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Dysregulation of Brain Stress Systems Mediates Compulsive Alcohol Drinking

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Abstract

The transition from moderate to compulsive alcohol drinking is driven by increasingly dysfunctional reward and stress systems. We review behavioral and pharmacological studies of alcohol self-administration in rats that were mainly conducted within the framework of the alcohol vapor model of dependence. We discuss neurotransmitter systems that are implicated in alcohol drinking, with a focus on contrasting those neurotransmitter systems that drive behavior in the dependent *vs.* nondependent states. We hypothesize that the identification of systems that become increasingly dysfunctional in alcohol dependence will reveal possible targets for successful interventions to reduce the motivation that drives compulsive alcohol drinking. In our opinion, drugs that (1) normalize, rather than block, a hypofunctional reward system via restoration of the function of hypothalamic stress systems, and (2) desensitize extrahypothalamic stress systems have the potential to selectively and effectively curb compulsive alcohol drinking.

Graphical Abstract



Neuroplasticity in hypothalamic and extrahypothalamic stress systems in alcohol dependence.

“Anxiety, yawning, rigor - wine drunk with an equal proportion of water, removes these complaints.” Hippocrates (400 B.C.E.) [1]

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Conflict of interest

The authors declare no conflicts of interest.

Introduction

Alcohol dependence (AD) is a major public health issue, the mortality and morbidity of which affects 6% of the global population [2]. Alcohol dependence has been conceptualized as a three-stage, recurring cycle that comprises *binge/intoxication*, *withdrawal/negative affect*, and *preoccupation/anticipation* (“craving”) stages. These stages involve neuroplastic changes in brain reward, stress, and executive function systems that are controlled by neurocircuits that involve the basal ganglia, extended amygdala, and prefrontal cortex, respectively [3]. Although medications currently exist for the treatment of AD, they are only moderately effective [4].

In this opinion article, we argue that AD is associated with (1) disruption of hypothalamic stress systems that contribute to brain reward hypofunction and (2) sensitization of extrahypothalamic stress systems. We propose that these processes lead to the negative emotional states that characterize motivational withdrawal and drive compulsive alcohol drinking via negative reinforcement (i.e., alcohol is consumed to alleviate negative feelings).

Vapor Model of Alcohol Dependence

Multiple rodent models of alcohol drinking exist. However, a major setback in the development of valid models of AD is that rodents will rarely voluntarily self-administer alcohol to the point of dependence without the use of prohibitively lengthy experimental designs. To overcome this obstacle, passive exposure to alcohol vapors has been used for over two decades to reliably create somatic signs of dependence (e.g., tail stiffness, abnormal gait/posture, and vocalization upon touch) and motivational signs of dependence (e.g., increased anxiety- and hypohedonic-like behavior). Typically, passive daily cycles of alcohol intoxication that produce blood alcohol levels around 150–250 mg/dl and withdrawal are used in combination with voluntary, operant alcohol self-administration to measure the motivation for alcohol during alcohol withdrawal. Compared with nondependent controls that are exposed to air, vapor-exposed rodents exhibit an escalation of intake and compulsive-like drinking behavior (for review, see [5,6]).

In the present article, we use the vapor model as a framework to discuss central neurotransmitter systems that are involved in normal, controlled *vs.* escalated, compulsive-like drinking. Most of the studies discussed herein tested the effects of acute drug treatments in rats on drinking during acute withdrawal (typically 2–8 h into withdrawal). Fig. 1 summarizes the dependent *vs.* nondependent specificity of the effects of systemically and intracerebroventricularly (but not site-specific brain infusions) delivered compounds that effectively reduced alcohol drinking in dependent and/or nondependent rats. We argue that compounds that preferentially reduce drinking in dependent rats may reveal targets for effective therapeutic intervention.

Neuropsychopharmacology of Alcohol Reinforcement

Catecholamines

Dopamine has long been suggested to be a common factor that mediates alcohol and drug addiction and is implicated in incentive salience and reinforcement learning in general. Although alcohol self-administration increases extracellular dopamine levels in the nucleus accumbens [7], dopamine is not critical for the maintenance of alcohol-reinforced behavior [8]. However, norepinephrine signaling appears to play a significant role in mediating AD. Administration of the β -adrenergic receptor antagonist propranolol reduced alcohol drinking to a greater extent in dependent than in nondependent rats [9]. The α 1-adrenergic receptor antagonist prazosin increased drinking in nondependent rats at a low dose, whereas it reduced drinking mainly in dependent rats when given at higher doses [10]. Intriguingly, the bidirectional modulation of drinking by noradrenergic receptor antagonists has also been observed in humans with AD. Antagonism of α -adrenergic receptors with doxazosin decreased alcohol drinking in AD patients with a family history of AD, whereas the same treatment increased drinking in AD patients without a family history of AD [11], suggesting a potential genetic component in the effects of this treatment.

