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Alcohol, Stress, and Glucocorticoids: From Risk to Dependence and Relapse in Alcohol Use Disorders

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Abstract

In this review, we detail the clinical evidence supporting the role of psychological and physiological stress in instrumental motivation for alcohol consumption during the development of mild to moderate alcohol use disorders (AUDs) and in the compulsive, habitual alcohol consumption seen in severe, chronic, relapsing AUDs. Traditionally, the study of AUDs has focused on the direct and indirect effects of alcohol on striatal dopaminergic pathways and their role in the reinforcing effects of alcohol. However, growing evidence also suggests that alcohol directly stimulates the hypothalamic pituitary adrenal (HPA) axis and has effects on glucocorticoid receptors in extrahypothalamic, limbic forebrain, and medial Prefrontal Cortex (PFC) circuits, which contribute to the development of AUDs and their progression in severity, chronicity, and relapse risk. Evidence indicates HPA axis, glucocorticoid, and PFC dysfunction during protracted withdrawal and under high arousal conditions in those with severe AUDs, and novel evidence is also emerging to suggest HPA axis dysfunction with binge/heavy drinking, which is associated with motivation for alcohol in non-dependent individuals. Specifically, alcohol-associated alterations in HPA axis responses to stress and alcohol cues may serve as interoceptive physiological signals and facilitate conditioning mechanisms to influence alcohol motivation. Thus, this dysfunction may serve as a potential biomarker of *both risk and of relapse*. Based on this emerging data, we conceptualize and present early evidence for treatment targets that may improve PFC function and/or normalize HPA axis functioning and may be beneficial in the treatment and relapse prevention of AUDs. Finally, we suggest that individual differences in alcohol-related pathophysiology in these circuits may modulate treatment and recovery response, thereby supporting the need for building personalized medicine algorithms to understand and treat AUDs.

Eighteen percent of Americans suffer from an alcohol use disorder (AUD) at some point during their lifetime and up to 8% of Americans go on to develop severe AUDs (Hasin et al.,

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2007). As a result, the United States loses more than 235 billion dollars a year in health related costs, loss of productivity, premature death, and legal costs (Whiteford et al., 2013). Current models of the development of severe AUDs posit that a shift occurs from alcohol consumption in impulsive binge intoxication episodes to compulsive use accompanied by cognitive preoccupation with alcohol (Koob and Le Moal, 1997). At first, when individuals impulsively consume alcohol, they are both positively reinforced by its euphoric effects and negatively reinforced by its anxiolytic effects. The relative importance of the initial positive vs. negative reinforcement may be linked to differences in the basal functioning of the peripheral stress pathways. However, as individuals progress into AUDs, alcohol consumption is driven more by negative reinforcement and less by the euphoric effects in all users, with alcohol providing relief from uncomfortable and unpredictable affective states (Koob, 2013). Clinical studies of compulsive users also suggest that alcohol does not provide the enjoyment or relief that it once did and that they are lacking any conscious desire to drink; instead, alcohol consumption becomes an automatic, habitual stimulus-response to alcohol-associated environmental cues (Heinz et al., 2009). Cognitive neuroscience approaches have also posited that subconscious attentional biases guide this behavior, instead of a conscious urge to continue or resume drinking (Claus and Hutchison, 2012). We and others have shown that increases in incentive salience drive both conscious craving and subconscious attentional biases, both of which are associated with escalation of alcohol use, abuse, and relapse, and are a result of progressive alcohol-related dysfunction in biological stress response and regulation pathways; changes in these circuits not only affect altered reactivity to and regulation of stress, and positive and negative reinforcing cues, but also promote incentive salience, compulsive motivation, and reductions in self -control (D'Sa et al., 2012; Rando et al., 2011; Sinha, 2013).

In this article, we highlight how alcohol affects the hypothalamic, extrahypothalamic limbic-striatal, and prefrontal stress pathways, acutely and chronically, to influence reward, incentive and compulsive motivation, and self-control processes in the development, progression, and chronicity of AUDs. We present evidence that changes in HPA axis and extrahypothalamic glucocorticoid pathways are not merely part of the compensatory allostatic consequences of excessive alcohol use and abuse, but these effects may play a role in reward, incentive salience, and compulsive alcohol motivation. Finally, it should be noted that while stress and alcohol both activate multiple neurobiological systems, which interact to coordinate behavioral, peripheral, and immune responses, a full discussion of these interactions and their effects is beyond the scope of this review. Rather, this review focuses primarily on stress and alcohol effects on the HPA axis, cortisol, and extrahypothalamic glucocorticoids, and not on alcohol effects on other neurotransmitter and brain systems involved in the stress response or the stress-related immune effects that are also affected by alcohol. For example, we only refer to corticotrophin releasing factor (CRF), opioid, gamma-aminobutryic acid (GABA), noradrenergic and autonomic alterations in reference to their influence on HPA axis and extrahypothalamic responses to alcohol and in the context of compounds and medications that may influence the HPA axis and affect cortisol responses and alcohol motivation and relapse.

1. Acute Stress activates the HPA Axis and Cortico-Striatal Motivation Pathways to Influence Alcohol Consumption

During acute stress, the HPA axis is activated by the corticotrophin releasing factor (CRF) that is released from the paraventricular nucleus (PVN) of the hypothalamus to stimulate the adrenocorticotrophin hormone (ACTH) from the anterior pituitary, which initiates the secretion of cortisol from the adrenal glands. Importantly, CRF also has extensive influence in extrahypothalamic regions and across the corticostriatallimbic pathways, as it modulates the levels of central catecholamines, particularly norepinephrine and dopamine in the Prefrontal Cortex (PFC; (Lavicky and Dunn, 1993). CRF in the amygdala and PFC has been linked to autonomic arousal and stress enhancement of PFC dependent memory via its effects on dopamine and norepinephrine (Herman et al., 2003; Herman et al., 2005; Roozendaal et al., 2002). Recent evidence from human studies suggests that acute stress-related increases in glucocorticoids and catecholamines are *both* required for encoding rewarding or aversive value and reinforcement learning, such as learning related to alcohol consumption as a stress-coping mechanism (Belujon and Grace, 2015; Schwabe et al., 2011).

