Published in final edited form as:

Neuropharmacology. 2022 May 01; 208: 108997. doi:10.1016/j.neuropharm.2022.108997.

Noradrenergic Circuits and Signaling in Substance Use Disorders

Anthony M. Downs, Ph.D.[1], **Zoe A. McElligott, Ph.D.**[1,2,3]

[1]Bowles Center for Alcohol Studies, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599

[2]Department of Psychiatry, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599

[3]Department of Pharmacology, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599

Abstract

The central noradrenergic system innervates almost all regions of the brain and, as such, is well positioned to modulate many neural circuits implicated in behaviors and physiology underlying substance use disorders. Ample pharmacological evidence demonstrates that α_1, α_2, and β adrenergic receptors may serve as therapeutic targets to reduce drug –seeking behavior and drug withdrawal symptoms. Further, norepinephrine is a key modulator of the stress response, and stress has been heavily implicated in reinstatement of drug taking. In this review, we discuss recent advances in our understanding of noradrenergic circuitry and noradrenergic receptor signaling in the context of opioid, alcohol, and psychostimulant use disorders.

Keywords

norepinephrine; opioids; psychostimulants; alcohol; locus coeruleus; nucleus of the tractus solitarius

INTRODUCTION

Norepinephrine (NE) is one of the most abundant neurotransmitters in the brain and periphery, and plays an important role in a variety of behavioral processes including, arousal, attention, appetite, and stress (Aston-Jones and Cohen, 2005; Berridge and Waterhouse, 2003; Rinaman, 2011; Sara and Bouret, 2012). The central noradrenergic system consists of six nuclei: A1/Rostroventrolateral medulla (RVLM), A2/Nucleus of the tractus solitarius (NTS), A5, A6/Locus coeruleus (LC), A7, and subcoeruleus. The cell bodies of all noradrenergic nuclei that innervate the brain are located in the medulla or pons. The A6/LC contains the largest number of central noradrenergic neurons and they project to almost all areas of the forebrain, including but not limited to the cortex, hippocampus,

Corresponding Authors: zoemce@email.unc.edu, Anthony_downs@med.unc.edu.

and central nucleus of the amygdala (CeA), via the dorsal noradrenergic bundle (DNB). The A1/RVLM and A2/NTS nuclei provide noradrenergic innervation to the paraventricular nucleus of the insular cortex, hypothalamus, bed nucleus of the stria terminalis (BNST), CeA, and basolateral amygdala (BLA) via the ventral noradrenergic bundle (VNB) (Moore and Bloom, 1979; Robertson et al., 2013).

NE modulates neurons via three main families of G-protein coupled receptors: the α_1, α_2, and β adrenergic receptors (ARs). The α_1 family consists of three different subtypes, α_{1a}, α_{1b}, and α_{1D}, all of which signal canonically through $G\alpha_q$ proteins and recruit phospholipase C and Ca^{2+} signaling. The α_2 family consists of 3 subtypes, α_{2a}, α_{2b}, and α_{2c}, which signal through the $G\alpha_i$ pathway and have the ability to suppress cAMP accumulation and/or alter the conductance of K^+ and Ca^{2+} channels. The β family also consists of three subtypes, named β_1, β_2, and β_3, which all signal canonically through $G\alpha_s$ proteins to enhance cAMP signaling promoting activation of protein kinase A. All three AR subtypes are found on postsynaptic neurons, where they modulate neuronal activity. However, α_2 ARs are also found on presynaptic terminals where they suppress the release of NE in an autocrine manner. α_2 ARs are also found presynaptically on glutamatergic and GABAergic terminals, where they suppress glutamate or GABA release respectively as heteroreceptors (Shields et al., 2009).

In recent history, the involvement of NE in substance use disorders (SUDs) has been overlooked in favor of dopamine (DA). However, several decades of research have clearly demonstrated that NE plays a critical role in some components of addiction-related behavior (Weinshenker and Schroeder, 2007). NE plays a significant role in stress-induced reinstatement of drug-seeking behaviors as well as withdrawal processes (Mantsch et al., 2016). Pharmacological data also support the importance of NE in substance use disorder (SUD), as drugs targeting α and/or β ARs modulate drug-seeking behaviors (Weinshenker and Schroeder, 2007). Indeed, recent clinical trials support the efficacy of α_1 AR antagonists and α_2 AR agonists in SUD (Kahn et al., 1997; Pergolizzi et al., 2019; Simpson et al., 2015; Simpson et al., 2018). Improving our understanding of how NE modulates neural circuitry during SUD may lead to the identification of new circuit interactions and novel therapeutics. This review will focus on recent advances in our understanding of how noradrenergic circuits modulate use of opioids, alcohol, and psychostimulants.

NOREPINEPHRINE, STRESS, AND SUBSTANCE USE DISORDER

SUD has been linked to brain systems that mediate both reward and stress. Logically this makes sense as both external and internal stress drives natural reward seeking (i.e. thirst drives the seeking of water.) Activation of these brain stress systems, however, is thought to be key to the negative emotional states (dysphoria, anxiety, and irritability) associated with drug misuse, and especially drug dependence, thus driving drug seeking through negative reinforcement learning (Koob and Le Moal, 1997; Koob and Le Moal, 2008). Life stress is also a well-known risk factor for the development of SUD and greatly increases the risk of relapse, and stress and anxiety disorders are highly comorbid with SUDs (Sinha, 2008).

NE is a key component of brain stress systems in large part due to NE's direct and indirect influence over the hypothalamic-pituitary-adrenal axis (HPA)(Herman et al., 2016). In brief, activation of the paraventricular nucleus of the hypothalamus causes synthesis and release of corticotropin releasing factor (CRF), which in turn stimulates adrenocorticotropic hormone (ACTH) production by the anterior pituitary gland. ACTH then enters the bloodstream to mediate production of glucocorticoids by the adrenal cortex. Glucocorticoids subsequently mediate the cellular stress response. Peripherally, NE is a key component in the sympathetic nervous system, which also mediates the stress response. In response to a stressful stimulus, preganglionic neurons originating in the interomediolateral gray matter of the spinal cord release acetylcholine, which drives peripheral NE release by either directly activating postganglionic NE neurons or stimulates epinephrine and norepinephrine production and release into the bloodstream by the adrenal medulla (Goldstein, 1987). Preganglionic sympathetic neurons also receive direct inputs from brain areas such as the paraventricular nucleus of the hypothalamus and insular cortex, as well as the noradrenergic A2/NTS and A1/RVLM areas (Fisher et al., 2009), and are indirectly influenced by other fear- and stress-related brain regions, such as the amygdala and BNST (Buijs and Van Eden, 2000; Crestani et al., 2013; Lebow and Chen, 2016). In an acute setting, peripheral NE signaling via the sympathetic nervous system, in concert with central NE signaling upon the HPA axis, instigate the "flight or fight" response. However, when chronically activated, central and peripheral signaling can lead to the development of neuropsychiatric disorders and can contribute to SUD (Sinha, 2008).

Ample epidemiological data links stress disorders, including post-traumatic stress disorder (PTSD), generalized anxiety disorders, and early childhood and adolescent exposure to traumatic events or abuse, to an increased risk for developing SUD (Sinha, 2008). This is likely explained by positive feedback interactions between activation of central and peripheral stress systems and the midbrain dopaminergic system, which is a brain region that directly mediates the reinforcing properties of many drugs of abuse (Di Chiara and Imperato, 1988; Volkow et al., 2007). Increased CRF and cortisol levels due to activation of the HPA axis during stress can directly modulate dopaminergic signaling and release in the ventral tegmental (VTA) and nucleus accumbens (NAcc) (Kalivas and Duffy, 1995; Piazza and Le Moal, 1996; Saal et al., 2003; Thierry et al., 1976). Further, both drug withdrawal and exposure to drug cues activates the HPA-axis. For example, in recently abstinent individuals with cocaine use disorder, exposure to a stress or drug cue results in a long-lasting activation of the HPA-axis, with increases in plasma cortisol, ACTH, norepinephrine, and epinephrine levels (Sinha et al., 2003). These studies demonstrate a pathway by which exposure to stress or drug withdrawal can activate central and peripheral stress systems to instigate or reinstate drug consumption through modulation of midbrain dopaminergic systems. In future sections, we will discuss studies investigating the role of the NE system in stress- or cue-induced reinstatement of drug consumption along with other roles of the noradrenergic system in other phases of SUD.

NOREPINEPHRINE IN OPIOID USE DISORDER

Significant pharmacological evidence links noradrenergic signaling and circuitry with opioid use disorder (OUD). The α_1 AR antagonist prazosin reduces heroin self-administration (SA)

in rats and blocks the somatic withdrawal symptoms of morphine in mice (Greenwell et al., 2009; Solecki et al., 2019b). Noradrenergic drugs are also used clinically to treat the symptoms of opioid withdrawal. The α_2 agonists clonidine and lofexidine are effective at reducing opioid withdrawal symptoms (Gish et al., 2010; Kahn et al., 1997; Pergolizzi et al., 2019). Taken together this suggests that reducing postsynaptic noradrenergic signaling by blocking α_1 ARs or inhibiting release of norepinephrine by activating presynaptic α_2 ARs may be important for alleviating opioid withdrawal. Additional studies have helped to better characterize the circuitry that mediates the effects of NE on opioid consumption and withdrawal.

Extended amygdala

The BNST, along with the CeA and the shell of the NAcc constitute the extended amygdala (Alheid, 2003). The BNST functions as an important integrator of stress and reward information (Jennings et al., 2013; Shackman and Fox, 2016). In the context of SUD, the BNST been implicated in withdrawal and is involved in stress-induced reinstatement of drug seeking behavior (Koob, 2009; Vranjkovic et al., 2017).

A combination of behavioral and physiological studies has implicated BNST noradrenergic signaling in many aspects of opioid use. Both mice lacking dopamine β-hydroxylase (*DBH*), the enzyme responsible for norepinephrine synthesis, and $\alpha 1_b$ AR knockout mice do not develop conditioned place preference (CPP) in response to morphine (Drouin et al., 2002; Olson et al., 2006). Restoration of *DBH* expression in the A2/NTS, but not the A6/LC, restores CPP in response to morphine (Olson et al., 2006). Due to the fact that the A2/NTS sends an extremely strong projection to the extended amygdala, and especially the BNST, these data suggest that NE signaling in the BNST may be necessary for CPP. This is highly probable because the BNST is strongly implicated in the seeking of cocaine, and ethanol, and in stress induced reinstatement to morphine seeking (Pina et al., 2015; Sartor and Aston-Jones, 2012; Wang et al., 2006). However, other A2/NTS targets like the basolateral amygdala and hypothalamus could also play a role in mediating this behavior.

Substantial evidence has linked NE signaling to stress-induced opioid reinstatement. Lesioning of the VNB, which carries most of the noradrenergic afferents from the A2/NTS and A1/RVLM, or infusion of the α_2 AR agonist clonidine into the BNST blocks stress-induced reinstatement of morphine CPP (Wang et al., 2001). However, microinjection of clonidine into the LC or lesion of the DNB, which carries most of the noradrenergic afferents from the LC, did not impact stress-induced maintenance of CPP in response to foot shock (Wang et al., 2001). In congruence, microinjection of clonidine into the LC did not impact reinstatement of heroin seeking in rats (Shaham et al., 2000). Taken together this suggests that the BNST and NE projections originating from the A2/NTS nucleus are necessary for stress induced reinstatement of opioid CPP and SA, but NE projections originating in the A6/LC are not.

