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Invited review

Influence of stress associated with chronic alcohol exposure on drinking

Howard C. Becker, PhD *

Charleston Alcohol Research Center, Department of Psychiatry and Behavioral Sciences, Department of Neuroscience, Medical University of South Carolina, RHJ Department of Veterans Affairs, Charleston, SC 29464, USA

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ABSTRACT

Stress is commonly regarded as an important trigger for relapse and a significant factor that promotes increased motivation to drink in some individuals. However, the relationship between stress and alcohol is complex, likely changing in form during the transition from early moderated alcohol use to more heavy uncontrolled alcohol intake. A growing body of evidence indicates that prolonged excessive alcohol consumption serves as a potent stressor, producing persistent dysregulation of brain reward and stress systems beyond normal homeostatic limits. This progressive dysfunctional (allostatic) state is characterized by changes in neuroendocrine and brain stress pathways that underlie expression of withdrawal symptoms that reflect a negative affective state (dysphoria, anxiety), as well as increased motivation to self-administer alcohol. This review highlights literature supportive of this theoretical framework for alcohol addiction. In particular, evidence for stress-related neural, physiological, and behavioral changes associated with chronic alcohol exposure and withdrawal experience is presented. Additionally, this review focuses on the effects of chronic alcohol-induced changes in several pro-stress neuropeptides (corticotropin-releasing factor, dynorphin) and anti-stress neuropeptide systems (nocicepton, neuropeptide Y, oxytocin) in contributing to the stress, negative emotional, and motivational consequences of chronic alcohol exposure. Studies involving use of animal models have significantly increased our understanding of the dynamic stress-related physiological mechanisms and psychological underpinnings of alcohol addiction. This, in turn, is crucial for developing new and more effective therapeutics for treating excessive, harmful drinking, particularly stress-enhanced alcohol consumption.

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Contents

Abbreviations: HPA, hypothalamic-pituitary-adrenocortical; CRF, corticotropin-releasing factor; DYN, dynorphin; KOR, kappa opioid receptor; CeA, central nucleus of the amygdala; BNST, bed nucleus of the stria terminalis.

* Charleston Alcohol Research Center, Departments of Psychiatry and Neuroscience, 67 President Street, MSC-861, Medical University of South Carolina, RHJ Department of Veterans Affairs, Charleston, SC 29425 USA.
E-mail address: beckerh@musc.edu.

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1. Introduction

It is generally acknowledged that stress is an important factor in alcohol abuse and alcohol use disorders. However, the influence of stress on alcohol drinking is complex and not fully understood. On the one hand, alcohol has anti-anxiety properties, serving as an effective anxiety-reducing (anxiolytic) agent. Hence, motivation for drinking may be driven, at least in part, by its ability to alleviate stress, including stress associated with periods of abstinence following bouts of heavy drinking (Cappell and Greeley, 1987; Sayette, 1999). This has been the cornerstone of the tension-reduction hypothesis of alcoholism (Conger, 1956). From a behavioral perspective, this defines how alcohol can serve as a negative reinforcer (i.e., alcohol consumption results in the removal (alleviation) of an aversive or unpleasant (anxiety) state).

At the same time, it is firmly established that alcohol, itself, is a stressor. Acute alcohol exposure activates the hypothalamic-pituitary-adrenocortical (HPA) axis, a major component of the neuroendocrine stress response (Smith and Vale, 2006). This effect has been shown to be mediated through direct stimulation of neurons in the paraventricular nucleus (PVN) of the hypothalamus, leading to the release of corticotropin-releasing factor (CRF) (and vasopressin) that induces secretion of adrenocorticotrophic hormone (ACTH) from the pituitary, which subsequently acts at the adrenal gland to release glucocorticoids into circulation (Lee et al., 2004; Rivier, 2014). It has been suggested that stress may increase motivation to imbibe through synergistic effects on reward circuitry in brain (e.g., mesolimbic dopamine transmission). That is, the activating effects of stress and alcohol on dopamine neurotransmission and on the HPA axis (elevated glucocorticoids) may combine to enhance the rewarding effects of alcohol, thereby facilitating greater propensity to drink (Stephens and Wand, 2012; Uhart and Wand, 2009).