A wealth of preclinical and clinical data indicates that acute stressors may play a role in the motivation for alcohol consumption in those with and without AUDs (Chaplin et al., 2008; Goeders, 2004; Sinha, 2001; Uhart and Wand, 2009). For example, findings from clinical studies of those with AUDs and ecological momentary assessment (EMA) in non-dependent drinkers generally support the notion that acute exposure to stress or high ratings of negative mood and stress are associated with alcohol use for coping (Breese et al., 2005; Cooney et al., 1997; Dvorak et al., 2014; Litt and Cooney, 1999; Serre et al., 2015; Todd et al., 2009). These findings corroborate well-established human models of addiction, such as the tension-reduction and self-medication models, which emphasize the basic need to boost positive affect via either positive (mood enhancement) or negative (relief from stress) reinforcement processes (Swendsen et al., 2000; Verheul et al., 1999; Weiss et al., 1992).

When alcohol is consumed, phasic bursts of activity from ventral tegmental area (VTA) GABAergic and dopamine neurons in the nucleus accumbens (NAcc) signal its positively reinforcing effects (Spanagel et al., 2014; Yorgason et al., 2014). This positive valence is further encoded by neuroplasticity in the afferent connections of the NAcc to PFC; over repeated use, these connections become overly sensitive to alcohol and increase the motivational drive to consume alcohol (Liu et al., 2011). Additionally, alcohol's initial stimulating effects include increased autonomic and HPA axis arousal and these effects may further potentiate both stress and alcohol-related striatal transmission to influence motivation and reward value of alcohol (Lee and Rivier, 1997). Thus, the initial stimulating effects of alcohol are similar to stress-related arousal, as both promote dopaminergic transmission to support reinforcement learning, thereby providing the basis for an association between stress and alcohol consumption, and alcohol use and abuse as a stress coping mechanism.

2. Acute Alcohol Consumption Co-Stimulates the HPA axis and Cortico-Striatal Motivation Pathways

Many of alcohol's acute effects are also linked to hypothalamic and extrahypothalamic stress regulation pathways. For example, acute intoxication at or above 0.08g% is associated with hypothalamically-driven rises in blood cortisol, ACTH, and norepinephrine (Allen et al., 2011; Borg et al., 1981; Frias et al., 2000; Gianoulakis et al., 1996; Howes and Reid, 1985; Magrys et al., 2013). However, these effects may be modulated by individual vulnerability factors. For example, previous studies suggest that the ACTH, cortisol, and norepinephrine responses to acute alcohol might depend upon family history of alcoholism. Some data show that greater stimulatory effects of mild intoxication (BAC=0.06g%) are seen in those who have positive family history for alcoholism (family history positive, FHP) than in those without family history of alcoholism (family history negative, FHN)(Söderpalm Gordh and Söderpalm, 2011). FHP participants without AUDs also experience greater stress-related craving and consume more alcohol in response to stress than those who are FHN (Söderpalm Gordh and Söderpalm, 2011; Zimmermann et al., 2004). The greater stimulating effects of alcohol consumption in FHP versus FHN subjects may be related to data showing that FHP adolescent boys have blunted basal (tonic) cortisol levels (Schuckit, 1987; Schuckit et al., 1996) and that blunted cortisol in boys promote alcohol and drug intake in adolescence (Moss et al., 1999). Additionally, one study showed that mild alcohol intoxication (average BAC=0.066g%) resulted in blunted HPA axis activity after alcohol consumption relative to placebo in FHN healthy participants, but an *increased* cortisol to ACTH ratio after alcohol consumption in all participants, suggesting that measures of adrenal sensitivity might be more indicative of HPA axis activation to acute alcohol than measures of cortisol or ACTH alone (Mick et al., 2013).

Other factors that may influence HPA axis response to alcohol include dose, acute stress, recent drinking history, and expectancies. Doses of alcohol below 0.08g% have been associated with a decreased HPA axis response in binge heavy drinkers, but greater increases in those with lower to moderate levels of drinking history (Allen et al., 2011; Blaine et al., 2016; Waltman et al., 1993; Zimmermann et al., 2004). A recent study showed that those who are able to mount a high cortisol response to stress also showed an increased cortisol response to low doses of alcohol, but report greater sedative effects with increasing doses of alcohol consumption, which correlates with increased cortisol responses at higher doses of alcohol (Brkic et al., 2016). On the other hand, those who were low cortisol responders to stress showed a blunted cortisol response to acute alcohol and reported significantly less sedation at the highest alcohol dose. The subjective stimulant response to acute alcohol is also blunted by greater recent drinking history, regardless of family history (Ramchandani et al., 2002). This blunted stimulant response is also related to greater acute tolerance to alcohol and thus may contribute to greater consumption (Ramchandani et al., 2002). Additionally, the amount of alcohol consumed within a drinking episode is enhanced via explicit expectancies regarding alcohol-induced increases in stimulation and these expectancies develop based on past experiences with alcohol (Kreusch et al., 2013). These findings suggest that there is a need to systematically examine the effects of acute alcohol doses alone on HPA axis and autonomic arousal during the stimulant and sedative phases of

the acute alcohol response in samples of FHP and FHN subjects matched for recent drinking history, cortisol response to stress, and explicit alcohol expectancies. Specifically, acute dose effects of alcohol and of stress on glucocorticoids and the related corticolimbic striatal circuits underlying stress, reward and motivation (shown in Figure 1) needs further examination to elucidate limbic-striatal interactions with acute alcohol intake, and the impact of alcohol history and individual difference variables on such responses.

3. Altered HPA axis response to Stress and Alcohol may Drive Alcohol Compulsion

After acute, moderate alcohol or stress exposure, the dopaminergic and hypothalamic pathways regain normal healthy basal tone and maintain the ability to phasically respond to novel stimuli. This return to a healthy normal set-point occurs via allostatic processes, which allow the brain and body to achieve physiological stability through challenges to homeostasis by altering cellular structure and function (McEwen, 1998). For example, in the healthy basal state, the number and sensitivity of dopaminergic, corticotropic, and glucocorticoid receptors in corticolimbic-striatal pathways return to pre-intoxication levels. On the other hand, binge/heavy and excessive alcohol consumption results in larger-scale adaptations and wear and tear (allostatic overload) to the reward and neuroendocrine regulation circuits (Koob and Le Moal, 2005; Sinha, 2001); these adaptations may represent the pathophysiology underlying the transition from controlled to compulsive alcohol-seeking in humans (Sinha, 2013; Sinha et al., 2013).