NE released in the BNST is also a critical mediator of the somatic and affective components of opioid withdrawal (Delfs et al., 2000). Abstinence from morphine enhances activation of the ventrolateral BNST and its afferents from the A2/NTS (Aston-Jones and Harris, 2004; Hamlin et al., 2004; Harris and Aston-Jones, 2007). In fact, NE release in the

BNST co-occurs during specific withdrawal behaviors in rats including, teeth chattering and swallowing movements, and withdrawal behaviors were exacerbated after co-administration of naloxone and the α_2 AR antagonist idazoxan following a single dose of morphine (Fox et al., 2017). This suggests that the amount of NE released in the BNST may correlate with the severity of withdrawal and that noradrenergic signaling in the BNST may contribute to the negative reinforcement and aversive learning associated with opioid withdrawal. Further, opioid withdrawal can induce plasticity in adrenergic circuitry itself. Chronic morphine withdrawal induces adrenergic plasticity in the BNST whereby α_2 AR become less effective at inhibiting NE release and norepinephrine transporter (NET) reuptake activity is decreased in rats (McElligott et al., 2013). We have observed similar reduced efficacy in α_2 ARs, and enhanced BNST NE release in chronically stressed mice (restraint, (Schmidt et al., 2019), demonstrating that across species opioid withdrawal and stress may result in common pathological mechanisms. In combination these effects may enhance BNST NE levels and potentially exacerbate symptoms of opioid withdrawal. As OUD is a chronically relapsing disorder, and α_2 AR antagonism is one of the main in-patient therapeutic treatments for withdrawal, this type of receptor desensitization could limit the therapeutic efficacy of these treatments. Individuals are now experiencing naloxone precipitated withdrawal to treat overdose at increasing rates with the availability of over-the-counter Narcan administration, Moreover the rates of patients receiving multiple doses of naloxone from emergency medical service (EMS) providers is on the rise (up 26% from 2012–2015, (Faul et al., 2017). This trend has only been exacerbated during the COVID-19 global pandemic. For example, EMS naloxone administration increased 57.8% and repeat administration increased 84.8% as compared to the pre-pandemic period in Guilford County, NC (Khoury et al., 2021). While, we emphasize that naloxone is life-saving treatment and should be readily available, we also wish to emphasize that the field needs to have a better mechanistic understanding of how both spontaneous, and rapid, precipitated opioid withdrawal alter neural circuits and plasticity.

Locus Coeruleus

The A6/LC provides noradrenergic input to most forebrain structures, and, as such, changes to A6/LC function are well positioned to modulate many different brain regions. Systemic or intracoeruleur administration of morphine directly inhibits LC neurons (Aghajanian, 1978; Bird and Kuhar, 1977; Korf et al., 1974; Valentino and Wehby, 1988). However, chronic opioid consumption induces tolerance which prevents morphine-induced LC neuron inhibition due to compensatory changes in cAMP/PKA signaling pathways (Ivanov and Aston-Jones, 2001; Kogan et al., 1992). Interestingly, chronic morphine exposure causes internalization of μ opioid receptor (OR) from the membrane of LC neurons in male rats, but not in females (Enman et al., 2019). This suggests there may be critical sex differences in LC plasticity in response to opioid exposure which may affect tolerance and/or withdrawal.

Like the BNST, most research into the role of the LC has focused on the withdrawal phase of opioid use disorder. The LC is activated above baseline levels by opioid withdrawal and opioid withdrawal alters excitability of LC neurons, which is likely a result of long-lasting changes in cAMP/PKA/CREB signaling pathways (Fig 1) (Han et al., 2006; Hayward et al., 1990; Mazei-Robison and Nestler, 2012; Rasmussen et al., 1990). Down regulation

of CREB in the LC/A6 using viral approaches attenuated some withdrawal behaviors associated with morphine withdrawal including, ptosis, wet dog shakes, and lacrimation, while upregulation of CREB enhanced those same withdrawal behaviors (Han et al., 2006). Further, a study using a LC slice culture model demonstrated that LC activity normalizes back to baseline levels following chronic morphine exposure, but LC activity is significantly enhanced following bath application of naloxone or washout of morphine. These effects on LC neuron activity are directly mediated by μ OR activation, suggesting an adaptive change in the valence of μ OR signaling (Cao et al., 2010). Overall, these findings conflict with early studies that found that lesion of the DNB, which contains NE projections from the LC, or LC proper did not attenuate somatic withdrawal behavior nor conditioned place aversion (CPA) after opioid withdrawal, suggesting that LC projections do not mediate all withdrawal-associated symptoms (Caillé et al., 1999; Delfs et al., 2000). However, these earlier studies may need to be reconsidered as more recent anatomical studies using modern genetic approaches have demonstrated that some LC neurons innervate the BNST and that the LC and A2/NTS innervate each other (Robertson et al., 2013). It is important to note, however, that there also may be species differences between rat and mouse that could account for these discrepancies.

The altered plasticity observed in the LC after chronic morphine exposure and withdrawal, may be a consequence of changes in inputs to the LC. There is an increase in excitatory input to the LC in chronically morphine-treated animals, as demonstrated by an increased frequency of spontaneous EPSCs (Torrecilla et al., 2008). However, the specific glutamatergic inputs to the LC that are enhanced is unknown, as the LC receives glutamatergic input from the paragigantocellularis nucleus, lateral habenula, and prefrontal cortex (Aston-Jones et al., 1986; Herkenham and Nauta, 1979; Jodo and Aston-Jones, 1997). Opioid use and withdrawal also modulate peptidergic inputs to the LC, including CRF and orexin. Stimulating the LC via orexin receptors promotes behaviors associated with opioid withdrawal in both morphine dependent and control rats, while blocking orexin receptor-1 (HCRTR1) prevents withdrawal behaviors (Davoudi et al., 2016; Ghaemi-Jandabi et al., 2017). Chronic morphine use sensitizes the LC to the effects of CRF and stress by recruiting CRF receptor 1 to the plasma membrane of LC neurons (Enman et al., 2019; Xu et al., 2004). Blocking CRF receptor 1 prevents both morphine CPP and withdrawal behaviors and also reduces NE turnover in the cerebral cortex (Funada et al., 2001; Lasheras et al., 2015). This demonstrates a mechanism by which stress can enhance LC activity and perhaps potentiate opioid-seeking activity and withdrawal.

Taken together, these preclinical rodent studies demonstrate a few anatomical locations where systemic administration of noradrenergic compounds may work to reduce the symptoms of opioid withdrawal in humans. Both blockade of α_1 ARs or activation of α_2 ARs in the BNST may be an important site of action to diminish the symptoms of opioid withdrawal. However, the observed desensitization of α_2 ARs in the BNST following repeated bouts of morphine withdrawal in rats may suggest that α_2 AR agonists potentially work in other brain regions as well (McElligott et al., 2013). Further, the association between opioid withdrawal and enhanced LC activation suggests that reducing postsynaptic noradrenergic signaling in brain regions that receive LC input, including CeA or mPFC, may play an important role in the therapeutic action of α_1 ARs antagonists or α_2 ARs agonists.

NOREPINEPHRINE AND ALCOHOL USE DISORDER

Noradrenergic signaling is also a critical mediator of the effects of ethanol. In clinical populations, reduced serum DBH activity is associated with alcohol use disorder (AUD) (Köhnke et al., 2002). Further, the *DBH*444G/A* allele, which causes a significant reduction in serum DBH activity, is associated with AUD but not with withdrawal symptom severity (Köhnke et al., 2006).

Alcohol consumption activates noradrenergic circuitry. Intraperitoneal injection and binge consumption (>80 mg/dL) of ethanol induces expression of the early immediate protein cFos in noradrenergic neurons in the LC and A2/NTS (Burnham and Thiele, 2017; Thiele et al., 2000). Acute ethanol exposure enhances NE release in the medial prefrontal cortex, basal forebrain, and BNST (Jadzic et al., 2021; Jaime et al., 2020). However, the increase in NE release in the medial prefrontal cortex (mPFC) was attenuated after one week of ethanol SA, which suggests adaptive changes in LC neuron activity, and/or terminal release mechanisms, following long-term ethanol use (Jaime et al., 2020). NE levels are elevated in both the CNS and periphery during alcohol withdrawal in mice (Kovács et al., 2002). In alcohol dependent patients undergoing alcohol withdrawal, NE levels are elevated in the cerebrospinal fluid and in plasma (Fitzgerald, 2013; Hawley et al., 1981; Patkar et al., 2003).

NE also modulates ethanol consumption. *DBH* KO mice have reduced ethanol consumption in a SA paradigm (Weinshenker et al., 2000). However, it is unclear if this reduction in ethanol consumption is due to a decrease in the rewarding properties of ethanol per se, or an increase in the aversive and/or interoceptive effects of ethanol, as *DBH* KO mice are more sensitive to ethanol-induced sedation and hypothermia (Weinshenker et al., 2000). It is worth noting that one of the only FDA approved treatments for AUD, the alcohol dehydrogenase inhibitor disulfiram, also is a potent inhibitor of DBH (for detailed discussion see: (Weinshenker and Schroeder, 2007) . Further, just as has been demonstrated with other misused substances, treatment with an α_2 AR agonist decreases alcohol SA while α_2 AR antagonist treatment increases alcohol consumption (Lê et al., 2005). However, these results should be interpreted with some caution because the α_2 antagonist used in the study, yohimbine, has significant off-target effects (Davis et al., 2008). Treatment with α_2 agonists also decreases stress-induced alcohol seeking behaviors due to footstock stress (Lê et al., 2005). A more recent study found that the α2 AR agonist clonidine reduced alcohol consumption in a genetically alcohol-preferring rats (Rasmussen et al., 2014). Clinical data supporting the use of α2 AR agonists is mixed. In a small clinical trial, clonidine did not significantly improve withdrawal symptoms relative to placebo (Adinoff, 1994). A clinical trial for the α2 AR agonist guanfacine for AUD in women is currently ongoing (NCT03137082), which is an interesting avenue to explore given that there are known sex differences in efficacy for drugs targeting the noradrenergic system (Fox et al., 2014; Fox and Sinha, 2009). Taken together these data suggest that reducing NE transmission with an α2 AR agonist may be an effective target for reducing alcohol consumption.

Blocking α_1 ARs has also been suggested as a therapeutic target in multiple clinical and preclinical studies. In fact, the α_1 AR antagonist prazosin has demonstrated efficacy in reducing the number of drinks and number of drinking days in a double-blind randomized

clinical trial in alcohol use disorder (Simpson et al., 2018). A recent clinical trial found that prazosin was more efficacious in patients suffering from more severe withdrawal symptoms. These patients experienced a significant reduction in heavy drinking days and alcohol cravings, while those with low or no withdrawal symptoms did not experience a benefit from prazosin (Sinha et al., 2021). Prazosin was also tested in AUD patients in a trial that used imagery exposure to stress and alcohol cues. Prazosin significantly decreased alcohol craving induced by both stress and alcohol cues, which suggests that prazosin may help to mitigate stress associated with early alcohol withdrawal (Fox et al., 2012; Milivojevic et al., 2020). A further clinical trial assessed the efficacy of prazosin in patients with comorbid AUD and PTSD. While prazosin reduced drinking outcomes in this study, it did not affect PTSD symptoms (where there have been promising but conflicting studies, see: (Raskind et al., 2018, 2013, 2003) and resulted in significant hypotensive side effects (Simpson et al., 2015). An additional small clinical study found that the α_1 AR antagonist, doxazosin, was more effective in reducing alcohol consumption in patients with high starting systolic blood pressure, which suggests that individual differences in sympathetic tone may account for the success or failure of α_1 AR antagonists in the clinic (Haass-Koffler et al., 2017). In preclinical studies, blocking α_1 ARs reduced alcohol self-administration in dependent animals and reduced alcohol consumption in a chronic intermittent access paradigm (Skelly and Weiner, 2014; Walker et al., 2008). Overall, these clinical and preclinical studies provide strong evidence that blocking α_1 ARs may be effective in AUD. However, the potential positive effects on alcohol consumption need to be balanced against potential negative hypotensive effects that may make these compounds undesirable for clinical use.

There is significantly less literature regarding the involvement of β ARs in AUD. Blocking central, but not peripheral, β ARs also reduced alcohol consumption in alcohol-dependent rats (Gilpin and Koob, 2010). Clinically, one early study found that the β AR antagonist propranolol was equally effective as diazepam at alleviating moderate withdrawal symptoms in AUD (Bailly et al., 1992). Two larger double-blind placebo control trial found that the β AR antagonist, atenolol, reduced withdrawal symptoms, alcohol cravings, and treatment failure in patients with mild withdrawal (Gottlieb et al., 1994; Horwitz et al., 1989). In the below sections, we will discuss circuit mechanisms that may mediate the effects of these noradrenergic drugs.

