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Norepinephrine at the Nexus of Arousal, Motivation and Relapse

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Abstract

Arousal plays a critical role in cognitive, affective and motivational processes. Consistent with this, the dysregulation of arousal-related neural systems is implicated in a variety of psychiatric disorders, including addiction. Noradrenergic systems exert potent arousal-enhancing actions that involve signaling at α_1 - and β -noradrenergic receptors within a distributed network of subcortical regions. The majority of research into noradrenergic modulation of arousal has focused on the nucleus locus coeruleus. Nevertheless, anatomical studies demonstrate that multiple noradrenergic nuclei innervate subcortical arousal-related regions, providing a substrate for differential regulation of arousal across these distinct noradrenergic nuclei. The arousal-promoting actions of psychostimulants and other drugs of abuse contribute to their widespread abuse. Moreover, relapse can be triggered by a variety of arousal-promoting events, including stress and re-exposure to drugs of abuse. Evidence has long-indicated that norepinephrine plays an important role in relapse. Recent observations suggest that noradrenergic signaling elicits affectively-neutral arousal that is sufficient to reinstate drug seeking. Collectively, these observations indicate that norepinephrine plays a key role in the interaction between arousal, motivation, and relapse.

Keywords

stimulants; addiction; amphetamine; catecholamines; noradrenergic; locus coeruleus

Introduction

Our ability to interact with the environment and, ultimately, to survive is highly dependent on the appropriate regulation of arousal. Noradrenergic systems are important modulators of arousal (Berridge et al., 2012). Cognitive and motivational processes display a pronounced dependency on arousal (Yerkes and Dodson, 1908). Clinically, dysregulated arousal and

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motivation are key features of a variety of behavioral disorders, including drug abuse disorders. Historically, dopamine has been the focus of research into the neurotransmitter regulation of motivation and drug taking. However, amassing evidence indicates a critical role for noradrenergic signaling in motivation, particularly in an arousal-sensitive context. In the following sections we briefly review evidence demonstrating an important influence of noradrenergic signaling in the modulation of arousal and motivated behavior that involves a network of noradrenergic nuclei and subcortical terminal fields. These observations suggest a likely prominent role of NE neurotransmission in disorders associated with dysregulated motivation, including addiction.

1. Noradrenergic Regulation of Arousal

1.1 Locus coeruleus-noradrenergic modulation of arousal

Evidence has long-implicated the noradrenergic nucleus, locus coeruleus (LC), in the regulation of arousal (for review, Berridge and Waterhouse, 2003). The LC is a small cluster of NE-synthesizing neurons located in the pontine brainstem adjacent to the fourth ventricle. Despite a restricted size, LC neurons extend immensely ramified axons that project widely throughout the neuraxis (Swanson and Hartman, 1975; Foote et al., 1983; Berridge and Waterhouse, 2003). Early observations suggested this nucleus was the sole source of the noradrenergic innervation of the hippocampus and neocortex (Foote et al., 1983; Robertson et al., 2013). However, recent studies indicate other noradrenergic nuclei provide a significant contribution to the noradrenergic innervation of select subfields of the prefrontal cortex and other neocortical sites (Robertson et al., 2013).

Seminal electrophysiological experiments first observed that LC neurons display state-dependent firing with higher discharge rates during waking than during sleep (Hobson et al., 1975). Importantly, changes in LC neuron discharge preceded transitions from sleep to waking and from waking to sleep (Hobson et al., 1975; Foote et al., 1980). Further evidence of state dependency in LC unit activity was also observed within waking, with increases in discharge rates observed during periods of elevated arousal, including those associated with reward or stress (Foote et al., 1980; Aston-Jones and Bloom, 1981; Abercrombie and Jacobs, 1987; Dunn, 1988). These observations gave rise to the hypothesis that NE exerts arousal-promoting actions.