Specifically, with binge and heavy alcohol use, a neuroendocrine tolerance response to stress and alcohol intake is observed (Allen et al., 2011; Heilig et al., 2010; Lovallo, 2006). A number of studies have demonstrated that binge/heavy drinkers show a blunted cortisol response to a fixed moderate or high dose oral alcohol administration and to pharmacological challenges, compared to moderate social drinkers (Allen et al., 2011; Frias et al., 2000; Mick et al., 2013; Söderpalm Gordh and Söderpalm, 2011; Thayer et al., 2006; Waltman et al., 1993). Additionally, neuroimaging research with acute oral and IV alcohol administration has shown blunted amygdala, nucleus accumbens, and prefrontal cortex responses to acute alcohol and negative emotion/fear responses in binge/heavy versus moderate drinking groups (Bjork and Gilman, 2014; Sripada et al., 2011). This blunted response may drive greater, binge/heavy levels of alcohol consumption aimed at reaching the “high” and reward state which was achieved when initial alcohol use led to higher glucocorticoid release (Koob et al., 2014). Therefore, binge and heavy alcohol-associated adaptations in HPA axis and glucocorticoids may not only represent an opponent process that promotes neuroendocrine tolerance, but also result in adaptations that increase compulsive motivation to restore reward tone or hedonic homeostasis (Koob, 1996).

Both preclinical and clinical evidence suggests a role for glucocorticoids in rewarding and subjective “high” states (Piazza and Le Moal, 1996). For example, positron emission tomography (PET) studies have shown that stress-induced cortisol levels positively correlate with amphetamine-induced dopamine release in the ventral striatum and amphetamine-induced “high” (Oswald et al., 2005; Wand et al., 2007). Also, the inability to resist nicotine

under stress is linked to cortisol release and the “high” feeling associated with return to cigarette smoking after stress exposure (McKee et al., 2011). Other evidence indicates that midbrain dopaminergic neurons are responsive to both aversive and rewarding stimuli that are salient and are of motivational significance (Bromberg-Martin et al., 2010; Levita et al., 2012). Together, these findings show that alcohol, stimulants, and stress activate the HPA axis and increase glucocorticoid transmission, which in turn, increases striatal activity by potentiating dopamine release to impact motivation, reinforcement learning, and goal-directed behaviors (Bjork and Gilman, 2014; Levita et al., 2009; Sinha, 2001). Thus, adaptations in biological stress pathways may potentiate anticipatory mesocortical dopamine release and drive compulsive motivation such that stress, alcohol cues, or alcohol itself trigger increases in alcohol craving with a progression from healthy desire without physiologic need or strong intent, to compulsive seeking and strong physiologic need for alcohol (Sinha, 2013). Craving therefore, may represent a relevant marker of the neuroendocrine tolerance and mesocortical sensitization that underlie the progression from use to abuse and to alcohol dependence.

Of note, the subjective experience of acute intoxication reported by binge drinkers matches predictions based on a state of mesocortical sensitization and neuroendocrine tolerance: binge drinkers report that one drink increases craving and stimulation, while light social drinkers report that one drink is anxiolytic and sedating (Holdstock et al., 2000). A recent longitudinal study suggested that those who persist in this behavior through their late twenties and early thirties show greater initial sensitivity to the stimulating effects of alcohol accompanied by lower cortisol release and lower sensitivity to the sedative effects of alcohol than those who do not continue binge drinking (King et al., 2015; King et al., 2011; King et al., 2014). Importantly, those who persist in binge drinking show this same physiological response to an alcohol challenge six years later at followup (King et al., 2014), with one third of the heavy drinking participants meeting criteria for current alcohol dependence at followup in this set of studies. Thus, based on the research cited above, we suggest that blunted HPA axis response to alcohol (and stress) is associated with an increased motivation for binge/heavy alcohol intake, perhaps to normalize or restore HPA axis and dopamine functioning, and may contribute to the transition from binge/heavy drinking to the compulsive loss of control over intake seen in severe AUDs.

4. Chronic Stress and Chronic Alcohol Promote Prefrontal Cortex Dysfunction

In addition to the promotion of HPA axis dysregulation, with both chronic stress and binge/heavy alcohol intake, there is also autonomic dysregulation and sympathetic nervous system over-activity. Sympathetic dominance may be both developed and perpetuated via alcohol and stress-related elevations of central norepinephrine in the PFC and noradrenaline in the circulation (Uylings et al., 2000). Chronic α1 receptor stimulation in the PFC is known to impair attentional processes by attenuating salient “signals” and increasing irrelevant “noise” (Birnbaum et al., 1999). When the PFC cannot distinguish between relevant and irrelevant stimuli, mesolimbic brain regions may show greater bottom-up influence on behavior. Increased noradrenaline peripherally and centrally may further prime the brain to

depend on instinctual and habit-based responding by keeping fight or flight bodily systems (i.e., the HPA axis) activated in the basal state. Furthermore, chronic basal cortisol and norepinephrine exposure from chronic alcohol or stress can maintain excitotoxic cascades that result in decreased dendritic length and decreased spine density of the dendrites in the PFC (Gamo and Arnsten, 2011; Karatsoreos and McEwen, 2013). These structural changes may underlie the PFC dysfunction associated with high levels of uncontrollable stress and AUDs, i.e., decreases in working memory function, poor attention and flexibility, lower behavioral control, and increases in impulsive responding (Arnsten, 2009a; Bechara, 2005; Koob and Le Moal, 2005; Matikainen et al., 1986; Piazza and Le Moal, 1997; Rosenkranz and Grace, 2002; Volkow et al., 2010). In this way, alterations in the HPA axis and autonomic and catecholaminergic pathways interact to take the PFC “off-line-” with a shift towards more habitual responding under these chronic conditions (Arnsten et al., 2012).