Extended and basolateral amygdala

Noradrenergic signaling in the extended amygdala has been specifically implicated in alcohol consumption. Acute ethanol administration increases NE output in the BNST (Jadzic et al., 2021). Microinjection of pindolol, a combined β AR antagonist and 5-$HT_{1A/B}$ agonist, into the BLA reduced long term ethanol consumption (Patkar et al., 2019; Patkar et al., 2017). Further, injection of the β AR antagonist propranolol into the BLA prevented reinstatement of alcohol seeking behaviors in a self-administration paradigm in rats (Chesworth and Corbit, 2018). This suggests that NE signaling in the BLA is a critical modulator of ethanol consumption, although the precise β AR subunit responsible for these effects is unknown.

Orbitofrontal cortex

Cortical regions, including the orbitofrontal cortex (OFC), have also been implicated in alcohol use disorder. The OFC mediates some components of choice behavior, reversal learning, and anticipation of expected outcomes in response to appetitive and aversive stimuli (Bissonette et al., 2008; Roesch and Olson, 2007; Schoenbaum et al., 1998). OFC dysfunction has also been implicated in neuropsychiatric diseases, including alcohol use disorder (Fortier et al., 2008; Verdejo-García et al., 2006). A recent study demonstrated that in non-alcohol exposed animals, monoamine receptors, including D2 DA receptors, α_2 AR, and 5-HT_{1A} receptors reduce OFC neuron excitability, mainly through activation of G-protein inwardly rectifying potassium (GIRK) channels. However, in chronic intermittent ethanol-treated mice, OFC neurons become more excitable and do not respond to D2 DA receptor, α_2 AR, or 5-HT_{1A} receptor activation (Nimitvilai et al., 2017). This demonstrates a mechanism by which chronic alcohol consumption can cause widespread disruption of cortical function.

Locus Coeruleus

NE signaling in the LC has also been implicated in alcohol use disorder. A recent study found that noradrenergic inputs from the LC to the VTA are required for the reinforcing effects of ethanol. Administration of α_1 AR agonists into the posterior VTA enhanced alcohol self-administration, while α_2 AR agonists decreased alcohol self-administration (Shelkar et al., 2017). Further, silencing of LC inputs to the posterior VTA with lidocaine blocked alcohol self-administration (Shelkar et al., 2017).

CRF and noradrenergic signaling in the LC are critical components for stress and are required for stress induced drug reinstatement (Smith and Aston-Jones, 2008). LC noradrenergic neurons are among the first to be recruited during a stressful event and increased NE release in the CeA enhances CRF-expressing GABAergic projection neuron activity in the CeA (Borodovitsyna et al., 2020; Campese et al., 2017; Finnell et al., 2019). In turn, CRF-expressing GABAergic neurons in the CeA project back to the LC and enhanced CRF input to LC neurons enhances LC neuron activity and anxiety like phenotypes (Koob, 1999; McCall et al., 2015; Reyes et al., 2011; Snyder et al., 2012). This interaction between LC neurons and CRF-expressing neurons in the CeA is disrupted by chronic ethanol consumption and creates a feed- forward loop that is activated following alcohol withdrawal and stress (Funk et al., 2006; Gilpin et al., 2015; Koob, 2015) (Fig 2). A recent study found that CRF receptor agonist administration in the CeA decreases NE release in the CeA in slice, which provides a local circuit mechanism of NE release inhibition. However, ethanol itself had no effect on NE release in the CeA (Hedges et al., 2020). In contrast, a previous study using *in vivo* microdialysis found that local infusion of CRF receptor agonist enhanced NE transmission in the CeA, an effect that would likely exacerbate stress response *in vivo* (Su et al., 2015). The differences between these two studies likely reflect the recruitment of additional circuits, perhaps connections from the PFC to the CeA, which are also regulated by LC noradrenergic inputs (Borodovitsyna et al., 2020). These long-loop connections would not be intact in the *ex vivo* slice preparation.

Non-neuronal cells

Non-neuronal cell types, including astrocytes and microglia, have also been implicated in alcohol use disorder (Adermark and Bowers, 2016). A recent study used 2-photon microscopy to investigate how ethanol and NE modulate vigilance-included changes in astrocytic Ca^{2+} signaling. NE triggers Ca^{2+} transients in astrocytes through activation of α_1 ARs. However, acute ethanol exposure causes a decrease in locomotor-induced increases in Ca^{2+} transients in astrocytes in both cerebellum and V1 cortex. The decrease in astrocyte Ca^{2+} is not due to direct effects of ethanol and astrocytes, but rather a decrease in LC activity by ethanol and a corresponding decrease in global NE release (Ye et al., 2020). This demonstrates how alcohol-induced changes in NE release from LC neurons can have physiological ramifications throughout the brain on both neurons and glia.

Taken together, these preclinical rodent studies demonstrate a few anatomical locations where systemic administration of noradrenergic compounds may work to treat AUD. Blockade of β ARs in the BLA may help to reduce alcohol consumption, although curiously β AR antagonists are the least well studied target from a clinical perspective. Further, the clear association between enhanced LC activation and stress-induced reinstatement of alcohol consumption suggests that α_1 AR antagonists or α_2 AR agonists may reduce alcohol consumption by blocking noradrenergic signaling in brain regions that receive LC projections such as the CeA or mPFC. Targeting these receptors in the CeA may help break the feedforward loop involving CRF-signaling between the CeA and LC to help relieve some of the aversive effects of alcohol withdrawal as well as stress-induced reinstatement. Further, blocking LC to VTA noradrenergic inputs may be effective in reducing the rewarding effects of alcohol by indirectly modulating NAcc DA signaling.

NOREPINEPHRINE AND PSYCHOSTIMULANT USE DISORDER

Psychostimulants, including amphetamine, methamphetamine, and cocaine, inhibit the norepinephrine transporter (NET), dopamine transporter (DAT), and serotonin transporter to modulate monoamine uptake in the brain. Early self-administration studies found that NE was not a mediator of the maintenance phase of psychostimulant self-administration. Rather, self-administration of psychostimulants depended on DA signaling. DA receptor antagonists reduced psychostimulant self-administration, but NE antagonists generally had no effect (Yokel and Wise, 1975; Yokel and Wise, 1976). Lesion of the VNB also had no effect on the maintenance phase of cocaine self-administration (Roberts et al., 1977). Further, selective NET inhibitors are generally not self-administered, while DAT inhibitors are self-administered (Skjoldager et al., 1993; Wee et al., 2006; Woolverton, 1987). Together, these data suggest that NE is not involved in the maintenance of psychostimulant self-administration.

However, NE signaling has been implicated in other models of psychostimulant use disorder. NET knockout mice show reduced CPP to amphetamine, likely a result of enhanced extracellular NE levels (Ventura et al., 2003). NE may also play a role in regulating locomotor and behavioral sensitization to psychostimulants. *DBH* knockout mice appear to be more sensitive to the locomotor effects of cocaine and amphetamine and are more sensitive to stereotypy following psychostimulant administration (Schank et al., 2006;

Weinshenker et al., 2002). NET knockout mice also demonstrate enhanced locomotor sensitization to cocaine and amphetamine (Xu et al., 2000). Some of these changes may be confounded by alterations in DA signaling in the NAc caused by *DBH* knockout. However, this strongly implicates that the NE system is regulating the mesolimbic DA system in profound ways.

Knockout studies have implicated the α_1 AR as a key postsynaptic mediator of behavioral sensitization to psychostimulants. Systemic or direct PFC administration of α_1 AR antagonists reduces cocaine or amphetamine locomotor sensitization (Drouin et al., 2002; Weinshenker et al., 2002; Wellman et al., 2002). Global knockout of α_{1b} ARs completely blocks psychostimulant induced locomotor activity (Auclair et al., 2004; Drouin et al., 2002; Salomon et al., 2006). In congruence, activating postsynaptic α_1 or α_2 ARs enhanced the locomotor effects of psychostimulants (Villégier et al., 2003). Taken together, these data suggest that enhanced NE signaling is critical for the locomotor effects of psychostimulants, although the effects on DA release caused by the manipulations in these experiments should be considered.

While NE does not appear to be involved in the maintenance phase of psychostimulant self-administration, NE is important for reinstatement of psychostimulant self-administration. Researchers have selectively bred a high responding rat line that exhibits enhanced levels of prolonged drug seeking behavior following long-term self-administration of cocaine, increased propensity for stress-induced reinstatement, and higher risk of relapse following abstinence (Flagel et al., 2016). These high responding rats have increased basal and cocaine-induced efflux of both DA and NE in the NAcc relative to low responding rats (Mabrouk et al., 2018). Intracerebroventricular injection of NE reinstates cocaine-seeking behavior (Brown et al., 2011), while inhibition of DBH with nepicastat reduced cocaine reinstatement following both stress and drug-associated cues (Schroeder et al., 2013). Further, systemic administration of α_2 AR agonists reduced stress induced reinstatement of cocaine seeking following foot shock (Erb et al., 2000). A recent clinical trial found that the α2 agonist guanfacine significantly reduced cocaine cravings and stress in female patients that were cocaine-dependent, while no effects were seen in cocaine-dependent male patients (Fox et al., 2014). The α_1 AR antagonist, doxazosin, also decreased cocaine use in a small clinical trial (Shorter et al., 2013). Doxazosin appears to be more effective in patients with lower noradrenergic tone caused by the (*C1021T*) variant in the *DBH* gene (Zhang et al., 2019). However, doxazosin is less effective in individuals with the (*T1848A*) variant in the *ADRA1D* gene, which encodes the α_{1D} AR (Shorter et al., 2020). These data demonstrate that enhanced NE release is an important mediator of stress-induced reinstatement. Further, the clinical trials for noradrenergic drugs demonstrate the importance of considering sex and genetic variants that may affect noradrenergic signaling/tone when evaluating the efficacy of these compounds.

Extended amygdala

Ample evidence has demonstrated that the extended amygdala is critical for the rewarding properties of psychostimulants (Li et al., 2015; Venniro et al., 2020). Both α and β ARs in the extended amygdala have been implicated in stress-induced reinstatement of cocaine

seeking behaviors. Microinjection of β AR antagonists into either the BNST or the CeA blocks cocaine reinstatement following foot shock or swim stress but does not block drug-induced reinstatement (Leri et al., 2002). The β2 AR selective antagonist ICI-118,551 also reduced *CRF* mRNA expression in the BNST following swim stress (McReynolds et al., 2014). Blockade of β2 ARs in the ventral BNST suppressed the activity of a ventral BNST to VTA circuit, which in turn suppressed both CRF receptor activation in the VTA and stress induced reinstatement of cocaine consumption (Vranjkovic et al., 2014) (Fig 3). However, β AR antagonists did not influence cocaine-induced reinstatement of cocaine seeking, suggesting a specific role of NE in response to stress-induced – but not drug-induced reinstatement (Leri et al., 2002).

α2 ARs have also been investigated in the context of cocaine use disorder in animal models, which is especially important given the interest in α2 AR agonists in the clinic. Postsynaptic excitatory $\alpha 2_a$ ARs are located in the BNST. A recent study found that global deletion of $\alpha 2_a$ ARs from the BNST blocked stress-induced cocaine reinstatement, but rescue of $\alpha 2_a$ AR signaling by mimicking its effect with $G_{\alpha i}$-DREADD expression specifically in the BNST restored stress-induced cocaine reinstatement (Perez et al., 2020). These data complicate the use of α2 AR agonists like guanfacine, because while guanfacine may inhibit stress-induced reinstatement by activating presynaptic α2 autoreceptors, it may also promote stress induced reinstatement by activation $\alpha 2_a$ ARs heteroreceptors in the BNST. However, the authors found that low dose guanfacine (0.15 mg/kg) did not enhance BNST activity as assessed by cfos staining but did suppress stress-induced cocaine reinstatement (Perez et al., 2020).

Chronic cocaine administration also induced plasticity in the BNST. Chronic (100-day) self-administration of cocaine in Rhesus monkeys resulted in a roughly 50% increase in NET-binding as assessed by *in vitro* autoradiography (Macey et al., 2003). These changes in noradrenergic plasticity may represent a pathological mechanism that contributes to stress-induced reinstatement and may be corrected by α1 and/or β AR antagonists.