Thus, the interaction between stress and alcohol is very complex. Alcohol can alleviate stress while at the same time provoke a stress response. The dynamic interplay between numerous biological and environmental variables along with experiential factors plays a critical role in defining subjective aspects of stress (i.e., perception and appraisal of a stressful event) as well as how response to stress impacts decisions about alcohol drinking and the manner in which alcohol consumption alters stress responsiveness. Recently, greater attention has focused on examining how a history of chronic alcohol exposure and withdrawal influences the capacity of stress to modulate alcohol consumption. Indeed, stress contributes to dynamic changes underlying transition to alcohol addiction and influences drinking at all stages of the addiction process.

Prolonged excessive alcohol consumption constitutes a potent stressor to the organism, setting in motion a host of neuroadaptive changes within brain reward and stress systems (Becker, 2012; Hansson et al., 2008; Koob, 2013; Koob and Le Moal, 2008; Vengeliene et al., 2008). Stress associated with chronic alcohol exposure and withdrawal experience continually challenges the organism through progressive dysregulation of brain reward and stress systems beyond normal homeostatic limits (Koob, 2003). These neuroadaptive changes are postulated to impact neural and physiological systems integral to the motivational effects of alcohol and, consequently, contribute to escalation of drinking and maintenance of sustained excessive alcohol consumption associated with dependence (Becker, 2012, 2013; Heilig et al., 2010; Koob, 2013). In this vein, alcohol dependence may be viewed as a persistent dysfunctional (allostatic) state, with the organism rendered ill-equipped to exert appropriate behavioral control over alcohol consumption, as well as appropriately respond to other (additional) stressful events that may provoke return to excessive drinking.

This article reviews literature indicating the complex reciprocal relationship between stress and alcohol, with particular emphasis on animal models demonstrating how stress associated with chronic alcohol exposure and withdrawal experience serves as a continual physiological, psychological, and behavioral challenge to the organism. Neuroadaptive (and maladaptive) mechanisms underlying a negative emotional state, altered stress responsiveness, and increased motivation to seek and consume alcohol are key components of the addiction process. The article highlights studies showing that prolonged exposure to alcohol produces perturbations in neuroendocrine and brain stress systems that interface with and influence motivational and reward circuitry in the brain, ultimately rendering subjects more vulnerable to relapse and driving excessive levels of alcohol consumption.

2. Stress associated with chronic alcohol exposure and withdrawal

As previously noted, alcohol activates the HPA axis, with the magnitude and response profile influenced by a host of variables (Lu and Richardson, 2014; Rivier, 2000; Wand, 2000). These include a number of alcohol-related factors (e.g., history of use, level and pattern of drinking, timing of accessibility of alcohol in relation to stress experience) as well as stress-related factors (e.g., type, chronicity, intermittency, predictability, controllability) that intersect with a number of biological variables (e.g., genetics, age, sex). As reported in clinical studies, experimental studies have documented profound disturbances in HPA axis function following chronic alcohol exposure and withdrawal. For example, studies in rodents have shown that chronic alcohol consumption results in a general elevation in blood corticosteroid levels, with a typical flattening of normal circadian fluctuations (Kakihana and Moore, 1976; Keith and Crabbe, 1992; Rasmussen et al., 2000; Tabakoff et al., 1978). At the same time, there is a dampened HPA response to subsequent CRF or stress challenge (Lee et al., 2000; Rivier et al., 1990). Additionally, the ability of alcohol to activate the HPA axis is blunted following chronic exposure to the drug (Richardson et al., 2008a), an effect thought to contribute to perpetuation of heavy drinking (Lu and Richardson, 2014).

Periods of abstinence (i.e., withdrawal) are characterized by elevated glucocorticoid levels that reflect increased HPA axis activity. This, along with increased activity of the sympathetic division of the autonomic nervous system, mediate an array of