Published in final edited form as:

Alcohol. 2015 December ; 49(8): 811–816. doi:10.1016/j.alcohol.2015.04.004.

Divergent Regulation of Distinct Glucocorticoid Systems in Alcohol Dependence

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Abstract

Chronic alcohol consumption disrupts glucocorticoid signaling at multiple physiological levels to interact with several disease-related processes associated with neuroendocrine and psychiatric disorders. Excessive alcohol use produces stress-related neuroadaptations at the level of the hypothalamic-pituitary-adrenal (HPA) axis as well as within central (extra-hypothalamic) neural circuitry, including the central amygdala (CeA) and prefrontal cortex (PFC). Altered glucocorticoid receptor (GR) signaling in these areas following excessive alcohol exposure is postulated to mediate the transition from recreational drinking to dependence, as well as the manifestation of a host of cognitive and neurological deficits. Specifically, a bidirectional regulation of stress systems by glucocorticoids leads to the development of an HPA axis tolerance and a concomitant sensitization of cortical and subcortical circuitries. A greater understanding of how hypothalamic and extra-hypothalamic glucocorticoid systems interact to mediate excessive drinking and related pathologies will lead to more effective therapeutic strategies for alcohol use disorder (AUD) and closely related comorbidities.

Keywords

alcohol-use disorder; amygdala; cognition; corticotropin-releasing factor; glucocorticoids; prefrontal cortex

Introduction

Since their original biological conceptualizations in the 1930s, scientists have intensively focused on the physiological basis of adaptive and maladaptive stress (Le Moal & Koob,

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2007; Sapolsky, Romero, & Munck, 2000). Numerous studies have described alterations in the hypothalamic-pituitary-adrenal (HPA) axis in various stress-related disorders such as major depression, post-traumatic stress disorder, and alcohol use disorder (AUD). The discovery of glucocorticoids by Hans Selye and the role of the HPA axis in the integrative stress response fostered the search for hypothalamic-releasing factors (Guillemin, 1978) and the discovery of corticotropin-releasing factor (CRF; Vale, Spiess, Rivier, & Rivier, 1981) as the primary stimulator of adrenocorticotrophic hormone (ACTH) release by the anterior pituitary. Cortisol in humans (or corticosterone in rodents) is the primary glucocorticoid released from the adrenal cortex in response to ACTH. Circulating glucocorticoids produce an array of physiological effects in response to external stressors, and under normal conditions are also responsible for termination of their own actions via negative feedback inhibition at multiple levels of the HPA axis. In the popular media, the concept of stress (and by extension, HPA axis function) has been largely debased from its original conceptualization by Selye as an adaptive response to environmental challenge. However, even Selye observed what he termed a “general adaptive syndrome” and “diseases of adaptation” (Selye, 1950). While HPA axis stimulation and termination provide a valuable mechanism for bodily homeostasis, repetitive activation is hypothesized to contribute to a cumulative load, termed allostatic load (McEwen & Stellar, 1993), onto this system that can tax it to the point of pathology (George, Le Moal, & Koob, 2012). Importantly, the gradual dysregulation of physiological stress mechanisms is postulated to include a functional potentiation of central brain stress circuitry that includes such regions as the central amygdala and prefrontal cortex (Koob et al., 2014; Myers, McKlveen, & Herman, 2014). Dysregulation of neuroendocrine systems has been associated with mental disorders ranging from major depression to drug addiction.

Alcohol-use disorder (AUD) represents a multifaceted psychiatric disease with few effective treatments. The Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5, 2013) stratifies AUD into mild, moderate, and severe forms based on the number of criteria met. These specifications include excessive drinking over extended periods, intense craving and desire to consume alcohol, and manifestation of a motivational withdrawal syndrome wherein alcohol is consumed via negative reinforcement processes (i.e., alcohol is consumed to relieve negative affective symptoms produced by abstinence). Importantly, HPA axis stimulation and glucocorticoid actions would appear to play a facilitative role in the development of each of these benchmarks (Becker, 2012), along with driving additional complications associated with excessive alcohol consumption. This review conceptualizes AUD as an unrelenting, relapsing disorder promoted and maintained via persistent alterations in hypothalamic and extra-hypothalamic stress signaling, yet offers hope based on an emerging intersection of preclinical and clinical studies that suggest the promise of effective therapeutic intervention aimed at correcting dysregulated glucocorticoid signaling.

