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ALCOHOL, STRESS HORMONES, AND THE PREFRONTAL CORTEX: A PROPOSED PATHWAY TO THE DARK SIDE OF ADDICTION

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Abstract—Chronic exposure to alcohol produces changes in the prefrontal cortex that are thought to contribute to the development and maintenance of alcoholism. A large body of literature suggests that stress hormones play a critical role in this process. Here we review the bi-directional relationship between alcohol and stress hormones, and discuss how alcohol acutely stimulates the release of glucocorticoids and induces enduring modifications to neuroendocrine stress circuits during the transition from non-dependent drinking to alcohol dependence. We propose a pathway by which alcohol and stress hormones elicit neuroadaptive changes in prefrontal circuitry that could contribute functionally to a dampened neuroendocrine state and the increased propensity to relapse—a spiraling trajectory that could eventually lead to dependence.

Key words: alcohol use disorders, hypothalamic pituitary adrenal axis, prefrontal cortex, animal models, dependence, glucocorticoids.

Contents

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Abbreviations: ACTH, adrenocorticotropic hormone; CRF, corticotropin-releasing factor; dmPFC, dorsal portion of the mPFC; GR, glucocorticoid type II receptor; HPA, hypothalamic pituitary adrenal; *iv*, intravenous; mPFC, medial prefrontal cortex, MR, mineralocorticoid receptor; PVN, paraventricular nucleus of the hypothalamus.

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OVERVIEW

Alcoholism is a neurobehavioral disorder characterized by compulsive seeking of alcohol, excessive and uncontrolled intake, and the emergence of a negative emotional state (e.g., irritability, anxiety, depression) when alcohol is unavailable (American Psychiatric Association, 1994). Preclinical studies in rodents suggest that the transition from alcohol *use* to *abuse* to *dependence* is due to alterations in stress-related neural pathways resulting from exposure to repeated cycles of alcohol intoxication and withdrawal (Heilig and Koob, 2007; Breese et al., 2011). Alcohol dependence is characterized by impaired functioning of the hypothalamic pituitary adrenal (HPA) axis (Adinoff et al., 1990; Wand and Dobs, 1991; Lovallo et al., 2000; Rasmussen et al., 2000; Zorrilla et al., 2001; Richardson et al., 2008). HPA dysfunction is thought to contribute to a number of symptoms, including dysphoria, alcohol craving, and enhanced propensity to relapse early in abstinence (Lovallo, 2006; Li et al., 2011; Sinha et al., 2011; Stephens and Wand, 2012).

Here we review alcohol use disorders and describe how preclinical and clinical studies together have implicated dysfunction of the HPA axis and prefrontal cortex in these disorders. We first provide an overview of some of the preclinical rodent models that have been designed to study drinking behavior at different stages of alcohol use disorders. With the focus on evidence from these drinking models, we discuss the bi-directional relationship between alcohol and stress hormones. The HPA axis undergoes adaptations from non-dependent drinking to alcohol dependence and we examine some of the mechanisms that may contribute to changes in stress hormone levels. Toward the end of the review, we pull together information from various studies that supports the following hypothesis: *continued heavy use of alcohol causes glucocorticoid-mediated adaptations within the HPA axis and upstream in the prefrontal cortex that lead to neuroendocrine dysfunction and a heightened propensity to relapse*. We posit that

the complex interplay between alcohol, stress hormones, and the prefrontal cortex may be a critical factor in the transition from social drinking to problematic drinking and alcoholism. More research should be directed toward exploring the possibility of adaptations in the HPA dysregulation driven by alterations in the prefrontal cortex regulation over time. These studies could provide a new avenue of therapeutic intervention that may be extremely effective, as prefrontal dysfunction and HPA dysregulation are both thought to play a functional role in escalation of drinking and relapse (Stephens and Wand, 2012).

ALCOHOL USE DISORDERS AND PREFRONTAL CORTEX

The prefrontal cortex integrates information from other cortical and subcortical regions to functionally contribute to working memory, emotion regulation, and behavioral control (Wilson et al., 2010; Kesner and Churchwell, 2011). Structural, physiological, and behavioral deficits related to the prefrontal cortex have been observed in alcohol use disorder patients. These functional changes include reduced glucose metabolic rates, cortical atrophy, decreased cognitive flexibility, and memory performance (reviewed in Fadda and Rossetti, 1998; Moselhy et al., 2001; Stephens and Duka, 2008). In addition, prefrontal deficits are tightly associated with HPA dysregulation in alcoholic men (Errico et al., 2002). Because the prefrontal cortex provides top-down control over the HPA axis, it is possible that neuroadaptive changes in this region could underlie some of the changes in stress hormones (Lovallo, 2006; Herman, 2012). Preclinical animal models can be useful tools for dissecting complex interaction between alcohol, stress hormones, and the prefrontal cortex. Below we briefly describe these models.

