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Alcohol, stress hormones, and the prefrontal cortex: a proposed pathway to the dark side of addiction

Yi-Ling Lu[a] and **Heather N. Richardson**[b,*]

[a]Neuroscience and Behavior Program, University of Massachusetts, Amherst, MA 01003, United States

[b]Department of Psychological and Brain Sciences, University of Massachusetts, Amherst, MA 01003, United States

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.

Keywords

alcohol use disorders; hypothalamic pituitary adrenal axis; prefrontal cortex; animal models; dependence; glucocorticoids

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,

*Correspondence to: H. N. Richardson, Department of Psychological and Brain Sciences, University of Massachusetts, Amherst, MA 01003, United States. hrichardson@cns.umass.edu (H. N. Richardson). Tel: +1-413-545-0166; Fax: +1-413-545-0996.

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 bidirectional 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 corticotropin-releasing factor (also known as corticotropin-releasing hormone) from axonal terminals in the median eminence (Vale et al., 1981). Corticotropin-releasing factor (CRF) travels through the short portal system, binds to its Type 1 G-protein coupled receptor (CRF1) (Chang et al., 1993; Chen et al., 1993; Perrin et al., 1993), and stimulates the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary gland (Rivier and Vale, 1983). ACTH is released into the bloodstream and within minutes this hormone reaches its target cells in the adrenal gland to stimulate the release of glucocorticoids (cortisol in primates, corticosterone in rodents, (Rivier and Vale, 1983).

The first line of evidence demonstrating that alcohol is an acute stressor that activates the HPA axis comes from studies in which alcohol-naïve animals are given a bolus dose of alcohol using “forced” delivery methods such as intragastric injection, *ig* (Ogilvie et al., 1997a), intubation/gavage (Pruett et al., 1998), intracerebroventricular injection (Selvage, 2012), intraperitoneal injection, *ip* (Rivier, 1993), and vapor inhalation (Rivier et al., 1984). This approach has been effective for identifying neural circuits that are activated by acute alcohol intoxication and exploring the molecular mechanisms by which alcohol can stimulate a stress hormone response. We briefly summarize these findings below (for a more detailed review, see Rivier, 2014).

Experimenter-administered alcohol dose dependently elicits elevations in PVN cellular activity and the release of ACTH and corticosterone in male and female rats (Ellis, 1966; Rivier, 1993; Rivier and Lee, 1996; Ogilvie et al., 1997a; Willey et al., 2012). The tight link between alcohol dose and HPA activity is further supported by correlated blood alcohol and stress hormone levels after an acute alcohol challenge (Ellis, 1966; Ogilvie et al., 1997a). These findings suggest that alcohol may directly activate HPA axis through regulating the PVN cellular activity. Indeed, *in vitro* application of alcohol to hypothalamic tissue or primary hypothalamic cells induces the release of CRF (Redei et al., 1988; Li et al., 2005). In addition, CRF heteronuclear RNA quickly elevates within 20 min after *in vivo* alcohol administration in rats (Rivier and Lee, 1996; Ogilvie et al., 1998). This transcriptional process is presumably initiated to replenish cellular stores of this peptide that were rapidly released from the nerve terminals in response to alcohol stimulation. CRF mRNA expression increases thereafter and remains elevated up to 6 hours following ethanol administration (Zoeller and Rudeen, 1992).

Alcohol is also known to activate cells outside the PVN. An intoxicating dose of alcohol administered *ip* or *ig* modulates Fos expression in the prefrontal cortex, bed nucleus of the stria terminalis, central nucleus of the amygdala, and locus coeruleus (Chang et al., 1995; Knapp et al., 2001). These targeted regions could regulate HPA reactivity through direct or indirect pathways and provide another layer of regulation in response to alcohol stimulation (Ulrich-Lai and Herman, 2009; Herman, 2012).

The acute effect of alcohol on stress hormones has been observed with voluntary drinking in humans and animals. Voluntary alcohol drinking activates the HPA axis in male rats (Richardson et al., 2008; although see Korányi et al., 1987) and in men and women (Jenkins and Connolly, 1968; Schuckit et al., 1987; Lex et al., 1991; Ekman et al., 1994; King et al., 2006). These key findings demonstrate that alcohol acts as a stressor, even if this drug is experienced through a natural route of administration. We and others postulate that the HPA axis is a biological system that is both sensitive to alcohol and may also play a functional role in the progression from non-dependent drinking to abuse and dependence (Koob and Kreek, 2007; Stephens and Wand, 2012; Vendruscolo et al., 2012; Koob et al., 2014). As mentioned earlier, binge drinking—but not moderate drinking—brings blood alcohol concentrations to a level of intoxication. Consequently, engaging in this type of hazardous drinking will activate a robust stress response, which could be costly to an individual if the pattern of abuse continues (Romero et al., 2009; Koob et al., 2014). Moreover, the effects alcohol abuse has on physiological and mental health may be more profound in individuals already sensitive to stress. Sex differences in HPA reactivity are thought to contribute to differential alcohol-related vulnerabilities in men and women (Adinoff et al., 2010; Lovallo et al., 2012; Stephens and Wand, 2012).

