof. Dr. Clemens Kirschbaum for advice concerning the cortisol assessment and analysis. This study was funded by a New Investigator grant to AEG from the Dutch Scientific Organization (NWO ZonMw, #91676084, 2007–10).

REFERENCES

Adinoff B, Martin PR, Eckardt MJ, Roehrich L, George DT, Moss HB, Eskay R, Linnoila M, Gold PW (1990) Hypothalamic-pituitary-adrenal axis functioning and cerebrospinal fluid corticotropin releasing hormone and corticotropin levels in alcoholics after recent and long-term abstinence. Arch Gen Psychiatry 47:325–330.

Bernardy NC, King AC, Parsons OA, Lovallo WR (1996) Altered cortisol response in sober alcoholics: an examination of contributing factors. Alcohol 13:493–498.

Boschloo L, Vogelzangs N, Licht CMM, Vreeburg SA, Smit JH, Van den Brink W, Veltman DJ, De Geus EJC, Beekman ATF, Penninx BWJH (2011) Heavy alcohol use, rather than alcohol dependence, is associated with dysregulation of the hypothalamic-pituitary-adrenal axis and the autonomic nervous system. Drug Alcohol Depend 116:170–176.

Brady KT, Waldrop AE, McRae AL, Back SE, Saladin ME, Upadhyaya HP, Anton RF, Randall PK (2006) The impact of alcohol dependence and posttraumatic stress disorder on cold pressor task response. J Stud Alcohol 67:700–706.

Bush K, Kivlahan DR, McDonnel MB, Fihn SD, Bradley KA (1998) The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. Ambulatory Care Quality Improvement Project (ACQUIP). Alcohol Use Disorders Identification Test. Arch Intern Med 158:1789–1795.

Coiro V, Casti A, Jotti GS, Rubino P, Manfredi G, Maffei ML, Melani A, Volta E, Chiodera P (2007) Adrenocorticotropic hormone/cortisol response to physical exercise in abstinent alcoholic patients. Alcohol Clin Exp Res 31:901–906.

Dickerson SS, Kemeny ME (2004) Acute stressors and cortisol responses: a theoretical integration and synthesis of laboratory research. Psychol Bull 130:355–391.

DiClemente CC, Carbonari JP, Montgomery RP, Hughes SO (1994) The alcohol abstinence self-efficacy scale. J Stud Alcohol 55:141–148.

Ehrenreich H, Schuck J, Stender N, Pilz J, Gefeller O, Schilling L, Poser W, Kaw S (1997) Endocrine and hemodynamic effects of stress versus systemic CRF in alcoholics during early and medium term abstinence. Alcohol Clin Exp Res 21:1285–1293.

Fowles DC, Christie MJ, Edelberg R, Grings WW, Lykken DT, Venables PH (1981) Committee report. Publication recommendations for electrodermal measurements. Psychophysiology 18:232–239.

Fox HC, Anderson GM, Tuit K, Hansen J, Kimmerling A, Siedlarz KM, Morgan PT, Sinha R (2012) Prazosin effects on stress- and cue-induced craving and stress response in alcohol-dependent individuals: preliminary findings. Alcohol Clin Exp Res 36:351–360.

Fox HC, Bergquist KL, Hong KA, Sinha R (2007) Stress-induced and alcohol cue-induced craving in recently abstinent alcohol-dependent individuals. Alcohol Clin Exp Res 31:395–403.

Gianoulakis C, Dai X, Brown T (2003) Effect of chronic alcohol consumption on the activity of the hypothalamic-pituitary-adrenal axis and pituitary beta-endorphin as a function of alcohol intake, age, and gender. Alcohol Clin Exp Res 27:410–423.

Heatherton TF, Kozlowski LT, Frecker RC, Fagerström KO (1991) The Fagerström Test for Nicotine Dependence: a revision of the Fagerström Tolerance Questionnaire. Br J Addict 86:1119–1127.

Het S, Rohleder N, Schoofs D, Kirschbaum C, Wolf OT (2009) Neuroendocrine and psychometric evaluation of a placebo version of the 'Trier Social Stress Test.' Psychoneuroendocrinology 34:1075–1086.