Glucocorticoid regulation of alcohol drinking, craving, and relapse

Alcohol intoxication and withdrawal serve as two distinct activators of the HPA axis to raise circulating corticosterone levels in rodents (Ellis, 1966; Rivier, Bruhn, & Vale, 1984; Tabakoff, Jafee, & Ritzmann, 1978) and cortisol levels in humans (Adinoff, Iranmanesh,

Veldhuis, & Fisher, 1998; Adinoff et al., 1990; Adinoff, Ruether, Krebaum, Iranmanesh, & Williams, 2003). Alcohol-induced glucocorticoid release may mediate some of alcohol's reinforcing effects because corticosterone is both reinforcing by itself (Piazza et al., 1993) and also increases alcohol drinking via actions in the ventral striatum (Fahlke & Hansen, 1999). In concert with corticosterone's ability to potentiate mesolimbic activation by excitatory amino acids (Cho & Little, 1999), this mechanism may play a role in the effects of various forms of stress to elevate drinking in non-dependent animals (e.g., Edwards et al., 2013; Little et al., 1999; Logrip & Zorrilla, 2012) via an interaction of stress and reinforcement circuitry. Indeed, Koenig and Olive (2004) found that systemic blockade of glucocorticoid receptors (GRs), but not mineralocorticoid receptors (MRs), significantly reduces alcohol drinking under putatively stressful limited-access conditions. These data indicate that alcohol intake is predominately under the influence of GRs versus MRs, despite the fact that MRs display a greater affinity for corticosterone and, like GRs, are located within limbic reward circuitry (McEwen, 2007; ter Heegde, De Rijk, & Vinkers, 2015).

The neurophysiological effects of glucocorticoids are complex, and plasma levels (especially in disease conditions) do not necessarily reflect brain levels. Little and colleagues (2008) conducted a comparative measure of plasma and brain corticosterone concentrations following chronic alcohol exposure. While corticosterone levels were similar in both brain and blood during alcohol intoxication, brain levels in specific limbic regions remained significantly elevated into long-term withdrawal (1 day to 2 months), indicating an important distinction between systemic and brain corticosterone synthesis and metabolism. Interestingly, the prefrontal cortex exhibited the greatest prolonged increases in corticosterone levels, and the same study found that nuclear localization of glucocorticoid receptors was increased in the prefrontal cortex (PFC) following chronic alcohol exposure. Such neuroadaptations are hypothesized to drive the transition to alcohol dependence by linking upstream PFC activity with downstream HPA function (Lu & Richardson, 2014). Importantly, individuals suffering from AUD are at a heightened risk of relapse drinking even after extended periods of successful abstinence. Alcohol-associated cues stimulate cortisol release in abstinent alcoholics (Fox, Bergquist, Hong, & Sinha, 2007; Sinha et al., 2009), suggesting that cortisol contributes to a conditioned, appetitive response to promote relapse. Interestingly, the same patients are less responsive to stress cue-induced cortisol induction than healthy controls, further indicative of a blunted HPA stress responsiveness in AUD. Central brain stress systems appear also to be regulated by glucocorticoid signaling during relapse-like behavior. Systemic GR antagonism with mifepristone reduces reinstatement to alcohol seeking produced by the chemical stressor yohimbine, and this effect is recapitulated by microinjection of mifepristone directly into the CeA (Simms, Haass-Koffler, Bito-Onon, Li, & Bartlett, 2012).

Neuroendocrine tolerance to alcohol

The repeated activation of the HPA axis by chronic alcohol drinking appears to produce a type of neuroendocrine tolerance, as glucocorticoid response to alcohol tends to be inversely related to alcohol drinking history. For example, Richardson, Lee, O'Dell, Koob, & Rivier (2008) discovered that low-drinking rats exhibited a higher corticosterone response to alcohol challenge vs. moderate-drinking (but non-dependent) animals, with alcohol-

dependent rats displaying a severely dampened corticosterone response. These effects were observed despite all animals reaching similar blood alcohol levels following the alcohol challenge, and were instead attributed to reductions in CRF levels in the paraventricular nucleus (PVN) of the hypothalamus that correlated with levels of alcohol exposure. Importantly, these results suggest that neuroendocrine deficits could be produced by episodes of heavy or binge drinking even before the transition to dependence, and this condition may even interact with low baseline HPA axis function in genetically predisposed individuals with a family history of alcoholism (Gianoulakis, Dai, Thavundayil, & Brown, 2005). Finally, a dampened neuroendocrine state is observed to last well into protracted abstinence in post-dependent animals (Zorrilla, Valdez, & Weiss, 2001), and may either strengthen the drive to escalate alcohol intake to compensate for its attenuated ability to activate the HPA axis or enhance the incentive salience of alcohol-paired cues that continue to stimulate corticosterone release as discussed above.