Chronic exposure to alcohol leads to neuroendocrine tolerance

Chronic heavy alcohol use eventually leads to dampened functioning of the neuroendocrine stress system and this dysregulated hormonal state may contribute to some of the symptoms of alcoholism (Lovallo, 2006; Li et al., 2011; Sinha et al., 2011; Stephens and Wand, 2012). Animal studies have elucidated some of the functional changes in the HPA axis that emerge after varying degrees of prolonged alcohol exposure in drinking models of addiction. Early in abstinence after chronic alcohol exposure, basal/resting levels of ACTH and corticosterone are significantly lower at the start of the inactive (light) phase of the light/dark cycle in dependent rats compared to non-dependent rats, but this difference in basal hormone levels was not measurable in the active (dark) phase (Richardson et al., 2008). Blunted basal levels of corticosterone have also been observed in both phases of the light/dark cycle in adult male rats weeks after removal from chronic alcohol liquid diet, as compared to alcohol naïve-controls (Rasmussen et al., 2000; Zorrilla et al., 2001).

The most reliable indicator of chronic alcohol-induced changes in HPA function is a reduced response of this neuroendocrine system to an acute challenge of alcohol—also known as “neuroendocrine tolerance.” Neuroendocrine tolerance emerges after prolonged drinking and the magnitude of decrease in neuroendocrine sensitivity to alcohol appears to be dose-dependently related to the overall amount of alcohol consumed. When animals are given an alcohol challenge of 1 g/kg *iv*—the dose of alcohol that dependent rats voluntarily binge drink in a single 30-min session (Heyser et al., 1997; Gilpin et al., 2009; Li et al., 2011)—HPA responses differ greatly across individuals depending on their previous experience with alcohol (Richardson et al., 2008). This 1 g/kg dose elicits binge-like blood alcohol levels in all animals (Fig. 2A). However, it stimulates robust ACTH and corticosterone responses in *low-drinking* non-dependent rats, mid-range responses in moderate drinking non-dependent rats, and blunted responses in high drinking dependent rats (Fig. 2A).

Adaptations have been found at multiple levels within the HPA axis, which may contribute to dampened neuroendocrine function after chronic alcohol. At the level of the hypothalamus, CRF mRNA expression is reduced in dependent animals 6–8 hours after withdrawal from chronic alcohol vapors compared to alcohol-naïve controls, and CRF mRNA expression in non-dependent animals is intermediate to these two groups (Fig. 2B). Chronic alcohol consumption appears to reduce responsiveness of pituitary corticotrophs to CRF peptide. A CRF challenge (0.3 μg/mL, *iv*, *intravenous*) elicits low ACTH responses in non-dependent and dependent drinking rats relative to the responses observed in alcohol-naïve rats (Fig. 2C). However, alterations in pituitary responsiveness does *not* appear to further progress with increased doses of alcohol, as non-dependent and dependent rats have comparable ACTH responses after a CRF challenge (Fig. 2C). Reduced pituitary responsiveness in drinking rats versus alcohol-naïve rats could be mediated by various mechanisms, including CRF1 receptor expression within pituitary cells and changes within the arginine vasopressin system (Ogilvie et al., 1997b; Zhou et al., 2000).

Although mechanisms downstream of the pituitary were not explored in Richardson et al. (2008), the fact that a 1 g/kg (*iv*) alcohol challenge in the dark cycle elicited a similar timeline of change in ACTH in the three drinking groups, but a much more prolonged corticosterone response in the low-drinking non-dependent rats suggests that even moderate drinking may alter adrenal sensitivity to ACTH (Fig. 2A). Alcohol-induced alterations in splanchnic innervation of the adrenal glands could explain such group differences (Ulrich-Lai et al., 2006). The mechanisms upstream of the hypothalamus are largely unknown, but enhanced inhibitory tone from peri-PVN GABA cells or other direct and indirect targets of the prefrontal cortex are possible candidates (Li et al., 2011; Herman, 2012). Later in this review, we discuss in detail a proposed role for the prefrontal cortex in neuroendocrine tolerance after chronic alcohol use and dependence (see Fig. 4).

Neuroendocrine tolerance may trigger relapse and heavy drinking

As described above, HPA dysregulation is a common symptom associated with chronic alcohol abuse and dependence. Reduced stress hormone levels may not only be reliable indicators of the addictive stage of an individual, but could also play a functional role in driving escalated drinking and enhanced relapse. In support of this hypothesis, blunted basal stress hormone levels in alcoholics predicts craving (Kiefer et al., 2002). There is also a strong temporal relationship between dampened HPA hormone levels and increases in heavy drinking and propensity to relapse early in abstinence in humans (Gianoulakis, 1998; Kiefer et al., 2002; Junghanns et al., 2003; Adinoff et al., 2005b; 2005c; 2005a; Sinha et al., 2011) and in rodents (Rasmussen et al., 2000; Richardson et al., 2008; Li et al., 2011). Additionally, the opiate receptor antagonist, naltrexone, stimulates the HPA axis and blocks alcohol craving and self-administration in alcohol-dependent human subjects (O'Malley et al., 2002).