1.2 Selective activation and suppression of LC alters EEG/behavioral state

Pharmacological studies provide strong evidence that the LC-NE system regulates sleep/wake processes. NE binds to three major receptor families, α_1 , α_2 , and β , each comprised of multiple subtypes, as well as the dopamine D4 receptor (Newman-Tancredi et al., 1997; Cummings et al., 2010). α_1 - and β receptors are thought to exist primarily postsynaptically whereas, α_2 -receptors are present both pre- and postsynaptically (see Berridge and Waterhouse, 2003). It has long been known that systemic or central treatment with α_2 agonists, which suppress NE release by activating presynaptic autoreceptors (Lavery and Taylor, 1969; Kleinlogel et al., 1975; Pastel and Fernstrom, 1984), or combined α_1 - and β -antagonists (Berridge and España, 2000) elicits profound sedation. However, these approaches lack the anatomical resolution to determine unambiguously the site of action

involved in the sedative actions of these noradrenergic drug manipulations. Subsequent research used electrophysiological recordings to guide small infusions (35–150 nl) of drugs immediately adjacent to the LC, to *selectively* examine the effects of LC activation and suppression on electroencephalographic (EEG) indices of arousal in anesthetized rats (Berridge and Foote, 1991; Berridge et al., 1993). It was observed that LC activation driven by peri-LC infusions of a cholinergic agonist elicited robust and bilateral activation of forebrain EEG that closely tracked the time-course of LC activation (Berridge and Foote, 1991). Conversely, pharmacological suppression of LC activity bilaterally elicited a robust increase in EEG indices of sedation (e.g. increased slow-wave activity) in lightly anesthetized rats that also tracked closely the time course of drug-induced suppression of LC discharge activity (Berridge et al., 1993). Importantly, less than 10% of LC neuronal activity in one hemisphere was sufficient to maintain EEG indices of arousal under these conditions.

More recent optogenetic activation and suppression of LC has yielded similar effects in unanesthetized animals (Carter et al., 2010). Brief optogenetic stimulation of the LC (1–10 seconds) elicited rapid transitions from sleep to waking and, within waking, prolonged time spent awake and increased behavioral activity. Conversely, 1 hour optogenetic inhibition of LC decreased time spent awake.

Collectively, these and other observations demonstrate that LC activity is both sufficient and necessary for the promotion and maintenance of alert waking.

1.3 Site of action: Noradrenergic α_1 - and β -receptors promote arousal in a network of subcortical regions

Subcortically, the general regions of the medial septal area (MSA), the substantia innominata (SI), the medial preoptic area (MPOA), and the lateral hypothalamus (LH; including LH proper, the dorsomedial hypothalamus, and the perifornical area) participate in the regulation of arousal (Buzsaki et al., 1983; Kumar et al., 1986; Buzsaki et al., 1988; Metherate et al., 1992). Each of these regions also receive LC-noradrenergic input (Swanson and Hartman, 1975; Zaborszky, 1989; Cullinan and Zaborszky, 1991; Zaborszky et al., 1991; Zaborszky and Cullinan, 1996; España and Berridge, 2006). To determine whether NE action in these regions modulates sleep-wake state, small volumes (150–250 nl) of NE, an α_1 -agonist, or a β -agonist were made in sleeping animals using remote controlled infusions designed to avoid waking/disturbing the animal (see Berridge and Foote, 1996). It was observed that α_1 - and β receptor activation in the MSA, the MPOA, or the LH produce robust and additive increases in EEG and behavioral indices of waking (Kumar et al., 1984; Berridge et al., 1996; Berridge and Foote, 1996; Sood et al., 1997; Berridge and O'Neill, 2001; Berridge et al., 2003; Schmeichel and Berridge, 2013). Infusions immediately outside these regions were devoid of wake-promoting actions (Berridge et al., 1996; Berridge and Foote, 1996; Berridge and O'Neill, 2001; Berridge et al., 2003; Schmeichel and Berridge, 2013). Within all regions the wake-promoting actions of α_1 - and β -receptor stimulation are additive (Berridge et al., 2003; Schmeichel and Berridge, 2013). Interestingly, the wake-promoting actions of NE within the LH are not associated with an activation of arousal-related hypocretin/orexin neurons (Schmeichel and Berridge, 2013).

