

Young Investigator Award Symposium

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Abstract

This article highlights the research presented at the inaugural meeting of *Alcoholism and Stress: A Framework for future Treatment Strategies*. This meeting was held on May 6–8, 2008 in Volterra, Italy. It is an international meeting dedicated to developing preventive strategies and pharmacotherapeutic remedies for stress- and alcohol-related disorders. For the first time, the National Institute on Alcohol Abuse and Alcoholism (NIAAA) conferred a Young Investigator Award to promote the work of young researchers and highlight their outstanding achievements in the fields of addiction medicine and stress disorders. The awardees were Dr. Katie Witkiewitz (University of Washington), Dr. Andrew Holmes (NIAAA), Dr. Lara A. Ray (Brown University), Dr. James Murphy (University of Memphis), and Dr. Heather Richardson (The Scripps Research Institute). The symposium was chaired by Drs. Fulton Crews and Antonio Noronha. © 2009 Published by Elsevier Inc.

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Introduction

Alcoholism and Stress: A Framework for Future Treatment Strategies is an international meeting dedicated to developing preventive strategies and pharmacotherapeutic remedies for stress- and alcohol-related disorders. To promote the work of young researchers and highlight their outstanding achievements in the fields of addiction medicine and stress disorders, the National Institute on Alcohol Abuse and Alcoholism (NIAAA) conferred a Young Investigator Award at the inaugural meeting in Volterra, Italy.

This is the first **Young Investigator Award** to be sponsored and funded by the NIAAA (AA017581). This award is intended to facilitate innovative research opportunities and support alcohol researchers. Applications were received from scientists throughout the United States and Europe.

Applications were reviewed by the conference organizers, Drs. Marisa Roberto and George Koob of The Scripps Research Institute (La Jolla, CA). The main criteria for selecting awardees were as follows: (1) scientific merit of the submitted abstract, (2) previous publication record, (3) present work in the alcohol research field, and (4) potential for development and contribution to alcohol and stress research. Those judged to be outstanding in quality were selected to be recipients of the Young Investigator Award.

Five Young Investigator Award recipients were selected and invited to give a presentation during the Young Investigator Symposium, chaired by Dr. Fulton Crews (University of North Carolina at Chapel Hill) and Dr. Antonio Noronha (NIH/NIAAA). Awardees also received a waiver of the meeting registration fee and an official certificate of merit from the meeting organizers.

Dr. Katie Witkiewitz (University of Washington) provided an overview of advanced statistical methods to study the correlation between stress and alcohol use across time. Dr. Andrew Holmes (NIAAA) showed data supporting

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the efficacy of novel antiglutamatergic and antidopaminergic drugs in the treatment of alcoholism. Dr. Lara Ray (Brown University) discussed the relationship between the clinical and diagnostic correlates of posttraumatic stress disorder (PTSD) and subsequent development of an alcohol use disorder (AUD). She also provided evidence for naltrexone (NTX) treatment for alcoholism. Dr. James Murphy (University of Memphis) presented data indicating that trauma, stress, and other psychiatric symptoms confer a high risk for alcohol-related problems in college students. Dr. Heather Richardson (The Scripps Research Institute) provided evidence of an imbalance of the hypothalamic and extrahypothalamic corticotropin-releasing factor (CRF) systems associated with alcohol dependence.

Examining the relationship between stress and alcohol use across time: recent advances in longitudinal data analyses

Katie Witkiewitz, Ph.D.

For over 30 years alcohol researchers have recognized the existence of multiple pathways in the relapse process. Yet, the statistical techniques used in the analysis of treatment outcome data have often failed to capture the individual variability in patterns of resumption after an initial lapse. Variation in drinking patterns is best demonstrated by examining individual differences in post-treatment drinking trajectories. There is tremendous variability both within and between individuals over time.

Fortunately, statistical techniques have been developed that can differentiate unique patterns in drinking and the risk factors that reliably predict these patterns. Two methods that have been increasingly used over the past few years in the alcohol and substance use literature, latent growth curve (LGC) models and growth mixture models (GMM; also latent class growth analysis), will be the focus of the present article. However, numerous other extensions of latent variable models are available (see Collins and Sayer, 2001; Hedeker and Gibbons, 2006; Rose et al., 2000; Singer and Willett, 2003).

