Published in final edited form as:

Psychoneuroendocrinology. 2017 February ; 76: 67–76. doi:10.1016/j.psyneuen.2016.10.011.

Adrenocortical Sensitivity, Moderated by Ongoing Stress, Predicts Drinking Intensity in Alcohol-Dependent Men

Bryon Adinoff, MD^{1,2}, David Leonard, PhD³, Julianne Price, MS², Martin A. Javors, PhD⁴, Robrina Walker, PhD², E. Sherwood Brown, MD, PhD², Hong Xiao, MD⁵, and Uma Rao, MD⁶

¹VA North Texas Health Care System, Dallas, Texas

²Department of Psychiatry, UT Southwestern Medical Center, Dallas, Texas

³David Leonard Statistical Consulting, Wichita Falls, TX

⁴Department of Psychiatry, University of Texas Health Science Center, 7703 Floyd Curl Drive, San Antonio, TX 78229, USA

⁵Fairway Family Medicine, Carrollton, Texas

⁶Center for Behavioral Health Research, University of Tennessee, Knoxville, TN

⁷Department of Pediatrics and Vanderbilt Kennedy Center, Vanderbilt University Medical Center, Nashville, TN

Abstract

Allostatic load from both environmental stressors and persistent glucocorticoid secretion has been associated with disease severity in alcohol dependence. Heightened relapse risk and/or drinking severity, in particular, may be a reaction to alcohol- and withdrawal-induced changes in physiological stress response systems coupled with ongoing life stress, although their shared

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Corresponding Author: Bryon Adinoff, M.D., 5323 Harry Hines Blvd., Dallas, TX 75390-8564, Bryon.adinoff@utsouthwestern.edu, Phone: 214-645-6975 Fax: 214-645-6975.

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Contributions:

BA was the senior investigator for the study, including developed study design, obtained funding, provided oversight for recruitment, assessment, analysis, data interpretation and manuscript preparation. DL developed statistical approach, conducted all statistical analyses, and contributed to manuscript preparation. JP conducted literature search and wrote initial draft and assisted with subsequent edits. MAJ contributed to initial study design, conducted all bioassays, assisted with interpretation of findings, and contributed to manuscript preparation. RW was responsible for primary oversight of participant recruitment and assessment and contributed to manuscript preparation. ESB and UR assisted in study design, data interpretation and manuscript preparation. HX assisted in participant recruitment and assessment and manuscript preparation.

Financial Disclosures

BA is employed by the Department of Veterans Affairs and UT Southwestern Medical Center. Funding has been received from the National Institute on Drug Abuse (NIDA) and the National Institute on Arthritis and Musculoskeletal and Skin Disorders. DL has been employed by UT Southwestern and is now employed as a statistical consultant. MAJ is employed by the UT Houston Health Science Center at San Antonio. ESB is employed by the UT Southwestern. Research funding has been received from the National Institute of Mental Health (NIMH), NIDA, National Center for Complementary and Alternative Medicine, National Heart Lung and Blood Institute, Stanley Medical Research Institute, Forest Laboratories and Sunovion Pharmaceuticals Inc. XH is employed by Fairway Family Medicine. UR is employed by the University of Tennessee and has received funding from NIDA, NIMH, and the Institute on Minority Health and Health Disparities. None of the authors have any commercial disclosures relevant to this manuscript.

contributions upon drinking severity have not been assessed. To investigate the combined contribution of hypothalamic-pituitary-adrenal (HPA) reactivity and environmental stressors (e.g., ongoing life stress) to relapse severity in alcohol-dependent men following treatment, plasma adrenocorticotropin (ACTH) and cortisol were obtained in 4-6 weeks abstinent alcohol-dependent men (n=41) following a psychosocial stressor [the Trier Social Stress Test (TSST)] and two pharmacological provocations [ovine corticotropin releasing factor (oCRH) and cosyntropin]. Following treatment discharge, drinking outcomes (primary outcome: drinks per drinking day (DDD); secondary outcomes: total drinks and drinking days) were assessed weekly and ongoing life stress was assessed biweekly for 24 weeks following treatment discharge. Generalized estimating equation models of drinking severity were fit with basal and stimulated ACTH and cortisol concentrations as predictors and ongoing life stress as the moderator. Greater levels of life stress were independently associated with greater drinking intensity (DDD and total drinks) but not frequency (days drinking). Higher basal cortisol:ACTH or provoked cortisol:ACTH ratios were strongly associated with greater post-treatment DDD in individuals who experienced higher levels of ongoing stress. In conclusion, ongoing life stress is associated with post-treatment drinking intensity in alcohol dependent men; stress also strengthens the relationship between adrenocortical sensitivity and post-treatment drinking. Physiological measures of allostatic load and environmental stressors conjointly increase relapse intensity.

Introduction

Allostasis is the process by which a new set-point of homeostasis is attained in response to persistent internal and/or external stressors (McEwen, 2008). A presumed source of allostatic load in alcohol-dependent individuals is the repetitive cortisol exposure associated with repeated bouts of alcohol and withdrawal-induced hypercortisolemia (Adinoff et al., 1998; Juster et al., 2010; Koob and Moal, 2001). This allostatic load is thought to induce alterations in hypothalamic-pituitary-adrenal (HPA) reactivity in actively drinking alcohol-dependent individuals, persisting into abstinence and heightening the risk of alcohol relapse and subsequent severity (Adinoff et al., 2005a; Breese et al., 2011; Stephens and Wand, 2012). A blunted cortisol response to either a public-speaking task or alcohol exposure, for example, predicts a more rapid return to drinking (Junghanns et al., 2003) and lower basal concentrations of adrenocorticotrophic hormone (ACTH) and cortisol have been associated with quicker relapse (Kiefer et al., 2002). Conversely, a heightened cortisol response to computerized psychological stress tasks predicted greater treatment dropout in an alcohol-dependent cohort (Daughters et al., 2009), and increased adrenal sensitivity, as assessed by the relationship of cortisol to ACTH release during a relaxing stimulus, also predicted alcohol relapse (Sinha et al., 2011). However, although there appears to be a significant relationship between peripheral stress-response systems and the persistence of drinking in this population, the strength and direction of this relationship remains uncertain.

