HHS Public Access

Author manuscript

Neuropharmacology. Author manuscript; available in PMC 2018 August 01.

Published in final edited form as:

Neuropharmacology. 2017 August 01; 122: 115–126. doi:10.1016/j.neuropharm.2017.04.028.

Influence of Stress Associated with Chronic Alcohol Exposure on Drinking

Howard C. Becker

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

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.

Keywords

Chronic alcohol exposure; alcohol withdrawal; stress; alcohol drinking; neuropeptides

Correspondence: Howard C. Becker, Ph.D. 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, South Carolina USA 29425 beckerh@musc.edu.

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 physiological symptoms of acute alcohol withdrawal (e.g., tachycardia, elevated blood pressure, diaphoresis, body temperature dysregulation) (Becker, 2000; Heilig et al., 2010). While heightened HPA axis activation associated with withdrawal usually resolves within a few days (Kakihana, 1979; Tabakoff et al., 1978), blunted HPA axis responsiveness appears to persist for a protracted period of time (Rasmussen et al., 2000; Zorrilla et al., 2001). In some cases, this may be accompanied by reduced basal levels of circulating corticosteroids (Rasmussen et al., 2000; Richardson et al., 2008a; Zorrilla et al., 2001). These perturbations

in HPA axis function align with findings reported in abstinent human alcoholics (Adinoff et al., 1990; Adinoff et al., 1991; Costa et al., 1996; Lovallo et al., 2000; Willenbring et al., 1984). Dysregulation of HPA axis function that extends into protracted phases of withdrawal is thought to contribute to dysphoria and negative affect associated with alcohol dependence (Heilig et al., 2010; Koob and Kreek, 2007; Koob, 2013). Further, persistent changes in HPA neuroendocrine function resulting from chronic alcohol exposure and withdrawal may activate brain stress systems outside the HPA axis (Koob, 2013; Vendruscolo et al., 2012).

Indeed, it is well established that chronic alcohol alters CRF activity independent from the HPA axis. CRF is a 41 amino acid neuropeptide that is widely distributed throughout mammalian brain. As noted above, CRF-containing neurons are found in high concentrations in the PVN of the hypothalamus where they play a primary role in regulating HPA axis activity, which is critical for orchestrating behavioral and physiological responses to stress. CRF-containing neurons are also found outside the neuroendocrine (HPA) axis. The extra-hypothalamic distribution of CRF includes an extensive network of interconnected neural structures (e.g., central amygdala (CeA), bed nucleus of the stria terminalis (BNST), prefrontal cortex) that are intimately associated with brain reward and stress pathways. The actions of CRF (and related peptides urocortin I, II, and III) are modulated by CRF-binding protein and mediated through interaction with two excitatory G-protein-coupled receptor subtypes (CRF_1 and CRF_2) (Bale and Vale, 2004). CRF_1 and CRF_2 receptors are distributed in overlapping yet distinct patterns within these brain reward and stress circuits. This anatomical distribution of CRF and its associated binding sites is congruent with the important role of both hypothalamic and extra-hypothalamic CRF in processing and regulating central, autonomic, and emotional/behavioral responses to stress as well as rewarding stimuli/events including alcohol and other drugs of abuse (Bruijnzeel and Gold, 2005; Ryabinin et al., 2002).

A large body of evidence has emerged indicating that CRF plays a critical role in alcohol (and other drug) addiction (Heilig and Koob, 2007; Koob and Zorrilla, 2010; Lowery and Thiele, 2010; Zorrilla et al., 2014). Aside from producing long-lasting dysregulation of HPA function, chronic alcohol exposure produces time-dependent changes in extracellular levels of extra-hypothalamic CRF during withdrawal (Merlo Pich et al., 1995; Olive et al., 2002; Zorrilla et al., 2001). Changes in CRF activity resulting from chronic alcohol exposure (increased CRF release along with an up-regulation in CRF_1 receptors) within the extended amygdala network is thought be key to the emergence of withdrawal symptoms reflective of a negative emotional state associated with alcohol dependence. For example, increased behavioral measures of anxiety associated with alcohol withdrawal is reduced by systemic (Breese et al., 2005; Sommer et al., 2008) and central (Baldwin et al., 1991; Rassnick et al., 1993; Valdez et al., 2003) administration of CRF receptor antagonists. This effect appears to be mediated by CRF_1 receptors (Overstreet et al., 2004), although a role for CRF_2 receptors cannot be ruled out (Valdez et al., 2004). Together, these findings indicate that chronic alcohol exposure and withdrawal experience can be viewed as a potent stressor that disrupts the functional integrity of the HPA axis while at the same time recruiting and sensitizing extra-hypothalamic CRF systems. The resultant allostatic state is characterized by progressive dysregulation of neuroendocrine and brain stress systems along with perturbations in brain reward pathways that contribute to dysphoric and negative affect

associated with alcohol dependence. Implications of these changes regarding motivation for alcohol self-administration as well as relapse vulnerability are discussed below.