Transgenic manipulations of CRF1 receptors in animals demonstrate that elimination of CRF1 receptors specifically from the central nervous system while leaving pituitary CRF1 receptor expression intact reduces relapse-like drinking (Molander et al., 2012). However, if pituitary CRF1 receptors are also eliminated—as with the CRF1 null knockout—HPA

hormones are dampened and relapse-like drinking increases (Molander et al., 2012). This is consistent with the hypothesis that during a drinking session alcohol-induced stimulation of ACTH and possibly its downstream hormone corticosterone curbs alcohol drinking. Other predictions of this hypothesis have been tested using pharmacological approaches. Blocking inhibitory tone on the PVN using $GABA_A$ receptor antagonists such as picrotoxin or bicuculline is known to increase HPA activity (indexed by elevated Fos-immunoreactivity in the PVN and elevated blood corticosterone levels) in alcohol-naïve rats (Cole and Sawchenko, 2002) and alcohol-dependent rats (Li et al., 2011). This treatment also prevents relapse-like drinking in animals exposed to an intermittent drinking paradigm (Li et al., 2011).

While the findings above suggest that dampened HPA activity may stimulate relapse and heavy drinking, the interplay between low peripheral glucocorticoid levels and drinking behavior is not so clear. Acute blockade of corticosterone synthesis through metyrapone administration fails to elevate (Besheer et al., 2013)—and may even block (Fahlke et al., 1994)—alcohol drinking behavior. This suggests that low glucocorticoid levels do not *cause* increases in drinking, at least under non-dependent conditions. Perhaps deficits in HPA reactivity upstream of the adrenal glands are driving forces in increased drinking (Li et al., 2011). In addition, dampened glucocorticoids may acutely drive heavy drinking and relapse only *after* key behavioral circuits have undergone significant neuroadaptive changes associated with dependence. To the best of our knowledge, this hypothesis has not been empirically tested.

Role of glucocorticoids in the transition to dependence

Even with chronic alcohol dampening the neuroendocrine stress system, glucocorticoids still play a powerful role in the transition to dependence. Chronic exposure to alcohol drinking or to vapor-induced bouts of intoxication leads to dampen peripheral glucocorticoid levels (Richardson et al., 2008; Silva et al., 2009), yet glucocorticoid signaling is required for the development of the physical, motivational, and cognitive syndromes associated with alcohol dependence in rodents (Sze, 1977; Jacquot et al., 2008; Vendruscolo et al., 2012). This seems paradoxical, but two important factors must be considered. First, chronic alcohol exposure reduces—but does not fully diminish—the ability of alcohol exposure to acutely elevate plasma levels of corticosterone (Rivier et al., 1984; Lee and Rivier, 1997; Richardson et al., 2008). In fact, corticosterone levels remain significantly elevated for several hours during the intoxication phase of chronic vapor treatment in neuroendocrine-tolerant animals (Rivier et al., 1984; Lee and Rivier, 1997). Second, as individuals experience repeated bouts of intoxication, the brain undergoes neuroadaptive changes that eventually promote the emergence of a withdrawal syndrome (Koob, 2013). It is thought that the withdrawal syndrome worsens over time, and at this point, periods of prolonged withdrawal could be a second phase in which brain circuits are exposed to high concentrations of glucocorticoids that may be synthesized centrally (Brooks et al., 2008; Little et al., 2008). Consequently, repeated cycling between binge intoxication and periods of withdrawal would conceivably give this stress hormone ample opportunity to act on its receptors in the brain and affect transcriptional regulation of multiple genes that could promote addiction.

To understand how glucocorticoid signaling could promote—and glucocorticoid type II receptor (GR) antagonists could block—the transition to dependence and increase the probability of relapsing after abstinence (Vendruscolo et al., 2012), we must consider the dynamic interplay between glucocorticoid levels and their receptors. As illustrated in Fig. 3, glucocorticoid signaling in the brain is thought to be a complex process as individual's transition from abuse to dependence. Blood levels of this stress hormone fluctuate with the pattern of alcohol exposure (Fig. 3B) and brain responsiveness to corticosterone also changes because of receptor auto-regulation (Sapolsky et al., 1984; Sapolsky and McEwen, 1985; Herman and Spencer, 1998). Accordingly, differential GR expression in the brain might give insight into which brain regions have high or low local concentrations of corticosterone during the intoxication and withdrawal phases of chronic alcohol exposure. GR expression levels differ in early versus late abstinence from chronic alcohol (Vendruscolo et al., 2012). GR mRNA expression is reduced in frontolimbic brain regions 24h into withdrawal from chronic intermittent vapors, but is normalized—or even elevated—in these same regions 3 weeks after cessation of chronic intermittent alcohol treatment (Vendruscolo et al., 2012). Down-regulated GR mRNA expression in early abstinence could reflect the recent hormonal environment in these frontolimbic regions during the 14-h intoxication phase of intermittent vapor treatment (Rivier et al., 1984).

