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Review

The locus coeruleus–noradrenergic system: modulation of behavioral state and state-dependent cognitive processes

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Abstract

Through a widespread efferent projection system, the locus coeruleus–noradrenergic system supplies norepinephrine throughout the central nervous system. Initial studies provided critical insight into the basic organization and properties of this system. More recent work identifies a complicated array of behavioral and electrophysiological actions that have in common the facilitation of processing of relevant, or salient, information. This involves two basic levels of action. First, the system contributes to the initiation and maintenance of behavioral and forebrain neuronal activity states appropriate for the collection of sensory information (e.g. waking). Second, within the waking state, this system modulates the collection and processing of salient sensory information through a diversity of concentration-dependent actions within cortical and subcortical sensory, attention, and memory circuits. Norepinephrine-dependent modulation of long-term alterations in synaptic strength, gene transcription and other processes suggest a potentially critical role of this neurotransmitter system in experience-dependent alterations in neural function and behavior. The ability of a given stimulus to increase locus coeruleus discharge activity appears independent of affective valence (appetitive vs. aversive). Combined, these observations suggest that the locus coeruleus–noradrenergic system is a critical component of the neural architecture supporting interaction with, and navigation through, a complex world. These observations further suggest that dysregulation of locus coeruleus–noradrenergic neurotransmission may contribute to cognitive and/or arousal dysfunction associated with a variety of psychiatric disorders, including attention-deficit hyperactivity disorder, sleep and arousal disorders, as well as certain affective disorders, including post-traumatic stress disorder. Independent of an etiological role in these disorders, the locus coeruleus–noradrenergic system represents an appropriate target for pharmacological treatment of specific attention, memory and/or arousal dysfunction associated with a variety of behavioral/cognitive disorders.

Theme: Neural basis of behavior

Topic: Monoamines and behavior

Keywords: Amphetamine; Arousal; Attention; Cognition; Learning; Memory; Norepinephrine; Perception; Sensory; Sleep; Stimulants; Stress; Vigilance; Waking

Contents

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1. Introduction

Norepinephrine (NE)-containing axons are distributed widely throughout the central nervous system (CNS), suggesting a prominent role of this neurotransmitter in CNS function and behavior. A majority of brain noradrenergic neurons are concentrated in the brainstem nucleus, locus coeruleus (LC). This nucleus is the primary source of an extensive, yet regionally-specialized, noradrenergic innervation of the forebrain. Importantly, the LC provides the sole source of NE to hippocampus and neocortex, regions critical for higher cognitive and affective processes. Despite intense examination of the LC–noradrenergic system and substantial progress in our understanding of the neurobiology of this system, the ultimate impact of LC neurotransmission on behavioral processes has, for the most part, remained unresolved.

This situation has changed gradually as relatively recent work provides unambiguous evidence that through a variety of actions, the LC–noradrenergic system exerts a widespread influence on neuronal circuits that are essential substrates of alert waking and state-dependent cognitive processes. Together with previous anatomical, electrophysiological and behavioral evidence, these observations indicate that the LC, and possibly other noradrenergic pathways, serves at least two general behavioral functions. First, this system contributes to the induction and maintenance of forebrain neuronal and behavioral activity states appropriate for the acquisition of sensory information (e.g. waking). Second, within the waking state, NE enhances and/or modulates the collection and processing of salient sensory information via actions on sensory, memory, attentional, and motor processes. Actions within this latter category can be both short-term and long-term in nature, and can occur within perceptual, attentional, and memory systems. Noradrenergic modulation of behavioral state and state-dependent processes involves actions distributed across multiple anatomical regions and multiple receptor subtypes. Based on these observations, it is posited that dysregulation of the LC–noradrenergic system may result in deficits in a variety of cognitive and affective processes that are, in turn, associated with numerous cognitive and affective disorders such as attention deficit/hyperactivity disorder (ADHD), narcolepsy, and stress-related disorders. Whether or not deficiencies in noradrenergic neurotransmission contribute to the etiology of these cognitive/affective disorders, actions of noradrenergic systems likely contribute to the efficacy of a variety of drugs used in the treatment of these conditions.