The SI, situated immediately lateral to both the MSA and MPOA, provides a potent activating influence on EEG, in part through the actions of cholinergic projections to the neocortex (Buzsaki and Gage, 1989; Metherate et al., 1992). Therefore, it is somewhat surprising that the SI is not a site of action for the arousal-promoting effects of NE, α_1 - or β -agonists, or the indirect NE agonist, amphetamine (Berridge et al., 1996; Berridge and Foote, 1996; Berridge et al., 1999; Berridge and O'Neill, 2001). The only exception to this was observed with a high concentration of NE that produced a moderate wake-promoting effect (Cape and Jones, 1998; Berridge and O'Neill, 2001). In this case, the latency to waking was substantially longer and the time spent awake substantially reduced, relative to infusion into the MPOA (Berridge and O'Neill, 2001). This pattern of results suggests that at high concentrations NE diffuses from the SI to the MPOA where it acts to increase waking.

1.4 Differential noradrenergic input across arousal promoting regions

The above-described observations provide clear evidence that LC neurons exert a robust excitatory influence on forebrain activity state that involves the additive actions of α_1 - and β -receptors located across a network of subcortical sites. However, anatomical tracing studies demonstrate that the LC is not the only source of noradrenergic innervation to these regions. Moreover, the proportion of NE innervation arising from the LC vs. other noradrenergic nuclei is not uniform across these arousal-related regions. For example, although the LC provides the majority (~50%) of noradrenergic input to the MSA and MPOA, significant noradrenergic innervation to these areas arises from the A1 and A2 noradrenergic nuclei (~25% each; España and Berridge, 2006). In the case of the LH, the LC provides a remarkably small proportion of innervation (~10%), with significantly larger contributions from A1 (~50%), and A2 (~22%; España et al., 2005; Yoshida et al., 2006). Thus, while it is clear that the LC exerts strong arousal modulatory actions, NE-dependent regulation of arousal and arousal-dependent processes likely involves multiple noradrenergic nuclei. It is important to note that the LC appears unique among noradrenergic nuclei in receiving prominent input from forebrain regions associated with higher cognitive and affective function (e.g., prefrontal cortex, amygdala; Arnsten and Goldman-Rakic, 1984; Berridge and Waterhouse, 2003). Together, these observations suggest that noradrenergic regulation of arousal and arousal-dependent processes involves a complex network of noradrenergic nuclei, receptors, and terminal fields that may be differentially recruited under varying conditions. The extent to which the LC, A1 and A2 are differentially activated across varying conditions is an important question for future studies.

1.5 Summary

Noradrenergic systems exert potent arousal promoting actions that involve α_1 and β -receptors in a network of subcortical regions. Although activation of either α_1 or β -receptors in any single region is *sufficient* to elevate behavioral and EEG/EMG indices under low-arousal conditions, blockade of both receptors globally in the brain is required to observe maximal sedation under conditions associated with higher arousal levels required for alert waking. The source of the noradrenergic innervation to subcortical NE-arousal regions varies across regions, with both the MSA and MPOA receiving the majority of input from the LC while the LHA receives a significantly smaller LC innervation.

2. Arousal-Related NE Contributions to Motivated Behavior

Drug addiction represents a significant public health problem, with considerable personal and economic costs. For many drugs, particularly psychostimulants and nicotine, the reinforcing¹ actions are superimposed on drug-induced elevations in arousal. Moreover, the arousal-promoting effects of these drugs contribute to their widespread use and abuse. As such, the ability of certain drugs of abuse to elevate arousal independent of their rewarding effects may represent a significant contributing factor in the development of addiction/abuse. Relapse represents one of the most significant impediments to the successful treatment of addiction. It is estimated that 40%–60% of abstinent drug addicts will relapse (McLellan et al., 2000). Further, it is well documented that relapse is highly sensitive to arousing, stressful conditions (e.g. Kosten et al., 1986; Koob, 1999; Kalivas and McFarland, 2003; Mantsch et al., 2015). Combined with the above-reviewed information, these observations suggest the hypothesis that through the modulation of arousal state, NE could participate in multiple aspects of addiction. Evidence related to this hypothesis is reviewed below.