After removal from chronic alcohol treatment, peripheral corticosterone levels can remain dampened for several weeks into abstinence (Rasmussen et al., 2000; Zorrilla et al., 2001)—perhaps resulting in a compensatory elevation in GR expression within some of these brain regions important for addiction. In animals that have been exposed to high levels of alcohol for several months, abstinence is characterized by increases in prefrontal concentrations of glucocorticoids and heightened glucocorticoid/GR signaling (Brooks et al., 2008; Little et al., 2008). This could explain why repeated periods of abstinence and relapse are key elements of alcoholism (Koob and Le Moal, 2001). Fig. 3C shows a hypothetical model of how GR expression may change in the brain in response to peripheral fluctuation of glucocorticoids throughout the induction of dependence and into early and late abstinence. The complex interplay between intermittent exposure to alcohol and changes of GR responsiveness in the brain may lead to further neuronal adaptation and behavioral changes such as escalated and compulsive drinking, and increased probability of relapse after abstinence.

Glucocorticoids may target the medial prefrontal cortex (mPFC) to produce some of the neuroendocrine and behavioral changes associated with dependence

Glucocorticoids initiate non-genomic and genomic cellular events that provide both immediate and long-term effects, respectively (Kolber et al., 2008). The fluctuating levels of glucocorticoids during alcohol intoxication and after abstinence, as described above, could induce assorted adaptation processes in the brain. Although there are most likely several targets undergoing GR-mediated neuroadaptive changes following chronic alcohol, here we focus on the prefrontal cortex—a region of the brain known for this role in executive

functions and regulation of emotions and behavior (Wilson et al., 2010; Kesner and Churchwell, 2011).

As shown in Fig. 4, mPFC may play a role in the long-loop negative feedback of the HPA axis (Sullivan and Gratton, 2002a). The GR has a four to five fold higher prevalence than mineralocorticoid receptor (MR) in the mPFC, which is notably different from the equal distribution of GR and MR in the hippocampus (Diorio et al., 1993; Cintra et al., 1994). Implantation of corticosterone pellets in the dorsal portion of the mPFC (dmPFC), to mimic high stress-like levels, attenuates HPA response to restraint stress (Diorio et al., 1993; Akana et al., 2001). Activation of the dmPFC dampens HPA responses, whereas lesions of the dmPFC produce exaggerated HPA responses (Diorio et al., 1993; Figueiredo et al., 2003; Radley et al., 2006; 2008; Jones et al., 2011). We hypothesize that corticosterone activates cells in the dmPFC that project to subcortical structures and inhibit HPA axis activity. *In vitro* studies support this hypothesis showing that corticosterone administration suppresses local GABA release in the dmPFC (prelimbic cortex)—a disinhibitory effect that would, in turn, lead to higher pyramidal cell activation and strengthen the overall dmPFC breaking effect on HPA activity (Hill et al., 2011).

In rodents, the mPFC is anatomically similar to the cingulate and premotor cortices of the frontal lobes in primates (Reep et al., 1987). The rodent mPFC also has functional similarity to the dorsolateral prefrontal cortex in primates (Kolb, 1984; Birrell and Brown, 2000; Barense et al., 2002; Seamans et al., 2008; Kesner and Churchwell, 2011). Chronic alcohol abuse and alcohol dependence can result in impaired performance on cognitive tasks associated with integrity of the mPFC (George et al., 2012; Kroener et al., 2012), suggesting that this region undergoes neuroadaptive change with prolonged exposure to moderate to high alcohol levels. We posit that repeatedly engaging in binge alcohol exposure stimulates HPA axis activity and leads to enduring GR signaling within the mPFC that produce changes in functions dependent on this region. In support of this hypothesis, mPFC GR mRNA expression is reduced and heavy, compulsive-like drinking is high early in abstinence from chronic alcohol, but prior chronic treatment with a GR antagonist prevents the development of this behavioral phenotype in rats (Vendruscolo et al., 2012). Acute treatment with a GR antagonist also reduce the mPFC-mediated memory deficit observed during acute withdrawal from chronic alcohol treatment in mice (Jacquot et al., 2008). Altogether, the findings suggest that prolonged exposure to alcohol impacts mPFC control of cognitive performance and addiction-related behaviors—at least in part—through glucocorticoid signaling.