Latent variable models, in general, assume that the relationship among observed measures can be explained by an underlying unobserved “latent” variable. In the case of LGC, the latent variables explain the repeated measurement of some observed variable, where the observed growth trajectory over time is modeled by a combination of fixed and random effects. Fixed-effects components are the mean values of the estimated trajectories and the random-effects components represent the variances around the mean trajectory. Growth mixture modeling (GMM) combines finite mixture modeling with LGC modeling by estimating a categorical latent variable that represents unobserved subpopulations of individuals with similar growth trajectories (Muthén, 2001; Muthén and Shedden, 1999). GMM enables the researcher to identify discrete typologies of mean growth trajectories

in the population and individual heterogeneity within each trajectory type (using continuous latent variables).

The present study provides an example of using LGC and GMM to examine variation in weekly perceived stress scale scores (Cohen et al., 1983) during treatment in the Combined Pharmacotherapies and Behavioral Intervention (COMBINE) study (COMBINE Study Group, 2003) as a predictor of percent drinking days during treatment through 68-weeks after treatment. A LGC model with linear and quadratic effects provided a good fit to weekly stress data (comparative fit index [CFI] = 0.97; root mean square error of approximation [RMSEA] = 0.03), which demonstrated a decreasing trend in stress scores over the course of 12 weeks (linear slope = -0.33 , $P < .005$). Treatment significantly predicted linear slope ($B = 0.15$ [SE = 0.04], $P < .005$), indicating that individuals who received the combined behavioral intervention (CBI) reported a greater decrease in stress over time, as compared with those who received medication management.

For the GMM analyses, a three-class model of drinking frequency (lapsers [8.6%], frequent drinkers [12.3%], and infrequent drinkers [79%]) provided the best fit to the observed data. Individuals with an increasing stress slope were 2.8 times more likely to be classified as lapsers and 3.2 times more likely to be classified as frequent drinkers, compared with infrequent drinkers. Receiving CBI was also related to drinking class membership, with lapsers having a lower odds of receiving CBI (odds ratio [OR] = 0.47, $P = .003$), as compared with infrequent drinkers; and frequent drinkers having a lower odds of receiving CBI (OR = 0.70, $P = .04$), as compared with lapsers. The results from this study suggest that assessing changes in stress during treatment could help identify individuals who are more or less likely to lapse after treatment. In addition, CBI was related to significant reductions in stress during treatment and less frequent drinking after treatment, compared with medication management.

Effects of antiglutamatergic drugs on sensitivity to ethanol's acute intoxicating effects in mice

Yi-Chyan Chen, M.D., and Andrew Holmes, Ph.D.

There is a growing evidence that the glutamate system plays a major role in the neural and behavioral actions of alcohol and the processes driving the development of alcoholism (Heilig and Egli, 2006; Spanagel and Kiefer, 2008). In rodents, pharmacological or genetic blockade of glutamate receptors alters the behavioral effects of ethanol (Boyce-Rustay and Holmes, 2005, 2006; Gass and Olive, 2008). This has led to growing interest in the potential efficacy of various clinically available drugs with “antiglutamatergic” properties for the treatment of alcoholism (Krupitsky et al., 2007). For example, six compounds (memantine, dextromethorphan, haloperidol, lamotrigine, oxcarbazepine, topiramate) with antiglutamatergic properties that are currently in clinical use for various indications (e.g., Alzheimer's disease,

epilepsy, psychosis, mood disorders) have been proposed as potential novel treatments for alcoholism.