Over the past 40 years, a large body of information has been garnered regarding the basic neurobiology of the LC–noradrenergic system, as reviewed in a number of excellent reviews [10,37,168,170,517]. The current report summarizes relatively recent anatomical, molecular, physiological and behavioral data demonstrating a role for the LC–noradrenergic system in the regulation of behavioral state and state-dependent cognitive processes and the neural circuitry underlying these actions. Within this framework we attempt to identify existing lacunae in our understanding of the neurobiology of this system and suggest potential implications of available information for better understanding the involvement of this neurotransmitter system in the etiology and treatment of a subset of cognitive/psychiatric disorders.

2. Anatomical and physiological attributes of the LC–noradrenergic system

2.1. Anatomical organization of the LC–noradrenergic system

The basic anatomical features of the LC–noradrenergic system have been defined in great detail by a variety of investigators [37]. The LC nucleus is a well-delineated cluster of NE-containing neurons, located adjacent to the fourth ventricle in the pontine brainstem. It is composed of a small number of neurons: approximately 1500 per nucleus in rat, several thousand in monkey, and 10,000–15,000 in human. However, these neurons possess immensely ramified axons such that the nucleus projects broadly throughout the neuraxis, from spinal cord to neocortex [170,280,504]. More recent anatomical findings provide important insights regarding the functional organization of the LC efferent system and its potential role in cognitive processes, as reviewed here in brief.

2.1.1. Distribution of NE-containing fibers

Despite a widespread efferent projection system, evidence suggests substantial regional specificity of noradrenergic fiber distribution within and across cortical and subcortical structures. For example, within neocortex, there is both regional and laminar variability in noradrenergic fiber density [280,282,352]. In general, cortical layers III and IV receive the densest innervation, whereas layer I receives a sparse innervation, with the majority of fibers contained within this layer oriented tangentially rather than randomly. This laminar specificity is evident in primates but less obvious or absent in rodent (reviewed in [172,280]).

Across functionally-distinct terminal fields, LC efferents display regional variations in NE-containing fiber density [352]. For example, within the primate visual system, NE fibers are more heavily represented in tecto–pulvinar–juxtastriate structures as contrasted with geniculo-striate and inferotemporate structures. On the basis of this distinction Morrison and Foote [352] suggested that, within the visual system, NE-containing fibers preferentially innervate regions involved in spatial analysis and visuomotor responses rather than areas involved in feature extraction and pattern analysis. Thus, on the basis of fiber distribution, the LC–NE system may potentially have a

selective influence on specific dimensions of visual signal processing. Although similar observations have not been forthcoming for other sensory systems, the expectation is that this pattern of NE fiber distribution represents a general feature of the LC efferent projection to auditory and somatosensory networks.

Although the LC–NE system innervates virtually the entire CNS, an exception to this is the basal ganglia (striatum, globus pallidus), which is nearly devoid of noradrenergic input. Recently, it has been determined that the nucleus accumbens can be divided into distinct subfields, delineated on the basis of histochemical markers as well as efferent and afferent projection patterns. The shell subregion has reciprocal connections with a variety of limbic and brainstem autonomic structures. Thus, it is of interest that the shell subregion of the nucleus accumbens is the only striatal subfield to receive a moderately dense noradrenergic innervation [54], although the majority of this arises from non-LC noradrenergic sources [130].

2.1.2. Adrenergic receptor distribution

Similar to other neurotransmitter systems, NE acts at multiple receptors in target tissues. Traditionally three noradrenergic receptor subtypes have been recognized: α_1, α_2, and β. α_1- and β-receptors are thought to exist primarily at postsynaptic sites, whereas α_2-receptors exist both pre- and postsynaptically. The distribution and second messenger coupling of these receptor subtypes vary within and across brain regions. For example, within neocortex, β-receptors appear to be more broadly distributed across laminae and are positively coupled to the Gs/cAMP second messenger system, whereas α_1- and α_2-receptors are concentrated in the superficial layers and are coupled to the phosphoinositol and Gi/cAMP systems, respectively [138]. Recently, molecular biological and pharmacological studies have revealed an even greater diversity of adrenergic receptors, with multiple subtypes each of β-, α_1-, and α_2-receptors identified [66,76,239]. Currently, three β-receptor subtypes (β1–3), three α_1 subtypes (α_{1a}, α_{1b}, α_{1d}) and four α_2-receptor subtypes (α_{2A-D}) are recognized. Suggesting an exception to the rule that β-receptors exist primarily postsynaptically are recent observations indicating β2-receptors act presynaptically to facilitate NE release [360,361,366].