3. Link Between Chronic Alcohol, Stress Response, and Motivation to Drink

The circumstances and manner in which stress influences alcohol drinking behavior has been extensively studied in humans and animal models (Brady and Sonne, 1999; Pohorecky, 1990, 1991; Sillaber and Henniger, 2004; Sinha, 2001, 2008). Over several decades, a wide array of animal models and experimental procedures have been employed in addressing this important issue. Unfortunately, this large body of literature has yielded equivocal results, most likely due to differences in a number of variables including genetic and other biological factors, environmental conditions, and a host of experimental procedural differences (Becker et al., 2011; Noori et al., 2014; Spanagel et al., 2014).

Recently, greater attention has focused on how stress associated with chronic alcohol exposure and withdrawal experience influences motivation to self-administer alcohol. Studies in mice and rats have demonstrated dependence-related excessive levels of alcohol consumption under a number of conditions (Becker, 2013; Becker and Ron, 2014; Vendruscolo and Roberts, 2014). These models not only demonstrate escalation of drinking, but perturbations in neuroendocrine and brain stress systems induced by chronic alcohol exposure and withdrawal have been linked to enhanced behavioral responsiveness to stress. For example, rats exhibit increased stress responsiveness following withdrawal from chronic alcohol exposure, as measured by several experimental procedures that provoke behavioral measures of stress/anxiety, such as reduced social interaction in a novel environment, reduced exploration in threatening circumstances (e.g., open, brightly illuminated spaces), and greater electroshock-induced suppression of ongoing behavior (Breese et al., 2005; Gehlert et al., 2007; Sommer et al., 2008). In a series of studies involving a mouse model of alcohol dependence and relapse drinking, repeated brief exposure to forced swim stress prior to alcohol drinking sessions significantly increased drinking in alcohol dependent mice, but did not alter intake in nondependent mice (Lopez et al., 2016). Interesting, this stress procedure did not further increase drinking in two other drinking models that typically engender high levels of alcohol intake – the drinking-in-the-dark (DID) model and the intermittent access (‘every-other-day’) model (Anderson et al., 2016a). These results suggest that stress may interact with chronic alcohol exposure and withdrawal in a unique manner to facilitate and further augment escalated drinking in dependent subjects (Anderson et al., 2016b). Further, behavioral sensitization to stress may be critical in rendering subjects more vulnerable to relapse. Indeed, experimental evidence suggests that stress can provoke relapse-like behavior more easily in subjects with a history of dependence (Liu and Weiss, 2002; Sommer et al., 2008).

4. Mechanisms Underlying Chronic Alcohol, Stress, and Drinking Relationship

4.1 Corticotropin-Releasing Factor (CRF)

Numerous studies involving rodent models have shown that such changes in brain CRF activity have important ramifications regarding alcohol self-administration behavior. For example, CRF infusion into the ventricles was shown to reduce voluntary alcohol intake in rats (Bell et al., 1998; Thorsell et al., 2005b). Likewise, transgenic CRF over-expressing mice exhibited reduced voluntary alcohol intake compared to non-transgenic controls (Palmer et al., 2004), while CRF deficient mice showed the opposite effect – increased alcohol drinking (Olive et al., 2003). Differences in brain CRF content have been observed in alcohol-naïve rats and mice known to differ in voluntary alcohol intake (Ehlers et al., 1992; George et al., 1990), although a recent report indicated no difference in brain regional expression of CRF between C57BL/6J (high alcohol drinking) and DBA/2J (low alcohol drinking) mice (Hayes et al., 2005). Additional studies in humans, monkeys, and rats suggest an association between genetic variants (single nucleotide polymorphisms) of the CRF and CRF_1 receptor genes and alcohol drinking (Barr et al., 2009; Barr et al., 2008; Blomeyer et al., 2008; Hansson et al., 2006; Schmid et al., 2010). Collectively, these findings indicate that genetic variations in the *Crf* and the *CrfR1* genes interact with stressful life events to influence age of drinking onset, progression of heavy drinking in adulthood, and general vulnerbaility to alcohol dependence.

Given its pivotal role in mediating neuroendocrine and brain (outside the HPA axis) responses to stress, it is not surprising that a large number of studies have examined the effect of chronic alcohol on CRF activity in relation to alcohol drinking. The non-selective peptide CRF antagonist (D-Phe-CRF_{12-41}) reduced excessive drinking in dependent animals when administered into the brain ventricles (Finn et al., 2007; Valdez et al., 2002) or into the CeA (Funk et al., 2006). Systemic administration of CRF_1 receptor-selective antagonists reduced up-regulated drinking in dependent mice (Chu et al., 2007) and rats (Funk et al., 2007; Gehlert et al., 2007; Gilpin et al., 2008b; Richardson et al., 2008b; Roberto et al., 2010; Sabino et al., 2006; Sommer et al., 2008).

