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Central Noradrenergic Interactions with Alcohol and Regulation of Alcohol-Related Behaviors

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Abstract

Alcohol use disorder (AUD) results from disruption of a number of neural systems underlying motivation, emotion, and cognition. Patients with AUD exhibit not only elevated motivation for alcohol but heightened stress and anxiety, and disruptions in cognitive domains such as decision-making. One system at the intersection of these functions is the central norepinephrine (NE) system. This catecholaminergic neuromodulator, produced by several brainstem nuclei, plays profound roles in a wide range of behaviors and functions, including arousal, attention, and other aspects of cognition, motivation, emotional regulation, and control over basic physiological processes. It has been known for some time that NE has an impact on alcohol seeking and use, but the mechanisms of its influence are still being revealed. This chapter will discuss the influence of NE neuron activation and NE release at alcohol-relevant targets on behaviors and disruptions underlying alcohol motivation and AUD. Potential NE-based pharmacotherapies for AUD treatment will also be discussed. Given the basic properties of NE function, the strong relationship between NE and alcohol use, and the effectiveness of current NE-related treatments, the studies presented here indicate an encouraging direction for the development of precise and efficacious future therapies for AUD.

Keywords

Adrenergic receptors; Allostasis; Dependence; Locus coeruleus; Nucleus tractus solitarius; Reward; Withdrawal

1 Introduction

Norepinephrine (NE) is a key neuromodulator in the CNS that originates from several hindbrain nuclei and projects widely across the brain. NE alters neural responsiveness in its targets, modifying activity of ongoing neural processes through pre- and postsynaptic G-protein-coupled receptors. As such, it can exert wide-reaching and complex influences over neural circuits involved in the regulation of alcohol-related behaviors. In the following chapter we discuss central noradrenergic systems, with a particular focus on NE from the locus coeruleus (LC) and nucleus tractus solitarius (NTS), their interactions with alcohol, and NE as a therapeutic target for alcohol use disorder (AUD).

2 Central Norepinephrine Systems

Central noradrenergic neurons in several small nuclei of the medulla and pons (A1–A7) use the enzyme dopamin- β -hydroxylase (DBH) to convert dopamine (DA) to NE for release (Dahlstrom and Fuxe 1964). Although their cell bodies number only in the thousands these neurons reach almost every region of the CNS through an extensively branching efferent network (Fuxe 1965). The largest population of noradrenergic neurons is the bilateral LC (A6) and subcoeruleus (A4) complex in the dorsal pons (Swanson and Hartman 1975). This population contains around half of all central NE neurons with each LC comprising ~1,500 neurons per side in rodents (Swanson 1976) and up to 50,000 per side in humans (Baker et al. 1989). Other noradrenergic nuclei are found within the lateral tegmental system that extends from the caudal midbrain and pons (A5, A7) through the medulla (A1–A3) (Moore and Bloom 1979).

In addition to descending spinal cord projections and local brainstem projections critical for autonomic regulation, NE populations show a diverse topography. The LC provides the vast majority of NE input to cerebral cortex, hippocampus, thalamus, and cerebellum, as well as innervating basal forebrain limbic structures including the amygdala, dorsal BNST, and some parts of the hypothalamus (Moore and Bloom 1979). Non-LC NE neurons, particularly those located in A1/A2 clusters in the medulla including the NTS (A2), provide input to homeostatic and limbic regions of the forebrain including the hypothalamus, amygdala, and extended amygdala, particularly the BNST (Moore and Bloom 1979). Although contributions of other NE nuclei cannot be ruled out, the majority of studies to date investigating the relationship between NE and alcohol use have focused on signaling emanating from either the NTS or the LC.

NTS and LC receive substantial convergent input, integrating information sent from multiple forebrain, thalamic and hypothalamic, midbrain, and brainstem nuclei, in addition to receiving inputs from spinal cord and cranial nerves (Cedarbaum and Aghajanian 1978; Rinaman 2011; Takigawa and Mogenson 1977). LC inputs include also ascending NE from the NTS (Levitt and Moore 1979). These afferents from diverse regions regulate NE neurons using a range of transmitters and modulators including glutamate and GABA, NE itself, and neuropeptides such as dynorphin (DYN), corticotropin releasing factor (CRF), pituitary adenylate cyclase-activating peptide (PACAP), and orexin/hypocretin, making NE neurons directly sensitive to multiple levels of modulation (Ennis and Aston-Jones 1988; Olpe and

Steinmann 1991; Valentino and Foote 1988). Of particular relevance to alcohol-associated studies, the NTS and LC are densely interconnected with frontal and insular cortex, amygdala, extended amygdala, and hypothalamus (reviewed in Berridge and Waterhouse 2003; Rinaman 2011). Finally, NE neurons co-express several additional neurotransmitters, modulators, and peptides including glutamate, neuropeptide Y (NPY), and galanin among a number of other peptides (Melandner et al. 1986; Rinaman 2011; Sawchenko et al. 1985; Stornetta et al. 2002). Thus, the medullary and brainstem NE populations are strongly regulated by a diverse set of inputs and, in return, project broadly, signaling with a complex conjunction of neurochemicals.

As noted above, NE neurons project widely across the extent of the brain, targeting cortical and subcortical regions. NE projections reach the forebrain primarily through two major ascending tracts, specifically the dorsal noradrenergic bundle (DNAB) from the LC and the ventral noradrenergic bundle (VNAB) from medullary NE neurons, including NTS. These tracts then converge within the medial forebrain bundle before reaching the hypothalamus and extended amygdala (Moore and Bloom 1979). An individual NE neuron may produce up to 30 cm of terminal arbors with ~100,000 axonal varicosities (Moore and Bloom 1979). NE is released extra-synaptically from these varicosities, in addition to synaptic release at axon terminals, further expanding the influence of NE through volume transmission (Aoki et al. 1998).

The distribution of norepinephrine projections allows these neurons to play a wide and diverse role in modulating key processes throughout the brain. The vast majority of NE efferents to cognitive and sensory cortical regions comes from LC, from which NE can modulate perception and decision making in response to alcohol-related stimuli (Aston-Jones and Cohen 2005; Berridge and Waterhouse 2003). LC also provides noradrenergic, and dopaminergic (Takeuchi et al. 2016), regulation to the hippocampus where it regulates memory function, including consolidation (Sara 2015). LC and medullary NE nuclei including NTS (and A1) project to paraventricular nucleus (PVN) of the hypothalamus where they regulate HPA signaling critical to ethanol responses (Moore and Bloom 1979). In each of these regions NE modulation provides a potent influence over physiological and behavioral responses to alcohol.

NE innervation of the forebrain is also well positioned to regulate motivational and emotional responses that drive alcohol consumption and craving. NE has a potent regulatory influence over limbic circuits, including control of anxiety and stress responses through LC inputs to basolateral amygdala, inputs to BNST from NTS, and to a lesser degree LC, in addition to reciprocal connections of both regions with central amygdala (Daniel and Rainnie 2016; Park et al. 2009; Phelix et al. 1992; Valentino and Van Bockstaele 2008). NE may also impact motivational drive for alcohol through modulation of lateral hypothalamus, ventral tegmental area, and other regions of the extended amygdala which are innervated by both LC and NTS NE (Moore and Bloom 1979). NTS NE additionally provides noradrenergic tone to the nucleus accumbens, an area heavily implicated in motivation for natural and drug rewards, including alcohol (Berridge et al. 1997; Chang 1989; Wang et al. 1992).

2.1 Central Norepinephrine Functions

The canonical role of NE modulation in these target regions is to enhance neuronal responses to other synaptic inputs. The enhancement can take the form of an inhibitory suppression of baseline noise, with or without a potentiation of discrete excitatory responses. NE achieves this complex modulatory regulation through several postsynaptic receptors; excitatory Gq-mediated $\alpha 1$ receptors, Gs-mediated β receptors (both $\beta 1$ and $\beta 2$ are prominent in CNS), or inhibitory Gi $\alpha 2$ receptors (MacDonald et al. 1997; Morrow and Creese 1986; Nicholas et al. 1993a, b). $\alpha 2$ receptors also play a prominent role in regulating NE transmission presynaptically by acting as autoreceptors on NE terminals and via local collaterals in NE nuclei (Aghajanian et al. 1977; Aoki et al. 1994). NE-mediated baseline suppression and excitatory potentiation can both lead to enhanced signal-to-noise of acute signaling at NE targets. The postsynaptic mechanisms of NE vary by target region with NE acting on target cells directly, or indirectly via postsynaptic GABAergic interneurons (Bevan et al. 1973; Foote et al. 1975; Waterhouse et al. 1980). In some target regions, such as the BNST, the presence of Gi-coupled $\alpha 2$ receptors on postsynaptic target cells or non-NE axon terminals predominates a net inhibitory effect upon NE release, suppressing both basal activity and incoming glutamatergic signaling (Daniel and Rainnie 2016; Shields et al. 2009).

The LC-NE system exerts profound influence on arousal, cognition, and behavioral regulation and is well poised to regulate responses to alcohol-related stimuli. A key feature of LC-NE signaling is dynamic modulation both through tonic baseline neuronal activity changes and through phasic bursting activity and NE release in response to behaviorally relevant or salient stimuli (Aston-Jones and Cohen 2005). Tonic LC neuron firing rates vary with arousal and are strongly influenced by peptidergic inputs, including stress-associated corticotrophin releasing factor (CRF) and dynorphin (DYN) from regions such as hypothalamus and extended amygdala (Valentino and Van Bockstaele 2008). In contrast, phasic responses are typically associated with salient stimuli, including conditioned salience, predictive cues, and aversive stimuli that require behavioral responses (Aston-Jones and Bloom 1981; Clayton et al. 2004; Kalwani et al. 2014).