Medial prefrontal cortex

Noradrenergic signaling in the mPFC has been implicated in psychostimulant use disorder. Selective depletion of NE in the prefrontal cortex prevents the formation of CCP to amphetamine (Ventura et al., 2003). Microinjection of the α_1 AR antagonist terazosin directly into the mPFC blocked cocaine-induced reinstatement of cocaine-seeking behaviors, but direct injection into either the NAc or VTA had no effect (Schmidt et al., 2017). This suggests that many of the effects of α_1 AR antagonists observed following systemic administration may be due to action of the drug in the mPFC. A recent study further characterized interactions between stress and cocaine CPP in the mPFC. Exposure to acute restraint stress enhanced cocaine CPP in rats (Shinohara et al., 2019). This was the result of synchronized transmission of both NE and DA in the mPFC, where DA was required for CPP, but NE enhanced that preference. This is likely driven by enhanced by cortical pyramidal cell excitability, through an α_1 AR-mediated mechanism (Shinohara et al., 2020; Wada et al., 2020).

Ventral tegmental area

While DA release in the NAc core mediates the rewarding properties of psychostimulants, noradrenergic innervation of the VTA plays an important modulatory role in drug preference. Conditioned stimulus-induced drug seeking, where drug use is paired with a conditioned stimulus, depends on phasic DA signaling in the NAc core (Solecki et al., 2013; Stuber et al., 2005). A recent study demonstrated that blocking α_1 ARs in the VTA attenuated conditioned stimulus-induced reinstatement of cocaine seeking (Solecki et al., 2019a). NE also interacts with CRF to modulate VTA excitability. Co-injection of a CRF receptor agonist and an α_1 AR agonist enhanced CPP for cocaine. This effect is mediated, at least in part, by potentiation of glutamatergic inputs onto VTA DA neurons via enhanced IP3-Ca^{2+} and NMDA receptor activity (Tovar-Díaz et al., 2018).

As was the case with OUD and AUD, clinical and preclinical studies suggest that α_1 AR antagonists, α_2 AR agonists, β AR antagonists may be useful for the treatment of psychostimulant use disorder. Data from rodent studies suggests that α_1 AR antagonists may work by blocking postsynaptic NE signaling in the mPFC or VTA. In particular, reducing NE signaling in the LC to mPFC pathway may be important for reducing cocaine-induced reinstatement f cocaine use. Further, blocking LC to VTA noradrenergic inputs may be effective in reducing the rewarding effects of cocaine and other psychostimulants by indirectly modulating NAcc DA signaling. α_2 AR agonists may work by acting presynatpically to reduce NE release in the BNST, which may impact downstream targets, including the VTA. While there is no clinical data investigating the use of β AR antagonists for psychostimulant use disorder, preclinical data in rodents suggests that blocking β_2 ARs in the BNST or CeA may be a useful target.

CONCLUSIONS AND FUTURE DIRECTIONS

The studies discussed in this review clearly demonstrate that NE signaling and circuitry is relevant for multiple misused drugs. NE is important for the rewarding properties of opiates, as demonstrated by alterations in opiate CPP when NE is altered experimentally, and NE is critical for stress-induced reinstatement of opioid seeking and opioid withdrawal. NE is necessary for voluntary consumption of ethanol and stress-induced reinstatement of ethanol seeking. NE is also necessary for psychostimulant CPP and stress-induced reinstatement.

Numerous pharmacological studies have demonstrated that ARs are critical mediators of stress-induced reinstatement of drug consumption and withdrawal from opioids. Further, the recent success of α_1 AR antagonists and α2 AR agonists in clinical trials suggests that preclinical animal studies are translatable to human substance use disorder (clinical trials summarized in Table 1) (Hendrickson and Raskind, 2016; Simpson et al., 2018). While ample clinical and preclinical evidence supports the use of noradrenergic compounds, there are still significant barriers to their clinical use. All of the noradrenergic drugs tested in clinical trials for SUD are also used to reduce blood pressure clinically, and, as such, can produce undesirable side effects associated with a reduction in blood pressure, including fainting, in SUD patients (Kahn et al., 1997; Keaney et al., 2001; Lin et al., 1997). As such, noradrenergic compounds may be more effective in SUD patients with co-occurring hypertension. Further, additional drug discovery efforts are needed to identify

noradrenergic signaling modulators that do not have hypotensive effects. Additionally, sex and pharmacogenetic effects, including polymorphisms in *DBH* and *ADRA1D*, also influence the efficacy of noradrenergic drugs in SUD, and should be considered when evaluating the success or failure of clinical trials (Fox et al., 2014; Shorter et al., 2020; Zhang et al., 2019).

Preclinical animal studies have greatly expanded our understanding of how noradrenergic signaling in specific brain regions including, BNST, VTA, mPFC, and LC, modulates different stages of SUD (summarized in Table 2). However, it is significantly less clear which specific cell types in these brain regions mediate these effects and how connections between these brain regions impact substance use disorders. For example, while β AR antagonist administration into the BLA reduces stress-induced reinstatement of alcohol-seeking behavior it is unclear which specific outputs of the BLA are affected by this treatment (Chesworth and Corbit, 2018). Likewise, while noradrenergic inputs from the LC/A6 to the BLA have been studied extensively, noradrenergic inputs from the A2/NTS have garnered significantly less scrutiny, even though A2/NTS inputs to the BLA are more extensive (Robertson et al., 2013). Furthermore, it is unclear if LC neurons projecting to the prefrontal cortex differ in their response to opioids/opioid withdrawal from the projections to the BLA (Uematsu et al., 2017). Likewise, α_2 AR agonists show great therapeutic promise for opioid use disorder. However, it is not clear which precise input or outputs in the BNST mediate their effects on stress-induced reinstatement of opioid seeking. Accordingly, future studies can use chemogenetic, optogenetic, fluorescent imaging, and other viral approaches to make further advances in our understanding of the precise circuitry that mediates the effects of noradrenergic drugs on substance use disorders.

FUNDING

This work was funded by R01DA049261, U01AA020911–08S1 and U01AA020911 (Z.A.M.) and T32AA007573 (A.M.D.). The authors have no competing interests to declare.

Abbreviations:

NE	norepinephrine
RVLM	rostroventrolateral medulla
NTS	nucleus of the tractus solitaries
LC	locus coeruleus
CeA	central nucleus of the amygdala
DNB	dorsal noradrenergic bundle
BNST	bed nucleus of the stria terminalis
BLA	basolateral amygdala
VNB	ventral noradrenergic bundle

AR	adrenergic receptor
DA	dopamine
SUD	substance use disorder
HPA	hypothalamic-pituitary-adrenal axis
CRF	corticotrophin releasing factor
ACTH	adrenocorticotropic factor
PTSD	post-traumatic stress disorder
VTA	ventral tegmental area
NAcc	nucleus accumbens
SA	self-administration
OUD	opioid use disorder
DBH	dopamine β-hydroxylase
CPP	conditioned place preference
NET	norepinephrine transporter
OR	opioid receptor
CPA	conditioned place aversion
AUD	alcohol use disorder
mPFC	medial prefrontal cortex
OFC	orbitofrontal cortex

LITERATURE CITED

Adermark L, Bowers MS, 2016. Disentangling the Role of Astrocytes in Alcohol Use Disorder. Alcohol Clin Exp Res 40, 1802–16. [PubMed: 27476876]

Adinoff B, 1994. Double-blind study of alprazolam, diazepam, clonidine, and placebo in the alcohol withdrawal syndrome: preliminary findings. Alcohol Clin Exp Res 18, 873–8. [PubMed: 7978098]

Aghajanian GK, 1978. Tolerance of locus coeruleus neurones to morphine and suppression of withdrawal response by clonidine. Nature 276, 186–8. [PubMed: 216919]

Alheid GF, 2003. Extended amygdala and basal forebrain. Ann N Y Acad Sci 985, 185–205. [PubMed: 12724159]

Aston-Jones G, Cohen JD, 2005. An integrative theory of locus coeruleus-norepinephrine function: adaptive gain and optimal performance. Annu Rev Neurosci 28, 403–50. [PubMed: 16022602]

Aston-Jones G, et al. , 1986. The brain nucleus locus coeruleus: restricted afferent control of a broad efferent network. Science 234, 734–737. [PubMed: 3775363]

Aston-Jones G, Harris GC, 2004. Brain substrates for increased drug seeking during protracted withdrawal. Neuropharmacology 47 Suppl 1, 167–79. [PubMed: 15464135]

Auclair A, et al. , 2004. 5-HT2A and alpha1b-adrenergic receptors entirely mediate dopamine release, locomotor response and behavioural sensitization to opiates and psychostimulants. Eur J Neurosci 20, 3073–84. [PubMed: 15579162]

Bailly D, et al. , 1992. Effects of beta-blocking drugs in alcohol withdrawal: a double-blind comparative study with propranolol and diazepam. Biomed Pharmacother 46, 419–24. [PubMed: 1363375]

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]

Bird SJ, Kuhar MJ, 1977. Iontophoretic application of opiates to the locus coeruleus. Brain Res 122, 523–33. [PubMed: 191143]

Bissonette GB, et al. , 2008. Double dissociation of the effects of medial and orbital prefrontal cortical lesions on attentional and affective shifts in mice. J Neurosci 28, 11124–30. [PubMed: 18971455]

Borodovitsyna O, et al. , 2020. Anatomically and functionally distinct locus coeruleus efferents mediate opposing effects on anxiety-like behavior. Neurobiol Stress 13, 100284. [PubMed: 33344735]

Brown ZJ, et al. , 2011. Central injections of noradrenaline induce reinstatement of cocaine seeking and increase c-fos mRNA expression in the extended amygdala. Behav Brain Res 217, 472–6. [PubMed: 20933023]

Buijs RM, Van Eden CG, 2000. The integration of stress by the hypothalamus, amygdala and prefrontal cortex: balance between the autonomic nervous system and the neuroendocrine system. Prog Brain Res 126, 117–32. [PubMed: 11105644]

Burnham NW, Thiele TE, 2017. Voluntary Binge-like Ethanol Consumption Site-specifically Increases c-Fos Immunoexpression in Male C57BL6/J Mice. Neuroscience 367, 159–168. [PubMed: 29111360]

Caillé S, et al. , 1999. Total neurochemical lesion of noradrenergic neurons of the locus ceruleus does not alter either naloxone-precipitated or spontaneous opiate withdrawal nor does it influence ability of clonidine to reverse opiate withdrawal. J Pharmacol Exp Ther 290, 881–92. [PubMed: 10411605]

Campese VD, et al. , 2017. Noradrenergic Regulation of Central Amygdala in Aversive Pavlovian-to-Instrumental Transfer. eneuro 4, ENEURO.0224–17.2017.

Cao JL, et al. , 2010. Essential role of the cAMP-cAMP response-element binding protein pathway in opiate-induced homeostatic adaptations of locus coeruleus neurons. Proc Natl Acad Sci U S A 107, 17011–6. [PubMed: 20837544]

Chesworth R, Corbit LH, 2018. Noradrenergic β-receptor antagonism in the basolateral amygdala impairs reconsolidation, but not extinction, of alcohol self-administration: Intra-BLA propranolol impairs reconsolidation of alcohol self-administration. Neurobiol Learn Mem 151, 59–70. [PubMed: 29649583]

Crestani CC, et al. , 2013. Mechanisms in the bed nucleus of the stria terminalis involved in control of autonomic and neuroendocrine functions: a review. Curr Neuropharmacol 11, 141–59. [PubMed: 23997750]

Davis AR, et al. , 2008. Yohimbine impairs extinction of cocaine-conditioned place preference in an alpha2-adrenergic receptor independent process. Learn Mem 15, 667–76. [PubMed: 18772254]

Davoudi M, et al. , 2016. The blockade of GABAA receptors attenuates the inhibitory effect of orexin type 1 receptors antagonist on morphine withdrawal syndrome in rats. Neurosci Lett 617, 201–6. [PubMed: 26879836]

Delfs JM, et al. , 2000. Noradrenaline in the ventral forebrain is critical for opiate withdrawal-induced aversion. Nature 403, 430–4. [PubMed: 10667795]

Di Chiara G, Imperato A, 1988. Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. Proc Natl Acad Sci U S A 85, 5274–8. [PubMed: 2899326]

Drouin C, et al. , 2002. Alpha1b-adrenergic receptors control locomotor and rewarding effects of psychostimulants and opiates. J Neurosci 22, 2873–84. [PubMed: 11923452]

Enman NM, et al. , 2019. Sex differences in morphine-induced trafficking of mu-opioid and corticotropin-releasing factor receptors in locus coeruleus neurons. Brain Res 1706, 75–85. [PubMed: 30391476]