Current models propose that alcohol abuse and alcoholism results from multiple risk factors, including a drive to alleviate the negative reinforcing effects of alcohol withdrawal (Koob, 2003) and a progressive impairment of executive control over alcohol seeking (Everitt and Robbins, 2005). Predisposition toward alcoholism is also associated with decreased sensitivity/increased acute tolerance to certain intoxicating (e.g., ataxic) effects of ethanol (Newlin and Thomson, 1990; Schuckit, 1994). However, although the preclinical literature supports a major interaction between experimental glutamate-acting compounds and ethanol, it is not yet clear whether clinically tolerated “antiglutamatergic” drugs also modulate (e.g., promote) the acute intoxicating effects of ethanol. A better understanding of such effects could provide insight into the mode of action and therapeutic profile of these drugs.

We examined memantine, dextromethorphan, haloperidol, lamotrigine oxcarbazepine, and topiramate for effects on the acute intoxicating effects of ethanol (ataxia, hypothermia, sedation/hypnosis) in C57BL/6J mice (Chen and Holmes, 2009). Because clinical and preclinical studies of topiramate have been the most extensive to date, we also tested whether topiramate’s effects on ethanol-induced sedation/hypnosis varied as a function of two major influences on risk and treatment for alcoholism: genetic background and stress history (Goldman et al., 2005; Grant et al., 2008; Koob, 2003). The influence of genetic background was tested via comparison of the 129S1, BALB/cJ, C57BL/6J, DBA/2J inbred strains, and the effects of prior stress history was tested by chronically exposing C57BL/6J to swim stress.

We found that one drug with *N*-methyl-D-aspartate receptor (NMDAR) antagonist properties, memantine, potentiated the ataxic but not hypothermic or sedative/hypnotic effects of ethanol, whereas another NMDAR antagonist, dextromethorphan, had no effects. The antipsychotic haloperidol, which also has some NMDAR antagonistic effects among its manifold actions, increased ethanol-induced ataxia and sedation/hypnosis to a similar extent as the prototypical NMDAR antagonist MK-801 (Palachick et al., 2008). Of the three anticonvulsants we tested, lamotrigine accentuated ethanol-induced sedation/hypnosis, whereas oxcarbazepine and topiramate were without effect, at least under baseline conditions in C57BL/6J mice. Taken together, these data show that, with the exception of haloperidol, the various compounds tested had either no significant or assay-selective effects on acute sensitivity to ethanol in the reference mouse strain C57BL/6J.

Interestingly, however, further experiments pointed to a more nuanced conclusion, at least with regards to topiramate. First, in C57BL/6J mice coadministration of topiramate and MK-801 had a synergistic effect on promoting ethanol-induced sedation/hypnosis. This could reflect the combined effects of glutamate release inhibition (by topiramate) and NMDAR

blockade (by MK-801), which would in turn suggest that topiramate effects can be unmasked under conditions of reduced NMDAR function. Second, despite showing no differences in baseline sleep responses to ethanol (consistent with previous reports, Boyce-Rustay et al., 2007; Boyce-Rustay et al., 2008) as compared with C57BL/6J, the BALB/cJ (but not 129S1 or DBA/2J) strain exhibited a clear ethanol-potentiating response to topiramate. The BALB/cJ strain is characterized as a relatively stress-reactive, “anxious” strain of mouse (e.g., Belzung, 2001; Norcross et al., 2008). This led us to test whether stress exposure could also render C57BL/6J sensitive to topiramate. Results of this experiment showed that topiramate increased ethanol-induced sedation/hypnosis in C57BL/6J mice after 14 daily sessions of forced swimming.

These findings raise a number of important issues for future research. For example, whether the other antiglutamatergic compounds tested herein also show interactions with stress and genetic background remains to be tested. Another key issue is whether the profile of topiramate or any of these drugs differs in C57BL/6J mice rendered ethanol-dependent (Becker and Lopez, 2004), because ethanol-dependence better models the clinical state, and current theories posit that the development of dependence is associated with increased glutamatergic signaling (Heilig and Egli, 2006; Koob, 2003; Spanagel and Kiefer, 2008). Notwithstanding, our findings lend tentative support for the hypothesis that topiramate, and possibly other clinically tolerated antiglutamatergic drugs, promote the intoxicating effects of alcohol in genetically- or life history-defined subpopulations, and that these actions may contribute to the drugs’ profile as treatments for alcoholism.