Opioids

Opioid signaling has consistently been shown to be involved in AD in a receptor-subtype specific manner. The μ -opioid antagonist naltrexone (Revia[®]) is an FDA-approved medication for AD that has been shown to decrease drinking in both nondependent and dependent rats, but nondependent rats were more sensitive to treatment [12]. The anti-craving effects of naltrexone may be attributable to activation of the hypothalamic-pituitary-adrenal (HPA) axis (discussed below). The mixed μ/κ -opioid receptor antagonist nalmeferone suppressed alcohol drinking to a similar extent in both dependent and nondependent rats [12]. However, selective κ -opioid antagonism by nor-binaltorphimine reduced drinking only in dependent rats [12,13]. Targeted blockade of κ -opioid receptor signaling in the nucleus accumbens selectively reduced drinking in dependent rats, suggesting a role for κ -opioid receptors in reward allostasis [14]. Recent work has also implicated κ -opioid receptor signaling in the central nucleus of the amygdala (CeA) in the mediation of intensification of the motivation to drink in dependent rats, a process that is distinct from somatic withdrawal [15]. The σ receptor antagonist BD-1063 decreased drinking specifically in dependent rats [16]. Thus, μ -opioid receptors likely decrease dependent and nondependent drinking by blocking alcohol's rewarding effects, whereas σ - and κ -opioid receptors become important during dependence.

Cannabinoids

The cannabinoid 1 (CB₁) receptor inverse agonist SR141716A (rimonabant) decreased drinking in dependent rats without affecting nondependent controls [17]. Rimonabant has also shown efficacy in decreasing drinking in humans with alcohol dependence. However, the blunting of natural reward mechanisms observed in preclinical studies and the incidence of potential severe side-effects in humans (e.g., suicide) limit its clinical use [18]. Endocannabinoids, particularly in the CeA, may mediate some of the anxiety-like effects of alcohol dependence [19]. As such, the modulation of endocannabinoids with novel "neutral"

antagonists or inhibitors of the degradation of endocannabinoids (which would increase CB1 signaling instead of blocking it) constitute potential targets for medication development and remain to be tested in the vapor model.

Glutamate and GABA

Acamprosate (Campral[®]) is an FDA-approved medication for AD. It is hypothesized to exert inhibitory effects on the modulation of *N*-methyl-D-aspartate (NMDA) receptors through interactions with metabotropic glutamate receptors that contribute to a hyperexcitable state in the absence of alcohol [20]. However, the precise mechanism of acamprosate's action is a subject of debate [21,22]. In rats with a history of vapor-induced alcohol dependence (i.e., protracted abstinence), acamprosate reduced escalated drinking to nondependent levels, without disrupting drinking in nondependent rats [23]. The effect of systemic acamprosate treatment in dependent rats during acute withdrawal has yet to be studied. The noncompetitive NMDA receptor antagonist memantine significantly decreased drinking in both dependent and nondependent rats but with a greater effect in nondependent rats [24].

The γ -aminobutyric acid B (GABA_B) receptor agonist baclofen decreased drinking in both dependent and nondependent rats but to a greater extent in dependent rats [25]. Intra-CeA administration of the GABA_A receptor agonist muscimol reduced drinking in dependent rats post-vapor, without affecting drinking in nondependent rats [26]. The indirect GABA modulator gabapentin, via actions on voltage-gated calcium channels, significantly reduced drinking in dependent rats, with no effects in nondependent rats [27]. A 2014 randomized clinical trial reported evidence of the safety and efficacy of gabapentin for the treatment of AD [28]. These findings provide translational evidence of the role of GABA transmission in AD. Altogether, these studies highlight the preferential effects of GABA modulators on drinking in dependent rats and suggest a potential clinical target.

Oxytocin, hypocretin, nociception, and substance P

Unpublished data from our laboratory indicated that oxytocin (Tunstall et al., unpublished data) and hypocretin receptor 2 (Schmeichel et al., unpublished data) are involved in dependent alcohol drinking. Based on the literature, we hypothesize that nociceptin and substance P may also be dysregulated in alcohol dependence [3,29]. The latter two systems remain to be tested in the vapor model.