Erb S, et al. , 2000. Alpha-2 adrenergic receptor agonists block stress-induced reinstatement of cocaine seeking. Neuropsychopharmacology 23, 138–50. [PubMed: 10882840]

Faul M, et al. , 2017. Multiple Naloxone Administrations Among Emergency Medical Service Providers is Increasing. Prehosp Emerg Care 21, 411–419. 10.1080/10903127.2017.1315203 [PubMed: 28481656]

Finnell JE, et al. , 2019. The contribution of the locus coeruleus-norepinephrine system in the emergence of defeat-induced inflammatory priming. Brain Behav Immun 79, 102–113. [PubMed: 30707932]

Fisher JP, et al. , 2009. Central sympathetic overactivity: maladies and mechanisms. Autonomic neuroscience : basic & clinical 148, 5–15. [PubMed: 19268634]

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, 171–83. [PubMed: 24151426]

Flagel SB, et al. , 2016. Genetic background and epigenetic modifications in the core of the nucleus accumbens predict addiction-like behavior in a rat model. Proc Natl Acad Sci U S A 113, E2861–70. [PubMed: 27114539]

Fortier CB, et al. , 2008. Delay discrimination and reversal eyeblink classical conditioning in abstinent chronic alcoholics. Neuropsychology 22, 196–208. [PubMed: 18331162]

Fox HC, et al. , 2012. Prazosin effects on stress- and cue-induced craving and stress response in alcohol-dependent individuals: preliminary findings. Alcohol Clin Exp Res 36, 351–60. [PubMed: 21919922]

Fox HC, et al. , 2014. Sex differences in guanfacine effects on drug craving and stress arousal in cocaine-dependent individuals. Neuropsychopharmacology 39, 1527–37. [PubMed: 24395021]

Fox HC, Sinha R, 2009. Sex differences in drug-related stress-system changes: implications for treatment in substance-abusing women. Harv Rev Psychiatry 17, 103–19. [PubMed: 19373619]

Fox ME, et al. , 2017. Reciprocal Catecholamine Changes during Opiate Exposure and Withdrawal. Neuropsychopharmacology 42, 671–681. [PubMed: 27461081]

Funada M, et al. , 2001. Involvement of corticotropin-releasing factor receptor subtype 1 in morphine withdrawal regulation of the brain noradrenergic system. Eur J Pharmacol 430, 277–81. [PubMed: 11711043]

Funk CK, et al. , 2006. Corticotropin-releasing factor within the central nucleus of the amygdala mediates enhanced ethanol self-administration in withdrawn, ethanol-dependent rats. J Neurosci 26, 11324–32. [PubMed: 17079660]

Ghaemi-Jandabi M, et al. , 2017. Intracoerulear microinjection of orexin-A induces morphine withdrawal-like signs in rats. Brain Res Bull 130, 107–111. [PubMed: 28093335]

Gilpin NW, et al. , 2015. The central amygdala as an integrative hub for anxiety and alcohol use disorders. Biol Psychiatry 77, 859–69. [PubMed: 25433901]

Gilpin NW, Koob GF, 2010. Effects of β-adrenoceptor antagonists on alcohol drinking by alcohol-dependent rats. Psychopharmacology (Berl) 212, 431–9. [PubMed: 20676608]

Gish EC, et al. , 2010. Lofexidine, an {alpha}2-receptor agonist for opioid detoxification. Ann Pharmacother 44, 343–51. [PubMed: 20040696]

Goldstein DS, 1987. Stress-induced activation of the sympathetic nervous system. Baillieres Clin Endocrinol Metab 1, 253–78. [PubMed: 3327494]

Gorodetzky CW, et al. , 2017. A phase III, randomized, multi-center, double blind, placebo controlled study of safety and efficacy of lofexidine for relief of symptoms in individuals undergoing inpatient opioid withdrawal. Drug Alcohol Depend 176, 79–88. [PubMed: 28527421]

Gottlieb LD, et al. , 1994. Randomized controlled trial in alcohol relapse prevention: role of atenolol, alcohol craving, and treatment adherence. J Subst Abuse Treat 11, 253–8. [PubMed: 8072054]

Greenwell TN, et al. , 2009. The alpha1 adrenergic receptor antagonist prazosin reduces heroin self-administration in rats with extended access to heroin administration. Pharmacol Biochem Behav 91, 295–302. [PubMed: 18703080]

Haass-Koffler CL, et al. , 2017. Higher pretreatment blood pressure is associated with greater alcohol drinking reduction in alcohol-dependent individuals treated with doxazosin. Drug Alcohol Depend 177, 23–28. [PubMed: 28551590]

Hamlin AS, et al. , 2004. Effect of naloxone-precipitated morphine withdrawal on c-fos expression in rat corticotropin-releasing hormone neurons in the paraventricular hypothalamus and extended amygdala. Neurosci Lett 362, 39–43. [PubMed: 15147776]

Han MH, et al. , 2006. Role of cAMP response element-binding protein in the rat locus ceruleus: regulation of neuronal activity and opiate withdrawal behaviors. J Neurosci 26, 4624–9. [PubMed: 16641242]

Harris GC, Aston-Jones G, 2007. Activation in extended amygdala corresponds to altered hedonic processing during protracted morphine withdrawal. Behav Brain Res 176, 251–8. [PubMed: 17123639]

Hawley RJ, et al. , 1981. CSF levels of norepinephrine during alcohol withdrawal. Arch Neurol 38, 289–92. [PubMed: 7224914]

Hayward MD, et al. , 1990. Induction of the c-fos proto-oncogene during opiate withdrawal in the locus coeruleus and other regions of rat brain. Brain Res 525, 256–66. [PubMed: 1701330]

Hedges DM, et al. , 2020. Corticotropin releasing factor, but not alcohol, modulates norepinephrine release in the rat central nucleus of the amygdala. Neuropharmacology 179, 108293. [PubMed: 32871155]

Hendrickson RC, Raskind MA, 2016. Noradrenergic dysregulation in the pathophysiology of PTSD. Exp Neurol 284, 181–195. [PubMed: 27222130]

Herkenham M, Nauta WJ, 1979. Efferent connections of the habenular nuclei in the rat. J Comp Neurol 187, 19–47. [PubMed: 226566]

Herman JP, et al. , 2016. Regulation of the Hypothalamic-Pituitary-Adrenocortical Stress Response. Compr Physiol 6, 603–21. [PubMed: 27065163]

Horwitz RI, et al. , 1989. The efficacy of atenolol in the outpatient management of the alcohol withdrawal syndrome. Results of a randomized clinical trial. Arch Intern Med 149, 1089–93. [PubMed: 2719503]

Ivanov A, Aston-Jones G, 2001. Local opiate withdrawal in locus coeruleus neurons in vitro. J Neurophysiol 85, 2388–97. [PubMed: 11387385]

Jadzic D, et al. , 2021. Nicotine, cocaine, amphetamine, morphine, and ethanol increase norepinephrine output in the bed nucleus of stria terminalis of freely moving rats. Addict Biol 26, e12864. [PubMed: 31849152]

Jaime S, et al. , 2020. Intravenous Ethanol Administration and Operant Self-Administration Alter Extracellular Norepinephrine Concentration in the Mesocorticolimbic Systems of Male Long Evans Rats. Alcohol Clin Exp Res 44, 1529–1539. [PubMed: 32573991]

Jennings JH, et al. , 2013. Distinct extended amygdala circuits for divergent motivational states. Nature 496, 224–8. [PubMed: 23515155]

Jodo E, Aston-Jones G, 1997. Activation of locus coeruleus by prefrontal cortex is mediated by excitatory amino acid inputs. Brain Res 768, 327–32. [PubMed: 9369332]

Kahn A, et al. , 1997. Double-blind study of lofexidine and clonidine in the detoxification of opiate addicts in hospital. Drug Alcohol Depend 44, 57–61. [PubMed: 9031821]

Kalivas PW, Duffy P, 1995. Selective activation of dopamine transmission in the shell of the nucleus accumbens by stress. Brain Res 675, 325–8. [PubMed: 7796146]

Keaney F, et al. , 2001. A double-blind randomized placebo-controlled trial of lofexidine in alcohol withdrawal: lofexidine is not a useful adjunct to chlordiazepoxide. Alcohol Alcohol 36, 426–30. [PubMed: 11524309]

Khoury D, et al. , 2021. Increases in Naloxone Administrations by Emergency Medical Services Providers During the COVID-19 Pandemic: Retrospective Time Series Study. JMIR Public Health Surveill 7, e29298. [PubMed: 33999828]

Kogan JH, et al. , 1992. Elevated basal firing rates and enhanced responses to 8-Br-cAMP in locus coeruleus neurons in brain slices from opiate-dependent rats. Eur J Pharmacol 211, 47–53. [PubMed: 1618268]

Köhnke MD, et al. , 2006. DBH*444G/A polymorphism of the dopamine-beta-hydroxylase gene is associated with alcoholism but not with severe alcohol withdrawal symptoms. J Neural Transm (Vienna) 113, 869–76. [PubMed: 16252068]

Köhnke MD, et al. , 2002. A genotype-controlled analysis of plasma dopamine beta-hydroxylase in healthy and alcoholic subjects: evidence for alcohol-related differences in noradrenergic function. Biol Psychiatry 52, 1151–8. [PubMed: 12488060]

Koob GF, 1999. Corticotropin-releasing factor, norepinephrine, and stress. Biol Psychiatry 46, 1167–80. [PubMed: 10560023]

Koob GF, 2009. Brain stress systems in the amygdala and addiction. Brain Res 1293, 61–75. [PubMed: 19332030]

Koob GF, 2015. The dark side of emotion: the addiction perspective. Eur J Pharmacol 753, 73–87. [PubMed: 25583178]

Koob GF, Le Moal M, 1997. Drug abuse: hedonic homeostatic dysregulation. Science 278, 52–8. [PubMed: 9311926]

Koob GF, Le Moal M, 2008. Addiction and the brain antireward system. Annu Rev Psychol 59, 29–53. [PubMed: 18154498]

Korf J, et al. , 1974. Noradrenergic neurons: morphine inhibition of spontaneous activity. Eur J Pharmacol 25, 165–9. [PubMed: 4435020]

Kovács GL, et al. , 2002. Plasma catecholamines in ethanol tolerance and withdrawal in mice. Eur J Pharmacol 448, 151–6. [PubMed: 12144935]

Lasheras MC, et al. , 2015. Corticotropin-releasing factor 1 receptor mediates the activity of the reward system evoked by morphine-induced conditioned place preference. Neuropharmacology 95, 168–80. [PubMed: 25556110]

Lê AD, et al. , 2005. Role of alpha-2 adrenoceptors in stress-induced reinstatement of alcohol seeking and alcohol self-administration in rats. Psychopharmacology (Berl) 179, 366–73. [PubMed: 15551068]

Lebow MA, Chen A, 2016. Overshadowed by the amygdala: the bed nucleus of the stria terminalis emerges as key to psychiatric disorders. Mol Psychiatry 21, 450–63. [PubMed: 26878891]

Leri F, et al. , 2002. Blockade of stress-induced but not cocaine-induced reinstatement by infusion of noradrenergic antagonists into the bed nucleus of the stria terminalis or the central nucleus of the amygdala. J Neurosci 22, 5713–8. [PubMed: 12097523]

Li X, et al. , 2015. The central amygdala nucleus is critical for incubation of methamphetamine craving. Neuropsychopharmacology 40, 1297–306. [PubMed: 25475163]

Lin SK, et al. , 1997. Double-blind randomised controlled trial of lofexidine versus clonidine in the treatment of heroin withdrawal. Drug Alcohol Depend 48, 127–33. [PubMed: 9363412]

Mabrouk OS, et al. , 2018. The in Vivo Neurochemical Profile of Selectively Bred High-Responder and Low-Responder Rats Reveals Baseline, Cocaine-Evoked, and Novelty-Evoked Differences in Monoaminergic Systems. ACS Chem Neurosci 9, 715–724. [PubMed: 29161023]

Macey DJ, et al. , 2003. Chronic cocaine self-administration upregulates the norepinephrine transporter and alters functional activity in the bed nucleus of the stria terminalis of the rhesus monkey. The Journal of neuroscience : the official journal of the Society for Neuroscience 23, 12–16. [PubMed: 12514195]