Stress and alcohol: from the laboratory to the clinic

Lara A. Ray, Ph.D.

Stress increases drug and alcohol use through multiple neurobiological and biobehavioral pathways (Koob and Kreek, 2007; Sinha, 2001). Understanding the link between stress and substance use is a challenging task that involves multiple levels of analyses such as the basic science level, the human laboratory level, and at the clinical and diagnostic level. This article describes two studies presented at the research meeting *Alcohol and Stress: A Framework for Future Treatment Strategies*, held in Volterra, Italy. The first study tested the effects of NTX on cortisol and its associations to subjective responses to alcohol and craving in a human laboratory design (Ray et al., 2008). The second study examined the relationship between PTSD with and without a comorbid AUD seeking to elucidate the clinical and diagnostic correlates of PTSD with subsequent development of an AUD (Ray et al., in press). These studies seek to elucidate the relationship between stress mechanisms and alcohol from different vantage points, one from a controlled behavioral pharmacology perspective and the other from the clinical and diagnostic viewpoint. The

integration of various clinical and experimental approaches holds promise to the overall understanding of these complex relationships and ultimately, to the translation of these findings into more effective treatment strategies.

From the laboratory: NTX effects on cortisol among hazardous drinkers

Opioid blockade has been found to increase blood levels of adrenocorticotropic hormone (ACTH), beta-endorphin, and cortisol in humans (Naber et al., 1981; Schluger et al., 1998). These findings suggest a potential role of the hypothalamo-pituitary–adrenocortical (HPA) axis activity in mediating the neurobiological effects of NTX. This is consistent with preclinical and clinical data suggesting that HPA-axis stimulation plays a role in the neurobiology of alcoholism itself (Adinoff et al., 1998; Adinoff et al., 2005) and findings that blunted HPA-axis response predicts alcohol preference in rodents (Olive et al., 2003) and an increased risk of early relapse in humans (Junghanns et al., 2003; Junghanns et al., 2005).

Acute neuroendocrine responses to NTX have been examined in a few laboratory studies (King et al., 2002; O'Malley et al., 2002) Inasmuch as controlled laboratory studies allow for the examination of the biobehavioral and neurobiological effects of NTX, results of such studies suggest that NTX-induced reductions in craving may be HPA-axis-mediated such that NTX could exert its therapeutic effect by restoring the blunted basal activity and reactivity of the HPA system (Adinoff et al., 2005; Kiefer et al., 2006). Subjective response to alcohol is a central biobehavioral mechanism of NTX's effects (King et al., 1997; Swift et al., 1994). To that end, the primary aim of this study is to examine the effects of NTX, as compared with placebo, on serum cortisol levels and their relation to alterations in subjective responses to alcohol and craving.

Participants were 37 (11 females) nontreatment-seeking drinkers who scored ≥ 8 on the Alcohol Use Disorders Identification Test (AUDIT), indicating a hazardous drinking pattern (Allen et al., 1997); as described elsewhere (Ray and Hutchison, 2007). Each participant completed two alcohol infusion sessions, one after taking NTX (50 mg) for 3 days and one after taking a matched placebo for 3 days. During the experimental sessions, participants received intravenous doses of alcohol. Participants completed assessments at baseline (BrAC = 0.00 g/dL) and at three points in the ascending arm of the BrAC (BrAC = 0.02, 0.04, and 0.06 g/dL). Blood samples for cortisol analyses were collected on both medication conditions (i.e., NTX and placebo) at *baseline* (BrAC = 0.00 g/dL) and at the *final target BrAC level* (i.e., 0.06 g/dL).