ANIMAL MODELS OF ALCOHOL USE, ABUSE, AND DEPENDENCE

Preclinical rodent models aim to emulate as much as possible the human experience with alcohol by capturing different drinking behaviors in the early, mid, and late stages of addiction (Brown et al., 1980). Fig. 1 provides an overview of commonly used rodent models of alcohol *use, abuse* and *dependence*. For more detailed discussion of the preclinical nonhuman primate models see (Grant and Bennett, 2003; Barr and Goldman, 2006). When people consume alcohol, most of them drink low-to-moderate amounts, which is less than three drinks per day for men and less than two drinks per day for women (Eckardt et al., 1998; Boschloo et al., 2011). Similarly, rodents can be used to model this type of non-dependent drinking (*Use*, left column, Fig. 1). The positive reinforcing properties of the drug, such as pleasure, disinhibition and social acceptance, are thought to be the primary forces driving motivation to consume alcohol under non-dependent conditions (Eckardt et al., 1998).

Rodent models of voluntary alcohol abuse are designed to capture more hazardous patterns of drinking (*Abuse*, middle column, Fig. 1). Abuse-like drinking patterns include escalations in intake, enhanced relapse after short or long withdrawal periods, stress/cue/alcohol-induced reinstatement, and episodic alcohol consumption resulting in some degree of intoxication. ''Binge drinking'' is an example of alcohol abuse. This is classified as the consumption of enough alcohol within a two-hour period to produce alcohol concentrations in the blood that reach an intoxication level of 0.08 g/dL or higher (~4 drinks in women, ~5 drinks in men, NIAAA, 2004). Non-dependent alcohol use can escalate to a pattern of abuse that may be brought on by additional factors such as social pressure, age, genetic predispositions, and gender (Chassin et al., 2004; Oei and Morawska, 2004; Ceylan-Isik et al., 2010; Silveri, 2012). Many of these same factors influence drinking patterns in rodents, and these preclinical models have aided in the identification of some of the neural correlates of risky drinking (Anacker and Ryabinin, 2010; Sherrill et al., 2011; Gilpin et al., 2012; Karanikas et al., 2013; McBride et al., 2014).

A variety of strategies can be used to elicit voluntary binge drinking in animals, but a common theme in most models is intermittent access to alcohol (Mcgregor and Gallate, 2004; Rhodes et al., 2005; Simms et al., 2008; Crabbe et al., 2009; Gilpin et al., 2012; Sharko et al., 2013). If this episodic pattern of drinking persists, animals may begin to show signs of motivational and emotional—but not physical—dependence (Cox et al., 2013). Stress regulatory systems begin to undergo neuroadaptive changes and although alcohol may still have positive reinforcing properties, the negative reinforcing properties of alcohol are starting to become powerful motivators driving excessive drinking (Baker et al., 1986; Koob, 2003; Sinha et al., 2009; Koob et al., 2014; Wise and Koob, 2014).

Chronic cycling between alcohol intoxication and withdrawal can cause an individual to become dependent on alcohol (Becker, 2008) (*Dependence*, right column, Fig. 1). This shift from non-dependence to dependence has been described as a transition from the *light side* to the *dark side* of addiction (Schulteis and Koob, 1994; Koob and Le Moal, 2005). Laboratory rodents without a predisposition for addiction are shifted from non-dependent baseline drinking to escalated and compulsive-like drinking by combining voluntary drinking and forced alcohol exposure that induces mild to moderate physical dependence (Roberts et al., 2000; Becker and Lopez, 2004; O'Dell et al., 2004; Richardson et al., 2008; Vendruscolo et al., 2012). By incorporating voluntary drinking into the experimental design, preclinical studies have been useful for identifying biological changes specifically associated with drinking behavior at these various stages of alcohol use disorders (Roberts et al., 1996; Knapp et al., 1998; Sidhpura et al., 2010; Gilpin et al., 2012; DePoy et al., 2013).

ALCOHOL STIMULATES THE RELEASE OF STRESS HORMONES

When an organism experiences a physical or psychological challenge, neurons in the paraventricular nucleus of the hypothalamus (PVN) release the 41-amino acid peptide corticotrophin-releasing factor (also known as corticotropin-releasing hormone) from