Glucocorticoid regulation of alcohol dependence

The development of animal models of alcohol dependence has driven the preclinical testing of hypotheses related to AUD development and expression (Gilpin & Koob, 2008; Gilpin, Richardson, Cole, & Koob, 2008). With the use of these preclinical models, multiple novel pharmacological targets have been revealed to target excessive drinking and alleviation of dependence-related conditions (Vendruscolo & Roberts, 2014). Rodents made dependent on alcohol via chronic, intermittent alcohol vapor exposure typically escalate their alcohol intake at withdrawal times associated with a spectrum of somatic and motivational symptoms of dependence (i.e., 6–10 h after the termination of alcohol vapor, when blood alcohol levels are diminished to near zero), whereas moderate levels of alcohol consumption are displayed by their non-dependent littermates. Under most experimental designs, researchers have described a reduction of elevated drinking in postdependent animals at this withdrawal time point via pharmacological intervention, revealing fundamental mechanisms that are responsible for the *maintenance* of dependent drinking (for review, see Vendruscolo & Roberts, 2014). In comparison, a select few studies have attempted to uncover the neurobiology associated with the *development* of escalated drinking. For example, Roberto and colleagues (2010) significantly attenuated the otherwise gradual increases in drinking in rats exposed to alcohol vapor via systemic, prophylactic treatment with a CRF receptor 1 (CRF1R) antagonist administered repeatedly before self-administration sessions. This study extended previous findings that established a role for CRF systems in driving alcohol dependence-related symptomatology (Funk, O'Dell, Crawford, & Koob, 2006; Heilig & Koob, 2007; Richardson, Zhao, et al., 2008), while also leaving open the question of which neurobiological mechanisms drive increased CRF expression to promote drinking escalation.

Given the regulation of CRF gene transcription by GRs, Vendruscolo and colleagues (2012) determined the effects of continuous, systemic blockade of GRs with mifepristone during the development of alcohol dependence in rats. Continuous release of subcutaneous mifepristone completely and specifically abolished the escalation of alcohol drinking in dependent animals, indicating a critical role for GR transcriptional mechanisms in the establishment of excessive drinking. Interestingly, alcohol-dependent rats exhibited

significant downregulation of GR expression in cortical and limbic regions, a result interpreted as a mechanism to partially counteract excessive HPA axis activation by chronic, intermittent alcohol exposure. Additionally, a rebound effect was observed during protracted abstinence (at least 3 weeks after rats were removed from alcohol exposure). At this later withdrawal time point, GR levels were increased in central brain regions (including the CeA, bed nucleus of the stria terminalis, and nucleus accumbens) that mediate relapse-like behaviors (Edwards & Koob, 2010) in alcohol-dependent rats. Consistent with the previous study, continuous mifepristone delivery normalized excessive drinking observed in dependent rats during protracted abstinence. Overall, these findings suggest that GR signaling is exacerbated during alcohol dependence and that dependent individuals may be more sensitive to glucocorticoid-induced relapse mechanisms even long into abstinence.

Potentiation of brain stress systems by alcohol

The intimate interaction between glucocorticoids and CRF in the regulation of stress signaling is partly mediated by the negative feedback mechanisms at the level of the HPA axis as described above. However, circulating glucocorticoids also appear to sensitize signaling in central stress circuitry, seemingly in opposition to its effects to dampen neuroendocrine mechanisms. For example, in contrast to reducing CRF expression in the PVN, high corticosterone levels increase CRF gene expression in the central amygdala (CeA; Makino, Gold, & Schulkin, 1994; Shepard, Barron, & Myers, 2000). As mentioned above, a host of studies has implicated CeA CRF action in the manifestation of excessive drinking. In addition, CRF signaling regulates a variety of emergent alcohol abuse-related behaviors ranging from relapse to hyperalgesia (Edwards et al., 2012b; Gehlert et al., 2007; Guerrero, Ghoneim, Roberts, & Koob, 2012; Marinelli et al., 2007; Valdez et al., 2002), and many of these behaviors are driven by CRF action within the CeA (Egli, Koob, & Edwards, 2012; Weiss et al., 2001).