Dysregulation of the HPA Axis and Extrahypothalamic Systems in Alcohol Dependence

Positive reinforcement and reward associated with alcohol involve the activity of multiple neurotransmitter systems (e.g., dopamine, μ -opioid, and CB₁). These neurotransmitter systems also mediate the rewarding effects of nondrug reinforcers. Therefore, blocking these systems is expected to have limited effectiveness in AD where reward processing is already compromised [30]. Conversely, correcting/boosting the reward system rather than blocking it may be more beneficial in AD, with the aim of improving mood and moderating compulsive drinking via an anti-dysphoria/anhedonia effect.

Similar to stress, acute alcohol intoxication activates the HPA axis in both humans and rodents. In rats, adrenalectomy abolished alcohol drinking in nondependent rats, which could be recovered by corticosterone replacement [31], indicating that glucocorticoids facilitate alcohol reinforcement. The bidirectional relationship between stress and alcohol reward is complicated. Low glucocorticoid levels or high glucocorticoid levels may have similar effects in disrupting alcohol self-administration. Within the functional range of HPA axis activity, increasing the level of stress has been shown to facilitate the self-administration of many drugs of abuse, including alcohol [32].

Chronic alcohol use, however, disrupts the HPA axis. Although some individuals with AD exhibit an altered stress response that is characterized by high glucocorticoid release (with symptomatology that mimics Cushing's syndrome), excessive HPA axis activation more commonly results in blunted HPA axis activity (for review, see [33]). Dysregulation of the HPA axis is thought to contribute to deficits in reward function that contribute to anhedonia/dysphoria and craving in AD (see graphical abstract and [34]). Thus, withdrawal is associated with opponent process-like rebound effects that occur during intoxication (i.e., excessive reward system activation), resulting in a hypohedonic-like emotional state. In this review, we focus on the role of blunted HPA axis activity in the persistence of reward hypofunction and stress sensitization.

A remarkable consequence of intense/frequent HPA axis activation (e.g., frequent excessive drinking) is opposing glucocorticoid receptor (GR)-mediated regulation of corticotropin-releasing factor (CRF) in the paraventricular nucleus (blunted activation) and extrahypothalamic stress systems (enhanced activation; for review, see [33]). Increases in extrahypothalamic CRF signaling, together with an increase in vasopressin (a co-regulator of the HPA axis that potentiates CRF's effects [35]), drive compulsive-like drinking. The CRF₁ receptor antagonists antalarmin, MJL-1-109-2, R121919, and MPZP selectively decreased alcohol drinking in dependent rats [36,37]. Selective blockade of alcohol drinking in dependent rats was also reported using intracerebroventricular [38] or direct injections of the CRF_{1/2} receptor antagonist D-Phe-CRF₁₂₋₄₁ in the CeA [39]. Here, intra-CeA but not intranucleus accumbens or intra-bed nucleus of the stria terminalis injections of CRF antagonists decreased escalated alcohol drinking in dependent but not nondependent rats [39]. Additionally, CRF₂ receptor agonism in the CeA [40], similar to CRF₁ antagonism, decreased alcohol drinking specifically in dependent rats. These findings suggest that CRF receptors are dysregulated in alcohol dependence, and the blockade of CRF₁ or activation of CRF₂ receptors selectively attenuates withdrawal-induced escalated alcohol drinking. Two recent laboratory human studies did not support the efficacy of CRF₁ antagonists in reducing alcohol craving in humans with AD [41,42]. These studies were conducted in treatment-seeking, detoxified subjects with alcoholism. In addition to differences in drinking patterns, treatment-seeking individuals, compared with non-treatment-seekers, present with more impulsivity, anxiety and mood disorders. However, both populations exhibit craving, compulsive seeking, and excessive drinking of alcohol, as well as the emergence of negative emotional states during withdrawal [43]. The effects of CRF₁ antagonism remain to be tested in non-treatment-seeking subjects with alcoholism who are currently drinking.

Even more intriguing, CRF and neuropeptide Y (NPY) have been found to have opposing behavioral effects. Central administration of CRF peptide (which is anxiogenic) decreased alcohol drinking in dependent and nondependent rats, whereas NPY (which is anxiolytic) reduced drinking only in dependent rats [44]. Thus, CRF appears to disrupt behavior in general, whereas NPY effectively reduces drinking via an opposing effect but only in dependent rats (i.e., rats that are highly “anxious”). This study also found that CRF and NPY co-administration had a clear interaction, leaving drinking in both groups unchanged compared with the control condition.