Conclusions

We propose that acute stimulation of the HPA axis during repeated bouts of intoxication and the subsequent adaptation within this neuroendocrine axis and upstream in the prefrontal cortex are key factors in the transition from alcohol use to abuse and eventually to dependence. As individuals engage in repeated cycles of intoxication, abstinence, and relapse, a dynamic cascade of glucocorticoid signaling could trigger a series of neuroadaptive events in the prefrontal cortex that have broad implications on neural functioning and behavior. Other important factors modulating the development of alcohol

use disorders are beyond the scope of the current review. However, these factors are worth noting and have been reported elsewhere: age onset of alcohol use/abuse (e.g. Dawson et al., 2008; Gilpin et al., 2012), substance co-use/abuse with alcohol (e.g. Hanson et al., 2008), genetic/epigenetic regulation (e.g. Tabakoff et al., 2009; Nieratschker et al., 2014), social components of drinking (e.g. Butler et al., 2014), sex differences (e.g. Fox et al., 2009; Wemm et al., 2013), other neurotransmitter/neuromodulator systems (e.g. Clapp et al., 2008; Gilpin, 2012) and the potential lateralized stress regulation in the prefrontal cortex (e.g. Sullivan and Gratton, 2002b). It is worth noting that the animal housing condition may be a factor that interacts with the alcohol drinking behavior and neural adaptations. The individual housing is often incorporated in the experimental during the drinking period or throughout the entire experiment. Single housing is known to induce stress (Greco et al., 1992) and increase voluntary alcohol consumption in rats (Yoshimoto et al., 2003). On the other hand, group housing may produce psychosocial stress from the hierarchy especially in male rodents (Pohorecky, 2010). Therefore, the potential stress effect from various housing conditions should be considered when interpreting alcohol effects in these studies.

Three important next steps in the field should be to (1) explore how glucocorticoid signaling changes within the prefrontal cortex during use, abuse, and dependence, (2) determine how alcohol and glucocorticoids interact to produce molecular and circuit-level neuroadaptive changes in the prefrontal cortex to impact downstream targets and alter neuroendocrine, autonomic, and behavioral functions related to stress and addiction, and (3) develop a deeper understanding and appreciation for the importance of sex, developmental status, and individual differences in this preclinical research, as most of the animal literature cited in this review was based on studies using adult male rodents. Gaining a new understanding the complex interplay among alcohol drinking, stress hormones, and the prefrontal cortex would provide further information in the development of new biomarkers to identify the progression of alcohol dependence and help guide the discovery of new promising treatments for alcohol use disorders.

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Use	Abuse	Dependence
Behavioral Characteristics and Symptoms		
When alcohol is available		
Baseline drinking	Escalated intake (relative to baseline) Enhanced relapse after deprivation from alcohol (tested every few days/weeks; increase relative to baseline or daily testing)	Drinking behaviors similar to those described for abuse (binge, relapse) Compulsive alcohol drinking (seek alcohol despite adverse consequences) Work harder for alcohol (increased progressive ratio break points)
When alcohol is not available		
No evidence of a physical or emotional/motivational dependence	No evidence of a physical dependence; possible emergence of emotional/motivational dependence	Withdrawal syndromes - Physical signs Hyperactivity (mild); seizures (severe) - Emotional/motivational signs Anxiety-like and depression-like behavior; Reward deficits (ICSS); heightened sensitivity to pain
Target Blood Alcohol Levels (BALs) during Drinking		
< 0.08 g/dL	≥ 0.08 g/dL	≥ 0.08 g/dL
Examples of Preclinical Drinking Models		
Operant self-administration of unsweetened alcohol (*e.g., Green and Grahame 2008, Weiss et al., 1993*) Home cage drinking of unswetened alcohol (*e.g., June et al., 1994; Avena et al., 2004*)	Drinking in the dark (DID) (*e.g., Rhodes et al., 2005, 2007; Cox et al., 2013*) Operant binge self-administration of sweetened alcohol (*e.g., Gilpin et al., 2012; Karanikas et al., 2013*) Home cage drinking of sweetened alcohol or beer (*e.g., Ji et al., 2008; McGregor and Gallate, 2004*) Chronic home cage drinking, intermittent access to 20% w/v ethanol (*e.g., Simms et al., 2008*)	Chronic exposure to alcohol diet, induction BAL is usually 0.15 - 0.25 g/dL (*e.g., Rassnick et al., 1992; Knapp et al., 1998*) Operant or home cage drinking followed by different dependence induction methods - alcohol vapor exposure, induction BAL is usually 0.15 - 0.25 g/dL (*e.g., Roberts et al., 1996, 2000; O'Dell et al., 2004; Becker and Lopez, 2004*) - gavage alcohol delivery, induction BAL is usually 0.20 - 0.45 g/dL (*e.g., Sidhpura et al., 2010*)

Fig. 1.

An overview of preclinical rodent models capturing different drinking behaviors in the early (*Use*), mid (*Abuse*), and late (*Dependence*) stages of alcohol addiction. Behavioral characteristics and symptoms are described for each phase under conditions when alcohol is available versus conditions when alcohol is unavailable (withdrawal). The blood alcohol levels reached during a drinking episode differs as well, with use always remaining below the "binge" limit (0.08 g/dL) during the *Use* phase, but exceeding this level during the phases of *Abuse* and *Dependence*. We have provided a few examples of models used to

capture drinking behavior at each phase, but it should be noted that this is not an exhaustive list. *Abbreviation:* ICSS, intracranial self-stimulation.