In this study, NTX significantly raised serum cortisol levels, compared with placebo, among hazardous drinkers. These findings advance previous work suggesting that NTX's neurobiological mechanisms involve HPA-axis activation (Kiefer et al., 2006; King et al., 2002; O'Malley et al., 2002). From the perspective of the biobehavioral mechanisms of action of

NTX, results indicated that basal cortisol levels are inversely related to some of the reinforcing effects of alcohol (i.e., high vigor) and positively associated with some of alcohol's unpleasant effects (i.e., sedation and subjective intoxication). This is relevant in light of the clinical literature suggesting that higher basal levels of cortisol may contribute to the relapse-preventing effects of NTX (Adinoff et al., 2005; Kiefer et al., 2006). Thus, it is plausible that the relapse-preventing effects of NTX may be because of differential responsivity to alcohol's reinforcing effects at higher basal levels of cortisol. However, there were no significant associations between cortisol levels and self-reported craving for alcohol, contrary to previous findings (O'Malley et al., 2002). Overall, results suggested that NTX alters cortisol levels and that its effects on subjective responses to alcohol may be related in part to NTX's ability to activate the HPA-axis.

From the clinic: PTSD and AUDs

In clinical populations, approximately 40% of patients presenting for substance abuse treatment meet criteria for co-occurring PTSD (Ouimette et al., 2005). Several models of addictions have attempted to delineate the relationship between PTSD and substance use. It has been argued that dysregulation of the HPA-axis in response to stress may provide a mechanistic link between the two disorders (Brady et al., 2006a; Brady et al., 2006b). The co-occurrence of PTSD and AUD has also been explained in the context of the self-medication hypothesis, by which the AUD develops as an attempt to alleviate symptoms of PTSD, particularly the symptoms of increased physiological hyperarousal (Kosten and Krystal, 1988). Examining differences in PTSD symptom profiles, diagnostic, and clinical variables, between PTSD patients with and without comorbid AUD has the potential to elucidate some of the clinical mechanisms underlying this comorbidity. This report from the Rhode Island Methods to Improve Diagnostic Assessment and Service (MIDAS) Project compared psychiatric outpatients with PTSD to those with PTSD + AUD on measures of PTSD symptomatology, diagnostic, and clinical variables.

Participants were recruited from the Rhode Island Hospital Department of Psychiatry's outpatient practice (Zimmerman, 2003). This report is based on 196 (84% female) patients who met criteria for PTSD in their lifetime, 158 of whom met criteria for PTSD without comorbid substance use disorder and 38 of whom met criteria for both PTSD and AUD. The average age was 36 years old and about 80% were Caucasian. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) Axis I diagnoses were obtained using the Structured Clinical Interview for DSM-IV Axis I Disorders and the Structured Interview for DSM-IV Personality assessed DSM-IV Axis II disorders.

The two groups did not differ significantly on symptom-level data, demographics, or Axis I diagnoses. However, analyses revealed that individuals with lifetime PTSD + AUD were more likely to meet criteria for cluster B

personality disorders, namely borderline personality disorder (BPD) and antisocial personality disorder (ASPD), as compared with individuals with PTSD alone. Although no causal links can be inferred, these results raise the question of whether emotion dysregulation and poor distress tolerance, associated with PDs such as BPD and ASPD, may be relevant in explaining the association between PTSD and the subsequent development of AUD. These features may also account for the maladaptive response to stress proposed in models of drug abuse and relapse (Sinha, 2001). Conversely, the diagnostic overlap observed in this study may reflect common etiological pathways. In short, these findings suggest that further examination of emotion regulation and distress tolerance may be useful in understanding the biobehavioral mechanisms underlying the risk for PTSD, AUD, and their comorbidity.

Conclusions

The relationship between stress processes and substance use is complex and multifaceted. Alterations in the stress response system may contribute to both the positive (i.e., binge of the addiction cycle) and negative (i.e., withdrawal and negative affect stage) reinforcement associated with substance use and abuse (Koob and Kreek, 2007). These altered stress response mechanisms may, in turn, be captured through both biological (e.g., neuroendocrine response) or psychosocial (e.g., emotion dysregulation) variables. Complex models of stress and addiction will require the translation to, and from, basic and applied levels of analyses. As a result, these models may be more complete and thus more useful in identifying treatment strategies combining both basic science and clinical manifestations of psychopathology.

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Alcohol use, stress, and psychiatric symptoms among trauma-exposed college students

James G. Murphy, Ph.D., Meghan E. McDevitt-Murphy, Ph.D.