The LC plays a major role in cognitive control. Physiological, pharmacological, and neurochemical techniques show that NE is associated with memory consolidation and executive function including response inhibition and behavioral flexibility, among others (reviewed by Aston-Jones and Cohen 2005; Robbins and Arnsten 2009). In addition to regulating cognitive function via PFC (and other areas), LC-NE plays a critical role in stress responses. LC neurons are reactive to both acute and chronic stress, in part due to strong CRF input (Valentino and Van Bockstaele 2008). CRF serves as a feedback mechanism whereby stress-related signaling dynamically regulates LC activity and, consequently, NE input back to stress-reactive systems (Van Bockstaele et al. 2001). Acute low level stress transiently increases tonic LC activity to facilitate alertness and scanning attention (Aston-Jones and Cohen 2005; Valentino and Van Bockstaele 2008). Exposure to prolonged, chronic stress dysregulates LC-NE function, and CRF mediated LC tone in a sex- and stressor-specific manner (Bangasser et al. 2010). We do not yet know if sex-dependent

regulation of LC-NE function impacts stress and alcohol interactions, although recent evidence suggests this is likely (Retson et al. 2015).

Within stress circuits, the LC sends robust projections to the basolateral amygdala (BLA) (Asan 1998; Jones and Moore 1977). BLA, LC, and other inputs regulate CRF containing neurons in the central amygdala (CeA). The CRF afferents from CeA innervate many regions, including LC, potentiating stress responses (Cui et al. 2015; Gilpin 2012). Stress-mediated dysregulation of LC, in addition to producing a feed-forward enhancement of anxiety and stress, disrupts NE regulation of cognitive function in PFC.

Medullary NE has a profound influence on homeostatic functions and emotional regulation and plays a prominent role in motivational drive related to the seeking of alcohol and other drugs of abuse (Rinaman 2011; Smith and Aston-Jones 2008). The A2 noradrenergic population plays a role in both the execution and inhibition of feeding behaviors, though the preponderance of studies to date emphasizes its role in suppression of feeding (Rinaman 2010, 2011; Roman et al. 2016; Wellman 2000). The NTS also plays an important role in emotional regulation and motivated behavior, in part through its connections with the NAc, CeA, PVN, and BNST (Delfs et al. 1998; Rinaman 2011; Sawchenko and Swanson 1981, 1982; Smith and Aston-Jones 2008). The main outcome of NTS innervation of such areas is primarily increased stress and behavioral inhibition, and some investigators have considered the NTS projections to limbic targets to be main activators of aversive emotional state, in contrast with LC-NE, the activation which ultimately promotes arousal and exploratory behavior (Rinaman 2011). In all likelihood both systems contribute to stress and anxiety, but the potent innervation of limbic structures such as those noted above, and the plethora of studies demonstrating a particularly influential role of the NTS over the HPA axis and behavioral components of stress indicate particularly privileged role for this system (Herman 2017; Rinaman 2011).

In general NE is broadly involved in multiple aspects of motivation, including driving behaviors associated with drugs of abuse. The history and current understanding of the role of NE in drug seeking have been the subject of a number of excellent recent reviews (Espana et al. 2016; Fitzgerald 2013; Smith and Aston-Jones 2008; Sofuoglu and Sewell 2009; Weinshenker and Schroeder 2007; Zaniowska et al. 2015). Although early studies of the neural circuitry of drug abuse highlighted a prominent role for NE, research gradually shifted focus to DA as a final common pathway underlying addiction (Weinshenker and Schroeder 2007). However, recent studies have demonstrated the importance of NE across multiple classes of drugs of abuse (psychostimulants, opiates, etc.), particularly with respect to relapse behaviors. The details underlying such lines of research are too extensive and diverse to consider here and, in focusing exclusively on the role of NE in alcohol-related behaviors and AUD, we refer readers to the reviews above for more detailed consideration.

3 Norepinephrine and Alcohol

The NE system in general is highly responsive to ethanol, and there is a growing appreciation that noradrenergic signaling may underlie substantial components of both controlled and excessive drinking. There have even been proposals that NE is more critical

than dopamine (DA) for ethanol reward (Amit and Brown 1982). Due in part to the organization and functions of noradrenergic systems described above, as well as effects of NE manipulation on alcohol seeking, described below, NE signaling has long been posited as a key neural mechanism involved in both positive and negative motivation for alcohol use (Koob 2014).

3.1 Changes in Noradrenergic Function Mediated by Acute and Chronic Alcohol

In early human studies, acute ethanol produced increases in NE and the NE metabolite 3-methoxy-4-hydroxy-phenylglycol (MHPG) measured in CSF (Borg et al. 1981) and plasma (Howes and Reid 1985). The acute increases in central NE were greater in alcoholic patients than in healthy controls and were correlated with blood alcohol levels. The increased levels observed in patients decreased significantly after multiple days of abstinence. These findings suggested that acute ethanol elevates the activity of central NE neurons, and the LC was proposed as a site of action (Borg et al. 1981). Further studies comparing MHPG levels between alcohol-dependent patients and healthy controls were inconclusive (Petrakis et al. 1999) and potentially depend on withdrawal state, indicating that further direct studies of central NE function are warranted.

Early investigations of NE and alcohol in animal models focused on the impact of alcohol administration on catecholamine metabolism. These studies found consistent changes in NE function during acute intoxication. At doses ranging from 1 to 5 g/kg of ethanol, brain NE content was reduced alongside increases in NE metabolites, specifically 3,4-dihydroxyphenylglycol (DHPG), and vanillomandelic acid (VMA). This was seen in both outbred and alcohol preferring P rats (Alari et al. 1987a; Karoum et al. 1976; Murphy et al. 1983). These increases in NE turnover during acute intoxication normalized 6 h after ethanol exposure and were consistently more pronounced than changes in dopamine turnover, particularly at lower doses of ethanol (Corrodi et al. 1966). Whether the increased turnover results from increased vesicular leakage or synaptic NE release remains unclear given conflicting findings from various approaches used to measure neuronal activity.

The idea that increased NE release and turnover is due to enhanced synaptic release is supported by increases in neuronal activation, often measured with c-Fos expression, within NE populations after acute ethanol exposure. c-Fos is an immediate early gene marker upregulated by neuronal activity and used as a post hoc proxy of recent activation (Dragunow and Faull 1989). Several studies have found an upregulation of c-Fos activity specifically in tyrosine hydroxylase (TH) or DBH positive neurons within the LC, RVLM (A1/C1) and NTS after intragastric or intraperitoneal injection of ethanol (Lee et al. 2011; Thiele et al. 2000). After high doses of acute ethanol, elevations in LC c-Fos are more pronounced in alcohol non-preferring strains than alcohol preferring strains of rats (Thiele et al. 1997). In the NTS, ethanol enhancement of GABAergic transmission, indirectly resulting in disinhibition of local TH positive neurons including NE, has been proposed as a mechanism for c-Fos induction by high doses in vivo (4 g/kg) (Aimino et al. 2017). A similar mechanism of disinhibition in LC-NE neurons is plausible, although GABAergic interneurons are not widely interdigitated within the nucleus. A pool of GABA neurons

within the dendritic fields of LC, however, would be capable of providing potent local regulation (Aston-Jones et al. 2004).

Direct recordings of NE neurons after acute alcohol have been made to confirm changes in activity indicated by NE turnover and c-Fos. The complexity of noradrenergic interactions with ethanol is highlighted by differential findings between electrophysiological studies and other measures neuronal activation. The majority of electrophysiological studies measuring responses of NE neurons to acutely administered ethanol have targeted LC-NE neurons, though similar effects have been demonstrated in an unidentified neuron population in NTS (Aimino et al. 2017). Systemic and direct local administration of relatively high doses of ethanol has elicited either no change, or suppression in LC unit activity via an enhancement of inwardly rectifying potassium currents (Aston-Jones et al. 1982; Osmanovic and Shefner 1994; Strahlendorf and Strahlendorf 1983; Verbanck et al. 1990). Even without direct changes in basal activity, LC signaling of salient sensory information is disrupted by low dose ethanol (1 g/kg). Acute ethanol delays, reduces the magnitude of, and slows LC-NE conduction velocity during LC signaling of sensory information (Aston-Jones et al. 1982). This difference between, on the one hand, suppression of NE unit activity or responsiveness and, on the other hand, evidence of neuronal activation using metabolite and c-Fos measures, has yet to be resolved. One potential explanation worth pursuing, however, comes from in vitro evidence for rebound activation in LC-NE neurons after acute ethanol washout which has been seen in multiple studies after acute suppression, or complete inhibition of firing by ethanol (Shefner and Tabakoff 1985; Verbanck et al. 1990).

There is additional evidence that environmental history may alter NE responses to acute alcohol, which has implications for interpretation of the above findings. Karkhanis et al. (2014, 2015) used microdialysis to measure NE release in the basolateral amygdala and NAc after low doses of acute ethanol (1 or 2 g/kg). No changes in NE release after alcohol were identified in group housed animals, but there was a significant enhancement of NE release within animals that had a history of social isolation. Just as environment might alter neural plasticity that contributes to changes in NE response to acute alcohol, chronic alcohol consumption also appears to alter the homeostatic balance within NE circuitry.