A key question is the way glucocorticoids produce a negative feedback at the HPA level but engender a positive feedback cycle within the CeA. Following glucocorticoid binding, the process of intracellular GR trafficking and nuclear gene expression is regulated by a host of chaperones and functional co-factors that could present a differential regulatory milieu between the hypothalamus and CeA (Fig. 1). One key regulatory molecule for GR efficacy is steroid receptor co-activator 1 (SRC-1), a histone acetyltransferase (Spencer et al., 1997). Interestingly, mice with a genetic deletion of SRC-1 fail to display natural changes in CRF gene expression after administration of dexamethasone (a synthetic glucocorticoid) in either the PVN or CeA (Lachize et al., 2009). That is, both reductions in PVN CRF mRNA and increases in CeA CRF mRNA following GR activation are dependent on SRC-1, suggesting a key role for this epigenetic factor in the differential response to stress (i.e., tolerance vs. sensitization) between the hypothalamic and extra-hypothalamic systems.

Glucocorticoid regulation of alcohol's effects on cognition and neurodegeneration

In addition to the development of pathological motivational states that drive the urge to drink, repeated binge or excessive alcohol use produces substantial and debilitating cognitive deficits (Hunt, 1993; Persidsky et al., 2011; Riege, Holloway, & Kaplan, 1981; Zorumski, Mennerick, & Izumi, 2014). Although some of these effects are due to alcohol-

related thiamine deficiency (Korsakoff's syndrome), evidence also points to a causative role for brain glucocorticoids in the exacerbation of neurocognitive deficits in alcoholism (Prendergast & Little, 2007; Rose, Shaw, Prendergast, & Little, 2010). Importantly, high cortisol levels during alcohol withdrawal correlated with the severity of cognitive problems in withdrawn alcoholics (Errico, King, Lovallo, & Parsons, 2002), while treatment with the GR antagonist mifepristone during acute withdrawal persistently reduced memory deficits observed in mice during later abstinence (Jacquot et al., 2008). Similar to its role in driving excessive alcohol drinking, a potentiation of CRF systems by GR signaling may underlie cognitive impairment during alcohol withdrawal (George, Sanders, et al., 2012).

In accordance with its deleterious effects on cognition, heavy alcohol use is also well known to produce direct neuronal damage, particularly within regions susceptible to excitotoxicity such as the hippocampus and prefrontal cortex. These regions also exhibit significant neurogenesis and gliogenesis (respectively) that is reduced by excessive alcohol exposure (Nixon & Crews, 2002; Richardson et al., 2009; Taffe et al., 2010). Corticosterone facilitates the effects of alcohol withdrawal to damage hippocampal slices (Mulholland et al., 2005), likely via enhancement of glutamatergic signaling (Abrahám, Harkany, Horvath, & Luiten, 2001; Butler, Berry, Sharrett-Field, Pauly, & Prendergast, 2013) that is already potentiated via chronic and intermittent alcohol exposure (Becker, Veatch, & Diaz-Granados, 1998). Importantly, treatment with mifepristone confers neuroprotection in the hippocampal dentate gyrus of binge alcohol-treated animals (Cippitelli et al., 2014), a brain region that displays robust neurogenesis (Mandyam, 2013). Together with mifepristone's demonstrated ability to reduce somatic symptoms of alcohol withdrawal in rats (Sharrett-Field, Butler, Berry, Reynolds, & Prendergast, 2013), these data suggest that GR antagonism would be capable of treating a full range of AUD symptoms.

Conclusions and future directions

In response to excessive drinking, a dysregulation of glucocorticoid function promotes neurocognitive deficits while locking individuals into dependent states by incentivizing the pursuit of alcohol to alleviate the negative motivational symptoms of withdrawal. The myriad effects of glucocorticoids on brain and HPA axis function contribute to AUD being a quintessential neurodegenerative and psychiatric disease.