We hypothesize that a reduction of GR signaling may block the sensitization of extrahypothalamic stress systems and, as a result, compulsive drinking. Glucocorticoid receptor blockade with either mifepristone (a GR and progesterone receptor antagonist) or CORT113176 (a selective GR antagonist) decreased alcohol drinking mainly in dependent rats, an effect that may involve the sensitization of GR signaling in the CeA [45]. Evidence also indicates a functional role for GR in escalated drinking in rats with a history of vapor-induced AD during protracted abstinence [46,47].

Carbenoxolone, a nonselective 11β -hydroxysteroid dehydrogenase (HSD) inhibitor, decreased drinking in both dependent and nondependent rats [48]. The inhibition of 11β -HSD₁ might be expected to selectively reduce drinking in dependent animals because it leads to a reduction of GR signaling in the brain. However, 11β -HSD₂ is expressed primarily in a subpopulation of neurons in the nucleus tractus solitarius that projects to both reward- and stress-related brain regions. Thus, the nonspecific inhibition of 11β -HSD isozymes may decrease alcohol reinforcement in general. Future experiments should evaluate the effects of inhibitors that are selective for 11β -HSD isozyme subtypes.

Continuous GR antagonism abolished the escalation of intake in rats that were exposed to alcohol vapor [47], suggesting that both genomic and non-genomic GR actions may be engaged in the chronic and acute effects of GR antagonism in escalated alcohol drinking. In addition to GR-mediated gene transcription, GR-mediated fast-acting CRF release has been reported [49]. Recently, a double-blind clinical and laboratory-based study demonstrated that individuals with AD who received 1-week treatment with mifepristone reported a reduction of alcohol drinking and craving for alcohol compared with placebo-treated subjects. Treated individuals also exhibited improvements in markers of liver function compared with placebo-treated subjects [45]. Mifepristone may exert therapeutic effects by restoring negative feedback along the HPA axis, which rescues reward function, and desensitizing extrahypothalamic stress systems (see Graphical Abstract).

Altogether, these findings suggest that initial HPA axis activation contributes to early drug use within the *binge/intoxication* stage of the addiction cycle, but chronic HPA axis activation sensitizes extrahypothalamic stress systems that characterize the *withdrawal/negative-affect* stage.

Summary

Alcohol dependence is associated with a decrease in reward function and sensitization of stress systems. These allostatic changes provide powerful incentives for compulsive alcohol drinking via negative reinforcement. Neurotransmitter systems, such as CRF, vasopressin, GABA, norepinephrine, glucocorticoids, NPY, and dynorphin (the endogenous ligand for κ -opioid receptors), create stress-like states that drive compulsive-like alcohol drinking. Supporting the predictive validity of the vapor model, initial studies in humans who suffer from AD indicated the potential of GABA (gabapentin), norepinephrine (doxazosin), and glucocorticoid (mifepristone) systems in the treatment of AD. Drugs that reset the function of the HPA axis and reward systems and desensitize extrahypothalamic stress systems may have the potential to treat AD. Future studies will be designed to test the efficacy of such compounds. Glucocorticoid receptor antagonists are an example of promising candidates for this dual approach.

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- * of special interest
- ** of outstanding interest
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reduced alcohol drinking in alcohol-dependent individuals who sought outpatient treatment with a high “family history of density of alcoholism,” but increased drinking in patients with a low “family history of density of alcoholism” Interestingly, using the vapor model of alcohol dependence, Walker et al. [10], reported that the α_1 -adrenergic blocker prazosin reduced alcohol drinking in dependent rats, whereas low doses of prazosin increased drinking in nondependent rats.

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- Remaining to be determined are the effects of CRF₁ receptor antagonists in individuals with AD that are currently drinkers and in alcohol-dependent patients during acute withdrawal
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Highlights

- Disruption of HPA axis leads to reward system hypofunction in alcohol dependence
- Extrahypothalamic stress systems are sensitized in alcohol dependence
- Loss of reward and stress sensitization drive compulsive alcohol drinking