Studies using operant conditioning procedures also have demonstrated an important role for CRF in mediating the ability of stress to trigger relapse-like behavior. For example, CRF antagonists have been shown to block stress-induced reinstatement of alcohol seeking behavior (Gehlert et al., 2007; Le et al., 2000; Liu and Weiss, 2002; Marinelli et al., 2007). This effect appears to be mediated by extra-hypothalamic CRF activity, since adrenalectomy (with or without corticosterone supplementation) did not affect reinstatement of alcohol responding induced by foot-shock stress (Le et al., 2000). In fact, direct infusion of a CRF antagonist into the median raphe nucleus blocked stress-induced alcohol seeking behavior (Funk et al., 2003; Le et al., 2002; Le et al., 2013). CRF_1 receptor antagonists injected into the ventral tegmental area reduced alcohol intake in high-drinking models, including stress-enhanced drinking (Hwa et al., 2016; Rinker et al., 2016). Overall, while a role for CRF_2 receptors cannot be ruled out (Funk and Koob, 2007; Valdez et al., 2004), the large preponderance of evidence suggests that CRF_1 receptors play an important role in regulating

alcohol consumption, especially excessive levels of drinking associated with dependence. Taken together, there is a large body of evidence indicating that chronic alcohol-induced changes in CRF function within brain/neuroendocrine systems may directly, and/or through mediating withdrawal-related anxiety and stress/dysphoria, promote excessive levels of drinking as well as influence relapse vulnerability (Heilig and Koob, 2007; Koob and Zorrilla, 2010; Lowery and Thiele, 2010; Zorrilla et al., 2014).

4.2 Dynorphin

Because both stress and chronic alcohol engage the DYN/KOR system, the role of this neuropeptide system in alcohol dependence-related stress/dysphoria and elevated drinking has gained increasing attention (Kissler et al., 2014; Wee and Koob, 2010). Dynorphins (DYN) are peptides derived from the precursor prodynorphin (Pdyn) that preferentially bind to kappa opioid receptors (KOR), producing physiological and behavioral effects via inhibitory G-protein (Gi) coupling and other signaling cascades (Bruchas and Chavkin, 2010; Bruchas et al., 2010; Crowley and Kash, 2015; Wee and Koob, 2010). KOR activation has been shown to produce aversive/dysphoric effects as indicated by measures of conditioned avoidance, anxiety-like, and depression-like behavior (Knoll and Carlezon, 2010; Van't Veer and Carlezon, 2013). Stress exposure activates the DYN/KOR system, eliciting dysphoria-like responses, increasing anxietylike behaviors (Land et al., 2008) and resulting in elevated DYN immunoreactivity in brain regions that are integral to reward and stress circuitries involved in alcohol/drug addiction (Shirayama et al., 2004). Further, pharmacological manipulation of KOR activity alters behavioral responses to stress and motivational effects of alcohol. For example, KOR agonists have been shown to produce a state of stress/dysphoria, mimicking effects of stress on alcohol drinking and conditioned reward (Anderson et al., 2016b; Sperling et al., 2010). Conversely, KOR antagonists attenuate stress-induced potentiation of conditioned alcohol reward (Sperling et al., 2010), yohimbine-induced reinstatement of alcohol seeking behavior (Funk et al., 2014), withdrawal-related negative affect and anxiety (Berger et al., 2013; Gillett et al., 2013; Rose et al., 2015; Schank et al., 2012; Valdez and Harshberger, 2012), and enhanced alcohol self-administration after exposure to a cue associated with a KOR agonist (Berger et al., 2013).

Structures within the extended amygdala circuitry that are intimately involved in mediating negative emotional and motivational states associated with stress and chronic alcohol exposure/withdrawal (e.g., CeA, BNST) are rich in DYN and KORs (Mansour et al., 1994; Marchant et al., 2007; Poulin et al., 2009). There is evidence that stress and chronic alcohol exposure increase DYN/KOR function in the CeA and BNST (Chung et al., 2014; Kissler et al., 2014). A number of studies have shown that this upregulation in DYN/KOR signaling contributes to escalated alcohol intake associated with dependence. For example, systemic administration of the KOR antagonist nor-binaltorphimine reduced escalated drinking in dependent rats while not altering more modest intake in nondependent rats (Kissler et al., 2014; Walker and Koob, 2008; Walker et al., 2011). Similar results were reported in mice (Rose et al., 2015). Pharmacological blockade of KORs by direct injection of a KOR antagonist into the CeA (Kissler et al., 2014) or into the nucleus accumbens (Nealey et al., 2011) also was shown to attenuate elevated alcohol consumption in dependent rats. Additionally, systemic administration of the novel short-acting KOR antagonist,

LY2444296, abolished the ability of stress (forced swim) to enhance drinking in dependent mice (Anderson et al., 2016b).