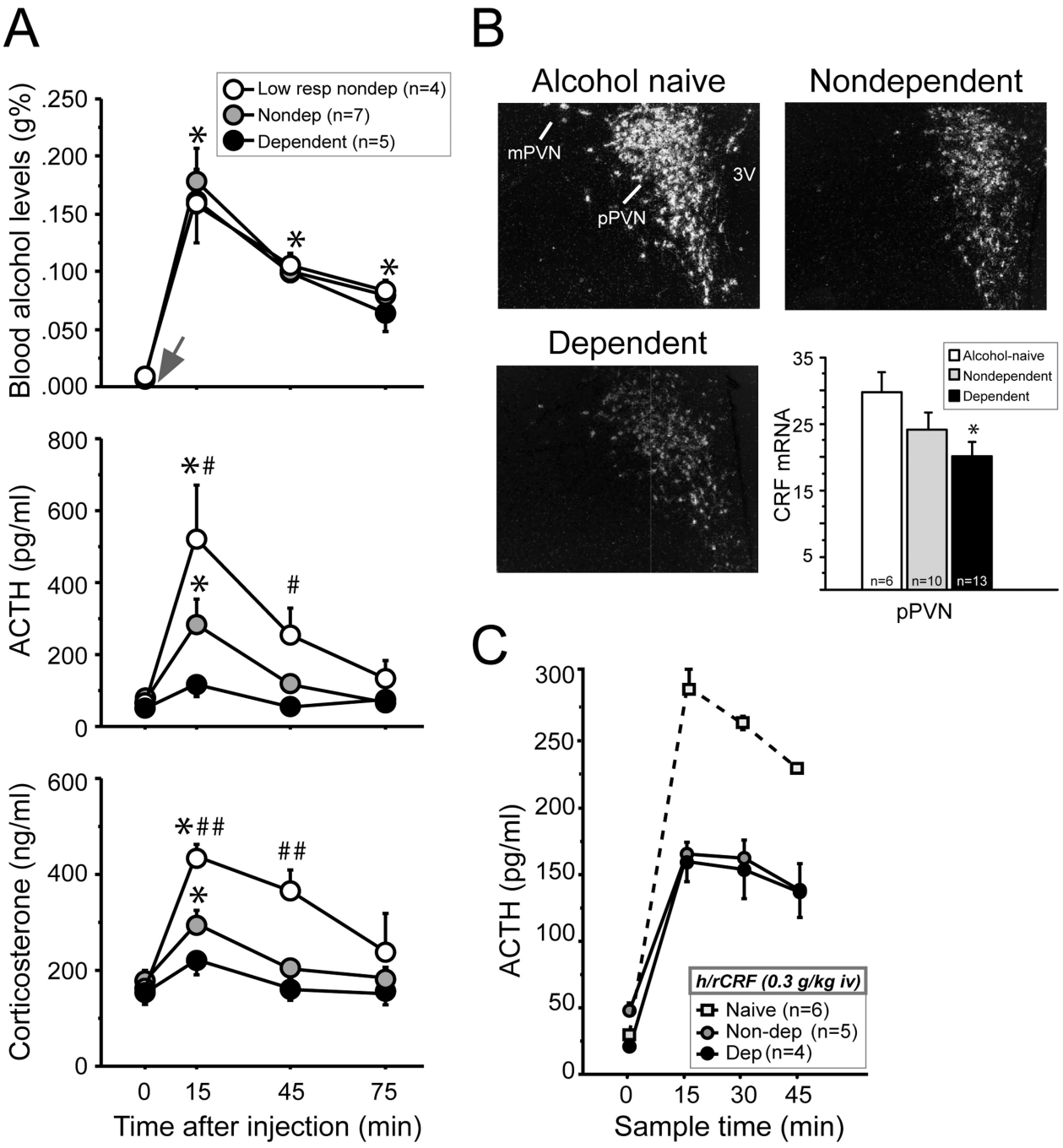

Fig. 2.

The hypothalamic pituitary adrenal (HPA) axis is functionally different depending on an individual's prior experience with alcohol. Data were obtained from adult male rats that were either *naïve* (no operant training or previous exposure to alcohol), *low-drinking non-dependent* (several weeks of low levels of alcohol-self administration), *non-dependent* (several weeks of moderate levels of alcohol-self administration), or *dependent* (several weeks of moderate levels of alcohol self-administration followed by chronic alcohol vapor-induced dependence). All measures were taken when dependent animals were in acute

withdrawal (6–8 hours after removal from chronic alcohol vapors). (A) The level of dampened HPA activity in response to 1 g/kg *iv* alcohol challenge depends on animals' alcohol responsiveness and the alcohol exposure history. (B) CRF mRNA expression is low in the hypothalamus of dependent compared to alcohol-naïve controls, and CRF mRNA expression in non-dependent animals is intermediate to these two groups. (C) A CRF challenge (0.3 μg/kg, *iv*) elicits a lower ACTH response in drinking rats relative to alcohol-naïve controls, but the non-dependent and dependent groups do not differ from one another. *Abbreviations: iv*, intravenous; pPVN, parvocellular division of paraventricular nucleus of the hypothalamus; mPVN, magnocellular division of PVN; 3V, third ventricle. [Adapted from Richardson et al., 2008 *European Journal of Neuroscience*.]