Importantly, recent evidence suggests that the ventromedial PFC, which encompasses the rostral anterior cingulate cortex (rACC) and the medial orbitofrontal cortex, influences behavioral and emotional coping responses to alcohol and related cues and stress via direct synaptic connections to the extended amygdala (Etkin et al., 2011; Seo and Sinha, 2011). Preclinical studies show that AUDs are associated with upregulated corticotrophin release factor receptor 1 (CRFR1) receptors throughout the extended amygdala (Heilig et al., 2010). If this upregulation in synaptic relays leads to damage via glucocorticoid -induced excitotoxicity, then self-directed behavior may be even more likely to be replaced by habit and sensory-driven automatic responding (Bechara, 2005; Ochsner and Gross, 2005; Ochsner et al., 2004; Rosenkranz and Grace, 2002; Thayer et al., 2009). For example, acute uncontrollable stress-such as with acute trauma- also up-regulates serine protease tissue-plasminogen activator in the amygdala, resulting in stress-related anxious behavior in mice (Pawlak et al., 2003) and elicits heightened amygdala response and subsequent indiscriminate hypervigilance in humans (van Marle et al., 2009). An increased amygdala response to aversive dangerous stimuli is a natural adaptive mechanism to protect the organism. However, sustained amygdala over-activity, as with trauma states, could debilitate prefrontal regulatory function. In support of this, it was demonstrated that hypersensitive amygdala activity blocks PFC inhibition in order to maximize external sensory input and respond to potential danger in the environment (Rosenkranz and Grace, 2002). These results suggest that continuous stimulation of the limbic-striatal circuit could lead to prefrontal regulatory impairment, which may further disinhibit the activity of amygdala and striatum and aggravate the severity of emotional distress, resulting in clinical conditions of post-traumatic stress states as well as increased alcohol craving and addiction.

Those who develop AUDs experience greater physiological stress than those who drink socially, both from the increased frequency of binge levels of alcohol consumption, from the associated psychological and interpersonal stress, which can then be worsened by maladaptive “drinking to cope” binges (Fox et al., 2007; Fox et al., 2005; Holahan et al., 2001; Park and Levenson, 2002; Sinha et al., 2009a; Thomas et al., 2003) (see Breese et al, 2011 for review). Complex behavioral responses, such as coping mechanisms, require critical input from the PFC, which plays a role in adaptive learning and executive function, including perceiving, modulating and appraising emotion and stress states and also exercising self-control over emotions, desires, and impulses (Maier and Watkins, 2010;

Roberts et al., 1998). Under normal conditions, the PFC can inhibit the physiological response to stress that is related to activation of the HPA axis and the autonomic nervous system (Spencer et al., 2005; Ulrich-Lai and Herman, 2009). Specifically, the PFC inhibits PVN activity via the GABAergic interneurons of the bed nucleus stria termanalis (Radley et al., 2009). Its output can therefore decrease HPA response to alcohol cues, including acute alcohol intake (Lu and Richardson, 2014). However, when one drinks to cope with stress, learning of the association between alcohol and relief, which begins as instrumental, becomes habitual. which may worsen one's ability to cope with stress, further strengthening the association between alcohol and relief, which begins as instrumental, and then becomes habitual. Such shifts from prefrontally-mediated, goal-directed responses to striatal, habit-based responding under stress were elegantly demonstrated in the laboratory by Schwabe et al., (2011). In this study, participants were trained in two instrumental responses associated with food rewards. Then, the food reward was no longer delivered after one of the responses, i.e., the response was devalued. After devaluation, participants received either a placebo injection, yohimbine (an alpha 2 inhibitor) alone, hydrocortisone alone, or both yohimbine and hydrocortisone. In contrast to all other conditions, when both hydrocortisone and yohimbine were given to participants, participants did not show evidence of learning which response was devalued; rather, perpetuation of habit-based responding occurred. In this way, the importance of both glucocorticoid and noradrenergic activity in the shift from prefrontally-mediated, goal directed to habit based responding was demonstrated (Schwabe et al., 2011). In turn, this loss of prefrontally- mediated executive function may support loss of control alcohol consumption in response to stress or alcohol cues.

In support of this, our recent work has also shown that those who show sustained prefrontal hypoactivation in response to stress show greater levels of maladaptive coping, including binge alcohol intake (Blaine et al., 2016; Sinha et al., 2016). Thus, binge alcohol intake and alcohol use disorders may develop as a result of dysfunctional stress biology including the HPA axis and the sympathetic nervous system, and PFC dysfunction in response to a *feed forward* loop of high levels of alcohol intake that leads to greater subjective stress and stress-induced alcohol craving and further increases in alcohol intake. Similarly, high levels of uncontrollable stress or trauma in those with chronic alcohol and/or chronic stress would promote the dysfunctional stress responses as outlined above and once again result in stress-induced alcohol craving and repeated bouts of high alcohol intake (Sinha, 2008a; Sinha, 2008b; Sinha, 2013).

5. HPA Axis and Prefrontal Dysregulation Increase Cue Reactivity and Predict Relapse

Once physical dependence, in addition to psychological dependence, is developed, the absence of alcohol in the nervous system induces allostatic overload in the form of withdrawal. Through repeated cycles of binge consumption and withdrawal, there are significant increases in neuroendocrine tolerance and basal state autonomic upregulation (Breese et al., 2011; Sinha et al., 2011). Specifically, acute withdrawal states are associated with increases in CRF levels in cerebrospinal fluid and blood plasma levels of ACTH, cortisol, norepinephrine, and epinephrine (Breese et al., 2011; D'Sa et al., 2012; Hawley et

al., 1985; Heilig et al., 2010; Markus et al., 2002). In addition, in several previous studies by our group, we have shown that early abstinence up to 4 weeks is associated with continued high basal ACTH and cortisol as well as higher basal heart rates, and blunted or suppressed ACTH, cortisol, and heart rate responses to pharmacological and psychological challenges in alcohol dependent individuals (Fox et al., 2012a; Fox et al., 2008; Sinha, 2012; Sinha et al., 2012; Sinha et al., 2011a; Sinha et al., 2009b). We also showed that both the persistent enhanced basal stress state and also the blunted responses to stress, along with high stress-induced alcohol craving, modulated the propensity for these early abstinent, treatment engaged AUD individuals to future alcohol relapse (Sinha et al., 2011b).