There is also evidence for interaction between the DYN/KOR system and CRF within extended amygdala circuitry that have implications for stress and chronic alcohol consequences. For example, these neuropeptides have been shown to be involved in chronic alcohol-induced alterations in synaptic plasticity in the CeA (Kang-Park et al., 2013, 2015; Roberto et al., 2010). Specifically, KORs were shown to modulate GABAergic transmission in a CRF_1 receptor-dependent manner (Kang-Park et al., 2015). Interestingly, CRF infusion into the CeA was reported to increase DYN release in a CRF_2 receptor-dependent manner (Lam and Gianoulakis, 2011). The aversive/anxiety-like behavioral effects of central CRF administration are attenuated by pretreatment with a KOR antagonist (Bruchas and Chavkin, 2010; Bruchas et al., 2010; Land et al., 2008). Conversely, a CRF_1 receptor antagonist blocked KOR agonist-induced reinstatement of alcohol seeking (Funk et al., 2014). Thus, while the precise nature of DYN/KOR-CRF interactions is not completely understood, behavioral and physiological evidence suggests that an interaction between these two stress-related neuropeptide systems within extended amygdala circuitry plays a significant role in mediating stress and motivational effects of chronic alcohol exposure.

4.3 Other Stress-Related Neuropeptides

Aside from CRF and DYN, several other neuropeptide systems in brain are involved in stress response as well as motivational effects of alcohol (Ciccocioppo et al., 2009; Martin-Fardon et al., 2010; Roberto et al., 2012). In some cases, these neuropeptide systems serve to dampen stress effects associated with chronic alcohol exposure, thereby modulating alcohol consumption in the context of dependence. Here we review three anti-stress neuropeptide systems (nociceptin, neuropeptide Y, and oxytocin) that are influenced by chronic alcohol exposure and contribute to withdrawal-related behavioral measures of dysphoria as well as motivation to self-administer alcohol. Of note, recent studies have pointed to several other neuropeptide systems that contribute to emotional and behavioral sequela that reflect the intersection of stress and chronic alcohol exposure/withdrawal, including orexin/hypocretin, neurokinins, and neuropeptide S (Schank et al., 2012).

4.3.1 Nociceptin—Nociceptin/orphanin FQ is a 17-amino acid peptide classified as being a member of the opioid family, but binds with high affinity to the nociception receptor (NOP; also referred to as the opioid receptor-like 1 - ORL1) rather than mu, delta, or kappa opioid receptors (Meunier et al., 1995; Reinscheid et al., 1995). Dense expression of the peptide and its receptor within cortical and limbic regions suggest its role in emotional and motivational behaviors, particularly those related to stress, chronic alcohol exposure/withdrawal, and drinking. Increased expression of nociception and NOP mRNA in the CeA of rats selectively bred for high alcohol preference is suggested to relate to the high-anxiety and stress responsiveness in these animals (Ciccocioppo et al., 2007; Economidou et al., 2008). Pharmacological studies have demonstrated a role for the nociceptin/NOP system in regulation of alcohol self-administration, as well as withdrawal-related anxiety and drinking. For example, infusion of nociceptin into brain ventricles reduced alcohol conditioned reward as well as relapse-like behavior provoked by either stress or alcohol-related cues

(Ciccocioppo et al., 2004; Martin-Fardon et al., 2000). Likewise, systemic administration of brain-penetrant nociception analogues reduced alcohol self-administration (Aziz et al., 2016; Ciccocioppo et al., 2014; Kuzmin et al., 2007). Direct injection of nociceptin into the CeA also was reported to reduce alcohol consumption (Economidou et al., 2008). This effect may be mediated by nociception interacting with alcohol-induced modulation of GABA and glutamate transmission in the CeA (Kallupi et al., 2014a; Kallupi et al., 2014b). Additionally, chronic alcohol exposure appears to enhance sensitivity to NOP activation, as nociceptin (or its analogues) were shown to be more effective as anxiolytics and reducing elevated drinking associated with dependence (Aujla et al., 2013; Aziz et al., 2016; de Guglielmo et al., 2015; Economidou et al., 2011; Martin-Fardon et al., 2010).