As noted above, NE metabolite levels in the CSF of alcohol-dependent subjects are higher compared to control subjects following acute ethanol administration (Borg et al. 1981). In dependent animals receiving daily ethanol gavage, NE metabolite levels remain high while intoxicated and through to withdrawal, indicating chronic increases in NE signaling (Karoum et al. 1976). Repeated alcohol administration has also been shown to sensitize NE neurons to release larger amounts of NE (Lanteri et al. 2008). Chronic alcohol differentially induces c-Fos signaling in the NTS (Ryabinin et al. 1997) of males and LC of females but not males (Chang et al. 1995; Retson et al. 2015) indicating some region-specific adaptations in NE signaling with chronic alcohol. However, withdrawal from chronic alcohol ubiquitously activates NE signaling across regions (Vilpoux et al. 2009).

Chronic alcohol use has long been associated with disruption of the HPA axis, although central NE is not necessarily a direct component (Richardson et al. 2008). As noted above, NE sources such as LC and NTS provide critical input to central HPA nuclei including the

paraventricular nucleus of the hypothalamus (PVN) as well as sites in the amygdala and extended amygdala (Moore and Bloom 1979). β -NE signaling within PVN is critical to ACTH production after ethanol administration (Selvage 2012). Alterations in NE signaling to HPA regions, combined with reciprocal connections between NE nuclei and CRF neurons that are activated after chronic ethanol in the central amygdala and other regions, generate feed-forward circuits for persisting NE dysfunction after chronic alcohol (Retson et al. 2016). Evidence for allostatic changes in NE signaling after chronic alcohol exposure and withdrawal indicates NE dysfunction as a key aspect of the negative affective state and a component driving relapse after abstinence (Koob 2014).

In summary, there is a wealth of studies demonstrating that both acute and chronic alcohol use has an impact on NE neuron function and NE release (see Table 1). Additionally, several peptides, such as NPY and galanin, which are expressed by NE neurons (and other populations) are known to be altered by alcohol exposure (Barson and Leibowitz 2016; Gilpin and Roberto 2012). The impact of co-transmitter/peptide release within NE circuits remains understudied in general. Most studies on these systems to date have focused on receptor signaling, and the source of these relevant co-transmitters/peptides, including whether or not they are originating in NE neurons, remains to be determined. There are also results that appear to conflict – the differences between decreased acute effects on NE neuron activity vs. increased c-Fos and NE release, for example. These differences may stem from experimental differences such as time points of intoxication and withdrawal, all of which have profound but potentially differential effects on NE systems. Future work dissecting the effects of acute vs. chronic alcohol at different stages of administration and withdrawal will help specify the precise effects of alcohol on NE neuron function and plasticity.

3.2 Effects of Noradrenergic Receptor Modulation on Alcohol-Related Behaviors and Neural Systems

Manipulation of noradrenergic signaling has provided some of the strongest evidence for a functional role of NE in alcohol-related behaviors and has demonstrated not only a mechanism for NE in stress-associated alcohol effects, but in positive motivational aspects of alcohol use as well (Table 2). Early studies using DBH inhibitors showed attenuation of voluntary ethanol consumption (Amit et al. 1977). More recently DBH knockout mice that are incapable of producing central NE have been shown to have a number of relevant phenotypes including reduced ethanol consumption in males but not females, and increased ethanol-related hypothermia and sedation in both sexes (Weinshenker et al. 2000). DBH knockout mice are hyperdopaminergic and release DA from NE terminals, suggesting the DA signaling through NE neurons may be a potential mechanism for these findings. However disruptions of DA signaling through lesioning of accumbens DA inputs do not impact voluntary ethanol intake (Rassnick et al. 1993). Lesions of ascending NE tracts can generate increases (Kiianmaa and Attila 1979; Kiianmaa et al. 1975) or decreases in ethanol intake (Brown and Amit 1977; Corcoran et al. 1983).

Whether NE-related changes in ethanol consumption are representative of reduced stress-driven drinking or reduced ethanol reward remain unclear. However, strong evidence for

rewarding components of NE in acute alcohol comes from a selective NE deafferentation of medial prefrontal cortex (mPFC) in mice which prevents ethanol-related conditioned place preference and reduces ethanol consumption (Ventura et al. 2006). This reinforces that the complexity of NE in alcohol-related behaviors is due in part to the broad efferent networks of NE and complex interactions at different targets.

A number of studies investigating the role of NE transmission in dependent subjects indicate a role for NE in pathological allostasis that is further exacerbated during withdrawal (Becker 2012; Koob 2014). NE-targeted therapies have demonstrated efficacy in improving symptoms associated with sympathomimetic overdrive and NE overactivation during withdrawal from chronic alcohol (Hawley et al. 1994; Rasmussen et al. 2006).

Polymorphisms in noradrenergic reuptake transporters or α_2 receptors, both mechanisms for terminating NE signaling, have been associated with familial history of, or individuals with, alcohol use disorders (Clarke et al. 2012). Studies in rodents and humans have shown value in the use of Gi-coupled ± 2 -adrenergic agonists (which activate postsynaptic and autoreceptors) as adjuncts for ameliorating ethanol withdrawal (Kostowski and Trzaskowska 1980; reviewed by Muzyk et al. 2011).

Preclinical evidence indicates an effect of NE pharmacotherapy both during acute withdrawal and in the maintenance of abstinence after chronic ethanol. α_2 agonists have shown further application in reducing operant self-administration of ethanol and reduce stress-induced reinstatement of ethanol seeking (Le et al. 2005). In alcohol preferring strains of P and AA rats, α_2 agonists reduce voluntary alcohol intake acutely and for several days after repeated administration (Opitz 1990; Rasmussen et al. 2014a). These effects are likely mediated by overall reductions in NE signaling due to presynaptic modulation as postsynaptic NE antagonists produce similar effects. Guanfacine, an α_{2a} agonist known for cognitive enhancing effects and currently being explored for treating ADHD (Ramos and Arnsten 2007), has been tested in rat models of drinking, producing decreased alcohol intake in high-drinking rats (Fredriksson et al. 2015) and in rats with elevated drinking resulting from social defeat stress (Riga et al. 2014). These results indicate a complex, but potentially important role for α_2 signaling in alcohol motivation and AUD. However, these agonist studies must be interpreted with caution, as α_2 agonists have known sedative properties via Gi-mediated inhibition of arousal circuits (Aoki et al. 1994) that may reduce a variety of volitional behaviors, particularly after systemic administration.

Chronic alcohol has been shown to disrupt α_1 -mediated NE signaling in the extended amygdala (McElligott et al. 2010), similar dysfunction likely occurs at other postsynaptic targets with extensive α_1 receptors including hypothalamus, amygdala, prefrontal cortex, and VTA (Domyancic and Morilak 1997; Sands and Morilak 1999). Prazosin, an α_1 NE inverse agonist, is a sympatholytic compound which is FDA approved to treat hypertension and has been well explored in relation to alcohol consumption. It has been shown to dose dependently reduce operant ethanol seeking in dependent animals (Walker et al. 2008), seeking in P rats (Verplaetse et al. 2012), and relapse in P rats (Froehlich et al. 2015), and it can also delay initiation of drinking in P rats (Froehlich et al. 2013). Prazosin also reduces anxiety-like behavior after chronic alcohol exposure and ongoing ethanol consumption in rats (Rasmussen et al. 2017; Skelly and Weiner 2014), and decreases sensitization to chronic

alcohol administration in mice (Kim and Souza-Formigoni 2013). Prazosin crosses the blood–brain barrier and is available as a clinical anti-hypertensive agent. Off-label studies have provided translational support for prazosin in the treatment of AUD. Prazosin has been shown to reduce stress- and cue-induced alcohol craving in abstinent individuals with AUD (Fox et al. 2012), as well as to reduce alcohol consumption and increase alcohol free days in treatment seeking individuals with AUD and those with AUD and comorbid PTSD (Simpson et al. 2009, 2015). Doxazosin, a long-lasting α_1 receptor antagonist, has shown preclinical efficacy in reducing alcohol consumption and yohimbine-induced reinstatement in alcohol preferring P rats (Funk et al. 2016; O’Neil et al. 2013). α_1 -mediated treatments such as prazosin and doxazosin may also come with potential side effects, such as orthostatic hypertension, and at high doses drowsiness, which may either limit their usefulness or patient compliance (see clinical efficacy review in this volume, Litten et al. 2018). However, both preclinical and human tests of α_1 antagonists appear to be efficacious, as described above, suggesting that refinement of α_1 -associated therapy may be a worthwhile pursuit.

Signaling through the β adrenergic receptor influences stress responses, indicating a potential mechanism to explain AUD-associated stress and anxiety (Do Monte et al. 2008; Giustino et al. 2016; Gorman and Dunn 1993; Steenen et al. 2016). However, the contributions of this system to AUD have been less thoroughly explored. Early studies suggested a beneficial role of propranolol, a nonselective β adrenergic antagonist, on decreasing withdrawal symptoms such as elevated anxiety and potentially reducing drinking in human alcoholic patients (Carlsson 1976; Sellers et al. 1977). Propranolol treatment also decreased alcohol preference in mice (Andreas et al. 1983). In rats, propranolol reduced operant self-administration of and motivation for alcohol in dependent animals at low doses and reduced moderate ethanol consumption in nondependent animals at high doses (Gilpin and Koob 2010). Combined α_1 and β adrenergic treatment with prazosin and propranolol is more effective at reducing alcohol consumption than either drug alone in rats (Rasmussen et al. 2014b), indicating that such a combination treatment may be useful in patients. However, this promising approach has not yet been investigated clinically. As noted with respect to α_1 -related treatments above, potential NE-related pharmacotherapies targeting β -adrenergic receptors must be considered with caution. Drugs targeting these receptors have potent hypotensive effects (Musini et al. 2017) which may limit their implementation and relevant dosing.