One additional mechanism by which the enhanced stress state seen in withdrawal leads to relapse may be through altered alcohol and stress cue reactivity. In a series of studies in our laboratory, participants were exposed to stress, alcohol cue, and neutral imagery paradigms both in the laboratory and during fMRI scans. Findings indicated that craving, adrenal sensitivity, and VmPFC hypoactivity following exposure to stress-related and alcohol cue-related imagery predicted shortened time to relapse, such that disrupted neutral state PFC function appears to mediate the relationship between adrenal sensitivity and future relapse risk (Blaine et al., 2015). Importantly, the study findings indicate that heightened peripheral tonic arousal may be associated with diminished prefrontal executive control over striatal and limbic circuits during stress in those with severe AUDs in early abstinence. Disrupted ventromedial and superior prefrontal executive control functioning occur with multiple detoxifications and each successive detoxification is also known to jeopardize abstinence and alcohol recovery, in addition to performance in emotion and incentive conflict tasks in alcohol dependent individuals (Duka et al., 2011; O'Daly et al., 2012). The associated lack of top-down inhibition may result in increased craving and a resumption of drinking behavior in newly abstinent patients (Heinz et al., 2009). The negative reinforcing effects of a return to drinking on a sensitized stress system have been broadly highlighted by the fact that treatment and laboratory studies have documented stress and negative mood as robust predictors of both medication response (Sofuoglu et al., 2013) and treatment outcome (Mulvaney et al., 1999). Relapse to resumed consumption of alcohol then further worsens autonomic and HPA axis dysfunction preventing restoration and recovery of the dysfunctional stress biology, making the next recovery attempt more difficult (Koob et al., 2014). In fact, these alterations in the

6. Summary of HPA axis dysfunction in Alcohol use, Abuse, and Relapse

In the previous sections, we described human studies on the effects of acute and chronic alcohol intake on the HPA axis, their association to brain prefrontal-limbic and striatal dysfunction, and the evidence that alcohol and stress-related dysfunctional tonic and phasic cortisol responses may not only represent biomarkers of central glucocorticoid adaptations but also may play a role in alcohol motivation. We discussed how acute alcohol's stimulating effects involve activation of sympathetic arousal and the HPA axis, but with binge/heavy use, autonomic nervous system and HPA axis tolerance develops, resulting in higher basal sympathetic and HPA axis tone, and blunted cortisol and heart rate responses to alcohol and stress. This blunted phasic effect has been associated with higher alcohol intake in binge/heavy drinkers, supporting the notion that such alcohol-related stress adaptations may

contribute to higher alcohol motivation and intake. Furthermore, acute alcohol withdrawal (both clinical and subclinical) and early abstinence, and repeated cycling through binge/heavy use and the associated withdrawal from alcohol, are also marked by higher tonic levels of heart rate and cortisol, along with an overactive, hyper-excitable VmPFC under basal and relaxed states, which are known to predict return to drinking and alcohol relapse. These tonic and phasic alterations are illustrated in a cartoon schematic shown in Figure 4, showing that binge/heavy and chronic alcohol use disrupts both tonic and phasic cortisol levels which in turn drives increased and compulsive behavioral alcohol motivation due to allostatic load in central homeostatic stress and arousal pathways. On the basis of these findings, we have suggested that normalizing both the tonic and phasic cortisol responses may be needed to successfully address alcohol use disorder risk and relapse (Milivojevic and Sinha, 2016).

7. Alcohol-related Stress Adaptations: Implications for Alcoholism Treatment and Prevention

Evidence in the previous sections outline the alcohol-related disruption in the HPA axis and the cortisol responses that are associated with decreased prefrontal executive control over stress and reward systems, which may result in increased craving and a greater susceptibility to habit-based maladaptive coping, i.e., relapse to drinking behavior (Heinz et al., 2009; Seo and Sinha, 2014; Sinha, 2008a). Resumed consumption of alcohol and the repeated cycles of binge/heavy alcohol intake along with associated withdrawal may eventually lead to even further decreased reward functioning and neuroendocrine tolerance. The allostatic overload in these systems may also weaken the regulatory influence of the PFC over hypothalamic and extrahypothalamic stress and reward circuits (Seo and Sinha, 2014; Sullivan and Pfefferbaum, 2014), and prevent restored functioning of these pathways to support alcoholism recovery. It follows that medications or behavioral strategies that normalize or improve PFC function and also reduce the HPA axis over-reactivity in the basal state, while also normalizing blunted HPA axis phasic responses may improve treatment outcomes. As discussed in other articles of this special issue, medications which target HPA axis and PFC dysfunction successfully reduce drinking behaviors in preclinical studies. Findings from these basic science studies have identified several pharmacological treatment targets to address stress-induced reinstatement of drug seeking and relapse susceptibility.

Human laboratory models can be effectively used to assess whether treatment with specific pharmacological compounds, versus placebo, can address alcohol-related disruptions in HPA axis function, as well as alcohol craving and intake (Sinha, 2009; Sinha et al., 2009a; Sinha et al., 2011c). A number of human laboratory and clinical outcome studies have been conducted to screen relevant compounds to assess the effects of stress, alcohol cues or alcohol intake exposure on intermediate markers of stress-related relapse susceptibility and available clinical outcome data. The results of these studies are also discussed in other articles in this special issue. Briefly, basic science data suggest CRF antagonists and noradrenergic agents could be promising in addressing stress-related relapse, but results from human laboratory studies using randomized, placebo controlled designs have been inconclusive. In this section, we briefly review the evidence in humans regarding

pharmacological agents and medications that affect the HPA axis and alter cortisol responses to alcohol, stress or alcohol cues, and also their potential effects on alcohol craving, intake and relapse. Table 1 presents a summary of these findings.