Higley A, Crane NA, Spadoni AD, Quello SB, Goodell V, Mason BJ (2011) Craving in response to stress induction in a human laboratory paradigm predicts treatment outcome in alcohol-dependent individuals. Psychopharmacology 218:121–129.

Junghanns K, Backhaus J, Tietz U, Lange W, Bernzen J, Wetterling T, Rink L, Driessen M (2003) Impaired serum cortisol stress response is a predictor of early relapse. Alcohol Alcohol 38:189–193.

Junghanns K, Horbach R, Ehrenthal D, Blank S, Backhaus J (2007) Cortisol awakening response in abstinent alcohol-dependent patients as a marker of HPA-axis dysfunction. Psychoneuroendocrinology 32:1133–1137.

Kirschbaum C, Hellhammer DH (1994) Salivary cortisol in psychoneuroendocrine research: recent developments and applications. Psychoneuroendocrinology 19:313–333.

Kirschbaum C, Pirke KM, Hellhammer DH (1993) The 'Trier Social Stress Test'—a tool for investigating psychobiological stress responses in a laboratory setting. Neuropsychobiology 28:76–81.

Klaver CHAM, de Geus EJC, de Vries J (1994) Ambulatory Monitoring System. Swets and Zeitlinger, Lisse.

Koob GF (2008) A role for brain stress systems in addiction. Neuron 59: 11–34.

Kudielka BM, Schommer NC, Hellhammer DH, Kirschbaum C (2004) Acute HPA axis responses, heart rate, and mood changes to psychosocial stress (TSST) in humans at different times of day. Psychoneuroendocrinology 29:983–992.

Lovallo WR, Dickensheets SL, Myers DA, Thomas TL, Nixon SJ (2000) Blunted stress cortisol response in abstinent alcoholic and polysubstance-abusing men. Alcohol Clin Exp Res 24:651–658.

Lowman C, Allen J, Stout RL (1996) Replication and extension of Marlatt's taxonomy of relapse precipitants: overview of procedures and results. The Relapse Research Group. Addiction 91:S51–S71.

Miller PM, Hersen M, Eisler RM, Hilsman G (1974) Effects of social stress on operant drinking of alcoholics and social drinkers. Behav Res Ther 12:67–72.

Pratt WM, Davidson D (2009) Role of the HPA axis and the A118G polymorphism of the mu-opioid receptor in stress-induced drinking behavior. Alcohol Alcohol 44:358–365.

Rehm J, Mathers C, Popova S, Thavornacharoensap M, Teerawattananon Y, Patra J (2009) Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. Lancet 373:2223–2233.

Richardson HN, Lee SY, O'Dell LE, Koob GF, Rivier CL (2008) Alcohol self-administration acutely stimulates the hypothalamic-pituitary-adrenal axis, but alcohol dependence leads to a dampened neuroendocrine state. Eur J Neurosci 28:1641–1653.

Schmand B, Bakker D, Saan R, Loumann J (1991) The Dutch Reading Test for Adults: a measure of premorbid intelligence level. Tijdschr Gerontol Geriatr 22:15–19.

Sinha R (2001) How does stress increase risk of drug abuse and relapse? Psychopharmacology 58:343–359.

Sinha R, Fox H, Hong KA, Bergquist K, Bhagwagar Z, Siedlarz KM (2009) Enhanced negative emotion and alcohol craving, and altered physiological responses following stress and cue exposure in alcohol dependent individuals. Neuropsychopharmacology 34:1198–1208.

Sinha R, Fox H, Hong KA, Hansen J, Tuit K, Kreek MJ (2011) Effects of adrenal sensitivity, stress- and cue-induced craving, and anxietey on subsequent alcohol relapse and treatment outcomes. Arch Gen Psychiatry 68:942–952.

Thomas SE, Bacon AK, Randall PK, Brady KT, See RE (2011) An acute psychosocial stressor increases drinking in non-treatment-seeking alcoholics. Psychopharmacology 218:19–28.

Uhart M, Wand GS (2009) Stress, alcohol and drug interaction: an update of human research. Addict Biol 14:43–64.

World-Health-Organization (1997) Composite International Diagnosis Interview—Version 2.1. World-Health-Organization, Geneva.

von Zerssen D (1986) Clinical Self-Rating Scales (CSRS of the Munich Psychiatric Information System). Springer, Berlin.