As is clear from studies involving manipulation of NE receptor signaling, there is a prominent role for this pathway in both human and animal models of alcohol use (Table 2). The potent effects of α_1 receptor blockade in animals and the promising impacts on human patients indicate that this may be a key mechanism in regulating aspects of AUD. However, modulation at α_2 or β receptors may play an equally potent role, and future therapies may benefit from combinations of receptor targeting. Although NE receptor pharmacotherapy appears to be particularly promising for AUD treatment, refinements are still required in order to develop therapies that are specific to dependence symptoms, including increased alcohol motivation, increased stress, and potentially cognitive disruptions impairing decision making. One possibility is that the AUD syndrome is a result of globally disrupted NE signaling, arguing that broad NE-associated treatments will be maximally efficacious. Alternately, only some aspects of the NE system may be disrupted in AUD, or AUD

subtypes, suggesting that future pharmacotherapy treatment should be refined. One way to refine future treatments, and a key action item for future research, is to determine functional consequences of the intersection between NE receptor subtypes and downstream neural systems influenced. Specific symptoms of AUD may result from disrupted NE signaling specifically in the BNST or amygdala or PFC, for example, but not in other areas. Individualized, highly specific treatment for subtypes of AUD may stem from characterizing precise interactions between NE release and NE-regulated neural networks. In addition to understanding specific circuits influenced by AUD-associated disruptions in NE release, future NE-related treatments may benefit from an understanding of interactions between NE signaling and other neuromodulatory or peptidergic pathways. Given the diverse set of systems associated with alcohol use and AUD, optimal treatments for alcohol-associated disorders will likely benefit from targeting multiple systems. One possibility is that these systems interact sequentially, such as in the proposal that the main motivational impact of NE is via the regulation of DA release, and the observation that neuropeptides such as DYN or CRF impact signaling in the LC, for example (Tjounmakaris et al. 2003). Alternately, these systems may influence alcohol use in a simultaneous, distributed, and potentially independent fashion, increasing the diversity of AUD subtypes depending on combinations of systems affected. Thus, in addition to specifying the precise nature of NE impact on alcohol use, potential treatment research will benefit from understanding the interaction (or lack thereof) between NE and the numerous other neural systems disrupted in AUD (Becker 2012; Koob 2014).

4 Summary: Norepinephrine in the Treatment of AUD

As discussed in the sections above, NE signaling exhibits a substantial degree of influence over alcohol use and its disruption contributes to AUD. Although its role in stress and anxiety is well documented, NE also appears to have an important role in the rewarding aspects of alcohol use. The NE system is also critical in a number of other behaviors and functions, in particular cognitive functions such as attention, memory, and decision making, as described above. Each of these elements of NE regulation contribute both to the role of NE signaling in regulated, nondependent, alcohol seeking and use, and in AUD symptoms resultant from chronic alcohol exposure. Given the prominent dysphoric disruptions that are a consequence of chronic alcohol use, elevated NE associated with (or even producing) increased stress in AUD may enhance motivation for alcohol in order to transiently relieve this negative hedonic state (Koob 2014). At the same time, disrupted NE control over cognitive functions such as response inhibition, behavioral flexibility, attention, and memory may result in compromised mechanisms that would normally allow individuals to regulate alcohol seeking behaviors. Pharmacotherapeutics specifically targeting the NE system, therefore, have the potential to ameliorate multiple key symptoms of AUD: motivation for alcohol, stress, and cognitive disruption. Supporting this hypothesis, initial results in human patients treated with prazosin, for example, appear promising. More specifically tailored treatments resulting from future research into the exact mechanisms of NE receptor subtypes and their interaction with other brain systems will enhance the effectiveness and selectivity of targeting the NE system. Additional issues remain to be explored at both basic and clinical levels, such as the interaction between NE signaling and other neuromodulators and

neuropeptides, clear sex differences in NE function in both humans and nonhuman models, and issues associated with individual heterogeneity in AUD symptoms in which some may be more NE-associated than others. Regardless, work to date has demonstrated that the NE system is both fundamentally involved in alcohol seeking behaviors and is disrupted following chronic alcohol and withdrawals in AUD and research for NE-targeted pharmacotherapies has strong potential for positive treatment outcomes.

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References

- Aghajanian GK, Cedarbaum JM, Wang RY (1977) Evidence for norepinephrine-mediated collateral inhibition of locus coeruleus neurons. *Brain Res* 136:570–577 [PubMed: 922502]
- Aimino MA, Coker CR, Silberman Y (2017) Acute ethanol modulation of neurocircuit function in the nucleus of the tractus solitarius. *Brain Res Bull.* 10.1016/j.brainresbull.2017.07.019
- Alari L, Lewander T, Sjoquist B (1987a) The effect of ethanol on the brain catecholamine systems in female mice, rats, and guinea pigs. *Alcohol Clin Exp Res* 11:144–149 [PubMed: 3296831]
- Alari L, Sjoquist B, Lewander T (1987b) Ethanol-induced hypothermia and biogenic amine metabolites. *Drug Alcohol Depend* 19:369–373 [PubMed: 2440656]
- Amit Z, Brown ZW (1982) Actions of drugs of abuse on brain reward systems: a reconsideration with specific attention to alcohol. *Pharmacol Biochem Behav* 17:233–238 [PubMed: 6127720]
- Amit Z, Brown ZW, Levitan DE, Ogren SO (1977) Noradrenergic mediation of the positive reinforcing properties of ethanol: I. Suppression of ethanol consumption in laboratory rats following dopamine-beta-hydroxylase inhibition. *Arch Int Pharmacodyn Ther* 230:65–75 [PubMed: 603310]
- Andreas K, Fischer HD, Schmidt J (1983) Effect of central effective substances on alcohol preference. *Biomed Biochim Acta* 42:391–398 [PubMed: 6138034]
- Aoki C, Go CG, Venkatesan C, Kurose H (1994) Perikaryal and synaptic localization of alpha 2A-adrenergic receptor-like immunoreactivity. *Brain Res* 650:181–204 [PubMed: 7953684]
- Aoki C, Venkatesan C, Go CG, Forman R, Kurose H (1998) Cellular and subcellular sites for noradrenergic action in the monkey dorsolateral prefrontal cortex as revealed by the immunocytochemical localization of noradrenergic receptors and axons. *Cereb Cortex* 8:269–277 [PubMed: 9617922]
- Asan E (1998) The catecholaminergic innervation of the rat amygdala. *Adv Anat Embryol Cell Biol* 142:1–118 [PubMed: 9586282]
- Aston-Jones G, Bloom FE (1981) Norepinephrine-containing locus coeruleus neurons in behaving rats exhibit pronounced responses to non-noxious environmental stimuli. *J Neurosci* 1:887–900 [PubMed: 7346593]
- Aston-Jones G, Cohen JD (2005) An integrative theory of locus coeruleus-norepinephrine function: adaptive gain and optimal performance. *Annu Rev Neurosci* 28:403–450 [PubMed: 16022602]
- Aston-Jones G, Foote SL, Bloom FE (1982) Low doses of ethanol disrupt sensory responses of brain noradrenergic neurones. *Nature* 296:857–860 [PubMed: 6280069]
- Aston-Jones G, Zhu Y, Card JP (2004) Numerous GABAergic afferents to locus ceruleus in the pericereular dendritic zone: possible interneuronal pool. *J Neurosci* 24:2313–2321 [PubMed: 14999082]
- Baker KG, Tork I, Hornung JP, Halasz P (1989) The human locus coeruleus complex: an immunohistochemical and three dimensional reconstruction study. *Exp Brain Res* 77:257–270 [PubMed: 2571514]
- Bangasser DA, Curtis A, Reyes BA, Bethea TT, Parastatidis I, Ischiropoulos H, Van Bockstaele EJ, Valentino RJ (2010) Sex differences in corticotropin-releasing factor receptor signaling and

trafficking: potential role in female vulnerability to stress-related psychopathology. *Mol Psychiatry* 15(877):896–904