Naltrexone (NTX) is an approved medication for AUDs and has been shown to have a modest, but significant effect as an anti-craving medication for AUDs (O'Brien et al., 1996; O'Malley et al., 1996; O'Malley et al., 1992; Volpicelli et al., 1992). In a laboratory study, O'Malley et al., (2002) gave non-treatment seeking alcohol dependent individuals 50 mg/day of naltrexone or placebo for 6 days in a double blind manner and assessed their responses to an initial alcohol priming drink that raised blood alcohol levels to 0.03 g/dl followed by a self-administration period with an opportunity to drink up to 8 drinks in a two-hour period (O'Malley et al., 2002). NTX treatment increased cortisol levels at baseline and decreased alcohol craving, while also increasing alcohol-stimulated ACTH and cortisol responses compared to placebo; these increases in HPA axis function were associated with less drinking in the NTX group compared to placebo. It appears that NTX may have reduced the alcohol-related neuroendocrine tolerance and improved alcohol's effects in stimulating the HPA axis, thereby reducing the blunted alcohol response on the HPA axis, which may contribute to NTX's AUD treatment efficacy and as an anti-craving agent. However, the findings also showed that NTX increased basal HPA axis tone and tonic cortisol levels relative to placebo, an effect that we speculate is detrimental for AUD individuals with higher subclinical and clinical HPA axis alcohol withdrawal/abstinence pathophysiology. It is possible that this aspect of NTX effects may make NTX not suitable for all AUD individuals, which may also contribute to its modest efficacy in AUDs. That is, one component of the HPA axis disruption, namely blunted HPA axis response to alcohol and possibly to stress is improved by NTX, but the high basal HPA axis tone is not addressed and maybe worsened by NTX.

Several laboratory studies have also examined compounds that directly act on the stress system for their effects on alcohol craving and stress responses. For example, 7 days of 300 mg/day of theCRF antagonist pexacerfont, followed by 100 mg/day for 23 days versus placebo, was assessed in a laboratory study of stress and cue-induced craving in anxious alcoholic patients. Findings indicated that pexacerfont did not reduce alcohol craving and had a transient, modest, but significant effect in reducing ACTH levels and in increasing cortisol responses to stress (Kwako et al., 2014). In another study by the same group, another CRF antagonist, verucerfont, or placebo was administered to anxious alcohol dependent women; they found that it potently reduced DEX-stimulated HPA axis response but did not significantly reduce alcohol craving and effects on alcohol intake were not studied (Schwandt et al., 2016).

In addition to CRF antagonists, noradrenergic compounds that have central effects on autonomic, HPA axis and prefrontal stress pathways have been studied, with some positive effects observed. In an inpatient laboratory study, abstinent AUD patients were titrated up to 16 mg/day of Prazosin, which is a alpha1-antagonist that reduces central adrenergic effects of stress (Arnsten, 2009b), or placebo over a 3 week period and then exposed to stress, alcohol cue, and neutral relaxing imagery on separate days and alcohol craving and HPA axis measures were assessed (Fox et al., 2012a). We found that prazosin reduced stress-

induced alcohol craving and negative emotions as well as reduced basal cortisol responses while increasing stress-induced cortisol responses. While alcohol consumption was not assessed in the study, Simpson et al., (2009) previously reported in a pilot study that Prazosin reduced alcohol intake (Simpson et al., 2009), and Prazosin and the related compound Doxazosin (Kenna et al., 2015) are both being assessed in clinical outcome studies.

We have also studied Guanfacine (2/3 mg/day), which is a alpha2 adrenergic agonist that reduces norepinephrine centrally and in prefrontal regions, versus placebo in cocaine dependent individuals who were also abusing alcohol and separately in tobacco dependent individuals. Findings indicated that Guanfacine reduced cue-induced drug and alcohol craving, and showed better self-control over nicotine lapse behavior after stress exposure, and interestingly, both improved prefrontal activation during stress and challenge states, as well as a reduction of baseline cortisol and improved stress-induced cortisol response (Fox et al., 2012b; Gaiser et al., 2015). However, there were dose related effects, with the 3 mg/day effect showing better outcomes and greater efficacy in cocaine and alcohol abusing women than men (Fox et al., 2015); some gender effects have also been noted in tobacco cessation effects (Glassman et al., 1993).These effects suggest the need to further explore guanfacine effects in alcohol dependence and specifically for alcoholic women.

As inhibitory GABAergic pathways are involved in modulating the HPA axis (Cullinan et al., 2008), we also assessed whether using the sex steroid hormone progesterone (as a probe for increasing the brain neurosteroid Allopregnenolone (ALLO)) could help in modulating both drug craving and HPA axis dysfunction in cocaine dependent, alcohol abusing individuals. Progesterone has been shown to decrease the subjective effects of cocaine (Sofuoglu et al., 2004) and improve cocaine use outcomes (Yonkers et al., 2014) and we previously showed that progesterone (400 mg/day) versus placebo administered for 7 days reduced cue-induced cocaine craving and improved prefrontal function as measured by Stroop performance (Fox et al., 2013). In a follow-up study, we measured basal levels of the neurosteroid ALLO while on 5 days of progesterone versus placebo to assess if progesterone effects in this study were due to increased levels of ALLO. Indeed, we found that the high ALLO group (treated with progesterone) versus the low ALLO group showed reduced overall drug and alcohol craving, improved Stroop performance, and both reductions in basal cortisol levels as well as increased cortisol in response to stress (Milivojevic et al., 2016). While there are no direct data on neurosteroid treatment in alcohol dependent individuals, these data support our notion that compounds and approaches that normalize HPA axis function need to be explored to fully test whether addressing this stress-related pathophysiology in alcohol use disorders with specific targeted treatments may be helpful in improving alcoholism relapse and recovery outcomes.

8. Conclusions and Future Directions

The previous sections cite evidence from laboratory and neuroimaging experimental studies, along with prospective clinical designs, indicating alcohol effects on the stress axis and its role in stress responses, alcohol craving, and risk of relapse. The psychobiological and neuroimaging research points to alcohol-related changes in brain and peripheral stress

pathways and the impact of those changes on increasing compulsive alcohol motivation, craving and relapse risk. We also discussed the state of research on acute alcohol stimulating effects on HPA axis responses and the influence of not only alcohol dose, but also alcohol drinking history, family history and gender on HPA axis and cortisol responses, as well as motivation for alcohol and alcohol use. We also presented evidence that binge heavy and chronic alcohol use is associated with blunted HPA axis responses to stress and to alcohol challenges relative to social drinkers. Furthermore, parallel hypoactivation in the amygdala and ventral striatum as well as prefrontal regions are associated with negative emotion, stress, and acute alcohol dose response in binge/heavy non-dependent drinkers. In alcohol dependent individuals relative to healthy controls, 4 weeks of abstinence from alcohol is associated with higher levels of anxiety when relaxed and when exposed to alcohol cues, greater emotional distress, and increased stress- and alcohol cue-induced craving. These states are accompanied by disruption in normal functioning of the peripheral stress pathways, with greater tonic cortisol and heart rate responses at baseline or during relaxed states and a blunted stress cortisol and heart rate response with exposure to stress and challenge states in AUD patients relative to controls.