There are high rates of alcohol abuse among traumatized persons (Stewart, 1996), and the link between trauma and

alcohol abuse appears to be mediated by symptoms of PTSD. Recent work also suggests a prominent role for the personality dimensions of negative emotionality and disinhibition (Miller et al., 2006). The utility of these dimensions in exploring alcohol abuse among college students has not been extensively investigated to date, but information about these relations could prove useful to better understand the determinants of hazardous drinking among students and to inform the development of appropriate interventions. In the present report, we investigated relations between personality and dimensions of psychopathology assessed by the Personality Assessment Inventory (PAI; Morey, 2006) and measures of alcohol consumption and related problems.

Method

Participants were 136 undergraduates (18 male and 82% female) ranging in age from 17 to 24 years old ($M = 19.7$). Most of them were Caucasian (83.8%), with some representation from other ethnic groups (African-American, 11.0%; Hispanic, 1.5%). Participants were nontreatment-seeking students recruited through psychology courses and postings around campus requesting research volunteers. The primary inclusion criterion for the study was exposure to at least one traumatic life event meeting Criterion A of the DSM-IV diagnostic criteria for PTSD (APA, 2001). Other inclusion criteria were aimed at ensuring a wide range of variability, including some well-adjusted students and some experiencing significant distress, assessed by brief self-report measures (see McDevitt-Murphy et al., 2007 for more details).

Personality and psychopathology dimensions were assessed with the PAI (Morey, 2006), a 344-item comprehensive self-report measure of personality and psychopathology that includes 11 clinical scales: somatic complaints, anxiety, anxiety-related disorders, depression, mania, paranoia, schizophrenia, borderline features, antisocial features, alcohol problems, and drug problems. The PAI has strong psychometric characteristics and has been studied extensively among trauma survivors (e.g., McDevitt-Murphy et al., 2005). Quantity and frequency of alcohol use over the previous 6 months were assessed using a single item each. Response options for the frequency item ranged from “I do not drink at all” to “I drink daily or almost daily.” Respondents were asked to indicate the number of standard drinks typically consumed per occasion. Participants who reported any alcohol use in the past 6 months completed the Rutgers Alcohol Problem Index (RAPI; White and Labouvie, 1989) as a measure of alcohol-related problems.

Results

Associations between psychopathology and alcohol consumption

We conducted a series of correlations to evaluate the relations between the 11 specific dimensions of psychopathology

as measured by the PAI and alcohol consumption. Because several previous studies revealed gender differences in these relations (Geisner et al., 2004), we conducted separate correlations for men ($n = 24$) and women ($n = 112$). The analyses with men were underpowered and should be considered preliminary. Among women, typical drinking quantity was significantly associated with the PAI antisocial personality ($r = 0.38$, $P < .01$), borderline personality ($r = 0.31$, $P < .01$), depression ($r = 0.27$, $P < .01$), and stress ($r = 0.21$, $P < .05$) scales. Drinking frequency was associated with the PAI antisocial personality ($r = 0.48$, $P < .01$), borderline personality ($r = 0.25$, $P < .05$), stress ($r = 0.21$, $P < .05$), and aggression ($r = 0.23$, $P < .05$) scales. Among men, typical drinking quantity was associated with the PAI antisocial personality ($r = 0.51$, $P < .01$), borderline personality ($r = 0.37$, $P < .1$), and aggression ($r = 0.48$, $P < .05$) scales. Drinking frequency was not associated with any PAI scales for men.

Associations between psychopathology and alcohol consumption

We conducted a series of hierarchical regression analyses to determine if specific dimensions of psychopathology showed unique associations with alcohol problems as previously mentioned and beyond the effect of alcohol consumption. The sample of male participants was inadequate for regression so we restricted our analysis to women. The first model examined the most established predictor of alcohol use and problems, antisocial personality traits, and revealed that antisocial scale scores predicted alcohol problems after controlling for alcohol consumption ($\Delta R^2 = 0.09$; $t = 3.90$, $P < .01$). Subsequent models evaluated the association between other dimensions of psychopathology after controlling for alcohol consumption and antisocial personality. The following scales predicted alcohol problems after controlling for alcohol consumption and antisocial scores: borderline personality ($\Delta R^2 = 0.14$; $t = 5.52$, $P < .01$), depression ($\Delta R^2 = 0.09$; $t = 4.34$, $P < .01$), PTSD ($\Delta R^2 = 0.08$; $t = 3.89$, $P < .01$), and stress ($\Delta R^2 = 0.06$; $t = 3.19$, $P < .01$).