- Barson JR, Leibowitz SF (2016) Hypothalamic neuropeptide signaling in alcohol addiction. *Prog Neuro-Psychopharmacol Biol Psychiatry* 65:321–329
- Becker HC (2012) Effects of alcohol dependence and withdrawal on stress responsiveness and alcohol consumption. *Alcohol Res* 34:448–458 [PubMed: 23584111]
- Berridge CW, Waterhouse BD (2003) The locus coeruleus-noradrenergic system: modulation of behavioral state and state-dependent cognitive processes. *Brain Res Brain Res Rev* 42:33–84 [PubMed: 12668290]
- Berridge CW, Stratford TL, Foote SL, Kelley AE (1997) Distribution of dopamine beta-hydroxylase-like immunoreactive fibers within the shell subregion of the nucleus accumbens. *Synapse* 27:230–241 [PubMed: 9329158]
- Bevan P, Bradshaw CM, Roberts MH, Szabadi E (1973) The excitation of neurons by noradrenaline. *J Pharm Pharmacol* 25:309–314 [PubMed: 4146683]
- Borg S, Kvande H, Sedvall G (1981) Central norepinephrine metabolism during alcohol intoxication in addicts and healthy volunteers. *Science* 213:1135–1137 [PubMed: 7268421]
- Brown ZW, Amit Z (1977) The effects of selective catecholamine depletions by 6-hydroxydopamine on ethanol preference in rats. *Neurosci Lett* 5(6):333 [PubMed: 19605016]
- Brown ZW, Amit Z, Levitan DE, Ogren SO, Sutherland EA (1977) Noradrenergic mediation of the positive reinforcing properties of ethanol: II. Extinction of ethanol-drinking behavior in laboratory rats by inhibition of dopamine-beta-hydroxylase. Implications for treatment procedures in human alcoholics. *Arch Int Pharmacodyn Ther* 230:76–82 [PubMed: 603311]
- Carlsson C (1976) Propranolol in the treatment of alcoholism: a review. *Postgrad Med J* 52(Suppl 4): 166–167 [PubMed: 787956]
- Cedarbaum JM, Aghajanian GK (1978) Afferent projections to the rat locus coeruleus as determined by a retrograde tracing technique. *J Comp Neurol* 178(1):16
- Chang HT (1989) Noradrenergic innervation of the substantia innominata: a light and electron microscopic analysis of dopamine beta-hydroxylase immunoreactive elements in the rat. *Exp Neurol* 104:101–112 [PubMed: 2707360]
- Chang SL, Patel NA, Romero AA (1995) Activation and desensitization of Fos immunoreactivity in the rat brain following ethanol administration. *Brain Res* 679:89–98 [PubMed: 7648269]
- Clarke TK, Dempster E, Docherty SJ, Desrivieres S, Lourdsamy A, Wodarz N, Ridinger M, Maier W, Rietschel M, Schumann G (2012) Multiple polymorphisms in genes of the adrenergic stress system confer vulnerability to alcohol abuse. *Addict Biol* 17:202–208 [PubMed: 21070505]
- Clayton EC, Rajkowski J, Cohen JD, Aston-Jones G (2004) Phasic activation of monkey locus coeruleus neurons by simple decisions in a forced-choice task. *J Neurosci* 24:9914–9920 [PubMed: 15525776]
- Corcoran ME, Lewis J, Fibiger HC (1983) Forebrain noradrenaline and oral self-administration of ethanol by rats. *Behav Brain Res* 8:1–21 [PubMed: 6405760]
- Corrodi H, Fuxe K, Hokfelt T (1966) The effect of ethanol on the activity of central catecholamine neurones in rat brain. *J Pharm Pharmacol* 18:821–823 [PubMed: 4381667]
- Cui C, Noronha A, Warren KR, Koob GF, Sinha R, Thakkar M, Matochik J, Crews FT, Chandler LJ, Pfefferbaum A, Becker HC, Lovinger D, Everitt BJ, Egli M, Mandyam CD, Fein G, Potenza MN, Harris RA, Grant KA, Roberto M, Meyerhoff DJ, Sullivan EV (2015) Brain pathways to recovery from alcohol dependence. *Alcohol* 49:435–452 [PubMed: 26074423]
- Dahlstrom A, Fuxe K (1964) Localization of monoamines in the lower brain stem. *Experientia* 20:398–399 [PubMed: 5856530]
- Daniel SE, Rainnie DG (2016) Stress modulation of opposing circuits in the bed nucleus of the Stria terminalis. *Neuropsychopharmacology* 41:103–125 [PubMed: 26096838]
- Delfs JM, Zhu Y, Druhan JP, Aston-Jones GS (1998) Origin of noradrenergic afferents to the shell subregion of the nucleus accumbens: anterograde and retrograde tract-tracing studies in the rat. *Brain Res* 806:127–140 [PubMed: 9739125]

- Do Monte FH, Canteras NS, Fernandes D, Assreuy J, Carobrez AP (2008) New perspectives on beta-adrenergic mediation of innate and learned fear responses to predator odor. *J Neurosci* 28:13296–13302 [PubMed: 19052221]
- Domyancic AV, Morilak DA (1997) Distribution of alpha1A adrenergic receptor mRNA in the rat brain visualized by in situ hybridization. *J Comp Neurol* 386:358–378 [PubMed: 9303423]
- Dragunow M, Faull R (1989) The use of c-fos as a metabolic marker in neuronal pathway tracing. *J Neurosci Methods* 29:261–265 [PubMed: 2507830]
- Ennis M, Aston-Jones G (1988) Activation of locus coeruleus from nucleus paragigantocellularis: a new excitatory amino acid pathway in brain. *J Neurosci* 8:3644–3657 [PubMed: 3193175]
- Espana RA, Schmeichel BE, Berridge CW (2016) Norepinephrine at the nexus of arousal, motivation and relapse. *Brain Res* 1641:207–216 [PubMed: 26773688]
- Fitzgerald PJ (2013) Elevated norepinephrine may be a unifying etiological factor in the abuse of a broad range of substances: alcohol, nicotine, marijuana, heroin, cocaine, and caffeine. *Subst Abuse* 7:171–183 [PubMed: 24151426]
- Foote SL, Freedman R, Oliver AP (1975) Effects of putative neurotransmitters on neuronal activity in monkey auditory cortex. *Brain Res* 86:229–242 [PubMed: 234774]
- Fox HC, Anderson GM, Tuit K, Hansen J, Kimmerling A, Siedlarz KM, Morgan PT, Sinha R (2012) Prazosin effects on stress- and cue-induced craving and stress response in alcohol-dependent individuals: preliminary findings. *Alcohol Clin Exp Res* 36:351–360 [PubMed: 21919922]
- Fredriksson I, Jayaram-Lindstrom N, Wirf M, Nylander E, Nystrom E, Jardemark K, Steensland P (2015) Evaluation of guanfacine as a potential medication for alcohol use disorder in long-term drinking rats: behavioral and electrophysiological findings. *Neuropsychopharmacology* 40:1130–1140 [PubMed: 25359257]
- Froehlich JC, Hausauer BJ, Federoff DL, Fischer SM, Rasmussen DD (2013) Prazosin reduces alcohol drinking throughout prolonged treatment and blocks the initiation of drinking in rats selectively bred for high alcohol intake. *Alcohol Clin Exp Res* 37:1552–1560 [PubMed: 23731093]
- Froehlich JC, Hausauer B, Fischer S, Wise B, Rasmussen DD (2015) Prazosin reduces alcohol intake in an animal model of alcohol relapse. *Alcohol Clin Exp Res* 39:1538–1546 [PubMed: 26207767]
- Funk D, Coen K, Tamadon S, Li Z, Loughlin A, Le AD (2016) Effects of prazosin and doxazosin on yohimbine-induced reinstatement of alcohol seeking in rats. *Psychopharmacology* 233:2197–2207 [PubMed: 27020784]
- Fuxe K (1965) Evidence for the existence of monoamine neurons in the central nervous system. 3. The monoamine nerve terminal. *Z Zellforsch Mikrosk Anat* 65:573–596 [PubMed: 14263017]
- Gilpin NW (2012) Corticotropin-releasing factor (CRF) and neuropeptide Y (NPY): effects on inhibitory transmission in central amygdala, and anxiety- & alcohol-related behaviors. *Alcohol* 46:329–337 [PubMed: 22560367]
- Gilpin NW, Koob GF (2010) Effects of beta-adrenoceptor antagonists on alcohol drinking by alcohol-dependent rats. *Psychopharmacology* 212:431–439 [PubMed: 20676608]
- Gilpin NW, Roberto M (2012) Neuropeptide modulation of central amygdala neuroplasticity is a key mediator of alcohol dependence. *Neurosci Biobehav Rev* 36:873–888 [PubMed: 22101113]
- Giustino TF, Fitzgerald PJ, Maren S (2016) Revisiting propranolol and PTSD: memory erasure or extinction enhancement? *Neurobiol Learn Mem* 130:26–33 [PubMed: 26808441]
- Gorman AL, Dunn AJ (1993) Beta-adrenergic receptors are involved in stress-related behavioral changes. *Pharmacol Biochem Behav* 45:1–7 [PubMed: 8100069]
- Hawley RJ, Nemeroff CB, Bissette G, Guidotti A, Rawlings R, Linnoila M (1994) Neurochemical correlates of sympathetic activation during severe alcohol withdrawal. *Alcohol Clin Exp Res* 18(6):1312 [PubMed: 7695023]
- Herman JP (2017) Regulation of hypothalamo-pituitary-adrenocortical responses to stressors by the nucleus of the solitary tract/dorsal vagal complex. *Cell Mol Neurobiol* 38(1):25–35 [PubMed: 28895001]
- Howes LG, Reid JL (1985) Changes in plasma free 3,4-dihydroxyphenylethylene glycol and noradrenaline levels after acute alcohol administration. *Clin Sci (Lond)* 69:423–428 [PubMed: 4042543]