2.1 NE contribution to psychostimulant-induced arousal

Psychostimulants are a widely abused class of drugs, originally defined by their potent arousal-enhancing, motor activating, and reinforcing actions. These drugs have long been used (both prescribed and illicitly) to sustain arousal beyond typical circadian rhythm, representing a potential ‘gateway’ for the development of abuse/addiction. Neurochemically, psychostimulants disrupt dopamine, NE, and serotonin transporters, thereby elevating extracellular levels of these transmitters (Florin et al., 1994; Florin et al., 1995). Given the strong arousal-promoting actions of NE combined with the NE-elevating actions of psychostimulants, it is not surprising that amphetamine-induced arousal involves drug action in all identified noradrenergic arousal-related terminal fields: MSA, MPOA and LH (Berridge et al., 1999; Schmeichel and Berridge, 2014). Consistent with this, the arousal-promoting effects of psychostimulants are closely aligned with elevations in extracellular NE levels (Berridge and Stalnaker, 2002) and, at least in anesthetized animals, can be blocked by pretreatment with α_1 - or β -receptor antagonists (Berridge and Morris, 2000). Together these observations, demonstrate that the arousal-promoting actions of psychostimulants involve, in part, elevated NE signaling in subcortical arousal-related regions. Interestingly, when infused directly into the MSA, MPOA and the LH, amphetamine lacks locomotor activating effects (Berridge et al., 1999; Schmeichel and Berridge, 2014), indicating the arousal-promoting and locomotor-activating actions of psychostimulants are dependent on distinct anatomical circuitry.

2.2 NE and the reinstatement of drug seeking: Potential role of arousal

Stress is a well-documented trigger for relapse (e.g. Kosten et al., 1986; Koob, 1999; Kalivas and McFarland, 2003). In animals, a variety of stressors have been documented to reinstate

¹We deliberately use the term ‘reinforcement’ over ‘reward’ as it can be challenging to measure the subjective experience typically denoted by the term ‘reward’, particularly in animals. In contrast, the reinforcing actions of drugs can be readily measured in both humans and animals, and can be either positive or negative. However, given multiple cognitive, affective and motivational processes participate in the reinforcing actions of drugs (see Berridge and Robinson, 2003; Salamone and Correa, 2012; Salamone et al., 2012; Schultz, 2015), it can be difficult to identify the underlying behavioral processes associated with alterations in drug seeking as measured in reinforcement paradigms.

previously extinguished drug seeking behavior, as measured in both conditioned place preference (CPP) and self-administration paradigms (for review, Koob, 1999; Shaham et al., 2000a; Kalivas and McFarland, 2003; Mantsch et al., 2014; Mantsch et al., 2015). Elevated arousal represents a critical aspect of stress. As reviewed above, NE systems are activated in stress and exert robust arousal-promoting actions (Berridge and Waterhouse, 2003). Consistent with these observations, substantial evidence indicates a prominent role of NE in stress-related *reinstatement* of drug seeking that is independent of stressor and whether drug seeking involves instrumental or classical conditioning (for review, Weinshenker and Schroeder, 2007; Mantsch et al., 2014). Given this has been reviewed extensively elsewhere, we only briefly review stress-related reinstatement herein.

Evidence for a noradrenergic contribution to stress-related reinstatement includes the ability of pharmacological suppression of NE release (α_2 -agonists), α_1 - or β -receptor blockade, or inhibition of NE synthesis to attenuate stressor-induced reinstatement of psychostimulant- (Erb et al., 2000; Schroeder et al., 2013), alcohol- (Lê et al., 2005; Lê et al., 2011) and opiate-seeking in rats (Shaham et al., 2000b; Leri et al., 2002; Ventura et al., 2005) in both CPP and self-administration paradigms. Similar observations have been made in human psychostimulant and opioid addicts (Sinha et al., 2007; Jobes et al., 2011). Together, these observations indicate that NE signaling *is necessary* for the ability of stress to reinstate previously extinguished drug seeking. Consistent with this, evidence demonstrates that increases in NE signaling *are sufficient* to reinstate psychostimulant- (Lee et al., 2004; Brown et al., 2009; Mantsch et al., 2010; Brown et al., 2011; Schroeder et al., 2013), and alcohol-seeking (Lê et al., 2005). Collectively, these observations indicate a significant role for NE in stress-related relapse of drug seeking.

CPP and self-administration involve at least partially distinct circuitry, as do the reinforcing effects of different drug classes (e.g. opiates vs. psychostimulants). The above-reviewed observations indicate that the ability of stress and NE to reinstate drug seeking is largely independent of reinforcement type or drug class. Therefore, NE modulation of arousal may represent a common mechanism by which noradrenergic signaling influences drug-related behavior, independent of drug type and associational process.