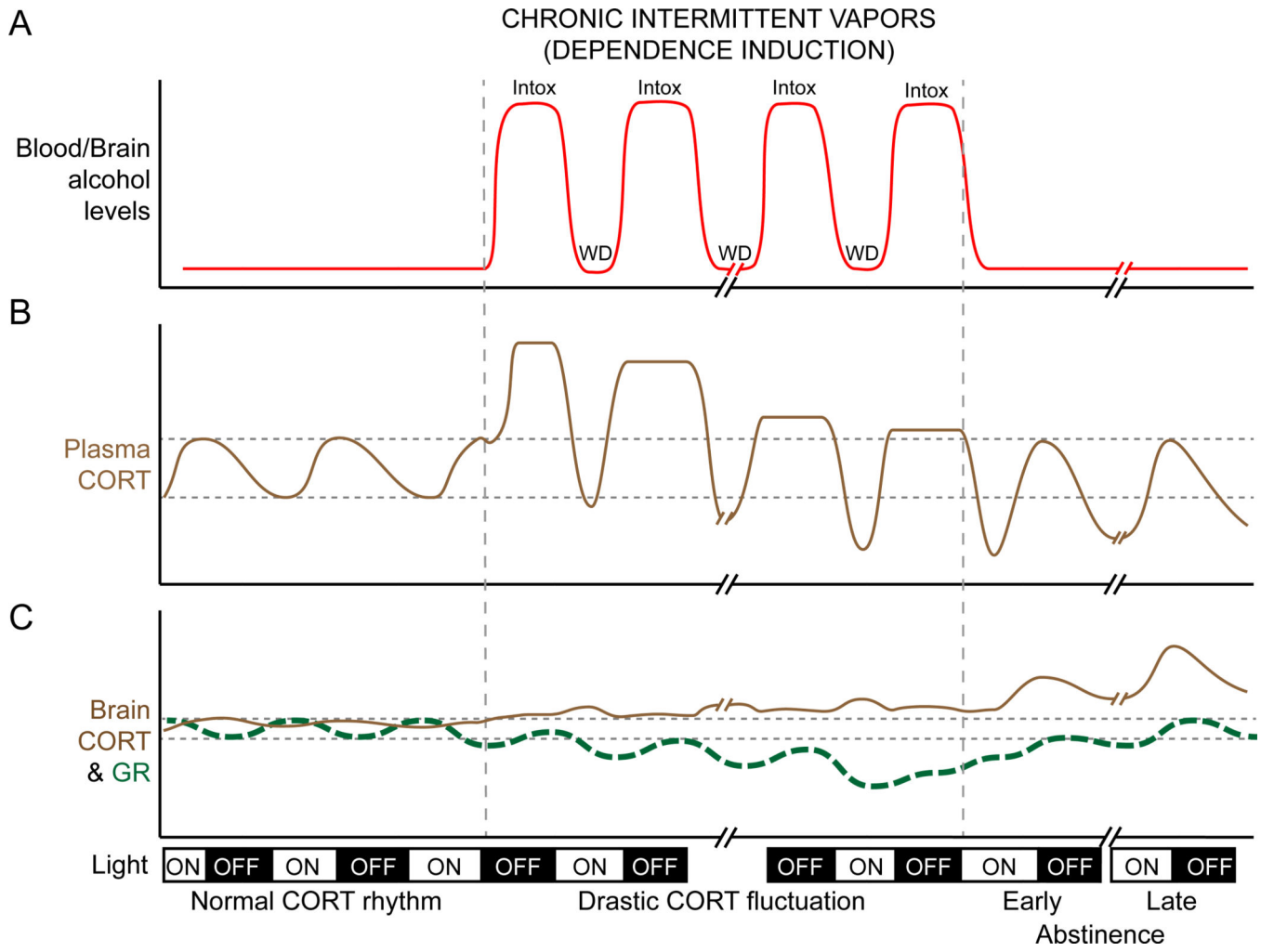

Fig. 3.

A schematic illustrating proposed alterations in alcohol levels in the blood, corticosterone (CORT) in the blood and brain, and glucocorticoid receptors (GR) in the brain before, during and after dependence induction. (A) Blood and brain alcohol levels are strongly fluctuated during the intermittent alcohol vapor exposure. In this example, vapors are delivered for 14 h, beginning at the onset of the dark cycle. (B) Alcohol vapor stimulates CORT release to levels far exceeding the normal diurnal rhythm of plasma CORT. Neuroendocrine tolerance develops through out the induction period and eventually leads to the dampened HPA activity. (C) GR level in the brain decreased in response to the high CORT during the high alcohol period. On the other hand, increased brain CORT after dependence is hypothesized to come from *de novo* local synthesis or alterations in blood brain-barrier permeability or both after alcohol dependence. *Abbreviations:* Intox, intoxication; WD, withdrawal.