Environmental stress, an allostatic stressor, has also long been posited as a precipitant for alcohol ingestion (Conger, 1956; Cooper et al., 1988; Hull, 1981; Pohorecky, 1991; Sher and Levenson, 1982; Wilson, 1983). Nevertheless, while multiple studies have shown a positive relationship between alcohol use and general life stress (Keyes et al., 2012), several prospective studies in non-alcohol dependent populations have reported either an inverse,

null, or limited relationship between daily stressors and alcohol intake (Breslin et al., 1995; Helzer et al., 2006; Rohsenow, 1982; Schroder and Perrine, 2007). Equally tenuous is the relevance of ongoing stress to drinking severity in individuals with an active alcohol use disorder. While environmental stress is often cited as a major provocation for relapse in alcohol-dependent populations (Marlatt and Gordon, 1985; Sinha, 2012), the supportive empirical literature is very limited. Studies in which alcohol-dependent patients are retrospectively queried about relapse precipitants tend to support a relationship between stressful life events and a return to drinking (Brown et al., 1990; Mattoo et al., 2003; Mattoo et al., 2009), although data from the National Epidemiological Survey on Alcohol and Related Conditions (NESARC) revealed that the only life event predicting relapse risk in remitted alcohol-dependent respondents was a divorce/separation during the index period (Pilowsky et al., 2013). In the laboratory setting, alcohol-dependent individuals exposed to a psychosocial stressor experience heightened craving (Sinha et al., 2009) and alcohol intake (Breese et al., 2005; Thomas et al., 2011). While suggestive of a relationship, these studies are limited either by a retrospective assessment of stress and/or alcohol use, laboratory measures of stress reactivity rather than ongoing life stress, or infrequent measures of prospective drinking behavior.

Although previous studies, as described above, have explored the role of either pituitary-adrenal reactivity or ongoing life stress in alcohol relapse, the interaction between these two processes has not been examined. We and others (Breese et al., 2011; Schepis et al., 2011; Stephens and Wand, 2012) have posited that a combination of factors (e.g., environmental stressors, cumulative cortisol stimulation), each increasing allostatic load, would heighten the risk of both the development and perpetuation of alcohol use disorders. This study was designed to explore whether allostatic load, as represented by basal and stimulated measures of the HPA axis, and by environmental stressors interacted to affect prospective drinking severity in alcohol-dependent men. The biologic component of allostatic load was determined by assessing ACTH and cortisol following a public-speaking task (to assess the pituitary-adrenal response to supratentorial stimulation) and the administration of oCRH and cosyntropin (to assess specific activation of pituitary corticotrophs and the adrenal cortex, respectively). Considered variables included the ratio of basal and provoked cortisol relative to basal and provoked ACTH, respectively. This allowed us to assess adrenocortical (glucocorticoid) sensitivity, with higher numbers revealing increased cortisol relative to a unit of ACTH. In addition, the simultaneous assessment of ACTH response to oCRH administration and the glucocorticoid response to cosyntropin administration allowed a measure of glucocorticoid sensitivity (cosyntropin-induced cortisol relative to oCRH-induced ACTH) uncontaminated by higher-level stimulation. Allostatic load due to environmental factors was determined by assessing ongoing life stress at biweekly intervals throughout a 24-week follow-up and daily alcohol consumption was assessed at weekly intervals. Due to marked gender differences in subjective stress reactivity (Uhart et al., 2006) and pituitary-adrenal reactivity in alcohol-dependent participants (Adinoff et al., 2010), the study was powered and funded to only include alcohol-dependent men.

We hypothesized that physiological measures of allostatic load (i.e., pituitary-adrenal reactivity) would predict post-treatment drinking severity and the additive (moderating)

effect of concurrent environmental allostatic load (i.e., ongoing stress) would further magnify drinking severity.

Methods and Materials

Alcohol-Dependent Participants

Sixty-three alcohol-dependent male patients were recruited from residential treatment programs at the VA North Texas Health Care System and Homeward Bound, Inc. Participants endorsed alcohol as their drug of choice, daily alcohol use of >80 gm a day (e.g., six-pack of beer or half of a pint of 100-proof liquor) for at least two weeks prior to admission, and 90 consecutive days of drinking up to the time of admission. Exclusionary criteria included the current diagnosis of another non-substance use Axis I disorder (with the exception post-traumatic stress disorder), use of medications known to affect the HPA axis or central nervous system (e.g. psychotropics, calcium channel blockers, hypoglycemics), and any medical condition affecting HPA function (e.g. diabetes). All three programs utilized the Minnesota Model psychosocial treatment approach. Urine drug screens were conducted throughout residential treatment to verify abstinence.

Clinical Assessment

The study was approved by the Institutional Review Boards at both the University of Texas Southwestern Medical Center and the VA North Texas Health Care System. Written informed consent was obtained from all participants. Participants met the Diagnostic and Statistical Manual of Mental Disorders–Version IV [DSM-IV(First et al., 2002)] as assessed using the Structured Clinical Interview for DSM–IV Axis I Disorders—Lifetime Version (SCID) (First et al., 1996). Additional assessments included the Beck Depression Inventory (BDI) (Beck et al., 1979), State Trait Anxiety Inventory (STAI-S) (Spielberger, 1971), and Drinking Inventory of Consequences (DrINc) (Miller et al., 1995). The Time Line Follow Back [TLFB (Sobell and Sobell, 1992)] estimated the number of drinking days and number of standardized drinks over the participants' lifetime and the day-by-day drinking over the 90 days prior to recent abstinence (Miller, 1996).