Re-exposure to drugs or drug-associated cues also reinstate drug seeking. Arguably, these relapse triggers are also of an arousing nature. Limited data support a role of NE in reinstatement elicited by drug-associated cues for psychostimulants (e.g. cocaine; Platt et al., 2007). The degree to which NE participates in drug-induced reinstatement is less clear, a topic that has been most commonly examined in the context of psychostimulants. In rodents and monkeys, α_1 -antagonists or α_2 -agonists, prevented the ability of noncontingent psychostimulant administration to reinstate cocaine self-administration (Zhang and Kosten, 2005; Platt et al., 2007). However, in other studies, neither α_1 -antagonists, β -antagonists, α_2 agonists (to suppress NE release) or NE synthesis inhibitors affected cocaine-induced reinstatement (Shaham et al., 2000a; Mantsch et al., 2010; Cooper et al., 2014). While the discrepant nature of the literature might indicate that NE does not play a prominent role in psychostimulant-induced reinstatement, there are a couple of important issues that need to be considered prior to drawing strong conclusions. First, the arousal-promoting actions of NE involve both α_1 and β -receptor signaling and blocking only one receptor can lack

significant impacts on behavioral and EEG/EMG measures of arousal (see above; Berridge and España, 2000). Thus negative effects of a single receptor-selective antagonist need to be interpreted cautiously. While α_2 agonists should suppress NE signaling at α_1 and β receptors, the degree to which this occurs in an unanesthetized animal treated under all relevant experimental conditions is unclear. Moreover, these drugs display a complex pharmacology (acting at post-synaptic and non-noradrenergic imidazoline receptors), which can cloud interpretation of experimental results obtained with their use (Arnsten et al., 1996). Second, the dose and frequency of psychostimulant used in a given study may be an important variable in the degree to which NE modulates drug-induced reinstatement. For example, the most robust suppression of cocaine-induced reinstatement of cocaine self-administration by an α_1 antagonist was observed at the lowest doses of cocaine (5 mg/kg vs. 20 mg/kg; Zhang and Kosten, 2005). As dose of psychostimulant increases, the concentration of NE increases (Kuczenski and Segal, 1992; Florin et al., 1994). Thus, at high doses, it may be difficult to fully block NE receptor signaling.

Finally, it is important to segregate the topics of sufficiency vs. necessity when discussing the involvement of NE in reinstatement/relapse. Multiple arousal-related systems are implicated in reinstatement/relapse, including CRF, dopamine and serotonin (for review, Lê et al., 2000; Shaham et al., 2000a; Self, 2004; Lê et al., 2006; Lê et al., 2009). Thus, blocking one transmitter alone may be insufficient to prevent drug-induced reinstatement, particularly at high doses of psychostimulants that are activating multiple reinstatement-related transmitter systems. The inability of a drug that interferes with NE neurotransmission to block drug-induced reinstatement demonstrates that target of that drug is not necessary for this form of reinstatement. However, given NE receptor activation is sufficient to induce reinstatement and at least some drugs of abuse increase NE signaling, one can reasonably conclude that NE likely contributes to some aspects of drug-induced reinstatement.

2.3 Arousal-related neurocircuitry involved in NE-related reinstatement

Consistent with the prominent role of NE in stress and arousal, evidence indicates that stress-related reinstatement of drug seeking involves subcortical arousal-related systems (e.g. MSA, bed nucleus of the stria terminalis, central nucleus of the amygdala, LHA; Highfield et al., 2000; Leri et al., 2002) for review, Stewart, 2000; Weinshenker and Schroeder, 2007). This suggests the hypothesis that stress-related reinstatement of drug seeking may involve arousal-related activation of motivational systems. However, given that negative affect is a known contributing factor in relapse (Baker et al., 2004; George and Koob, 2010), stress-related reinstatement of drug seeking could reflect the induction of a negative affective state independent of fluctuations in arousal.

Related to this issue, we recently observed that amphetamine acts within the LH to promote affectively-neutral arousal (Schmeichel and Berridge, 2013; Schmeichel and Berridge, 2014). Specifically, intra-LH amphetamine infusions elicited a robust increase in time spent awake (Figure 1), while lacking reinforcing or aversive actions as measured in CPP (Figure 2). Nonetheless, intra-LH amphetamine infusion produced a robust reinstatement of a previously extinguished CPP produced with systemic amphetamine treatment (Schmeichel and Berridge, 2014).

