Divergent regulation of distinct glucocorticoid systems in alcohol dependence

Scott Edwards [a,*], Hilary J. Little [b], Heather N. Richardson [c], Leandro F. Vendruscolo [d]

[a] Department of Physiology, Alcohol and Drug Abuse Center of Excellence, Louisiana State University Health Sciences Center, 1901 Perdido St., New Orleans, LA 70112, USA
[b] Institute of Psychiatry, Psychology & Neuroscience, King's College, London, UK
[c] University of Massachusetts, Department of Psychological and Brain Sciences, Amherst, MA, USA
[d] National Institute on Drug Abuse, National Institutes of Health, Baltimore, MD, USA

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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.

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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, 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 et al. (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–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, and 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 et al. (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