Contrary to these findings, recent reports suggest that blocking, rather than activating, NOP receptors may be effective in reducing alcohol self-administration. Genetic deletion of the nociception receptor in rats resulted in lower alcohol consumption compared to wildtype controls, while saccharin intake was unaltered (Kallupi et al., 2017). Further, systemic administration of NOP antagonists reduced alcohol self-administration in wildtype rats but was without effect in NOP-deficient rats (Kallupi et al., 2017). These results align with another report showing that oral administration of a NOP antagonist reduced alcohol consumption, motivation to work for alcohol, and stress (yohimbine)-induced reinstatement of alcohol-seeking behavior in rats (Rorick-Kehn et al., 2016). These effects produced by the nociceptin receptor antagonist were attributed to the drug blocking alcohol-induced dopamine release in the nucleus accumbens. Several explanations have been postulated to address these apparent contradictory results (NOP agonists and antagonists reduce alcohol consumption), including receptor translocation, ligand-biased receptor signaling, and brain regional differences in receptor variants (Rorick-Kehn et al., 2016). Future studies will need to resolve this issue as well as address the therapeutic potential of this target for treating alcohol use disorders and stress-related drinking in particular.

4.3.2 Neuropeptide Y—Neuropeptide Y (NPY) is known to mediate anti-stress effects, typically opposing behavioral actions of CRF (Sajdyk et al., 2006). NPY, a 36-amino acid peptide, produces these effects primarily through actions at Y1 and Y2 receptors in brain. NPY exerts anxiolytic effects in a number of behavioral tasks, an effect thought to be mediated by interaction with Y1 receptors in the amygdala (Heilig et al., 1993; Thorsell, 2008). There is evidence indicating a relationship between NPY activity (primarily in the CeA) and alcohol consumption. For example, rats selectively bred for high alcohol preference exhibit low NPY mRNA and peptide levels in the CeA, an effect that was reversed when the rats were given the opportunity to consume alcohol (Pandey et al., 2005). Viral mediated overexpression of NPY in the amygdala was shown to reduce alcohol drinking in rats identified as being highly anxious (Primeaux et al., 2006) or following periods of forced abstinence (Thorsell et al., 2007). Also, infusion of NPY in brain ventricles (icv.) reduced stress-induced relapse-like behavior in rats (Cippitelli et al., 2010).

Pharmacological studies also support a role for NPY in the regulation of alcohol consumption, although there is some contradictory evidence regarding the role of Y1 and Y2 receptor subtypes. For example, systemic (ip.) and central (icv.) administration of a Y1R antagonist reduced alcohol intake in C57BL/6J mice (Sparta et al., 2004). In contrast,

another study showed that central injection (icv.) of a Y1R agonist reduced binge-like alcohol intake in mice in a dose-related manner (Sparrow et al., 2012). Further, a Y1R antagonist (icv.) increased alcohol consumption (Sparrow et al., 2012), supporting an earlier report indicating that Y1R knockout mice exhibited increased alcohol intake (Thiele et al., 2002). A Y2 antagonist given directly into brain (icv.) reduced ethanol intake in rats (Thorsell et al., 2002), and sensitivity to this effect was greater is dependent rats (Rimondini et al., 2005). A similar finding was reported in mice (Sparrow et al., 2012), corroborating results from a study showing reduced ethanol intake in Y2R knockout mice (Thiele et al., 2002). However, in another study systemic (sc.) or central (icv.) administration of a brain-penetrant Y2 antagonist did not alter operant responding for alcohol or stress (foot-shock)-induced reinstatement of alcohol responding in rats, although the drug was effective reducing withdrawal-related anxiety (Cippitelli et al., 2011).

Studies have shown that chronic alcohol exposure alters NPY function and this may contribute to increased stress/anxiety associated with dependence as well as increased propensity to drink. Early studies indicated that NPY administration reduced elevated drinking in dependent animals (Thorsell et al., 2005a, c). More recent work has focused on NPY actions in the CeA in the context of dependence (Gilpin et al., 2015). For example, increased anxiety during withdrawal from chronic alcohol exposure was associated with decreased NPY expression in CeA (Roy and Pandey, 2002). Further, direct injection of NPY into the CeA reduced excessive alcohol consumption in dependent rats (Gilpin et al., 2008a), an effect possibly related to modulation of GABA transmission in the CeA (Gilpin et al., 2011). Recent work also points to interactions between NPY and CRF within the BNST as a site important for mediating stress influences on alcohol drinking (Pleil et al., 2015).