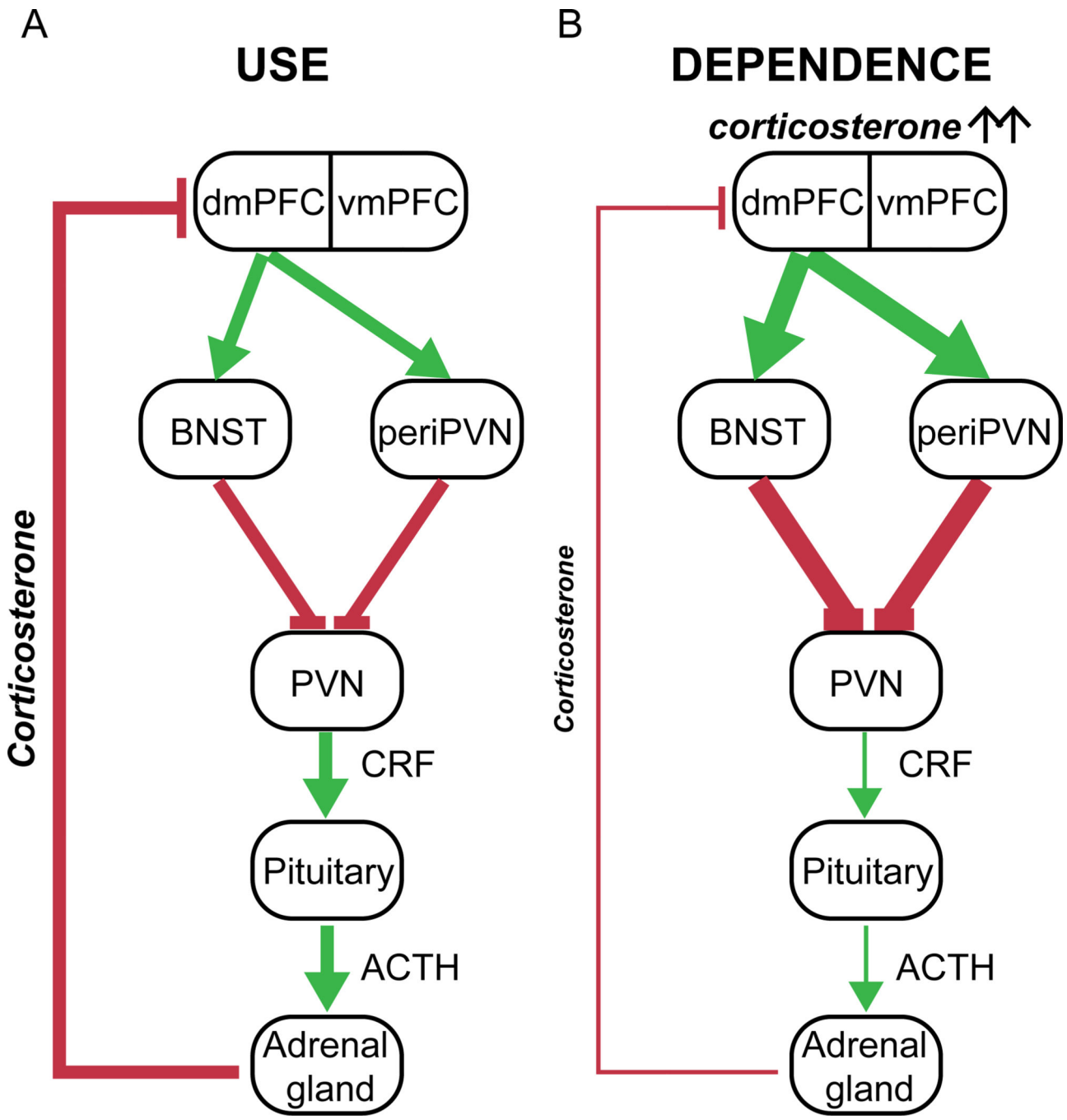

Fig. 4.

A proposed model illustrating differential prefrontal regulation of the HPA axis after alcohol use (A) versus alcohol dependence (B). Dorsomedial prefrontal cortex (dmPFC) in rats modulates HPA activity by activating the inhibitory control over PVN via the BNST or periPVN (Radley et al., 2006; 2009). Chronic alcohol exposure has been proposed to increase the local *de novo* glucocorticoid synthesis in the PFC (Little et al., 2008). Additionally, *ex vitro* studies demonstrates that glucocorticoids reduce GABA inhibition of layer V pyramidal cells in the dmPFC (Hill et al., 2011). Thus, the chronic alcohol-induced

overflow of glucocorticoids in the dmPFC could strengthen its output to downstream targets such as the BNST and periPVN, resulting in stronger inhibition of the PVN and neuroendocrine tolerance. *Abbreviations:* dmPFC, dorsal medial prefrontal cortex; vmPFC, ventral medial prefrontal cortex; BNST, bed nucleus of the stria terminalis, periPVN, peri-paraventricular nucleus of the hypothalamus, PVN, parventricular nucleus of the hypothalamus; ACTH, adrenocorticotropic hormone; CRF, corticotropin releasing factor.