Procedure (Figure 1)

Participants were recruited following admission to one of two residential substance use disorder treatment programs in Dallas, Texas and were admitted as soon as possible after their last reported use of alcohol. Both programs utilized the Minnesota Model psychosocial treatment approach. Urine drug screens were conducted throughout residential treatment to verify abstinence from alcohol and other substances. All procedures were performed four to six weeks following admission to the treatment program (participants typically continued drinking until treatment admission but were free from substance use for at least four weeks before the administration of research procedures). Because of our interest in assessing the relevance of the HPA axis to prospective drinking behavior following treatment, we measured basal and HPA axis reactivity during a period of relative quiescence, i.e. after four weeks of abstinence. As the HPA axis may continue to equilibrate with abstinence (Ehrenreich et al., 1997), our window of assessment was limited to four to six weeks abstinence. This avoided the acute alcohol withdrawal phase that is known to be associated

with marked HPA axis activation (Adinoff et al., 1991; Adinoff et al., 2003), limited our assessment period to a relatively confined time period to minimize variability, provided a feasible method of monitoring abstinence (as participants were able to remain in a residential setting for the 4-6 week period) and duplicated the design used in our previous studies (Adinoff et al., 2005b, c).

The Trier Social Stress Test (TSST) (Kirschbaum et al., 1993), cosyntropin, and oCRH infusion, infusion were performed in three sequential evening sessions, respectively. Procedures were conducted in the evening, allowing basal measures to be assessed during the diurnal period of stable quiescent and provoked concentrations to be assessed in the absence of ACTH and cortisol morning escalations. Nicotine-dependent patients were provided a nicotine patch. An intravenous (IV) line was placed one hour prior to each study. The Brief Symptom Inventory (BSI) (Derogatis and Melisaratos, 1983) was obtained just prior to each procedure. Studies were performed at the Clinical and Translational Research Center at the University of Texas Southwestern Medical Center.

TSST—The task was performed as described by Kirschbaum et al. (Kirschbaum et al., 1993) Basal ACTH and cortisol plasma concentrations were obtained at 1850 and 1900 hr; post-task measures were obtained at 1920, 1930, 1940, 1950, 2000, and 2010 hr. Participants were then asked “How stressful did you experience the experiment?” (score ranged from 1 to 5).

Cosyntropin Stimulation—Basal measures of ACTH and cortisol were obtained every 10 min from 1930 to 2000 hr. IV cosyntropin (0.01 µg/kg) was administered over one min at 2001; blood samples were obtained every 10 minutes from 2000 to 2100 hr. and every 20 minutes from 2100 to 2200 hr.

oCRH Stimulation—oCRH 0.4 µg/kg was administered at 2001 hr. over one min. Other procedures replicated those of the cosyntropin stimulation test.

Follow-up assessments

Following discharge, participants were interviewed weekly. In-person interviews were conducted every other week (for TLFB and UCLA Life Stress interview); TLFB was obtained by phone on the other week. Financial compensation was based on the number of completed assessments (Peirce et al., 2006). TLFB was obtained weekly to record daily drinking (days drinking and number of days drinking) since the prior session. The UCLA Life Stress interview (Hammen et al., 1995), a semi-structured interview that obtains information on ongoing and episodic/acute stress (only ongoing stress is considered here), was conducted in biweekly (every two week) sessions. “Ongoing stress” was defined as “ongoing, persistent stress” (e.g., ongoing marital discord) within a specified period of time as opposed to “episodic stress”, defined as “discrete events with a distinct onset and offset (e.g., marital separation)” (Hammen, 2002). Ongoing stress was assessed across ten domains over the previous two weeks: family relationships, independence from family, close friendships, romantic relationships, social life, work, finances, health of subject, and health of family. Reliability for interpersonal domains range from 0.82 to 0.91 and from 0.72 to

0.95 for chronic stress interviews (Hammen, 2002; Hammen et al., 2012) and validity of the UCLA Life Stress Interview has been demonstrated in a number of studies (Adrian and Hammen, 1993; Hammen, 1991; Rao et al., 1999). Participants and interviewers rated levels of stress (1=none to 5=high) for each domain and averaged within and across domains to determine total stress for the 2-week period. Drinking severity was determined for each two-week interval by dividing number of total drinks by the number of drinking days (drinks per drinking day, or DDD).

BioAssay

All ACTH and cortisol samples were tested in duplicate at the Biological Psychiatry Analytical Labs at the University of Texas Health Science Center (MAJ). For %CV values greater than 20%, a second set of duplicate samples were tested and the median of the four results was reported. Plasma (EDTA) ACTH was measured using an ELISA kit (Biomerica, Newport, CA). Calibrators included a 0 pg/mL sample, spiked calibrators ranged from 5 to 165 pg/mL, the lowest detectable concentration was 0.46 pg/mL. Intra-assay variability was 3.1% CV at 35.7 pg/mL (N=21) and inter-assay variability was 5.8% CV at 35.2 pg/mL (N=21). Plasma (EDTA) cortisol was quantified using an ELISA kit (Diagnostic Systems Labs, Webster, TX). Calibrators included a 0 µg/dL sample and spiked calibrators ranged from 0.5 to 60 µg/dL. The minimum detectable concentration was 0.1 µg/dL. Intra-assay variability was 5.0% CV at 15.9 µg/dL (N=12) and inter-assay variability was 6.1% CV at 11.4 µg/dL (N=12).

