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Review

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.

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Contents

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1. 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 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 norepinephrine (NE) neurotransmission in disorders associated with dysregulated motivation, including addiction.

2. Noradrenergic regulation of arousal

2.1. *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.

2.2. *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 (Laverty 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