Discussion

Antisocial personality symptoms showed the strongest relations with alcohol use among men and women. This finding is consistent with other studies indicating that the closely related construct of sensation seeking predicts alcohol use and abuse (Baer, 2002). Borderline personality symptoms also showed strong relations to drinking and accounted for unique variance in women's levels of alcohol-related problems. Students with marked interpersonal conflict, impulsiveness, and emotional dysregulation may be especially prone to drink and to experience negative outcomes resulting from drinking (Chabrol et al., 2005). Stress and depression were associated with alcohol use among women but not men. Stress, depression, and PTSD accounted for unique variance in women's levels of alcohol problems. This is consistent with previous research suggesting that individuals with high levels

of negative affect are especially susceptible to alcohol-related problems (Geisner et al., 2004).

These results suggest that, among college students exposed to trauma, symptoms of depression, PTSD, borderline personality, and life stress confer unique risk for alcohol-related problems. These findings parallel previously reported results from adult samples documenting the role of personality factors and acute trauma-related symptoms in substance abuse among adult sample (Miller et al., 2006). College counseling personnel should assess for alcohol abuse in students with mental health concerns. Alcohol prevention and intervention programs should target students with mental health issues and include a focus on ameliorating psychiatric symptoms as a means of achieving a reduction in alcohol-related problems.

The neuroendocrine stress system and alcohol dependence

Heather N. Richardson, Ph.D.

CRF is a 41 amino-acid residue peptide that mediates neuroendocrine responses to stress through regulation of the HPA-axis (Vale et al., 1981) and behavioral responses to stress through action outside the hypothalamus, primarily targeting cell groups in the limbic system (Britton et al., 1986a, b; Sutton et al., 1982). Hormones of the HPA-axis have been linked to alcohol dependence (Froehlich et al., 2003; Koob and Kreek, 2007; Wand and Dobs, 1991). A dampened ability to cope with stress and negative correlations between cortisol and craving and relapse has been observed in alcoholics (Adinoff et al., 2005; Heinz et al., 1995; Keedwell et al., 2001; Kiefer and Wiedemann, 2004; Lovallo et al., 2000; O'Malley et al., 2002; although see Sher, 2007). It remains unknown whether functional differences in the HPA-axis precede (and possibly drive) alcohol abuse and dependence or result from chronic exposure to this drug.

We hypothesized that voluntary alcohol drinking acutely activates the neuroendocrine stress system, and long-term exposure to alcohol can lead to impaired neuroendocrine function (see Richardson et al., 2008a for details). This hypothesis was tested using an animal model of alcohol dependence (Funk et al., 2006; Gilpin et al., 2008; O'Dell et al., 2004; Richardson et al., 2008b; Walker and Koob, 2007; for related models, see Overstreet et al., 2002; Roberts et al., 1996; Rimondini et al., 2002; Valdez et al., 2002). In this model, rats trained to self-administer alcohol and exposed for several weeks to bouts of high alcohol (e.g., vapors) exhibit an alcohol dependence syndrome characterized by somatic and motivational withdrawal symptoms and engage in excessive drinking when alcohol is made available again ("dependent animals"). Rats trained to self-administer alcohol but exposed for several weeks to control air do not exhibit the dependence syndrome and continue to respond for alcohol at baseline levels when alcohol is made available again

(“nondependent” animals). Serial blood levels were taken via the jugular vein to measure ACTH and corticosterone levels before, during, and after self-administration of alcohol in nondependent and dependent adult male rats. Blood sampling in all animals occurred at a time in which dependent animals were in acute withdrawal (6–8 h after removal from chronic intermittent alcohol vapors). This is a well-studied period of withdrawal when animals made dependent by chronic exposure to alcohol display robust signs of motivational withdrawal, including increased expression of anxiety-like behavior (Baldwin et al., 1991; Rassnick et al., 1993) and elevations in brain reward thresholds (“reward deficits;” Schulteis et al., 1995), and engage in high drinking behavior (Gilpin et al., 2008; Richardson et al., 2008b; Walker and Koob, 2007).