Statistical Analyses

Neuroendocrine Studies—Missing values were estimated based on the mean of hormone measures taken directly before and after the missing values. ACTH and cortisol secretion were expressed using the area-under-the-curve (AUC) method, or net integrated response: area beneath the concentration-time curve from 0 to 60 min (for TSST) or 0 to 120 min (for oCRH and cosyntropin) minus the area corresponding to the mean of the baseline values $\times$ 60 (TSST) or 120 minutes (oCRH, cosyntropin).

Multiple Regression Models—DDD was modeled by fitting Poisson regression models to the number of drinks (total drinks) with the logarithm of the number of drinking days specified as an offset to the logarithm-linked response. Each bi-weekly interval with at least one drinking day was included as a separate observation in the regression models, and we used the Generalized Estimating Equations (GEE) method to account for correlation among multiple observations within each subject (Zeger and Liang, 1986). (As the DDD outcome is undefined in the absence of drinking days, bi-weekly intervals with no drinking day were excluded from these analyses. Consequently, participants abstinent through the 24-week follow-up were excluded.) It was assumed that the correlation structure of the observations was independent between participants and exchangeable within participants. Models included age, race and baseline drinking (DDD for 90 days prior to admission) as covariates to control for these between-subjects effects; all models included stress and neuroendocrine variables as main effects along with the stress $\times$ neuroendocrine variable interactions. Stress and the neuroendocrine variables were standardized to zero mean and unit standard deviation, which, due to the logarithmic link function, allows a regression parameter to be

interpreted as the fractional increment in the expected number of DDD for each standard deviation increment of the corresponding covariate. For the secondary outcomes of total drinks and drinking days, Poisson regression models were fit to the sample included in the DDD models and also to the sample including participants and intervals with zero drinking days. Corresponding measures of drinking over the 90 days prior to treatment were included as covariates. These secondary outcome models both allowed the inclusion of participants remaining abstinent throughout the follow-up period and assisted in determining whether significant findings with DDD were due to primarily to drinking intensity (total drinks) and/or frequency (drinking days). This approach also allowed the subgroup without abstinent intervals to be directly compared with the DDD models.

Four GEE models were constructed, each model containing two to four neuroendocrine variables (see Table 1). The first two models explored variation in outcomes explained by basal and TSST-provoked ACTH and cortisol measures.

- Model 1 (TSST) - Basal and TSST-induced ACTH and cortisol
- Model 2 (TSST reactivity) – pre-TSST (basal) cortisol relative to ACTH and TSST-induced cortisol and relative to TSST-induced ACTH

The next two models explored variation in outcomes explained by basal and cosyntropin-induced cortisol and basal and oCRH-induced ACTH.

- Model 3 (Cosyn_oCRH) – ACTH prior to oCRH infusion (basal), oCRH-induced ACTH, cortisol prior to cosyntropin infusion (basal), and cosyntropin-induced cortisol.
- Model 4 (Cosyn_oCRH reactivity) - basal and cosyntropin-induced cortisol relative to basal and oCRH-induced ACTH.

For each model, cluster Cook's D statistics was calculated for each subject to assess their influence on the fit (Preisser and Qaquish, 1996). Sensitivity analyses were performed by excluding subjects with cluster Cook's D > 1 and refitting the models. All analyses were programmed in SAS/STAT®, version 9.4 (SAS Institute, Inc., Cary NC, USA). Since several analyses were conducted for each model, a more conservative threshold was used to define statistical significance ($p < 0.01$).

RESULTS

Demographic and Clinical Information

Eight participants were not included in the study due to failure to meet inclusion/exclusion criteria, early discharge, declining to participate further in the study, or were missing critical neuroendocrine variables. 10 participants did not return for follow-up. A total of 45 subjects were therefore included in the analyses.

Of the 45 participants included in the analysis, most were Caucasian (67.7%) or African-American (22.2%), and single (44.4%) or divorced (42.2%). Participants were 43.1 ± 9.3 years old (range 20-59) and had, on average, a 12th grade education (± 1.7). The average number of lifetime drinks was $116,083 \pm 87,286$ and number of drinking days was

7459±3416. Over the 90 days prior to their most recent abstinence period, participants reported drinking 1462.3±1053.6 drinks on 76.9±17.4 days, resulting in 18.6±11.9 standardized DDD. DrINC scores were 38.6±5.8; BDI and STAI scores were 10.7±7.7 and 41.6±12.8, respectively. Two participants met active DSM-IV criteria for cocaine abuse, two for cannabis dependence, two for cannabis abuse, and two for PTSD.

Mean measures of days drinking per week, number of drinks per week, and ongoing stress, over the 24-week post-resident treatment follow-up period are shown in Fig. 2. Six participants of the 41 participants were abstinent throughout the 24-week follow-up period.

Basal and Stimulated ACTH and Cortisol Concentrations

Mean±SD ACTH and cortisol concentrations for each HPA axis test are shown in Figure 3. To assess the stability of basal measures over the three study days, basal concentrations of ACTH and cortisol were compared. Mean basal concentrations of ACTH were similar on the TSST, oCRH, and cosyntropin study days (mean±SD 16.4±9.8; mean±SD 15.4±10.0; mean±SD 13.6±9.5, respectively). However, basal ACTH concentrations on TSST study day were not highly correlated with ACTH prior to oCRH ($r=0.31$, $p=0.049$, $n=40$) or cosyntropin ($r=0.28$, $p=0.076$, $n=41$) [basal ACTH prior to oCRH and cosyntropin was significantly correlated ($r=0.75$, $p<.0001$, $n=42$)]. Basal cortisol was significantly higher ($p<0.005$) on the TSST study day relative to the other two days (mean±SD 11.1±14.3; mean±SD 7.7±6.6; mean±SD 7.4±6.6, respectively), but cortisol concentrations were highly correlated on each study day (TSST vs. oCRH: $r=0.757$, $n=41$, $p<.0001$; TSST vs. cosyntropin: $r=0.89$, $n=41$, $p<.0001$; oCRH vs. cosyntropin: $r=0.88$, $n=43$, $p<.0001$). The relationship of the basal TSST cortisol:TSST ACTH ratio (from Model 2) and the basal cosyn cortisol:oCRH ACTH ratio (from Model 4) was $r=0.72$, $n=40$, $p<.0001$; the provoked cortisol:ACTH response to TSST and cosyn/oCRH was also highly correlated ($r=0.72$, $n=40$, $p=0.001$).

