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Invited review

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.

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Contents

Eighteen percent of Americans suffer from an alcohol use disorder (AUD) at some point during their lifetime and up to 8% of

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Americans go on to develop severe AUDs (Hasin et al., 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 corticostriatal-limbic 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, 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 0.08 g% 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 = 0.06 g%)