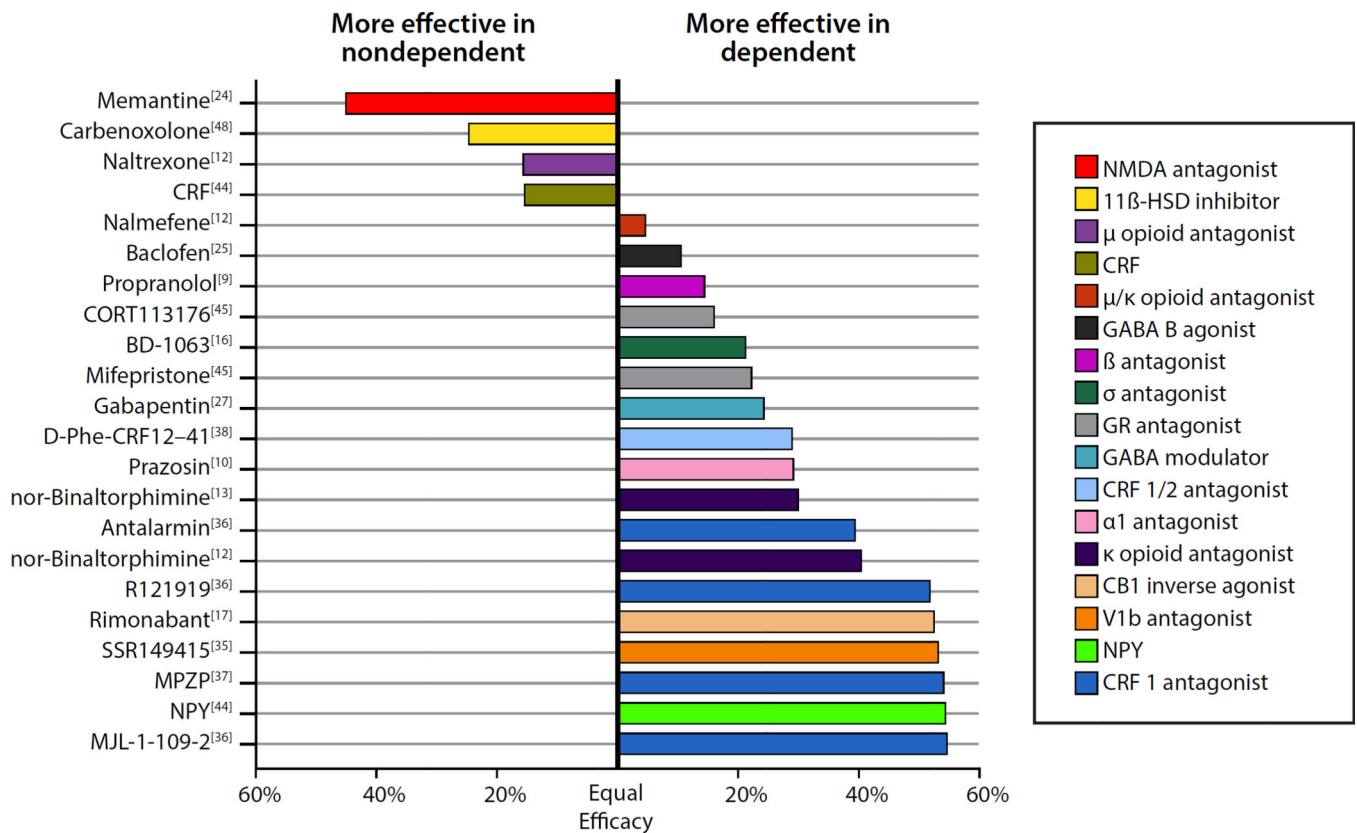


Fig. 1.

Effect of drugs reported to have acute effects in the alcohol-vapor dependence model of escalated alcohol drinking. To be included in this analysis, the studies had to include both dependent and nondependent rats and report a significant effect on alcohol drinking in either group. Studies were included that tested alcohol drinking during acute withdrawal (typically 2–8 h into withdrawal; memantine was tested at 24 h into withdrawal). The figure shows the difference in sensitivity between groups (i.e., percent change in drinking in the dependent group [drug relative to vehicle] minus the percent change in drinking in the nondependent group). We chose the highest dose of the drug that caused a group-specific effect. If not available (i.e., equally effective in both groups), we used the first effective dose to compare groups. Because none of the treatments caused large increases in alcohol drinking, the bars that are plotted can generally be interpreted as showing the relative effectiveness of each compound in reducing drinking in the two groups. Bars to the left of the “Equal Efficacy” line indicate compounds that are more effective in nondependent animals. Bars that are close to the “Equal Efficacy” line indicate that the treatment was similarly effective in both groups. Bars to the right of the “Equal Efficacy” line indicate compounds that are more effective in dependent animals. To collect numerical values for this analysis, figures from published reports were analyzed using a freely available tool for extracting raw data from scientific figures (Web Plot Digitizer, Version 3.9, <http://arohatgi.info/WebPlotDigitizer>).