Main Effects of Stress on Drinking Severity (Table 2)

Stress significantly predicted DDD in all four models ($p<0.007$). When total drinks were considered with and without abstinent intervals, similar findings were observed in all but one model [$p=0.028$, Model 4 (cosyn_oCRH reactivity)]. In contrast, stress only predicted drinking days in one model [Model 2 (TSST reactivity), only with non-abstinent intervals included]. Thus, drinking intensity (DDD, total drinks) but not frequency (drinking days) was predicted by ongoing stress.

Main effects of pituitary-adrenal predictors of drinking severity (Table 2)

Only lower basal ACTH prior to TSST predicted greater DDD independent of stress ($z=-4.33$, $p<.0001$; Model 1). Excluding non-drinking intervals, lower basal cortisol prior to cosyntropin also predicted total drinks ($z=-3.44$, $p=.0006$; Model 3). Neither TSST-induced or oCRH-induced measures of ACTH or cortisol, nor their basal or provoked cortisol:ACTH ratios, predicted drinking severity (Models 2-4). Overall, basal and stimulated neuroendocrine measures were not, when isolated from stress, useful predictors of drinking outcome.

Pituitary-adrenal predictors of drinking severity moderated by stress (Table 2)

Higher concentrations of basal cortisol prior to the TSST, moderated by increased stress, predicted greater DDD ($z=2.83$, $p<0.004$; Model 1), i.e. the higher the basal cortisol and more ongoing stress, the higher the DDD. The relationship of basal TSST cortisol to basal ACTH ($z=3.99$, $p<0.0001$; Model 2) (Figure 3, top panel) revealed that increased adrenocortical sensitivity, when moderated by greater stress, resulted in increased DDD.

Models exploring the relative contributions of oCRH-related ACTH (pituitary reactivity) and cosyntropin-related cortisol (adrenocortical reactivity), coupled with stress, showed that cosyntropin-induced cortisol relative to oCRH-induced ACTH was associated with higher drinking severity when moderated by stress ($z=3.53$, $p=0.0004$; Model 4) (Figure 3, lower panel).

These findings were, in part, confirmed when total drinks were considered as the outcome variable. Excluding non-drinking intervals, the findings of Model 1 and 2 were confirmed (basal cortisol prior to TSST ($z=3.99$, $p<0.0001$) and TSST-induced cortisol/ACTH ($z=4.18$, $p<0.0001$), when moderated by stress, predicted drinking). The latter finding was also observed when non-drinking intervals were included. Basal ACTH, prior to both TSST ($z=-3.20$, $p<0.0001$; Model 1) and oCRH ($z=-3.60$, $p=0.0003$; Model 3), predicted drinking days when moderated by stress in drinking participants only.

DISCUSSION

Post-treatment biological measures of HPA reactivity, as assessed by three distinct levels of pituitary-adrenal stimulation, and ongoing environmental stressors were used as prospective predictors of drinking severity over a six-month period in alcohol-dependent men. Our most consistent finding was that ongoing life stress moderated drinking intensity. In addition, relatively higher basal and stimulated adrenocortical reactivity, moderated by ongoing stress, prospectively and positively predicted post-treatment drinking intensity.

All four models demonstrated that ongoing life stress was positively associated with increased drinking intensity following discharge from a residential treatment program. This relationship was evident when drinking was assessed by drinks per drinking day and total drinks but not drinking days, indicating that ongoing stress moderated *how much* alcohol was consumed but not how frequently. Although the moderating effect of stress on alcohol intake was not unexpected, it has not, to our knowledge, been prospectively demonstrated in a population of alcohol dependent individuals. It is consistent with our previously reported findings (from this same study) that the positive relationship between childhood early life stress and pre-treatment drinking was moderated by pre-treatment chronic stress; higher early life stress plus higher ongoing stress was associated with higher amounts of drinking (Eames et al., 2014). A similar finding was reported by Kim et al., who found that ongoing stress interacted with childhood maltreatment to predict heightened craving in adult drinkers (Kim et al., 2014). Although specific types of stressors have been noted to increase drinking in general (Keyes et al., 2012) and alcohol dependent (Eames et al., 2014) populations, our approach only assessed for general estimates of stress. Thus, the collapse of all domains did not allow us to determine whether specific domains were more predictive of drinking

severity than other domains. This approach avoided the attribution of stress to any specific event or events and questions relevant to the severity of any specific stressor were avoided; stress ratings were obtained from participants and provided by interviewers only after questions regarding the participant's experience in each domain were posed and answered. While this approach did not entirely avoid “effort after meaning” (e.g., the tendency to explain recent drinking as a result of heightened stress) (Allan and Cooke, 1985), the paradigm – coupled with collecting drinking (weekly) and stress (biweekly) measures at different intervals – minimized this potential confound.