Mantsch JR, et al. , 2016. Stress-Induced Reinstatement of Drug Seeking: 20 Years of Progress. Neuropsychopharmacology 41, 335–356. [PubMed: 25976297]

Mazei-Robison MS, Nestler EJ, 2012. Opiate-induced molecular and cellular plasticity of ventral tegmental area and locus coeruleus catecholamine neurons. Cold Spring Harb Perspect Med 2, a012070. [PubMed: 22762025]

McCall JG, et al. , 2015. CRH Engagement of the Locus Coeruleus Noradrenergic System Mediates Stress-Induced Anxiety. Neuron 87, 605–20. [PubMed: 26212712]

McElligott ZA, et al. , 2013. Noradrenergic synaptic function in the bed nucleus of the stria terminalis varies in animal models of anxiety and addiction. Neuropsychopharmacology 38, 1665–73. [PubMed: 23467277]

McReynolds JR, et al. , 2014. Beta-2 adrenergic receptors mediate stress-evoked reinstatement of cocaine-induced conditioned place preference and increases in CRF mRNA in the bed nucleus of the stria terminalis in mice. Psychopharmacology (Berl) 231, 3953–63. [PubMed: 24696080]

Milivojevic V, et al. , 2020. Effects of Prazosin on Provoked Alcohol Craving and Autonomic and Neuroendocrine Response to Stress in Alcohol Use Disorder. Alcohol Clin Exp Res 44, 1488–1496. [PubMed: 32449942]

Moore RY, Bloom FE, 1979. Central catecholamine neuron systems: anatomy and physiology of the norepinephrine and epinephrine systems. Annu Rev Neurosci 2, 113–68. [PubMed: 231924]

Nimitvilai S, et al. , 2017. Ethanol Dependence Abolishes Monoamine and GIRK (Kir3) Channel Inhibition of Orbitofrontal Cortex Excitability. Neuropsychopharmacology 42, 1800–1812. [PubMed: 28139680]

Olson VG, et al. , 2006. Role of noradrenergic signaling by the nucleus tractus solitarius in mediating opiate reward. Science 311, 1017–20. [PubMed: 16484499]

Patkar AA, et al. , 2003. Changes in plasma noradrenaline and serotonin levels and craving during alcohol withdrawal. Alcohol Alcohol 38, 224–31. [PubMed: 12711656]

Patkar OL, et al. , 2019. Modulation of serotonin and noradrenaline in the BLA by pindolol reduces long-term ethanol intake. Addict Biol 24, 652–663. [PubMed: 30022582]

Patkar OL, et al. , 2017. The antihypertensive drug pindolol attenuates long-term but not short-term binge-like ethanol consumption in mice. Addict Biol 22, 679–691. [PubMed: 27273539]

Perez RE, et al. , 2020. α(2A)-adrenergic heteroreceptors are required for stress-induced reinstatement of cocaine conditioned place preference. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology 45, 1473–1481. [PubMed: 32074627]

Pergolizzi JV Jr., et al. , 2019. The Role of Lofexidine in Management of Opioid Withdrawal. Pain Ther 8, 67–78. [PubMed: 30565033]

Piazza PV, Le Moal ML, 1996. Pathophysiological basis of vulnerability to drug abuse: role of an interaction between stress, glucocorticoids, and dopaminergic neurons. Annu Rev Pharmacol Toxicol 36, 359–78. [PubMed: 8725394]

Pina MM, et al. , 2015. The bed nucleus of the stria terminalis regulates ethanol-seeking behavior in mice. Neuropharmacology 99, 627–38. [PubMed: 26302652]

Raskind MA, Peskind ER, Chow B, Harris C, Davis-Karim A, Holmes HA, Hart KL, McFall M, Mellman TA, Reist C, Romesser J, Rosenheck R, Shih M-C, Stein MB, Swift R, Gleason T, Lu Y, Huang GD, 2018. Trial of Prazosin for Post-Traumatic Stress Disorder in Military Veterans. N Engl J Med 378, 507–517. 10.1056/NEJMoa1507598 [PubMed: 29414272]

Raskind MA, et al. , 2003. Reduction of nightmares and other PTSD symptoms in combat veterans by prazosin: a placebo-controlled study. Am J Psychiatry 160, 371–373. [PubMed: 12562588]

Raskind MA, et al. , 2013. A trial of prazosin for combat trauma PTSD with nightmares in active-duty soldiers returned from Iraq and Afghanistan. Am J Psychiatry 170, 1003–1010. [PubMed: 23846759]

Rasmussen DD, et al. , 2014. The α2-adrenergic receptor agonist, clonidine, reduces alcohol drinking in alcohol-preferring (P) rats. Alcohol 48, 543–9. [PubMed: 25085719]

Rasmussen K, et al. , 1990. Opiate withdrawal and the rat locus coeruleus: behavioral, electrophysiological, and biochemical correlates. J Neurosci 10, 2308–17. [PubMed: 2115910]

Reyes BA, et al. , 2011. Amygdalar peptidergic circuits regulating noradrenergic locus coeruleus neurons: linking limbic and arousal centers. Exp Neurol 230, 96–105. [PubMed: 21515261]

Rinaman L, 2011. Hindbrain noradrenergic A2 neurons: diverse roles in autonomic, endocrine, cognitive, and behavioral functions. Am J Physiol Regul Integr Comp Physiol 300, R222–35. [PubMed: 20962208]

Roberts DC, et al. , 1977. On the role of ascending catecholaminergic systems in intravenous self-administration of cocaine. Pharmacol Biochem Behav 6, 615–20. [PubMed: 122445]

Robertson SD, et al. , 2013. Developmental origins of central norepinephrine neuron diversity. Nat Neurosci 16, 1016–23. [PubMed: 23852112]

Roesch MR, Olson CR, 2007. Neuronal activity related to anticipated reward in frontal cortex: does it represent value or reflect motivation? Ann N Y Acad Sci 1121, 431–46. [PubMed: 17846160]

Saal D, et al. , 2003. Drugs of abuse and stress trigger a common synaptic adaptation in dopamine neurons. Neuron 37, 577–82. [PubMed: 12597856]

Salomon L, et al. , 2006. Behavioral sensitization to amphetamine results from an uncoupling between noradrenergic and serotonergic neurons. Proc Natl Acad Sci U S A 103, 7476–81. [PubMed: 16648258]

Sara SJ, Bouret S, 2012. Orienting and reorienting: the locus coeruleus mediates cognition through arousal. Neuron 76, 130–41. [PubMed: 23040811]

Sartor GC, Aston-Jones G, 2012. Regulation of the ventral tegmental area by the bed nucleus of the stria terminalis is required for expression of cocaine preference. Eur J Neurosci 36, 3549–58. [PubMed: 23039920]

Schank JR, et al. , 2006. Dopamine beta-hydroxylase knockout mice have alterations in dopamine signaling and are hypersensitive to cocaine. Neuropsychopharmacology 31, 2221–30. [PubMed: 16395294]

Schmidt KT, et al. , 2017. Norepinephrine regulates cocaine-primed reinstatement via α1-adrenergic receptors in the medial prefrontal cortex. Neuropharmacology 119, 134–140. [PubMed: 28392265]

Schmidt KT, et al. , 2019. Stress-Induced Alterations of Norepinephrine Release in the Bed Nucleus of the Stria Terminalis of Mice. ACS Chem Neurosci 10, 1908–1914. [PubMed: 30252438]

Schoenbaum G, et al. , 1998. Orbitofrontal cortex and basolateral amygdala encode expected outcomes during learning. Nat Neurosci 1, 155–9. [PubMed: 10195132]

Schroeder JP, et al. , 2013. The selective dopamine β-hydroxylase inhibitor nepicastat attenuates multiple aspects of cocaine-seeking behavior. Neuropsychopharmacology 38, 1032–8. [PubMed: 23303068]

Shackman AJ, Fox AS, 2016. Contributions of the Central Extended Amygdala to Fear and Anxiety. J Neurosci 36, 8050–63. [PubMed: 27488625]

Shaham Y, et al. , 2000. Clonidine blocks stress-induced reinstatement of heroin seeking in rats: an effect independent of locus coeruleus noradrenergic neurons. Eur J Neurosci 12, 292–302. [PubMed: 10651884]

Shelkar GP, et al. , 2017. Noradrenergic inputs from locus coeruleus to posterior ventral tegmental area are essential to support ethanol reinforcement. Addict Biol 22, 291–302. [PubMed: 26549324]

Shields AD, et al. , 2009. alpha2A-adrenergic receptors heterosynaptically regulate glutamatergic transmission in the bed nucleus of the stria terminalis. Neuroscience 163, 339–51. [PubMed: 19527774]

Shinohara F, et al. , 2020. Noradrenaline enhances the excitatory effects of dopamine on medial prefrontal cortex pyramidal neurons in rats. Neuropsychopharmacol Rep 40, 348–354. [PubMed: 32897002]

Shinohara F, et al. , 2019. Stress augments the rewarding memory of cocaine via the activation of brainstem-reward circuitry. Addict Biol 24, 509–521. [PubMed: 29480583]

Shorter D, et al. , 2013. The alpha-1 adrenergic antagonist doxazosin for treatment of cocaine dependence: A pilot study. Drug Alcohol Depend 131, 66–70. [PubMed: 23306096]

Shorter DI, et al. , 2020. Doxazosin treatment in cocaine use disorder: pharmacogenetic response based on an alpha-1 adrenoreceptor subtype D genetic variant. Am J Drug Alcohol Abuse 46, 184–193. [PubMed: 31914324]

Simpson TL, et al. , 2015. A pilot trial of prazosin, an alpha-1 adrenergic antagonist, for comorbid alcohol dependence and posttraumatic stress disorder. Alcohol Clin Exp Res 39, 808–17. [PubMed: 25827659]

Simpson TL, et al. , 2018. Double-Blind Randomized Clinical Trial of Prazosin for Alcohol Use Disorder. Am J Psychiatry 175, 1216–1224. [PubMed: 30153753]

Sinha R, 2008. Chronic stress, drug use, and vulnerability to addiction. Ann N Y Acad Sci 1141, 105–30. [PubMed: 18991954]

Sinha R, et al. , 2003. Hypothalamic-pituitary-adrenal axis and sympatho-adreno-medullary responses during stress-induced and drug cue-induced cocaine craving states. Psychopharmacology (Berl) 170, 62–72. [PubMed: 12845411]

Sinha R, et al. , 2021. Moderation of Prazosin's Efficacy by Alcohol Withdrawal Symptoms. Am J Psychiatry 178, 447–458. [PubMed: 33207935]

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, 468–83. [PubMed: 25161814]

Skjoldager P, et al. , 1993. Effects of GBR 12909 and cocaine on cocaine-maintained behavior in rhesus monkeys. Drug Alcohol Depend 33, 31–9. [PubMed: 8370338]

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]

Snyder K, et al. , 2012. Corticotropin-releasing factor in the norepinephrine nucleus, locus coeruleus, facilitates behavioral flexibility. Neuropsychopharmacology 37, 520–30. [PubMed: 21993205]

Solecki W, et al. , 2013. Differential role of ventral tegmental area acetylcholine and N-methyl-d-aspartate receptors in cocaine-seeking. Neuropharmacology 75, 9–18. [PubMed: 23850572]

Solecki WB, et al. , 2019a. Alpha(1)-adrenergic receptor blockade in the ventral tegmental area modulates conditional stimulus-induced cocaine seeking. Neuropharmacology 158, 107680. [PubMed: 31247269]

Solecki WB, et al. , 2019b. Noradrenergic and corticosteroid receptors regulate somatic and motivational symptoms of morphine withdrawal. Behav Brain Res 360, 146–157. [PubMed: 30500430]

Stuber GD, et al. , 2005. Extinction of Cocaine Self-Administration Reveals Functionally and Temporally Distinct Dopaminergic Signals in the Nucleus Accumbens. Neuron 46, 661–669. [PubMed: 15944133]

Su J, et al. , 2015. Injection of corticotropin-releasing hormone into the amygdala aggravates visceral nociception and induces noradrenaline release in rats. Neurogastroenterology & Motility 27, 30–39. [PubMed: 25359531]