As a transcription factor, dysregulation of GR activity would be expected to modulate a wide variety of neurotransmitter systems that regulate stress and alcohol use (Koob, 2009; Silberman et al., 2009). For example, it is noteworthy that in addition to CRF, the role of GR in the modulation of vasopressin gene expression and function may explain some of the effects of glucocorticoid dysregulation on stress responsiveness and alcohol dependence (Daubert, Looney, Clifton, Cho, & Scheuer, 2014; Kim, Summer, Wood, & Schrier, 2001; Rabadan-Diehl & Aguilera, 1998; Zhou & Kreek, 2014). Along with CRF, vasopressin is present in parvocellular PVN neurons and acts as a co-regulator of the HPA axis (Sawchenko, Swanson, & Vale, 1984; Whitnall, Mezey, & Gainer, 1985) through its actions on V1b receptors. Glucocorticoids exert a negative feedback on PVN vasopressin release (Liu, Wang, & Chen, 1995), while central brain vasopressin circuitry promotes a host of anxiety- and depression-like behaviors (Salomé, Stemmellin, Cohen, & Griebel, 2006;

Stemmelin, Lukovic, Salome, & Griebel, 2005). Importantly, vasopressin acting through V1b receptors has been demonstrated to participate in the manifestation of excessive drinking in alcohol-dependent and alcohol-preferring rats (Edwards et al., 2012a; Zhou et al., 2011).

AUD is frequently associated with the use of commonly abused drugs such as nicotine (Little, 2000; Leão et al., 2015). Like virtually all drugs of abuse, nicotine both stimulates the HPA axis (Armario, 2010) and potentiates CRF systems in the CeA during dependence (Cohen et al., 2013; George et al., 2007). The restoration of adaptive glucocorticoid signaling may therefore represent a simple and comprehensive treatment strategy for drug and alcohol co-dependence, along with a host of psychiatric conditions co-morbid with AUD (Pettinati, O'Brien, & Dundon, 2013). In this regard, the demonstrated efficacy of the GR antagonist mifepristone in psychiatric disease and neurocognitive disorders (DeBattista & Belanoff, 2006) warrants additional investigation into its beneficial use in AUD populations that may suffer from these devastating conditions.

Finally, the interaction of glucocorticoids in so many areas of stress signaling has also been suggested to play a role in resilience factors against psychiatric disease (Srinivasan, Shariff, & Bartlett, 2013). For example, differential cortisol levels and responsiveness contribute to individual vulnerability in the development of PTSD (Whitaker, Gilpin, & Edwards, 2014), while GR-associated cofactors such as FKBP51 appear to influence affective disorder development and even medication responsiveness in individuals (Galigniana et al., 2012; Wilker et al., 2014). Animal models of PTSD have demonstrated both the central role of GR signaling in the delineation of resilient vs. susceptible individuals (Daskalakis, Cohen, Cai, Buxbaum, & Yehuda, 2014), as well as the heightened propensity for escalation of alcohol drinking in traumatic stress-sensitive populations (Edwards et al., 2013). Further study into the role of individual differences in glucocorticoid signaling in relation to AUD may provide better insight into individualized therapies (e.g., pharmacogenetic strategies) and also help return us to the original conceptualizations of adaptive versus maladaptive stress in health and disease as intended by Selye and colleagues.

Acknowledgments

Preparation of this review was supported by the National Institute on Alcohol Abuse and Alcoholism (AA020839, SE) and the National Institute on Drug Abuse, Intramural Research Program (LFV). We thank Dr. Marisa Roberto and all of the individuals who allowed us to share our work at the 2014 Alcoholism and Stress Conference in Volterra, Italy (supported by AA017581).

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Fig. 1.

Distinct regulatory environments exist for glucocorticoid receptor (GR)-mediated gene expression in the hypothalamic paraventricular nucleus and the central amygdala (CeA). Specific epigenetic elements (e.g., steroid receptor co-activator 1, SRC-1) drive corticotropin-releasing factor (CRF) expression in opposite directions within these two stress-regulatory regions, mediating a negative feedback along the hypothalamic-pituitary-adrenal (HPA) axis but a positive feedback in the CeA. In combination with alterations in GR activity within the prefrontal cortex (PFC) that may promote cognitive disruption in heavy drinkers, these neuroadaptations in glucocorticoid signaling are hypothesized to drive the transition from recreational alcohol drinking to alcohol-use disorder (AUD).