We further noted that basal and relaxed state corticostriatal hyperactivity in the VmPFC and ventral striatum (VS), and blunted neural responses in these regions during stress and alcohol cue exposure, predicted alcohol relapse and severity of relapse in those with AUDs. Furthermore, there is an association between the high tonic HPA axis and sympathetic basal overactivity and neural hyperactivity in the VmPFC and VS regions during early abstinence. Such relationships highlight a connection between HPA axis dysregulation and alcohol-related brain dysfunction in extrahypothalamic and cortico-striatal pathways involved in biobehavioral regulation of the stress response. A lack of normal stress regulation during this early abstinence period leaves the recovering alcoholic highly vulnerable to high craving, anxiety, and risk of relapse, particularly under stressful conditions and when faced with alcohol-related stimuli in the environment. Finally, we suggested that these biological stress dysfunction measures may serve as biomarkers and used clinically to identify people at high risk of relapse. Thus, individuals who show chronic alcohol-related effects on neural and biobehavioral aspects of stress and craving could benefit from treatments that target stress effects on craving and alcohol seeking. Several novel medications that target the stress pathways are now being tested and a brief summary of these targets for their effects on the specific relapse risk measures identified were presented in the section above. Development of such treatment strategies may be of tremendous help in normalizing stress responses and decreasing alcohol craving and improving brain recovery from alcohol use disorders.

Lastly, it should be noted that individual differences in chronic alcohol-related adaptations in stress pathways would be important considerations in evaluating alcohol-related stress system effects and their impact on relapse and treatment outcomes. The development of compulsive motivation and the role of cortisol in preoccupation/anticipation may differ among individuals due to genetic, epigenetic, and environmental differences. It is also important, therefore, to recognize that AUD-related changes exist on a continuum and that individual differences in genes and environment may moderate the response to medication. The effects of individual differences in alcohol-related genes, their expression patterns, and alcohol and stress effects on epigenetic changes may modulate the neural and biobehavioral

stress system markers to influence treatment outcomes. Furthermore, sex differences in these responses as well as the influence of trauma, adversity, and co-morbid health conditions are also important factors that impact the alcohol-stress interactions and may moderate potential treatment effects of compounds that target the alcohol-related stress dysfunction described in previous sections. Consideration of all of these genetic, individual, and environmental factors on risk and relapse in AUDs further support the need for a personalized medicine framework in reducing risk of development of AUDs as well as in improve treatment and recovery outcomes in AUDs.

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Highlights

- Stress and alcohol's acute and chronic effects are linked to stimulation and alterations in the hypothalamic and the prefrontal-limbic-striatal stress and reward regulation pathways.
- In the development of AUDs, craving and compulsive motivation are linked to altered alcohol cue-related signals with dysfunctional hypothalamic and medial prefrontal responses to these arousal states.
- In severe AUDs, altered basal hypothalamic and prefrontal function are linked to the chronic, relapsing nature of the disorder.

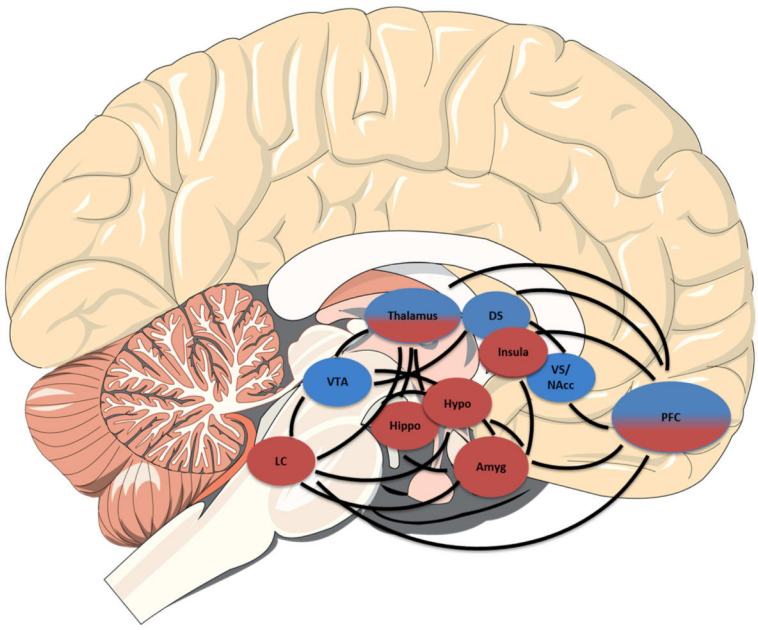

Figure 1.

Specific regions of the corticolimbic striatal circuitry that are influenced by alcohol (in blue) and by stress (in red) to identify the overlapping hypothalamic and extra-hypothalamic brain pathways underlying stress, reward, and motivation.

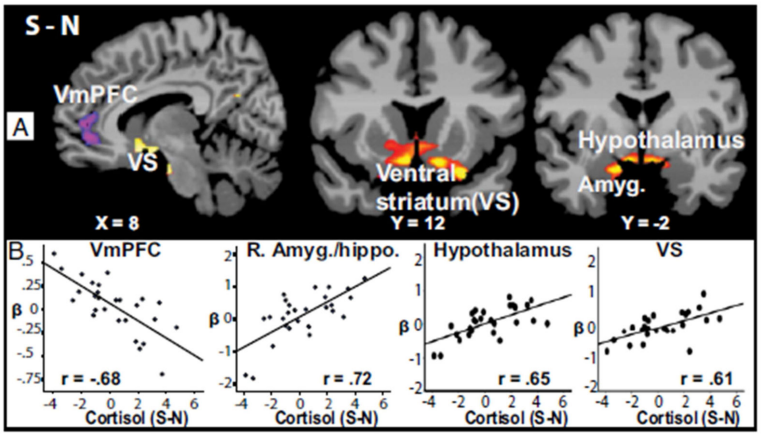

Figure 2.