4.3.3 Oxytocin—A growing body of literature suggests that oxytocin plays a significsant role in alcohol (and othe drug) addiction, as well as neuropsychiatric disorders that involve deficits in social behaviors (Baskerville and Douglas, 2010; Lee and Weerts, 2016). Oxytocin, a nonapeptide, is an endogenous neurohormone synthesized in the paraventricular and supraoptic nuclei of the hypothalamus and released by the posterior pituitary into peripheral circulation. In addition, oxytocin is released by neurons in the hypothalamus that project to numerous extra-hypothalamic regions in the brain (e.g., cortical, limbic, basal ganglia structures) where it mediates an array of behavioral effects via interaction with G(q)-coupled oxytocin receptors (Lee et al., 2016). Aside from its known hormonal role in parturition and maternal behaviors, oxytocin also regulates a number of behaviors that involve social interactions (e.g., pair-bonding, social reward processing, aggression) and nonsocial behaviors, including anxiety and stress responses (Baskerville and Douglas, 2010; Bowen et al., 2011; Neumann and Landgraf, 2012).

Preclinical evidence indicates that oxytocin influences a number of behavioral and physiological effects of alcohol, including tolerance, withdrawal, and motivational effects (Lee and Weerts, 2016). For example, systemic administration of oxytocin reduces alcohol preference and intake in a variety of drinking models in rats (Bowen et al., 2011; MacFadyen et al., 2016; McGregor and Bowen, 2012) and mice (King et al., 2017; Peters et al., 2013). Direct injection of oxytocin into brain ventricles reduced alcohol consumption and alcohol-induced dopamine efflux in the nucleus accumbens in rats (Peters et al., 2016).

Few studies have examined the role of oxytocin receptors in mediating the neuropeptide's effects on motivational actions of alcohol. Recent studies involving viral-mediated overexpression of oxytocin receptors in the nucleus accumbens core have implicated a role for these receptors in alcohol drinking and conditioned reward (Bahi, 2015; Bahi et al., 2016). However, it is noteworthy that oxytocin was shown to block alcohol-induced ataxic and sedative/hypnotic effects via an apparent direct interaction with delta-subunit containing GABA-A receptors (Bowen et al., 2015). Thus, there remains some abiguity as to the role of oxytocin receptors in mediating the neuropeptide's effects on physiological effects of alcohol and, in particular, alcohol-related reward and self-administration behavior.

Oxytocin is known to exert stress-bufferring effects, and this may be of relevance to its role in influencing stress-alcohol interactions. For example, oxytocin decreases stress-induced HPA axis activation and behavioral (anxiety) responses (Neumann et al., 2000; Windle et al., 1997). Systemic oxytocin treatment was also shown to temper stress-related increases in alcohol consumption (Peters et al., 2013). Finally, in a recent clinical study, Pedersen and colleagues demonstrated that intranasal oxytocin treatment attenuated alcohol withdrawal symptoms in treatment-seeking human subjects compared to placebo (Pedersen et al., 2013). Taken together, there is emerging evidence that oxytocin may hold promise as a therapeutic for treating alcohol use disorders and, in particular for mitigating stress effects on alcohol drinking and relapse.

4.4 Glucocorticoids

Alcohol-induced activation of the HPA axis results in elevated circulating glucocorticoids and it has been suggested that this may contribute to amplified motivation to drink through an interaction with brain reward circuitry (Piazza and Le Moal, 1997; Uhart and Wand, 2009). Central and systemic administration of corticosterone has been shown to increase alcohol consumption, whereas adrenalectomy or administration of a corticosteroid synthesis inhibitor (i.e., metyrapone) decreased alcohol intake in rodents (Fahlke et al., 1995; Fahlke et al., 1996). Likewise, a glucocorticoid receptor antagonist (i.e., mifepristone) reduced alcohol self-administration behavior in rats (Koenig and Olive, 2004). Furthermore, mifepristone administered systemically or into the central nucleus (but not the basolateral nucleus) of the amygdala attenuated stress-induced reinstatement of alcohol seeking behavior (Simms et al., 2012).

Stress associated with chronic alcohol exposure and withdrawal results in a dysregulated HPA axis. Resultant elevated glucocorticoids dampen HPA activity through negative feedback, but there is evidence that glucocorticoids induce CRF activity in extra-hypothalamic sites such as the amygdala (Sawchenko, 1987). Thus, chronic alcohol exposure may ultimately dampen HPA axis while accentuating extra-hypothalamic CRF activity. This, in turn, may contribute to chronic alcohol-induced negative affect and increased motivation to drink (Koob, 2013; Lu and Richardson, 2014).