Heightened adrenocorticoid reactivity, as evidenced by higher cortisol, lower ACTH, and/or increased glucocorticoid relative to ACTH secretion (basal and stimulated) was associated with higher drinking intensity (either DDD or total drinks) only in the presence of ongoing stress (with one exception). The strongest findings revealed that adrenocortical reactivity (the ratio of cortisol to ACTH), in particular, coupled with ongoing stress was associated with drinking. Furthermore, these findings were most evident for basal endocrine measures and not provoked responses. The most consistent finding was observed for basal adrenocortical reactivity prior to TSST, which was observed for DDD and total drinks (with and without abstinent participants). The heightened adrenocortical responsiveness may be an allostatic response to both early and adult life stress and the frequent and persistent bouts of alcohol intoxication and alcohol withdrawal experienced in alcohol-dependent individuals (Koob and Moal, 2001; Schepis et al., 2011). These findings support previous work demonstrating that the elevated cortisol was associated with the onset of substance use disorder in adolescents, and that this relationship was moderated by stressful life experiences (Rao et al., 2009). Our findings confirm and extend the work of Sinha et al. (2011), who observed that a heightened glucocorticoid:ACTH response to a relaxing stimulus was predictive of alcohol relapse as assessed 14, 30 and 90 days post-discharge. Lower basal ACTH (Kiefer et al., 2002) and ACTH reactivity (Brady et al., 2006) and heightened cortisol reactivity (Kiefer et al., 2002) have also been found to predict relapse or relapse severity in alcohol-dependent individuals. The moderating effects of stress in the current study suggest that physiological measures of allostatic load should optimally not be assessed in isolation, but considered in tandem with prospective environmental stressors. In addition, our findings uniquely suggest that the combination of neuroendocrine and environmental allostatic load is not only a risk factor for relapse (as shown by others) but of more severe drinking once a return to drinking has occurred.

The interactive effects of ongoing stress with ambient and reactive pituitary-adrenal concentrations emphasize the relevance of biological stress systems in alcohol relapse severity. Notably, the best predictors of drinking severity, when coupled with ongoing stress, were cortisol:ACTH ratios, limiting the utility of either neuroendocrine measure in isolation. It is also worth noting that, although basal cortisol measures were higher pre-TSST than pre-oCRH and -cosyntropin (we suspect due to some participant anxiety in anticipation of the TSST) and there was generally a good correlation between the basal concentrations over the three study days, and – importantly – there was a very high correlation between the two ratios most predictive of drinking severity when stress was considered as a moderator (basal TSST cortisol:ACTH and integrated cosyn cortisol/integrated oCRH ACTH ($r=0.49$, $n=40$,

$p=0.001$). Thus, there appears to be some consistency in the predictive utility of both basal and provoked measure.

Heightened cortisol:ACTH ratios may be a result of biologic (e.g., alcohol- and withdrawal-induced glucocorticoid elevation) and environmental (e.g., trauma) allostatic stressors. These stressors may produce an adaptive down-regulation of basal or stimulated ACTH concentrations, coupled with a persistent “normal” glucocorticoid response – thus resulting in a relative increase in the cortisol:ACTH ratio. This relationship may indicate increased glucocorticoid sensitivity of the pituitary corticotrophs, such that negative feedback of cortisol upon induces rapid suppression of the ACTH response, a finding consistent with our observation of accentuated dexamethasone-induced ACTH suppression in alcohol-dependent men (Adinoff et al., 2005b). While alterations in the basal and/or stimulated cortisol:ACTH concentrations may not be problematic in a non-stressed environment, an abnormal adrenocortical response to stressors may exacerbate an already fragile physiologic milieu. The ultimate behavior response (in this case, drinking alcohol) to heightened adrenocortical reactivity would be further influenced by specific alleles (e.g., CRH1, 5-HTTLPR (Covault et al., 2007; Hansson et al., 2006)), central (e.g., amygdala, hippocampus) and peripheral (e.g., pituitary) glucocorticoid receptor sensitivity, and other associated biological factors. Finally, an interaction between stress, glucocorticoid reactivity and alcohol reinforcement may underlie the observed moderating effect of stress on drinking severity (as opposed to drinking frequency) (Stephens and Wand, 2012).

Individuals with higher glucocorticoid:ACTH ratios, particularly those endorsing significant stress, may require targeted pharmacological interventions. Naltrexone disinhibits the tonic opioid restraint of pituitary corticotrophs, thus allowing increased CRH responsivity to CNS stimulation (Hernandez-Avila et al., 2002). Prazosin (Simpson et al., 2009), an α -1 antagonist, NK1 antagonists (George et al., 2008), and oCRH antagonists (Gilpin et al., 2008) all target biological stress-response systems. Caution is advised, however, as pharmacological amelioration of glucocorticoid sensitivity in the presence of muted ACTH reactivity may interfere with an adaptive response that is presently modulating integrated HPA reactivity.

The alcohol-dependent population studied were abstinent at least four weeks when neuroendocrine procedures were conducted, thus minimizing the potential influences of recent alcohol use and withdrawal. The exclusion of major ongoing psychiatric disorders as well as medications or medical illnesses that might interfere with HPA axis functioning allowed assessment of this biological system with minimal confounds, although this approach limited the generalizability of our findings to typical clinical populations. Several of the participants initially studied did not follow-up with study staff, again limiting the generalizability of our findings. Nevertheless, the returning participants reported high amounts of drinking, indicating our population was not limited to low-risk patients. As there are significant gender differences in stress reactivity (Uhart et al., 2006), the present findings in men only cannot be extended to women. The use of prospective, frequent, and multiple (up to 13 over 26 weeks) alcohol intake (weekly) stress ratings (every two weeks) were major strengths of our approach, although these reports were retrospective over the past 7 to 14 days. Our use of the same time epoch to assess both stress and drinking also did not allow

a causal model to be tested. The most recent research using ecologically momentary assessments (EMA), using real-time assessments of mood and drinking, has found that both positive and negative mood states are associated with drinks per drinking day in heavily drinking young adults, coupled with complex interactions with gender, response inhibition and drinking motives (Dvorak et al., 2016; Smit et al., 2015). The use of EMA in an alcohol-dependent population to assess real-time stress measures in relationship to drinking may help clarify persistent questions regarding the temporal connection between stress and drinking. Previous life trauma/adversity, not considered in this study, may also influence the interaction of stress and drinking