- Jones BE, Moore RY (1977) Ascending projections of the locus coeruleus in the rat. II. Autoradiographic study. *Brain Res* 127:25–53 [PubMed: 301051]
- Kalwani RM, Joshi S, Gold JJ (2014) Phasic activation of individual neurons in the locus ceruleus/subceruleus complex of monkeys reflects rewarded decisions to go but not stop. *J Neurosci* 34:13656–13669 [PubMed: 25297093]
- Karkhanis AN, Locke JL, McCool BA, Weiner JL, Jones SR (2014) Social isolation rearing increases nucleus accumbens dopamine and norepinephrine responses to acute ethanol in adulthood. *Alcohol Clin Exp Res* 38:2770–2779 [PubMed: 25421514]
- Karkhanis AN, Alexander NJ, McCool BA, Weiner JL, Jones SR (2015) Chronic social isolation during adolescence augments catecholamine response to acute ethanol in the basolateral amygdala. *Synapse* 69:385–395 [PubMed: 25963724]
- Karoum F, Wyatt RJ, Majchrowicz E (1976) Brain concentrations of biogenic amine metabolites in acutely treated and ethanol-dependent rats. *Br J Pharmacol* 56:403–411 [PubMed: 769883]
- Kiianmaa K, Attila LM (1979) Alcohol intake, ethanol-induced narcosis and intoxication in rats following neonatal 6-hydroxydopamine or 5, 7-dihydroxytryptamine treatment. *Naunyn Schmiedeberg's Arch Pharmacol* 308:165–170 [PubMed: 574195]
- Kiianmaa K, Fuxe K, Jonsson G, Ahtee L (1975) Evidence for involvement of central NA neurones in alcohol intake. Increased alcohol consumption after degeneration of the NA pathway to the cortex cerebri. *Neurosci Lett* 1:41–45 [PubMed: 19604750]
- Kim AK, Souza-Formigoni ML (2013) Alpha1-adrenergic drugs affect the development and expression of ethanol-induced behavioral sensitization. *Behav Brain Res* 256:646–654 [PubMed: 24036170]
- Knapp DJ, Duncan GE, Crews FT, Breese GR (1998) Induction of Fos-like proteins and ultrasonic vocalizations during ethanol withdrawal: further evidence for withdrawal-induced anxiety. *Alcohol Clin Exp Res* 22:481–493 [PubMed: 9581657]
- Kolodziejska-Akiyama KM, Cha YM, Jiang Y, Loh HH, Chang SL (2005) Ethanol-induced FOS immunoreactivity in the brain of mu-opioid receptor knockout mice. *Drug Alcohol Depend* 80:161–168 [PubMed: 15893889]
- Koob GF (2014) Neurocircuitry of alcohol addiction: synthesis from animal models. *Handb Clin Neurol* 125:33–54 [PubMed: 25307567]
- Kostowski W, Trzaskowska E (1980) Effects of lesion of the locus coeruleus and clonidine treatment on ethanol withdrawal syndrome in rats. *Pol J Pharmacol Pharm* 32:617–623 [PubMed: 7196574]
- Lanteri C, Salomon L, Torrens Y, Glowinski J, Tassin JP (2008) Drugs of abuse specifically sensitize noradrenergic and serotonergic neurons via a non-dopaminergic mechanism. *Neuropsychopharmacology* 33:1724–1734 [PubMed: 17805311]
- Le AD, Harding S, Juzysch W, Funk D, Shaham Y (2005) Role of alpha-2 adrenoceptors in stress-induced reinstatement of alcohol seeking and alcohol self-administration in rats. *Psychopharmacology* 179:366–373 [PubMed: 15551068]
- Lee S, Craddock Z, Rivier C (2011) Brain stem catecholamines circuitry: activation by alcohol and role in the hypothalamic-pituitary-adrenal response to this drug. *J Neuroendocrinol* 23:531–541 [PubMed: 21447066]
- Levitt P, Moore RY (1979) Origin and organization of brainstem catecholamine innervation in the rat. *J Comp Neurol* 186:505–528 [PubMed: 15116686]
- Litten RZ, Falk DE, Ryan ML, Fertig J, Leggio L (2018) Advances in pharmacotherapy development: human clinical studies. *Handb Exp Pharmacol*. 10.1007/164_2017_79
- MacDonald E, Kobilka BK, Scheinin M (1997) Gene targeting – homing in on alpha 2-adrenoceptor-subtype function. *Trends Pharmacol Sci* 18:211–219 [PubMed: 9227000]
- McElligott ZA, Klug JR, Nobis WP, Patel S, Grueter BA, Kash TL, Winder DG (2010) Distinct forms of Gq-receptor-dependent plasticity of excitatory transmission in the BNST are differentially affected by stress. *Proc Natl Acad Sci U S A* 107:2271–2276 [PubMed: 20133871]
- Melander T, Hokfelt T, Rokaeus A, Cuello AC, Oertel WH, Verhofstad A, Goldstein M (1986) Coexistence of galanin-like immunoreactivity with catecholamines, 5-hydroxytryptamine, GABA and neuropeptides in the rat CNS. *J Neurosci* 6:3640–3654 [PubMed: 2432203]

- Moore RY, Bloom FE (1979) Central catecholamine neuron systems: anatomy and physiology of the norepinephrine and epinephrine systems. *Annu Rev Neurosci* 2:113–168 [PubMed: 231924]
- Morrow AL, Creese I (1986) Characterization of alpha 1-adrenergic receptor subtypes in rat brain: a reevaluation of [3H]WB4104 and [3H]prazosin binding. *Mol Pharmacol* 29:321–330 [PubMed: 3010073]
- Murphy JM, McBride WJ, Lumeng L, Li TK (1983) Monoamine and metabolite levels in CNS regions of the P line of alcohol-preferring rats after acute and chronic ethanol treatment. *Pharmacol Biochem Behav* 19:849–856 [PubMed: 6196794]
- Musini VM, Gueyffier F, Puil L, Salzwedel DM, Wright JM (2017) Pharmacotherapy for hypertension in adults aged 18 to 59 years. *Cochrane Database Syst Rev* 8:CD008276 [PubMed: 28813123]
- Muzyk AJ, Fowler JA, Norwood DK, Chilipko A (2011) Role of alpha2-agonists in the treatment of acute alcohol withdrawal. *Ann Pharmacother* 45:649–657 [PubMed: 21521867]
- Nicholas AP, Pieribone V, Hokfelt T (1993a) Distributions of mRNAs for alpha-2 adrenergic receptor subtypes in rat brain: an in situ hybridization study. *J Comp Neurol* 328:575–594 [PubMed: 8381444]
- Nicholas AP, Pieribone VA, Hokfelt T (1993b) Cellular localization of messenger RNA for beta-1 and beta-2 adrenergic receptors in rat brain: an in situ hybridization study. *Neuroscience* 56:1023–1039 [PubMed: 8284033]
- O'Neil ML, Beckwith LE, Kincaid CL, Rasmussen DD (2013) The alpha1-adrenergic receptor antagonist, doxazosin, reduces alcohol drinking in alcohol-preferring (P) rats. *Alcohol Clin Exp Res* 37:202–212 [PubMed: 22758213]
- Olpe HR, Steinmann M (1991) Responses of locus coeruleus neurons to neuropeptides. *Prog Brain Res* 88:241–248 [PubMed: 1813923]
- Opitz K (1990) The effect of clonidine and related substances on voluntary ethanol consumption in rats. *Drug Alcohol Depend* 25:43–48 [PubMed: 1969792]
- Osmanovic SS, Shefner SA (1994) Ethanol enhances inward rectification in rat locus ceruleus neurons by increasing the extracellular potassium concentration. *J Pharmacol Exp Ther* 271:334–342 [PubMed: 7965733]
- Park J, Kile BM, Wightman RM (2009) In vivo voltammetric monitoring of norepinephrine release in the rat ventral bed nucleus of the stria terminalis and anteroventral thalamic nucleus. *Eur J Neurosci* 30:2121–2133 [PubMed: 20128849]
- Petrakis IL, Trevisan L, D'Souza C, Gil R, Krasnicki S, Webb E, Heninger G, Cooney N, Krystal JH (1999) CSF monoamine metabolite and beta endorphin levels in recently detoxified alcoholics and healthy controls: prediction of alcohol cue-induced craving? *Alcohol Clin Exp Res* 23:1336–1341 [PubMed: 10470976]
- Phelix CF, Liposits Z, Paull WK (1992) Monoamine innervation of bed nucleus of stria terminalis: an electron microscopic investigation. *Brain Res Bull* 28:949–965 [PubMed: 1379113]
- Putzke J, Spanagel R, Tolle TR, Zieglgansberger W (1996) The anti-craving drug acamprosate reduces c-fos expression in rats undergoing ethanol withdrawal. *Eur J Pharmacol* 317:39–48 [PubMed: 8982717]
- Ramos BP, Arnsten AF (2007) Adrenergic pharmacology and cognition: focus on the prefrontal cortex. *Pharmacol Ther* 113:523–536 [PubMed: 17303246]
- Rasmussen DD, Wilkinson CW, Raskind MA (2006) Chronic daily ethanol and withdrawal: 6. Effects on rat sympathoadrenal activity during “abstinence”. *Alcohol* 38:173–177 [PubMed: 16905443]
- Rasmussen DD, Alexander L, Malone J, Federoff D, Froehlich JC (2014a) The alpha2-adrenergic receptor agonist, clonidine, reduces alcohol drinking in alcohol-preferring (P) rats. *Alcohol* 48:543–549 [PubMed: 25085719]
- Rasmussen DD, Beckwith LE, Kincaid CL, Froehlich JC (2014b) Combining the alpha1-adrenergic receptor antagonist, prazosin, with the beta-adrenergic receptor antagonist, propranolol, reduces alcohol drinking more effectively than either drug alone. *Alcohol Clin Exp Res* 38:1532–1539 [PubMed: 24891220]
- Rasmussen DD, Kincaid CL, Froehlich JC (2017) Prazosin prevents increased anxiety behavior that occurs in response to stress during alcohol deprivations. *Alcohol Alcohol* 52:5–11 [PubMed: 27797712]