There is also evidence that chronic alcohol exposure alters corticosteroid levels and glucocorticoid receptors in brain. Recent studies have shown that glucocorticoid receptor expression (mRNA levels) and phosphorylation were elevated in the central (but not basolateral) amygdala in dependent compared to nondependent rats (Vendruscolo et al.,

2012; Vendruscolo et al., 2015). Further, systemic and direct (central amygdala) injection of mifepristone was shown to reduce alcohol self-administration in dependent but not nondependent rats (Vendruscolo et al., 2015). Mifepristone treatment was also reported to reduce alcohol craving and consumption in a double-blind clinical laboratory-based study of alcohol dependent human subjects (Vendruscolo et al., 2015). Finally, studies in mice and rats have shown that withdrawal following prolonged alcohol consumption produced elevated corticosterone levels in certain brain regions (i.e., the prefrontal cortex and hippocampus) that persisted long after plasma corticosterone levels returned to baseline levels (Little et al., 2008). Elevations in brain glucocorticoid concentrations following chronic alcohol exposure and withdrawal not only may have significant implications for motivation to drink, but also may contribute to the cognitive deficits and neurotoxic damage that is commonly associated with alcohol dependence (Rose et al., 2010).

4.5 Autonomic Nervous System

An important component of stress associated chronic alcohol exposure and withdrawal is activation of the autonomic nervous system. In particular, increased noradrenergic output from locus coeruleus activation plays an important role in mediating both somatic and affective aspects of alcohol withdrawal (Heilig et al., 2010). Beyond withdrawal symptoms, changes in central noradrenergic activity also has been implicated in stress-related psychiatric illnesses as well as alcohol use disorders. For example, the noradrenergic alpha-1 receptor antagonist prazosin has been shown to be efficacious in treating various PTSD-related symptoms (Germain et al., 2012; Raskind et al., 2007; Raskind et al., 2013). Another noradrenergic alpha-1 receptor antagonist with a more favorable pharmacokinetic profile, doxazosin, was shown to reduce symptoms of PTSD as well (De Jong et al., 2010).

Drugs targeting the noradrenergic system also has been reported to reduce alcohol consumption in a number of preclinical studies. Prazosin reduced alcohol drinking in rats selectively bred for high alcohol preference (Froehlich et al., 2013a; Rasmussen et al., 2009). The drug also was effective in reducing intake in relapse models involving repeated alcohol deprivation periods (Froehlich et al., 2015) and stress-induced reinstatement of alcohol seeking behavior (Le et al., 2011). Prazosin treatment prior to stress (restraint) exposure during repeated deprivation periods prevented increased anxiety-like behaviors during a subsequent deprivation period (Rasmussen et al., 2017). Additionally, several studies found prazosin in combination with naltrexone to be more effective in reducing drinking than either drug given alone (Froehlich et al., 2013b; Rasmussen et al., 2015; Verplaetse and Czachowski, 2015). Studies also have shown prazosin reduces alcohol self-administration in dependent rats (Walker et al., 2008), and a similar effect was obtained with the beta-adrenergic antagonist propranolol (Gilpin and Koob, 2010). Given this preclinical and clinical evidence, there is active interest in the potential for drugs targeting central adrenergic receptors in the treatment of alcohol use disorders and the high prevalence of its comorbidity with stress-related illnesses such as PTSD (Kenna et al., 2016; Simpson et al., 2015).

5. Summary

The relationship between stress and alcohol is complex, with a wide array of factors (genetic, biological, and environmental) playing a role in contributing to the outcome of stress-alcohol interactions. While stress may interact with alcohol during the initial stages of drinking to enhance its rewarding effects, persistent excessive alcohol consumption serves as a potent stressor itself, continually challenging and ultimately compromising the physiological integrity of the subject. Prolonged alcohol exposure leads to fundamental changes in brain reward and neuroendocrine/stress systems beyond normal homeostatic limits (i.e., a state of allostasis), which, in turn, impacts physiological and brain motivational systems that are integral to control and regulation of ethanol consumption. As reviewed in this article, substantial evidence has accrued demonstrating that chronic alcohol exposure produces profound dysregulation in the neuroendocrine (HPA axis) stress system while at the same time recruiting and sensitizing extra-hypothalamic stress circuitry in the brain. Use of animal (primarily rodent) models has been critical to advancing our understanding about how chronic alcohol-induced changes in neuroendocrine and brain stress systems, particularly those intertwined with reward circuitry, underlie expression of withdrawal symptoms reflective of a negative affective state (i.e., dysphoria, anxiety), along with increased motivation to self-administer alcohol (Figure 1). As highlighted in this review, elevated glucocorticoids, along with activation of several pro-stress neuropeptides (CRF, DYN) and anti-stress neuropeptide systems (nociceptin, NPY, oxytocin) have been shown to play a significant role in these dynamic aspects of the addiction process. Heightened autonomic (sympathomimetic) effects also contribute to the stress, negative emotional, and motivational consequences of chronic alcohol exposure. Future studies aimed at elucidating mechanisms of engagement and timing of these (and other) stress-related systems will be critical in providing a more comprehensive understanding of the dynamic physiological and psychological underpinnings of alcohol addiction. Use of animal models also will be key to identifying new targets and evaluating potential therapeutics for treating problem drinking, particularly stress-related excessive alcohol consumption. This research also has important implications for developing more effective treatments for those individuals presenting with comorbidity of alcohol use disorder and a stress-related illness, such as PTSD.