In summary, comprehensive assessment of pituitary-adrenal axis reactivity to hypothalamic, pituitary and adrenal provocation, coupled with prospective, biweekly measures of both ongoing stress and drinking, revealed that stress moderated the effects of muted ACTH and higher glucocorticoid reactivity upon drinking severity in alcohol-dependent men. The glucocorticoid:ACTH relationship, and its interaction with stress and drinking, may be particularly useful measures of allostatic load. Future studies would benefit from the use of real-time assessments of stress and drinking to identify specific causal determinants as well as the effects of behavioral and pharmacologic interventions.

Acknowledgements

This work was funded by INIAStress U01AA016668, the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Clinical Sciences Research and Development and the UT Southwestern Center for Translational Medicine UL1TR000451. The authors gratefully acknowledge the assistance of the substance abuse team at the VA North Texas Health Care System and at Homeward Bound, Inc. for their support in the screening and recruitment of study subjects.

Funding Source

This work was funded by INIAStress U01AA016668, the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Clinical Sciences Research and Development and the UT Southwestern Center for Translational Medicine UL1TR000451.

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Highlights

- Allostatic load from stress and cortisol secretion may worsen course of alcoholism.
- Effects of HPA axis activity and ongoing stress upon drinking severity were assessed.
- Life stress and drinking assessed biweekly for 6 months post-treatment discharge.
- Adrenocorticoid reactivity, moderated by stress, predicted drinking intensity.
- Addressing both glucocorticoid and stress reactivity may lessen relapse severity.

Figure 1.

Study Design: Treatment-seeking alcohol-dependent individuals were admitted into one of three public sector residential treatment programs and recruited into the study. Participants were monitored for abstinence throughout the program. Between 4 to 6 weeks of abstinence, participants were transferred to the University of Texas Southwestern Medical Center inpatient Clinical Research Unit. Three assessments of hypothalamic-pituitary-adrenal (HPA) axis functioning (predictor variables) were obtained over three days, each at 2000 hr. Assessments were conducted in sequential order: Trier Social Speaking Task (TSST), cosyntropin administration, and ovine corticotrophin releasing hormone (oCRH) administration. Following discharge from the Clinical Research Unit, participants were assessed weekly as outpatients. Timeline follow back for alcohol use was obtained weekly (outcome variable); ongoing stress was obtained every other week (moderator variable).

Figure 2.

Drinking and stress during the 24-week post-residential treatment follow-up. Left panel: Mean number of drinks per week (circles, dashed line, left y axis) and days drinking per week (squares, solid line, right y axis). Right panel: Mean measure of ongoing stress.

Figure 3.

Plasma adrenocorticotropin hormone (ACTH) (black circles) and cortisol (gray triangles) response to Trier Social Speaking Task and ovine corticotrophin releasing hormone (oCRH) and cosyntropin administration (n=41). Black box (left panel) notes when speaking task administered. Arrows points to time of administration (2000 hr) of 0.4 $\mu\text{g/kg}$ oCRH (middle panel) and 0.01 $\mu\text{g/kg}$ cosyntropin (right panel). Error bars denote standard deviation.

Figure 4.

Adrenocortical reactivity, as measured by cortisol/ACTH, predicts drinking intensity (measured by drinks per drinking day; DDD) when moderated by ongoing life stress. *Top panel:* Basal concentrations of cortisol:ACTH prior to TSST, moderated by ongoing life stress, predict DDD (Model 2, $z=3.99$, $p<.0001$). *Bottom panel:* Cosyntropin-induced cortisol relative to oCRH-induced ACTH, moderated by ongoing life stress, predict DDD (Model 4, $z=3.53$, $p=.0004$). Surface plots (on left) show the interpolated surface; scatter plots (on right) interval data points. ACTH and cortisol concentrations (z axis) are reported as z scores. AUC = area under the curve, or net integrated response.

Table 1

Basal and stimulated ACTH and Cortisol as predictors of drinking severity, moderated by ongoing stress. Significant findings are bolded and italicized. Statistical significance was defined as $p < 0.01$.