Collectively, these observations indicate that *affectively-neutral* arousal is sufficient to reinstate psychostimulant seeking. As reviewed above, NE acts at α_1 and β receptors in the LH to similarly promote arousal. Given amphetamine infusions into the LH elevate extracellular NE levels, it is posited that NE plays a significant role in the arousal-related reinstating effects of intra-LH amphetamine infusions. These observations raise important questions for future studies. These include whether the arousal-promoting actions of NE signaling in the LH or other subcortical regions associated with NE-driven arousal (e.g. MSA, MPOA) are: 1) affectively neutral; 2) *sufficient* to trigger reinstatement, and 3) *necessary* for the reinstating effects of either local or systemic psychostimulant treatment. It is important to note that the posited role of NE-dependent arousal in the reinstatement of drug seeking does not argue against a role of either negative affect or other neurotransmitter (e.g. dopamine) signaling in drug/psychostimulant relapse. Indeed, evidence strongly indicates an involvement of these other processes in drug addiction. However, the evidence reviewed above additionally suggests a potentially important role of the (affectively-neutral) arousal-promoting actions of NE in the reinstatement of drug seeking.

2.4 NE involvement in the reinforcing actions of drugs of abuse

The above-described observations indicate that NE-dependent elevation in arousal likely contributes to stress-related and potentially other forms of reinstatement. A separate question is whether NE contributes to the reinforcing actions of drugs of abuse. This is a topic that has not received extensive exploration in part given limited and mixed results of early studies (see Weinshenker and Schroeder, 2007). It is important to note, as reviewed above, the arousal-promoting actions of NE involve multiple receptor subtypes acting in multiple brain regions. Thus, negative observations with methods that only partially impair NE signaling need to be interpreted cautiously.

Nonetheless, several observations indicate that disruption of NE signaling reduces drug taking and seeking, in both self-administration and CPP paradigms. In terms of self-administration, disruption to NE neurotransmission has been shown to reduce intake of a variety of drugs of abuse. Specifically, inhibition of NE synthesis has been observed to reduce morphine (Brown et al., 1978) and ethanol administration (Amit et al., 1977; Brown et al., 1977; Weinshenker et al., 2000), while reduced NE transmission via activation of α_2 autoreceptors attenuated alcohol intake (Lê et al., 2005). Likewise, blockade of either α_1 or β receptors reduced intake of cocaine and ethanol (Goldberg and Gonzalez, 1976; Harris et al., 1996; Gilpin and Koob, 2010; Skelly and Weiner, 2014). Additionally, mice engineered to lack α_1 receptors display reduced oral cocaine and morphine preference relative to their wild-type counterparts (Drouin et al., 2002). Of course, the knockout approach is subject to long-term compensatory responses that may modify normal physiology, complicating interpretation of results obtained with this approach. Finally, increasing NE activity via NE transporter (NET) knockouts or α_2 -receptor antagonists has been observed to increase cocaine and alcohol intake, respectively (Rocha, 2003; Lê et al., 2005).

Similar effects of NE disruption are observed when the rewarding actions of drugs of abuse are measured using CPP. For instance, depletion of NE, suppression of NE release, or blockade of α_1 - or β -receptors blocks CPP for psychostimulants and opiates (Hand et al.,

1989; Zarrindast et al., 2002; Ventura et al., 2003; Sahraei et al., 2004; Ventura et al., 2005; Fitzgerald et al., 2016). Consistent with this, DBH or α_1 -receptors knockout mice display reduced CPP for morphine (Drouin et al., 2002; Olson et al., 2006). Importantly, the attenuation of CPP elicited by the disruption of NE signaling does not appear to be related to generalized failures in learning given DBH knockout mice are capable of expressing CPP for food and conditioned taste aversion to lithium chloride (Weinshenker et al., 2000; Olson et al., 2006; Schank et al., 2006). In contrast to the effects of NE disruption, enhanced NE signaling in NET knockouts or via α_2 -antagonist treatment increases CPP for psychostimulants and opiates (Xu et al., 2000; Zarrindast et al., 2002; Sahraei et al., 2004).