Thiele TE, et al. , 2000. Ethanol-induced c-fos expression in catecholamine- and neuropeptide Y-producing neurons in rat brainstem. Alcohol Clin Exp Res 24, 802–9. [PubMed: 10888068]

Thierry AM, et al. , 1976. Selective activation of mesocortical DA system by stress. Nature 263, 242–4. [PubMed: 958479]

Torrecilla M, et al. , 2008. Pre- and postsynaptic regulation of locus coeruleus neurons after chronic morphine treatment: a study of GIRK-knockout mice. Eur J Neurosci 28, 618–24. [PubMed: 18702733]

Tovar-Díaz J, et al. , 2018. Cooperative CRF and α1 Adrenergic Signaling in the VTA Promotes NMDA Plasticity and Drives Social Stress Enhancement of Cocaine Conditioning. Cell Rep 22, 2756–2766. [PubMed: 29514102]

Uematsu A, et al. , 2017. Modular organization of the brainstem noradrenaline system coordinates opposing learning states. Nat Neurosci 20, 1602–1611. [PubMed: 28920933]

Valentino RJ, Wehby RG, 1988. Morphine effects on locus ceruleus neurons are dependent on the state of arousal and availability of external stimuli: studies in anesthetized and unanesthetized rats. J Pharmacol Exp Ther 244, 1178–86. [PubMed: 3252031]

Venniro M, et al. , 2020. Abstinence-dependent dissociable central amygdala microcircuits control drug craving. Proc Natl Acad Sci U S A 117, 8126–8134. [PubMed: 32205443]

Ventura R, et al. , 2003. Norepinephrine in the prefrontal cortex is critical for amphetamine-induced reward and mesoaccumbens dopamine release. J Neurosci 23, 1879–85. [PubMed: 12629192]

Verdejo-García A, et al. , 2006. Executive dysfunction in substance dependent individuals during drug use and abstinence: an examination of the behavioral, cognitive and emotional correlates of addiction. J Int Neuropsychol Soc 12, 405–15. [PubMed: 16903133]

Villégier AS, et al. , 2003. Stimulation of postsynaptic alpha1b- and alpha2-adrenergic receptors amplifies dopamine-mediated locomotor activity in both rats and mice. Synapse 50, 277–84. [PubMed: 14556232]

Volkow ND, et al. , 2007. Dopamine in drug abuse and addiction: results of imaging studies and treatment implications. Arch Neurol 64, 1575–9. [PubMed: 17998440]

Vranjkovic O, et al. , 2014. Stress-induced cocaine seeking requires a beta-2 adrenergic receptor-regulated pathway from the ventral bed nucleus of the stria terminalis that regulates CRF actions in the ventral tegmental area. J Neurosci 34, 12504–14. [PubMed: 25209288]

Vranjkovic O, et al. , 2017. The bed nucleus of the stria terminalis in drug-associated behavior and affect: A circuit-based perspective. Neuropharmacology 122, 100–106. [PubMed: 28351600]

Wada S, et al. , 2020. Acute restraint stress augments the rewarding memory of cocaine through activation of α(1) adrenoceptors in the medial prefrontal cortex of mice. Neuropharmacology 166, 107968. [PubMed: 32035731]

Walker BM, et al. , 2008. alpha1-noradrenergic receptor antagonism blocks dependence-induced increases in responding for ethanol. Alcohol 42, 91–7. [PubMed: 18358987]

Wang J, et al. , 2006. Region-specific effects of brain corticotropin-releasing factor receptor type 1 blockade on footshock-stress- or drug-priming-induced reinstatement of morphine conditioned place preference in rats. Psychopharmacology (Berl) 185, 19–28. [PubMed: 16374599]

Wang X, et al. , 2001. Noradrenaline in the bed nucleus of the stria terminalis is critical for stress-induced reactivation of morphine-conditioned place preference in rats. Eur J Pharmacol 432, 153–61. [PubMed: 11740951]

Wee S, et al. , 2006. Role of the increased noradrenergic neurotransmission in drug self-administration. Drug Alcohol Depend 82, 151–7. [PubMed: 16213110]

Weinshenker D, et al. , 2002. Mice with chronic norepinephrine deficiency resemble amphetamine-sensitized animals. Proc Natl Acad Sci U S A 99, 13873–7. [PubMed: 12370425]

Weinshenker D, et al. , 2000. Ethanol-associated behaviors of mice lacking norepinephrine. J Neurosci 20, 3157–64. [PubMed: 10777779]

Weinshenker D, Schroeder JP, 2007. There and back again: a tale of norepinephrine and drug addiction. Neuropsychopharmacology 32, 1433–51. [PubMed: 17164822]

Wellman P, et al. , 2002. Cocaine-induced hypophagia and hyperlocomotion in rats are attenuated by prazosin. Eur J Pharmacol 455, 117–26. [PubMed: 12445577]

Woolverton WL, 1987. Evaluation of the role of norepinephrine in the reinforcing effects of psychomotor stimulants in rhesus monkeys. Pharmacol Biochem Behav 26, 835–9. [PubMed: 3496618]

Xu F, et al. , 2000. Mice lacking the norepinephrine transporter are supersensitive to psychostimulants. Nat Neurosci 3, 465–71. [PubMed: 10769386]

Xu GP, et al. , 2004. Chronic morphine sensitizes the brain norepinephrine system to corticotropin-releasing factor and stress. J Neurosci 24, 8193–7. [PubMed: 15385601]

Ye L, et al. , 2020. Ethanol abolishes vigilance-dependent astroglia network activation in mice by inhibiting norepinephrine release. Nat Commun 11, 6157. [PubMed: 33268792]

Yokel RA, Wise RA, 1975. Increased lever pressing for amphetamine after pimozide in rats: implications for a dopamine theory of reward. Science 187, 547–9. [PubMed: 1114313]

Yokel RA, Wise RA, 1976. Attenuation of intravenous amphetamine reinforcement by central dopamine blockade in rats. Psychopharmacology (Berl) 48, 311–8. [PubMed: 823588]

Yu E, et al. , 2008. A Phase 3 placebo-controlled, double-blind, multi-site trial of the alpha-2-adrenergic agonist, lofexidine, for opioid withdrawal. Drug Alcohol Depend 97, 158–68. [PubMed: 18508207]

Zhang X, et al. , 2019. Pharmacogenetics of Dopamine β-Hydroxylase in cocaine dependence therapy with doxazosin. Addict Biol 24, 531–538. [PubMed: 29498170]

Highlights

- Anatomical and pharmacological discussion of the noradrenergic system and circuits.
- Discussion of the role of various components of the noradrenergic system in models of opioid, alcohol, and psychostimulant use disorders.
- Discussion of the clinical studies that have targeted noradrenergic receptors and systems to alleviate substance use disorders.

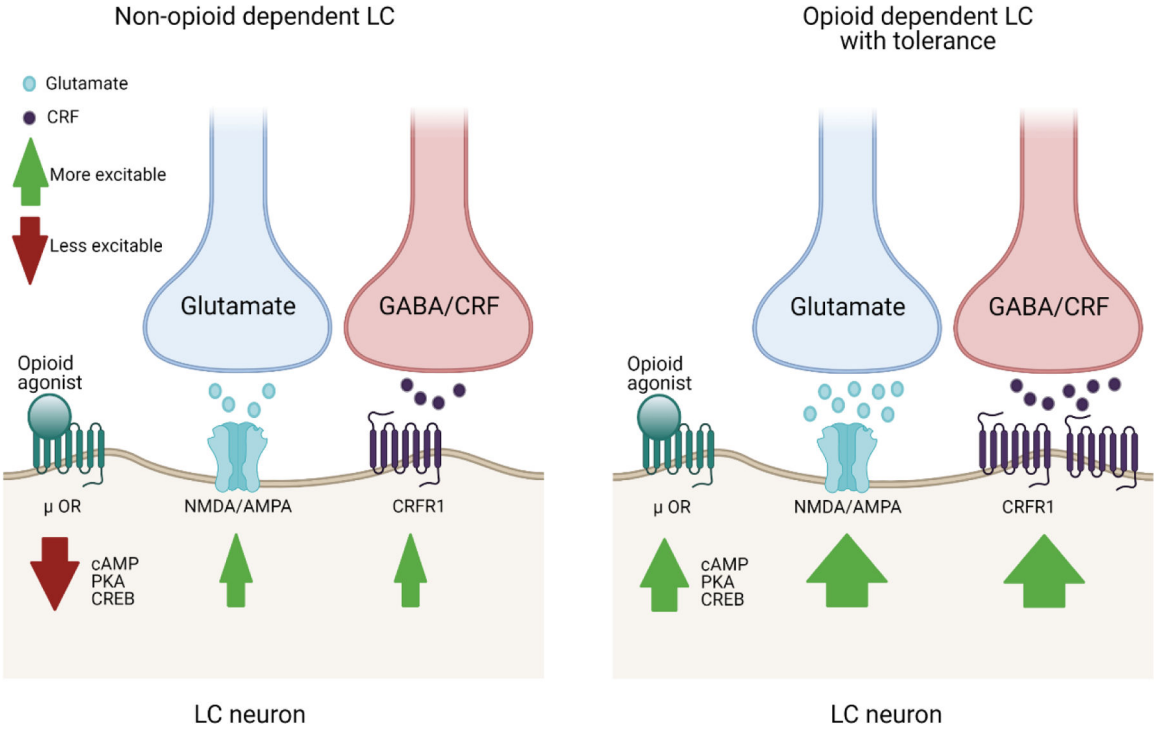

Fig 1.

Plasticity in LC neuron following opioid dependence and tolerance. In the non-opioid dependent LC, activation of μ ORs normally decreases cAMP/PKA signaling and depresses LC excitability. The LC also receives glutamatergic input from the paragigantocellularis nucleus, lateral habenula, and prefrontal cortex and GABA/CRF input from the CeA. Under normal conditions, glutamatergic and CRF inputs enhance LC neuron activity. In the opioid dependent LC, the valence of μ OR activity changes, whereby activation of μ ORs enhances cAMP/PKA and CREB signaling. Glutamatergic inputs to the LC are also enhanced and drive increased LC excitability. There is also an increase in CRFR1 receptors which may potentiate the activity on CRF on LC excitability.

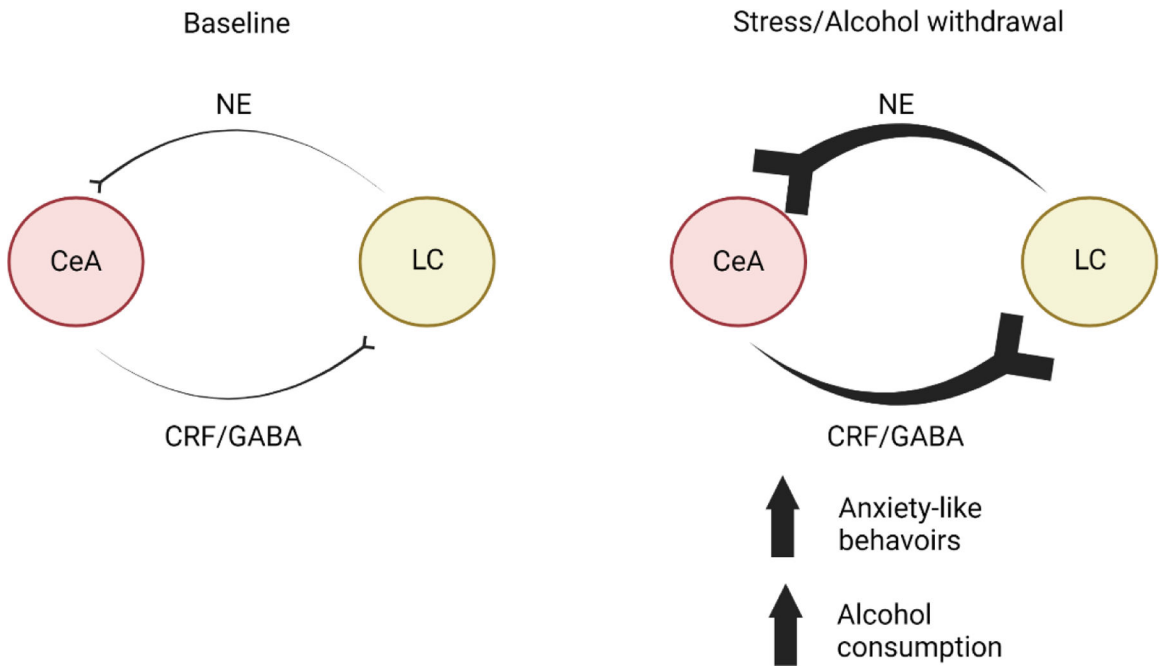

Figure 2.