	Drinks per Drinking Day			Total Drinks			Total Drinks (including abstinent intervals)			Drinking Days			Drinking Days (including abstinent intervals)		
	$PE^{\dagger}$	Z-score	p-value	$PE^{\dagger}$	Z-score	p-value	$PE^{\dagger}$	Z-score	p-value	$PE^{\dagger}$	Z-score	p-value	$PE^{\dagger}$	Z-score	p-value
<i>Model 1: Basal and TSST-induced Cortisol and ACTH</i>															
	(n=31; observations=334)			(n=32; observations=374)			(n=39; observations=773)			(n=32; observations=356)			(n=39; observations=773)		
Stress	0.13	2.60	0.009	0.24	3.99	<0.0001	0.29	3.45	0.0006	0.05	0.82	0.41	0.14	1.50	0.13
Basal cortisol	-0.10	-1.35	0.18	0.03	0.18	0.86	-0.23	-0.71	0.47	-0.01	-0.09	0.93	-0.21	-0.95	0.34
*stress	0.10	2.83	0.004	0.21	2.85	0.004	0.06	0.49	0.63	0.05	1.08	0.28	-0.03	-0.29	0.77
Basal ACTH	-0.25	-4.33	<0.0001	-0.21	-1.30	0.19	-0.23	0.93	0.35	-0.16	-1.20	0.23	0.09	0.35	0.73
*stress	-0.07	-1.67	0.09	-0.13	-1.44	0.15	-0.21	-1.21	0.22	-0.28	-3.20	0.001	-0.16	-0.92	0.36
Net integrated cortisol	0.20	1.16	0.25	-0.14	-0.54	0.59	-0.05	-0.21	0.83	-0.08	-0.58	0.56	-0.19	-0.71	0.48
*stress	-0.04	-0.58	0.56	-0.37	-2.19	0.03	-0.13	-1.45	0.15	0.03	0.39	0.70	-0.09	-1.31	0.19
Net integrated ACTH	-0.45	-2.23	0.03	0.19	0.57	0.57	0.15	0.49	0.62	0.29	1.74	0.08	0.47	1.59	0.11
*stress	-0.07	-0.60	0.55	0.12	0.87	0.38	-0.07	-0.71	0.47	-0.07	-1.06	0.29	-0.03	-0.45	0.65
<i>Model 2: Basal and TSST-induced cortisol relative to basal and TSST-induced ACTH</i>															
	(n=30; observations=360)			(n=32; observations=374)			(n=37; observations=725)			(n=32; observations=373)			(n=38; observations=749)		
Stress	0.20	2.92	0.004	0.32	0.09	0.0003	0.60	3.87	0.0001	0.02	0.15	0.88	0.37	2.76	0.006
Basal cortisol/ACTH	-0.08	-1.16	0.24	0.15	0.76	0.44	0.18	0.56	0.57	-0.05	-0.43	0.67	-0.05	-0.25	0.80
*stress	0.16	3.99	<0.0001	0.23	4.18	<0.0001	0.28	3.13	0.002	0.04	0.61	0.54	0.15	0.50	0.01
Net integrated cortisol/ACTH	0.08	0.38	0.70	0.07	1.15	0.25	-0.21	-0.69	0.49	-0.36	-1.04	0.30	-0.26	-0.85	0.40
*stress	0.49	1.46	0.14	0.45	1.81	0.07	0.13	2.52	0.012	-0.32	-0.51	0.61	1.06	2.07	0.04
<i>Model 3: Basal and cosyntropin-induced Cortisol, basal and oCRH-induced ACTH</i>															
	(n=32; observations=357)			(n=34; observations=391)			(n=41; observations=821)			(n=32; observations=391)			(n=41; observations=821)		
Stress	0.12	2.69	0.007	0.22	2.88	0.004	0.27	2.93	0.003	0.11	1.93	0.05	0.11	1.34	0.18
Basal Cortisol	-0.15	-0.58	0.56	-0.52	-3.44	0.0006	-0.25	-1.08	0.28	-0.22	-2.48	0.013	-0.13	-0.65	0.52
*stress	-0.03	-0.23	0.82	-0.12	-1.58	0.12	-0.07	-1.33	0.18	-0.05	-1.78	0.07	-0.09	-2.09	0.04
Basal ACTH	-0.16	-1.90	0.06	-0.44	-2.53	0.012	-0.27	-0.92	0.36	-0.15	-1.33	0.18	0.01	0.04	0.97
*stress	-0.04	-1.06	0.29	-0.26	-2.83	0.005	-0.25	-1.80	0.28	-0.23	-3.60	0.0003	-0.26	-2.29	0.02
Net integrated cortisol	0.09	1.07	0.28	0.08	0.83	0.41	0.18	1.08	0.28	-0.03	-0.32	0.75	-0.07	-0.41	0.68

	Drinks per Drinking Day			Total Drinks			Total Drinks (including abstinent intervals)			Drinking Days			Drinking Days (including abstinent intervals)		
	$PE^{\dagger}$	Z-score	p-value	$PE^{\dagger}$	Z-score	p-value	$PE^{\dagger}$	Z-score	p-value	$PE^{\dagger}$	Z-score	p-value	$PE^{\dagger}$	Z-score	p-value
*stress	-0.01	-0.22	0.83	-0.08	-1.99	0.05	0.02	0.41	0.68	-0.06	-1.79	0.07	0.11	1.89	0.06
Net integrated ACTH	-0.17	-0.87	0.38	-0.55	-2.25	0.02	-0.03	-0.09	0.93	-0.20	-1.08	0.28	0.08	0.23	0.82
*stress	-0.18	-2.52	0.012	-0.23	-2.18	0.03	-0.06	-0.66	0.51	0.00	-0.02	0.98	0.13	2.06	0.04
Model 4: Basal and cosyntropin-induced Cortisol relative to basal and oCRH-induced ACTH															
	(n=32; observations=356)			(n=33; observations=380)			(n=40; observations=800)			(n=33; observations=380)			(n=40; observations=800)		
Stress	0.14	3.40	0.0007	0.15	2.19	0.03	0.20	3.60	0.0003	0.05	0.86	0.39	0.10	1.13	0.26
Basal cortisol/ACTH	-0.07	-1.05	0.29	-0.14	1.04	0.30	0.00	0.00	0.99	0.17	1.38	0.17	-0.96	-1.00	0.32
*stress	0.07	1.60	0.11	0.01	0.08	0.94	0.05	0.30	0.76	0.07	2.16	0.03	0.20	0.92	0.36
Net integrated cortisol/ACTH	0.00	0.04	0.97	-0.25	-1.25	0.21	-0.19	-0.50	0.61	-0.21	-1.87	0.06	-0.26	-0.99	0.32
*stress	0.08	3.53	0.0004	0.06	0.72	0.47	-0.02	-0.33	0.74	-0.01	-0.26	0.79	-0.14	-1.65	0.10

[†]PE: Parameter estimates are fractional increments in the expected number of drinks per drinking day (total drinks/days drinking) per standard deviation increment of the effect.