The relationship of simultaneous measurement of cortisol during brief sustained stress exposure relative to no-stress neutral exposure with key corticolimbic-striatal brain regions are shown. Correlation images from whole brain regression analysis showing association between stress-neutral (S-N) brain activity and cortisol response (S-N) are shown in *A* ($p<0.05$, whole brain corrected). Corresponding scatterplots from extracted beta weights of key corticostriatal-limbic regions of interest (ROIs) indicate areas of association from the S-N regression map and the S-N cortisol responses are shown in *B*. Red/yellow, positive correlation; blue/purple, negative correlation. (Reproduced with permission from Sinha et al., 2016, Proceedings of the National Academy of Sciences).

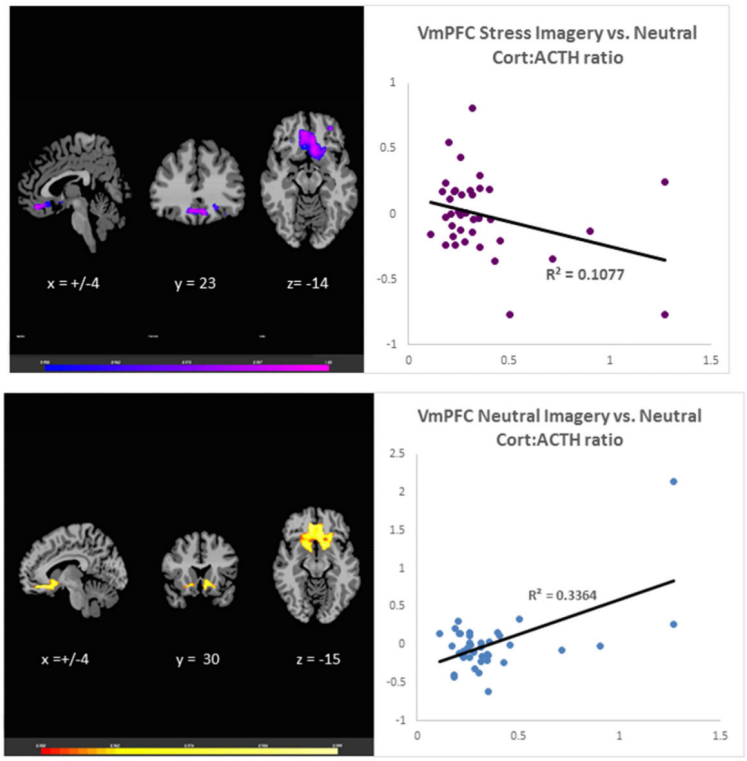

Figure 3.

Whole brain correlation between disrupted adrenal sensitivity (Cortisol:ACTH ratio) and VmPFC and ventral striatal dysfunction during neutral (tonic) and stress (phasic) responses in 4-week abstinent recovering alcoholics. Both responses predicted future return to alcohol intake (Reproduced with permission from Blaine et al., Addiction Biology, 2015).

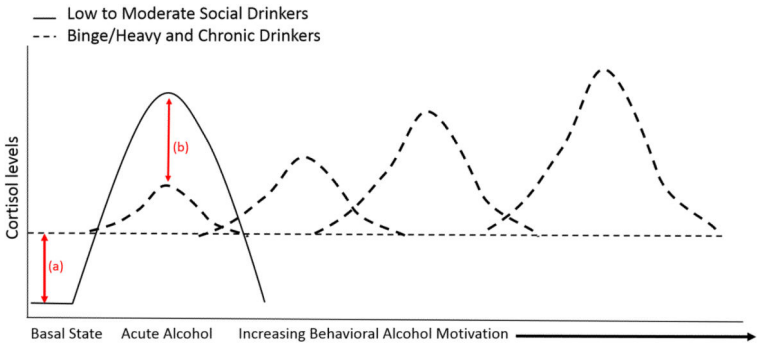

Figure 4.

Schematic Model Positing the Relationship between Tonic and Phasic Cortisol and Increased Alcohol Motivation and Intake. The solid line indicates the response to acute consumption in Low to Moderate Social Drinkers with less behavioral motivation and low self-administration of alcohol, whereas the dashed lines indicate high behavioral motivation and thus increased acute alcohol intake in Binge/Heavy and Chronic Drinkers. (a) A higher basal cortisol level is shown in Binge/Heavy and Chronic Drinkers relative to low-moderate, and (b) illustrates greater behavioral motivation and higher level of alcohol intake in Binge/Heavy and Chronic Drinkers with higher self-administered alcohol intake required to increase initial blunted cortisol responses towards more normal levels.

Table 1

Medications that have been tested for their effects on HPA axis function, craving, and/or substance abuse (drug/alcohol) intake in those with addictive disorders.

	Tonic Cortisol Level	Phasic Cortisol Response	Alcohol/Drug Craving[a]	Alcohol/Drug Intake[b]
Naltrexone[1-5]	↑	↑	↓	↓
Progesterone[6-8]	↓	↑	↓	↓
Allopregnanalone[9]	↓	↑	↓	?
Prazosin[10-11]	↓	↑	↓	↓
Guanfacine[12-15]	↓	↑	↓	↓
Verucerfont[16]	?	↓	-	?
Pexacerfont[17]	-	↑	-	?

Note: It is hypothesized that interventions that normalize the high tonic and blunted phasic cortisol response by both reducing the tonic level as well as increasing the phasic response to alcohol and stress may effectively address the stress-related pathophysiology in AUDs.

Citations are as follows:

[1] O'Malley et al., 2002.

[2] O'Brien et al., 1996,

[3] O'Malley et al., 1992

[4] O'Malley et al., 1996

[5] Volpicello, 1992.

[6] Fox et al., 2015.

[7] Yonkers et al., 2014.

[8] Sofuoglo et al.,2004.

[9] Milivojevic et al, 2016.

[10] Fox et al., 2012.

[11] Simpson et al., 2009.

[12] Fox et al., 2012.

[13] Gaiser et al., 2015.

[14] Fox et al., 2015.

[15] Glassman et al., 1993.

[16] Schwandt et al., 2016.

[17] Kwako et al., 2014.

[a] Response to Stress/Cues

[b] Clinical or Lab Study Outcome

- Null findings

~Equivocal findings