We found that voluntary consumption of alcohol acutely stimulated the HPA-axis in nondependent and dependent animals, but chronic exposure, sufficient to produce dependence, led to a dampened neuroendocrine state. Although dependent animals consumed enough alcohol to produce blood alcohol levels twofold higher than nondependent animals, blood levels of ACTH and corticosterone remained lower than nondependent animals throughout the self-administration session. Notably, self-administration of alcohol elicited relatively mild elevations in HPA hormones in nondependent rats compared with previous reports using forced alcohol in drug-naïve rats (Lee and Rivier, 1997; Lee et al., 2000); thus, we next investigated whether neuroendocrine tolerance functional changes in the HPA-axis may be initiated before dependence onset. Indeed, the same dose of alcohol elicited vastly different HPA responses in trained groups of animals depending on drinking history. ACTH and corticosterone elevations were indeed most robust in “low-responding” nondependent animals (averaging < 0.2 mg/kg/session), intermediate in nondependent animals (averaging ~0.4 mg/kg/session), and most blunted in dependent animals (averaging ~1.0 mg/kg/session) after several weeks of daily 30-min self-administration sessions, suggesting that neuroendocrine tolerance can be initiated before dependence and relates to the amount of alcohol consumed. CRF transcript levels in the hypothalamus and responsivity of the pituitary gland to CRF were next investigated to determine possible mechanisms by which chronic alcohol may downregulate HPA function. Data indicated that decreased expression of CRF mRNA in the paraventricular nucleus of the hypothalamus and reduced sensitivity of the pituitary to CRF may contribute to tolerance early on in the addiction cycle, but these mechanisms do not completely explain the severe impairment in the neuroendocrine stress system observed in the dependent state.

In summary, the present study investigated the relationship between alcohol drinking, chronic alcohol exposure, and the HPA-axis using an animal model of alcohol dependence and combined behavioral, neuroendocrine, and molecular approaches (Richardson et al., 2008a). Operant self-administration of alcohol acutely elevated HPA

hormone levels, but chronic exposure resulted in significant impairment of HPA function, extending earlier studies showing blunted HPA hormones several weeks after withdrawal from chronic alcohol liquid diet compared with alcohol-naïve rats (Rasmussen et al., 2000; Zorrilla et al., 2001; although see Roberts et al., 1992; Tabakoff et al., 1978). Interestingly, although the neuroendocrine stress system is downregulated at this withdrawal time, extrahypothalamic stress responsivity appears to be upregulated, indicated by elevations in extracellular levels of CRF in the central nucleus of the amygdala (Merlo-Pich et al., 1995), and lateral bed nucleus of the stria terminalis (Olive et al., 2002). Furthermore, excessive drinking is specifically sensitive to the blockade of excessive drinking by CRF type I (CRF₁) receptor antagonists in dependent animals (Gilpin et al., 2008; Richardson et al., 2008b). Thus, the present data (Richardson et al., 2008a) in conjunction with several other reports (Chu et al., 2007; Funk et al., 2007; Gehlert et al., 2007; Hansson et al., 2006; Merlo-Pich et al., 1995; Olive et al., 2002; Overstreet et al., 2004; Richardson et al., 2008b; Sabino et al., 2006) suggests a pathway from causal drinking to dependence by which chronic heavy use eventually leads to an imbalance of the hypothalamic and extrahypothalamic CRF systems. Multiple adaptations to stress regulatory systems may be brought about by excessive drinking, including a compromised hormonal response and a sensitized brain stress response, which together contribute to dependence. Supported by NIAAA grants AA06420, AA08459, and AA12602.

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