LC and CeA circuitry in stress and alcohol use disorder. The LC sends noradrenergic projections to the CeA, while the CeA sends GABAergic and CRF-positive projections to the LC. During stress or alcohol withdrawal, LC activity increases and sends enhanced noradrenergic input to the CeA. This in turn increases GABA/CRF neuron activity in the CeA resulting in a feedforward-loop causing enhanced LC and CeA activity in stress and alcohol withdrawal. This enhanced activity contributes to an increase in both anxiety-like behaviors and alcohol consumption in rodents.

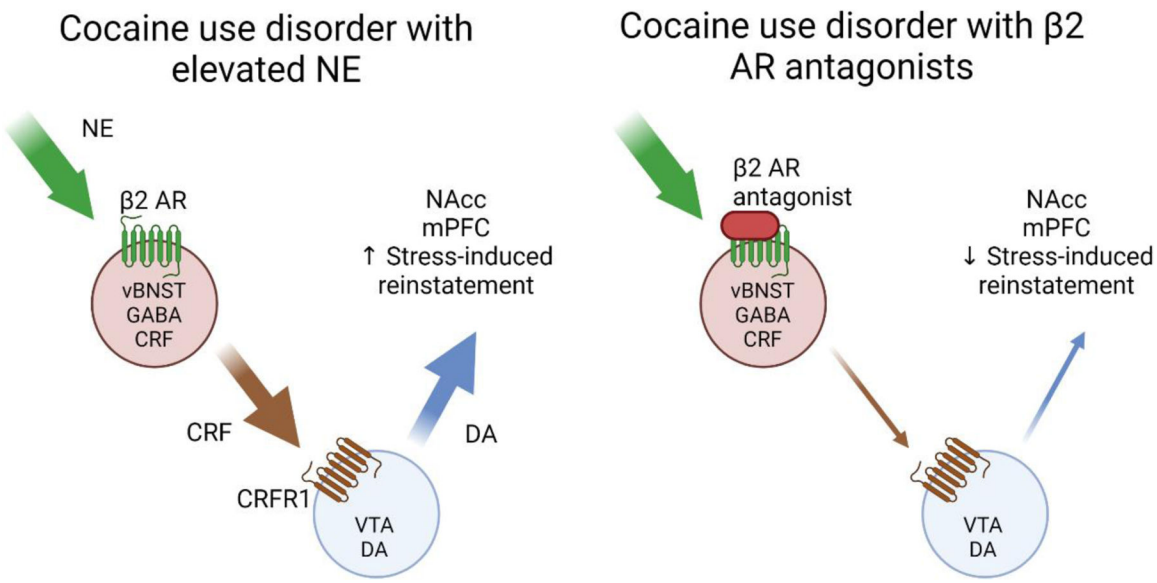

Figure 3.

vBNST to VTA circuitry in cocaine use disorder. In CUD, noradrenergic innervation of the vBNST is increased, which leads to increased activity of CRF-expressing GABAergic BNST neurons via activation of β_2 ARs. These BNST neurons project to the VTA and release elevated amounts of CRF. CRFR1 is activated which stimulates dopaminergic VTA neurons and results in increased DA release in the NAcc and mPFC which contributes to stress-induced reinstatement. This pathway is inhibited following β_2 AR antagonist treatment. CRF innervation from the vBNST to VTA is inhibited which decreases dopaminergic VTA neuron activity. This ultimately results in reduced DA release in the NAcc and mPFC and opposes stress-induced reinstatement of cocaine seeking.

Table 1.

Clinical trials of noradrenergic drugs in SUD

Substance use disorder studied	Type of study	Number of subjects	Compound tested	Outcome	Reference
Opioid Use Disorder	Double-blind trial	28	Lofexidine Clonidine	Decreased self-reported withdrawal symptoms with both compounds. Fewer adverse hypotensive events with lofexidine.	(Kahn et al., 1997)
	Double-blind randomized trial	80	Lofexidine Clonidine	Equal decrease in withdrawal symptoms for clonidine & lofexidine. Fewer hypotensive effects with lofexidine with better treatment retention	(Lin et al., 1997)
	Randomized multi-center double-blind placebo-controlled trial	264	Lofexidine	Significant decrease in withdrawal scoring in lofexidine vs placebo. Improved treatment retention in lofexidine vs placebo	(Gorodetzky et al., 2017)
	Randomized multi-center double-blind placebo-controlled trial	68	Lofexidine	Significant decrease in withdrawal scoring in lofexidine vs placebo. Improved treatment retention in lofexidine vs placebo	(Yu et al., 2008)
Alcohol Use Disorder	Double-blind randomized Placebo controlled trial	180	Atenolol	Reduced percentage of treatment failure and alcohol cravings in patients that received atenolol versus placebo.	(Horwitz et al., 1989)
	Double-blind randomized placebo-controlled trial	120	Atenolol	Reduced withdrawal symptoms, alcohol cravings, and treatment failure in patients that received atenolol versus placebo.	(Gottlieb et al., 1994)
	Double-blind comparative trial	28	Propranolol	Propranolol and diazepam were equally effective in diminishing alcohol withdrawal symptoms And anxiety	(Bailly et al., 1992)
	Double-blind randomized placebo-controlled trial	72	Chlordiazepoxide + lofexidine	Chlordiazepoxide + lofexidine group had significantly worse withdrawal symptoms, more adverse hypotensive effects, and similar treatment retention compared to chlordiazepoxide alone	(Keaney et al., 2001)
	Double-blind randomized Placebo-controlled trial	30 (AUD + PTSD)	Prazosin	Prazosin had fewer drinking days and fewer heavy drinking days per week than placebo. No effect on PTSD symptoms.	(Simpson et al., 2015)
	Double-blind randomized placebo-controlled trial	92	Prazosin	Prazosin had a decrease in number of drinks and heavy drinking days over the 12-week course of treatment than placebo. Moderate drowsiness in prazosin group.	(Simpson et al., 2018)
	Double-blind randomized placebo-controlled trial	100	Prazosin	Individuals with severe withdrawal symptoms had a significant reduction in drinking days, heavy drinking days, and drinks per week after prazosin treatment. Individuals with low or no withdrawal symptoms had no benefit from prazosin.	(Sinha et al., 2021)
	Double-blind randomized placebo-controlled trial	25	Clonidine vs diazepam or alprazolam	Prazosin did not significantly improve withdrawal symptoms versus placebo. Both benzodiazepines significantly improved withdrawal symptoms.	(Adinoff, 1994)
	Double-blind randomized placebo-controlled trial	40	Prazosin	Prazosin reduced stress cue-induced alcohol craving, alcohol cue-induced anxiety, basal cortisol, and cue-induced increases in cortisol versus placebo.	(Milivojevic et al., 2020)
	Double-blind randomized placebo-controlled trial	41	Doxazosin	Doxazosin reduced alcohol consumption and heavy drinking days versus placebo. Doxazosin was most effective in individuals with high blood pressure.	(Haass-Koffler et al., 2017)

Substance use disorder studied	Type of study	Number of subjects	Compound tested	Outcome	Reference
Cocaine Use Disorder	Double-blind randomized placebo-controlled trial	40	Guanfacine	Guanfacine significantly decreased cocaine cravings and negative emotions in response to a drug cue in females but had no effect in males.	(Fox et al., 2014)
	Double-blind randomized placebo-controlled trial	35	Doxazosin	Doxazosin significantly increased the number of drug free days versus placebo.	(Shorter et al., 2013)
	Double-blind randomized placebo-controlled trial	76	Doxazosin	Doxazosin was less effective in individuals with the (*T1848A*) variant in the *ADRA1D* gene.	(Shorter et al., 2020)
	Double-blind randomized placebo-controlled trial	76	Doxazosin	Doxazosin was more effective in patients with lower noradrenergic tone caused by the (*C1021T*) variant in the *DBH* gene	(Zhang et al., 2019)

Table 2.

Summary of animal studies examining noradrenergic system in SUD

Substance Use Disorder Type	Model	Brain region(s) targeted	Manipulation/ drug used	Consumption	CPP	Stress-induced reinstatement	Drug cue-induced reinstatement	Withdrawal	Reference
Opioid Use Disorder	Mouse	Global	*DBH KO*	n/a	↓	n/a	n/a	n/a	(Olson et al., 2006)
	Mouse	Global	*ADRA1A KO*	n/a	↓	n/a	n/a	n/a	(Drouin et al., 2002)
	Mouse	A2/NTS	Restoration DBH expression in *DBH KO* mouse	n/a	↑	n/a	n/a	n/a	(Olson et al., 2006)
	Rat	VNB	Lesion	n/a	n/a	↓	n/a	n/a	(Wang et al., 2001)
	Rat	BNST	Clonidine	n/a	n/a	↓	n/a	n/a	(Wang et al., 2001)
	Rat	DNB	Lesion	n/a	n/a	–	n/a	n/a	(Wang et al., 2001)
	Rat	LC	Clonidine	n/a	n/a	–	n/a	n/a	(Shaham et al., 2000)
	Rat	Global	Idazoxan following morphine naloxone	n/a	n/a	n/a	n/a	↑	(Fox et al., 2017)
	Rat	LC	Downregulation of CREB	n/a	n/a	n/a	n/a	↓	(Han et al., 2006)
	Rat	LC	Orexin 1 receptor antagonist (SB-334867)	n/a	n/a	n/a	n/a	↓	(Davoudi et al., 2016)
Alcohol Use Disorder	Mouse	Global	*DBH KO*	↓	n/a	n/a	n/a	n/a	(Weinshenker et al., 2000)
	Rat	Global	Lofexidine	↓	n/a	↓	n/a	n/a	(Lê et al., 2005)
	Rat	Global	Clonidine	↓	n/a	n/a	n/a	n/a	(Rasmussen et al., 2014)
	Rat	Global	Prazosin	↓	n/a	n/a	n/a	n/a	(Walker et al., 2008)
	Rat (CIE)	Global	Prazosin	↓	n/a	n/a	n/a	n/a	(Skelly and Weiner, 2014)
	Rat	Global	Propranolol	↓	n/a	n/a	n/a	n/a	Gilpin and Koob, 2010)
	Mouse	BLA	Pindolol	↓	n/a	n/a	n/a	n/a	Patkar et al., 2019)
	Rat	BLA	Propranolol	↓	n/a	n/a	↓	n/a	Chesworth and Corbit, 2018)
	Rat	VTA	Prazosin	↓	n/a	n/a	n/a	n/a	Shelkar et al., 2017)
Psychostimulant Use Disorder	Mouse	Global	*NET KO*	n/a	↓	n/a	n/a	n/a	Ventura et al., 2003)

Substance Use Disorder Type	Model	Brain region(s) targeted	Manipulation/ drug used	Consumption	CPP	Stress-induced reinstatement	Drug cue-induced reinstatement	Withdrawal	Reference
	Rat	Global	Nepicastat (DBH inhibitor)	↓	n/a	↓	↓	n/a	Schroeder et al., 2013)
	Rat	Global	Clonidine Lofexidine Guanabenz	n/a	n/a	↓	n/a	n/a	Erb et al., 2000)
	Rat	BNST or CeA	Betaxolol & ICI-118,551 (β2 AR antagonist)	n/a	n/a	↓	–	n/a	Leri et al., 2002)
	Rat	BNST	ICI-118,551 (β2 AR antagonist)	n/a	n/a	↓	n/a	n/a	Vranjkovic et al., 2014)
	Mouse	BNST	Rescue of *ADRA2A KO* with DREADD	n/a	n/a	↑	n/a	n/a	Perez et al., 2020)
	Rat	mPFC	Terazosin	n/a	n/a	n/a	↓	n/a	Schmidt et al., 2017)
	Rat	NAcc	Terazosin	n/a	n/a	n/a	–	n/a	Schmidt et al., 2017)
	Rat		Terazosin	n/a	n/a	n/a	–	n/a	Schmidt et al., 2017)
	Rat	VTA	Terazosin	n/a	n/a	–	↓	n/a	Solecki et al., 2019a)