- Rassnick S, Stinus L, Koob GF (1993) The effects of 6-hydroxydopamine lesions of the nucleus accumbens and the mesolimbic dopamine system on oral self-administration of ethanol in the rat. *Brain Res* 623:16–24 [PubMed: 8221085]
- Retson TA, Reyes BA, Van Bockstaele EJ (2015) Chronic alcohol exposure differentially affects activation of female locus coeruleus neurons and the subcellular distribution of corticotropin releasing factor receptors. *Prog Neuro-Psychopharmacol Biol Psychiatry* 56:66–74
- Retson TA, Sterling RC, Van Bockstaele EJ (2016) Alcohol-induced dysregulation of stress-related circuitry: the search for novel targets and implications for interventions across the sexes. *Prog Neuro-Psychopharmacol Biol Psychiatry* 65:252–259
- Richardson HN, Lee SY, O'Dell LE, Koob GF, Rivier CL (2008) Alcohol self-administration acutely stimulates the hypothalamic-pituitary-adrenal axis, but alcohol dependence leads to a dampened neuroendocrine state. *Eur J Neurosci* 28:1641–1653 [PubMed: 18979677]
- Riga D, Schmitz LJ, van der Harst JE, van Mourik Y, Hoogendijk WJ, Smit AB, De Vries TJ, Spijker S (2014) A sustained depressive state promotes a guanfacine reversible susceptibility to alcohol seeking in rats. *Neuropsychopharmacology* 39:1115–1124 [PubMed: 24192553]
- Rinaman L (2010) Ascending projections from the caudal visceral nucleus of the solitary tract to brain regions involved in food intake and energy expenditure. *Brain Res* 1350:18–34 [PubMed: 20353764]
- Rinaman L (2011) Hindbrain noradrenergic A2 neurons: diverse roles in autonomic, endocrine, cognitive, and behavioral functions. *Am J Physiol Regul Integr Comp Physiol* 300:R222–R235 [PubMed: 20962208]
- Robbins TW, Arnsten AF (2009) The neuropsychopharmacology of fronto-executive function: monoaminergic modulation. *Annu Rev Neurosci* 32:267–287 [PubMed: 19555290]
- Rodberg EM, den Hartog CR, Anderson RI, Becker HC, Moorman DE, Vazey EM (2017) Stress facilitates the development of cognitive dysfunction after chronic ethanol exposure. *Alcohol Clin Exp Res* 41:1574–1583 [PubMed: 28753742]
- Roman CW, Derkach VA, Palmiter RD (2016) Genetically and functionally defined NTS to PBN brain circuits mediating anorexia. *Nat Commun* 7:11905 [PubMed: 27301688]
- Ryabinin AE, Criado JR, Henriksen SJ, Bloom FE, Wilson MC (1997) Differential sensitivity of c-Fos expression in hippocampus and other brain regions to moderate and low doses of alcohol. *Mol Psychiatry* 2:32–43 [PubMed: 9154216]
- Sands SA, Morilak DA (1999) Expression of alpha1D adrenergic receptor messenger RNA in oxytocin- and corticotropin-releasing hormone-synthesizing neurons in the rat paraventricular nucleus. *Neuroscience* 91:639–649 [PubMed: 10366021]
- Sara SJ (2015) Locus Coeruleus in time with the making of memories. *Curr Opin Neurobiol* 35:87–94 [PubMed: 26241632]
- Sawchenko PE, Swanson LW (1981) Central noradrenergic pathways for the integration of hypothalamic neuroendocrine and autonomic responses. *Science* 214:685–687 [PubMed: 7292008]
- Sawchenko PE, Swanson LW (1982) The organization of noradrenergic pathways from the brainstem to the paraventricular and supraoptic nuclei in the rat. *Brain Res* 257:275–325 [PubMed: 6756545]
- Sawchenko PE, Swanson LW, Grzanna R, Howe PR, Bloom SR, Polak JM (1985) Colocalization of neuropeptide Y immunoreactivity in brainstem catecholaminergic neurons that project to the paraventricular nucleus of the hypothalamus. *J Comp Neurol* 241:138–153 [PubMed: 3840810]
- Sellers EM, Zilm DH, Degani NC (1977) Comparative efficacy of propranolol and chlordiazepoxide in alcohol withdrawal. *J Stud Alcohol* 38:2096–2108 [PubMed: 592834]
- Selva D (2012) Roles of the locus coeruleus and adrenergic receptors in brain-mediated hypothalamic-pituitary-adrenal axis responses to intracerebroventricular alcohol. *Alcohol Clin Exp Res* 36:1084–1090 [PubMed: 22236039]
- Shefner SA, Tabakoff B (1985) Basal firing rate of rat locus coeruleus neurons affects sensitivity to ethanol. *Alcohol* 2:239–243 [PubMed: 4015846]

- Shields AD, Wang Q, Winder DG (2009) α 2A-adrenergic receptors heterosynaptically regulate glutamatergic transmission in the bed nucleus of the stria terminalis. *Neuroscience* 163:339–351 [PubMed: 19527774]
- Simpson TL, Saxon AJ, Meredith CW, Malte CA, McBride B, Ferguson LC, Gross CA, Hart KL, Raskind M (2009) A pilot trial of the α -1 adrenergic antagonist, prazosin, for alcohol dependence. *Alcohol Clin Exp Res* 33:255–263 [PubMed: 18945226]
- Simpson TL, Malte CA, Dietel B, Tell D, Pocock I, Lyons R, Varon D, Raskind M, Saxon AJ (2015) A pilot trial of prazosin, an α -1 adrenergic antagonist, for comorbid alcohol dependence and posttraumatic stress disorder. *Alcohol Clin Exp Res* 39:808–817 [PubMed: 25827659]
- Skelly MJ, Weiner JL (2014) Chronic treatment with prazosin or duloxetine lessens concurrent anxiety-like behavior and alcohol intake: evidence of disrupted noradrenergic signaling in anxiety-related alcohol use. *Brain Behav* 4:468–483 [PubMed: 25161814]
- Smith RJ, Aston-Jones G (2008) Noradrenergic transmission in the extended amygdala: role in increased drug-seeking and relapse during protracted drug abstinence. *Brain Struct Funct* 213:43–61 [PubMed: 18651175]
- Sofuoglu M, Sewell RA (2009) Norepinephrine and stimulant addiction. *Addict Biol* 14:119–129 [PubMed: 18811678]
- Steenen SA, van Wijk AJ, van der Heijden GJ, van Westrhenen R, de Lange J, de Jongh A (2016) Propranolol for the treatment of anxiety disorders: systematic review and meta-analysis. *J Psychopharmacol* 30:128–139 [PubMed: 26487439]
- Stornetta RL, Sevigny CP, Schreihöfer AM, Rosin DL, Guyenet PG (2002) Vesicular glutamate transporter DNPI/VGLUT2 is expressed by both C1 adrenergic and nonaminergic presympathetic vasomotor neurons of the rat medulla. *J Comp Neurol* 444:207–220 [PubMed: 11840475]
- Strahlendorf HK, Strahlendorf JC (1983) Ethanol suppression of locus coeruleus neurons: relevancy to the fetal alcohol syndrome. *Neurobehav Toxicol Teratol* 5:221–224 [PubMed: 6306495]
- Swanson LW (1976) The locus coeruleus: a cytoarchitectonic, Golgi and immunohistochemical study in the albino rat. *Brain Res* 110:39–56 [PubMed: 776360]
- Swanson LW, Hartman BK (1975) The central adrenergic system. An immunofluorescence study of the location of cell bodies and their efferent connections in the rat utilizing dopamine-beta-hydroxylase as a marker. *J Comp Neurol* 163:467–505 [PubMed: 1100685]
- Takeuchi T, Duszkievicz AJ, Sonneborn A, Spooner PA, Yamasaki M, Watanabe M, Smith CC, Fernandez G, Deisseroth K, Greene RW, Morris RG (2016) Locus coeruleus and dopaminergic consolidation of everyday memory. *Nature* 537:357–362 [PubMed: 27602521]
- Takigawa M, Mogenson GJ (1977) A study of inputs to antidromically identified neurons of the locus coeruleus. *Brain Res* 135:217–230 [PubMed: 922473]
- Thiele TE, van Dijk G, Bernstein IL (1997) Ethanol-induced c-Fos expression in rat lines selected for low and high alcohol consumption. *Brain Res* 756:278–282 [PubMed: 9187343]
- Thiele TE, Cubero I, van Dijk G, Mediavilla C, Bernstein IL (2000) Ethanol-induced c-fos expression in catecholamine- and neuropeptide Y-producing neurons in rat brainstem. *Alcohol Clin Exp Res* 24:802–809 [PubMed: 10888068]
- Tjoumakaris SI, Rudy C, Peoples J, Valentino RJ, Van Bockstaele EJ (2003) Cellular interactions between axon terminals containing endogenous opioid peptides or corticotropin-releasing factor in the rat locus coeruleus and surrounding dorsal pontine tegmentum. *J Comp Neurol* 466:445–456 [PubMed: 14566941]
- Valentino RJ, Foote SL (1988) Corticotropin-releasing hormone increases tonic but not sensory-evoked activity of noradrenergic locus coeruleus neurons in unanesthetized rats. *J Neurosci* 8:1016–1025 [PubMed: 3258021]
- Valentino RJ, Van Bockstaele E (2008) Convergent regulation of locus coeruleus activity as an adaptive response to stress. *Eur J Pharmacol* 583:194–203 [PubMed: 18255055]
- Van Bockstaele EJ, Bajic D, Proudfit H, Valentino RJ (2001) Topographic architecture of stress-related pathways targeting the noradrenergic locus coeruleus. *Physiol Behav* 73:273–283 [PubMed: 11438352]
- Ventura R, De Carolis D, Alcaro A, Puglisi-Allegra S (2006) Ethanol consumption and reward depend on norepinephrine in the prefrontal cortex. *Neuroreport* 17:1813–1817 [PubMed: 17164670]