Despite this evidence, several other studies indicate that disruptions to NE signaling fail to alter cocaine or ethanol self-administration (Roberts et al., 1977; Richardson and Novakowski, 1978; Wee et al., 2006). Moreover, inhibition of NE signaling has also been noted to decrease food intake, an observation that has been interpreted to argue against a role of NE, specifically in the reinforcing actions of drugs of abuse (Weinshenker and Schroeder, 2007). However, if a minimal arousal level is required for motivated behavior, NE contributions to motivation may not be selective to drug-related motivation.

While the available evidence argues for a role of NE signaling in the reinforcing actions of drugs of abuse, the nature of this involvement, including the extent to which this reflects NE-modulation of arousal, is unclear and represents an important area for future study.

3. Conclusions

In conclusion, arousal is known to impact motivated behavior and a large body of evidence demonstrates a critical role of central noradrenergic systems in the regulation of arousal. NE-dependent modulation of arousal involves multiple noradrenergic nuclei that display differential innervation patterns across arousal related regions. Intriguingly, limited data suggest the hypotheses that affectively-neutral arousal contributes to relapse and that NE α_1 - and β -receptors located in subcortical arousal-related regions play an important role in this process. The degree to which NE-signaling in arousal-related regions contributes to drug reinforcement and the reinstatement of drug seeking for varying classes of drugs and differing forms of reinforcement is an important topic for future research.

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Highlights

- Arousal is a critical component of motivational processes
- Norepinephrine (NE) promotes arousal via action in a network of subcortical regions
- Relapse likely involves NE-dependent increases in affectively-neutral arousal

Figure 1. The lateral hypothalamus (LH) is a site involved in the arousal promoting actions of norepinephrine (NE) and amphetamine (AMPH)

A: Dashed lines indicate a region within general LH area (LHA) in which infusions of NE, α_1 -agonist and β -agonist infusion elicits an increase in waking. This region encompasses LH proper as well as the dorsomedial hypothalamus (DMH). For this schematic, circles indicate location of amphetamine infusions that elicited waking depicted in Panel C. Numbers are proportional to time awake. Numbers >2 indicate time spent awake following the infusion that exceed that seen in baseline conditions and following vehicle infusions. α_1 - and β -receptors within this region exert additive wake-promoting effects. Similar wake-promoting effects of NE manipulations are observed with infusions into the medial septal area and the medial preoptic area. 3V, third ventricle; fx, fornix; VMH, ventromedial hypothalamus. **B:** Symbols indicate time (seconds) spent awake in 30-minute epochs before (PRE) and following (POST) remote-controlled infusions of vehicle (VEH) or varying concentrations of the NE α_1 -agonist, phenylephrine (PHEN). All infusions were unilateral within the LHA except for a group receiving 20 nmol PHEN bilaterally. PHEN produced a dose-dependent increase in time spent awake. Bilateral infusions elicited a larger increase in waking than unilateral infusions. **C:** Intra-LH AMPH infusions elicited a dose-dependent increase in waking identical to that seen with NE receptor activation. AMPH induced waking occurred in the absence of a pronounced locomotor activation. See B for description of axis labels. * P <0.05; ** P <0.01, relative to PRE1. Figures modified from (Schmeichel and Berridge, 2013; Schmeichel and Berridge, 2014).

Figure 2. Arousal promoting intra-lateral hypothalamus (LH) infusions of amphetamine (AMPH) are affectively neutral while reinstating AMPH seeking

A: Left panel demonstrates that systemic treatment with 0.25 mg/kg subcutaneous AMPH elicited a significant conditioned place preference (CPP) as measured by a significant increase in time spent in the drug-paired chamber in a post-conditioning test (POST COND) relative to a pre-conditioning test (PRE COND). In contrast, intra-LH infusion of an arousal promoting concentration of AMPH (25 nmol, bilaterally) failed to produce either a CPP or conditioned place aversion. These observations indicate that AMPH acts in the LH to elicit affectively neutral arousal. **B:** Intra-LH AMPH infusion reinstates (AMPH REINST) an extinguished CPP (EXTINCTION) elicited by systemic treatment with AMPH (0.25 mg/kg; PRE COND vs. POST COND). ** $P < 0.01$ vs. PRE COND; ## $P < 0.01$ vs. POST COND; % $P < 0.05$ vs. EXTINCTION. Data from (Schmeichel and Berridge, 2014).