Acknowledgments

This work was supported by the National Institutes of Health [National Institute on Alcohol Abuse and Alcoholism grants: P50 AA010761, U01 AA014095, and U01 AA020929], Department of Defense/U.S. Army Institute for Molecular Neuroscience [grant: 803-94], and Department of Veterans Affairs [grant: BX000813].

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Abbreviations

HPA	hypothalamic-pituitary-adrenocortical
CRF	corticotropin-releasing factor
DYN	dynorphin
KOR	kappa opioid receptor
CeA	central nucleus of the amygdale
BNST	bed nucleus of the stria terminalis

Highlights

- Stress alters drinking and progression of addiction in a complex manner
- Prolonged excessive alcohol consumption is a potent stressor
- Chronic alcohol produces persistent dysregulation of brain reward and stress systems
- Chronic alcohol engages stress and anti-stress neuropeptide systems
- chronic alcohol adaptations underlie stress, negative affect, and motivational behaviors

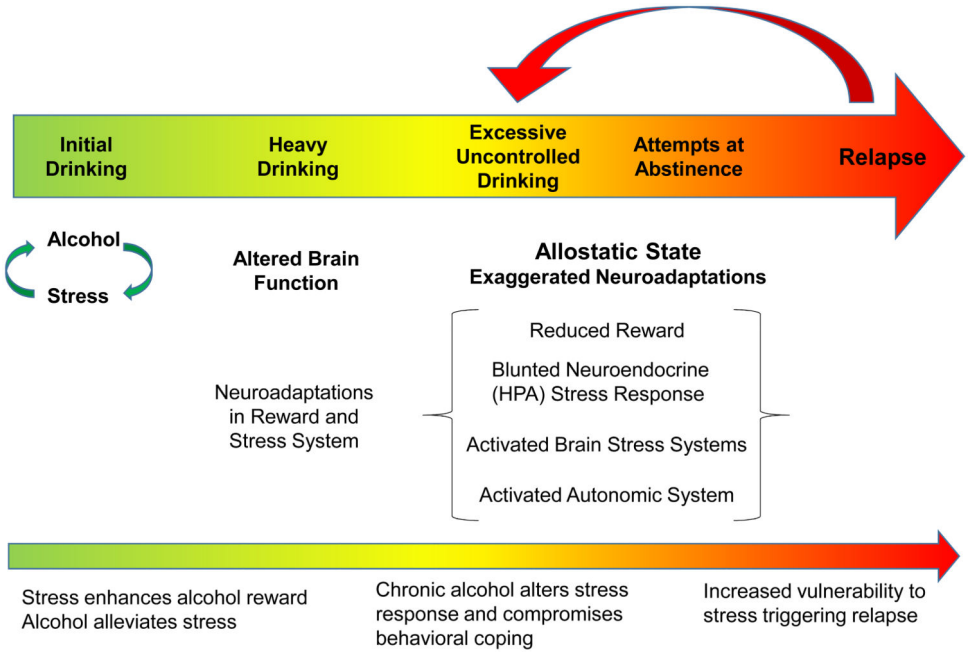

Figure 1.

Stress Influences on the Progression of Alcohol Addiction.

When drinking is first initiated and regulated, alcohol and stress interact in a complex manner. Stress may promote alcohol consumption via glucocorticoid interactions with brain reward systems and, for some individuals, the anxiolytic (stress-alleviating) effect alcohol may influence motivation to drink. Continued heavy drinking results in fundamental changes in brain function. Under assault from continued alcohol exposure, the brain engages a host of adaptations in brain reward and stress systems that contribute to the perpetuation of excessive levels of drinking. Stress associated with heavy bouts of drinking and repeated failed attempts at abstinence fuel progressive dysregulation of these brain systems beyond normal homeostatic limits, setting the stage for a persistent dysfunctional (allostatic) state. This is characterized by exaggerated neuroadaptations that manifest as reduced reward processing, a blunted neuroendocrine stress response, engagement of extra-hypothalamic stress (e.g., CRF, dynorphin) and anti-stress (e.g., nociceptin, NPY, oxytocin) systems, and heightened autonomic nervous system (sympathomimetic) function. Collectively, these changes contribute to a persistent negative emotional (affective) state along with compromised executive function that renders individuals ill-equipped to exert appropriate behavioral control over alcohol consumption, as well as appropriately respond to stressful events that may provoke return to excessive drinking.