- Verbanck P, Seutin V, Dresse A, Scuvee J, Massotte L, Giesbers I, Kornreich C (1990) Electrophysiological effects of ethanol on monoaminergic neurons: an in vivo and in vitro study. *Alcohol Clin Exp Res* 14:728–735 [PubMed: 2176067]
- Verplaetse TL, Rasmussen DD, Froehlich JC, Czachowski CL (2012) Effects of prazosin, an alpha1-adrenergic receptor antagonist, on the seeking and intake of alcohol and sucrose in alcohol-preferring (P) rats. *Alcohol Clin Exp Res* 36:881–886 [PubMed: 21981346]
- Vilpoux C, Warnault V, Pierrefiche O, Daoust M, Naassila M (2009) Ethanol-sensitive brain regions in rat and mouse: a cartographic review, using immediate early gene expression. *Alcohol Clin Exp Res* 33:945–969 [PubMed: 19302091]
- Walker BM, Rasmussen DD, Raskind MA, Koob GF (2008) alpha1-noradrenergic receptor antagonism blocks dependence-induced increases in responding for ethanol. *Alcohol* 42:91–97 [PubMed: 18358987]
- Wang ZJ, Rao ZR, Shi JW (1992) Tyrosine hydroxylase-, neurotensin-, or cholecystokinin-containing neurons in the nucleus tractus solitarii send projection fibers to the nucleus accumbens in the rat. *Brain Res* 578:347–350 [PubMed: 1380865]
- Waterhouse BD, Moises HC, Woodward DJ (1980) Noradrenergic modulation of somatosensory cortical neuronal responses to iontophoretically applied putative neurotransmitters. *Exp Neurol* 69:30–49 [PubMed: 7389849]
- Weinshenker D, Schroeder JP (2007) There and back again: a tale of norepinephrine and drug addiction. *Neuropsychopharmacology* 32:1433–1451 [PubMed: 17164822]
- Weinshenker D, Rust NC, Miller NS, Palmiter RD (2000) Ethanol-associated behaviors of mice lacking norepinephrine. *J Neurosci* 20:3157–3164 [PubMed: 10777779]
- Wellman PJ (2000) Norepinephrine and the control of food intake. *Nutrition* 16:837–842 [PubMed: 11054588]
- Zaniewska M, Filip M, Przegalinski E (2015) The involvement of norepinephrine in behaviors related to psychostimulant addiction. *Curr Neuropharmacol* 13:407–418 [PubMed: 26411968]

Table 1

Summary of the impact of ethanol on NE neuronal function

Change	Region	Measurement	Species	References
NE neuron activity				
<i>Acute ethanol</i>				
Decrease	LC	Electrophysiology (in vivo)	Rodent	Aston-Jones et al. (1982), Strahlendorf and Strahlendorf (1983), and Verbanck et al. (1990)
Decrease	LC	Electrophysiology (ex vivo)	Rodent	Osmanovic and Shefner (1994), Shefner and Tabakoff (1985), and Verbanck et al. (1990)
Rebound increase	LC	Electrophysiology (ex vivo)	Rodent	Shefner and Tabakoff (1985) and Verbanck et al. (1990)
Increase	LC, NTS	c-Fos	Rodent	Aimino et al. (2017), Chang et al. (1995), Kolodziejska-Akiyama et al. (2005), Lee et al. (2011), Ryabinin et al. (1997), and Thiele et al. (1997, 2000)
<i>Chronic ethanol</i>				
Increase	LC	c-Fos	Rodent	Males (Knapp et al. 1998; Putzke et al. 1996; Ryabinin et al. 1997) females but not males (Retson et al. 2015)
Decrease	LC	c-Fos	Rodent	Males (Rodberg et al. 2017)
NE release/measurement				
<i>Acute ethanol</i>				
Increase	CSF/plasma	NE, metabolites (MHPG)	Human	Borg et al. (1981) and Howes and Reid (1985)
Increase	Whole brain	Metabolites (DHPG, VMA)	Rodent	Alari et al. (1987b), Corrodi et al. (1966), Karoum et al. (1976), and Murphy et al. (1983)
Decrease	Whole brain	NE	Rodent	Alari et al. (1987a) and Murphy et al. (1983)
<i>Chronic ethanol</i>				
Increase	CSF	Metabolites (MHPG)	Human	Borg et al. (1981)
Increase	Whole brain	Metabolites (DHPG, VMA)	Rodent	Karoum et al. (1976)
Increase	PFC	Evoked extracellular NE	Rodent	Lanteri et al. (2008)

As discussed in the text above, there has been longstanding interest in understanding how ethanol alters noradrenergic activity, and norepinephrine release/turnover. Some key findings are summarized in this table

BLA basolateral amygdala, *CSF* cerebrospinal fluid, *DHPG* 3,4-dihydroxyphenylglycol, *MHPG* 3-methoxy-4-hydroxy-phenylglycol, *NAc* nucleus accumbens, *LC* locus coeruleus, *NTS* nucleus tractus solitarius, *PFC* prefrontal cortex, *VMA* vanillomandelic acid

Table 2

Summary of the impact NE manipulations on ethanol-related behavior

<i>Direct NE disruption</i>				
Manipulation	Measurement	Effect on ethanol-related behavior	Species	References
DBH knockout	Ethanol intake	Decreased consumption	Rodent	Males but not females (Weinshenker et al. 2000)
DBH inhibition	Ethanol intake	Decreased consumption	Rodent	Brown et al. (1977)
DNAB lesion	Ethanol intake	Increased consumption	Rodent	Kiianmaa et al. (1975)
DNAB lesion	Ethanol intake and initiation	Decreased consumption/initiation	Rodent	Brown and Amit (1977) and Corcoran et al. (1983)
NE lesion in PFC	Ethanol intake and CPP	Decreased consumption/preference	Rodent	Ventura et al. (2006)
LC lesion	Withdrawal symptoms	Decrease	Rodent	Kostowski and Trzaskowska (1980)
<i>NE receptor disruption</i>				
Target/manipulation (compound)	Measurement	Effect on ethanol-related behavior	Species	References
<i>α_2 – Gi coupled</i>				
Agonist (lofexidine, guanfacine)	Ethanol SA, cue/stress-induced reinstatement	Decreased ethanol seeking	Rodent	Fredriksson et al. (2015), Le et al. (2005), and Riga et al. (2014)
Agonist (clonidine, guanfacine)	Ethanol intake	Decreased consumption	Rodent	Fredriksson et al. (2015), Opitz (1990), and Rasmussen et al. (2014a)
Agonist (clonidine)	Withdrawal symptoms	Decrease acute withdrawal	Rodent	Kostowski and Trzaskowska (1980)
<i>α_1 – Gq coupled</i>				
Inverse agonist (prazosin)	Cue/stress-induced craving	Decreased ethanol craving	Human	Fox et al. (2012)
Inverse agonist (prazosin)	Ethanol intake	Decreased consumption	Human	Simpson et al. (2009, 2015)
Inverse agonist (prazosin)	Ethanol intake and initiation	Decreased consumption	Rodent	Froehlich et al. (2013, 2015) and Skelly and Weiner (2014)
Inverse agonist (prazosin)	Ethanol SA, cue/stress-induced reinstatement	Decreased ethanol seeking	Rodent	Funk et al. (2016), Verplaetse et al. (2012), and Walker et al. (2008)
Antagonist (doxazosin)	Ethanol intake	Decreased consumption	Rodent	O'Neil et al. (2013)
Antagonist (doxazosin)	Cue/stress-induced ethanol reinstatement	Decreased ethanol seeking	Rodent	Funk et al. (2016)
<i>β – Gs coupled</i>				
Antagonist (propranolol)	Withdrawal symptoms	Decrease withdrawal	Human	Carlsson (1976) and Sellers et al. (1977)
Antagonist (propranolol)	Ethanol SA	Decreased ethanol seeking	Rodent	Gilpin and Koob (2010)
Antagonist (propranolol)	Ethanol intake	Decreased consumption	Rodent	Andreas et al. (1983)
<i>α_1 and β antagonist cocktail</i>				
Prazosin + propranolol	Ethanol intake	Decreased consumption	Rodent	Rasmussen et al. (2014b)

NE-targeted manipulations have been shown to have a number of effects on ethanol-related behavior. The vast majority of interventions have targeted reductions in NE transmission/signaling and a summary of some key effects are included in this table

CPP conditioned place preference, DBH dopamine- β -hydroxylase, DNAB dorsal noradrenergic bundle, PFC prefrontal cortex, SA self-administration (operant)