The distinct cellular and behavioral functions mediated by each receptor subtype, across multiple terminal fields and different classes of neurons, have been only partially elucidated. For example, despite the ubiquitous nature of the noradrenergic innervation of the six layered neocortex in rat, this heterogeneous population of cortical neurons may vary in their responsiveness to synaptically released NE as a function of their adrenergic receptor complement. Such a view is supported by the ever increasing body of evidence that suggests within a heterogeneous population of neurons, such as exists in cerebral cortex, there are neuronal subtypes with different intrinsic membrane properties and different complements of membrane receptors, signal transduction mechanisms and ion channels [110,111,270,315,324]. Consistent with these observations, differential distribution of α- and β-adrenergic receptors across cortical laminae has been described [189,406,407,578]. Likewise, mRNA localization studies have revealed differential distributions of α-and β-receptor subtypes throughout the brain [327,362,363,387]. These observations suggest that different adrenoceptor subtypes mediate distinctive actions within noradrenergically-innervated circuits by virtue of their differential localization across neuronal subpopulations and/or neuronal compartments. Still others have shown that adrenergic receptors reside on glial cells, prompting speculation regarding the influence of the LC–noradrenergic system on glial function and the impact of such actions on neighboring neurons [13,485,487,491]. Thus, a proposition that has not been fully tested is that the net outcome of NE release in the neocortex or elsewhere in the forebrain is highly dependent upon the receptor complement of not only neuronal but also non-neuronal elements within that circuitry. Such receptor diversity could clearly account for the diversity of postsynaptic responses that have been reported following local administration of NE or activation of the LC efferent pathway, as reviewed below. Further, the differential distribution of adrenoceptor subtypes provides a mechanism for local specificity of NE action following what appears to be ubiquitous and simultaneous release of this transmitter/modulator from a widespread and diffuse network of NE-containing fibers.

A further issue for consideration is the short- and long-term plasticity of receptor expression in cell membranes. Considerable evidence indicates that the number and functional status of membrane-bound β-adrenergic receptors are subject to regulation by multiple intracellular mechanisms [447]. Accordingly, β-receptor-mediated neurotransmission would be dictated, perhaps on a moment to moment or longer basis, by the number of functional β-receptors within the postsynaptic membrane. Receptor plasticity could be a function of developmental state, circadian rhythms, circulating hormonal influences or, as already shown [447], receptor activation states.

2.1.3. Efferent topography of LC

Longstanding evidence from many retrograde tracer studies suggests that the LC exhibits a rough topographic organization with respect to its efferent targets [296,297,316,544,546]. In the coronal plane the nucleus is divided into dorsal and ventral zones by cells of the medial vestibular nucleus [501]. Likewise, there is a prominent, but scattered cluster of NE-containing cells just ventral and lateral to the LC proper referred to as the sub-coeruleus [501]. An early retrograde tracing study in rat [316] demonstrated an internal organization within the LC nucleus such that cells projecting to hippocampus and septum were concentrated in the dorsal LC, those project-

ing to cerebellum were located in both dorsal and ventral LC, and those projecting to the thalamus and hypothalamus were found in the caudal and rostral poles of the nucleus, respectively. In this study cortical and amygdala projection cells were scattered throughout the nucleus. Later work showed that cortically-projecting LC neurons are more prominent within the caudal portion of the nucleus and these neurons project in a predominantly ipsilateral (>95%) manner [546].

In addition to an anterocaudal organization, cortically-projecting LC neurons display a moderate dorsoventral organization with neurons located dorsally within LC projecting towards occipital cortex and neurons located ventrally projecting towards the prefrontal cortex [546]. In contrast to that observed in cortex, subcortical structures receive a bilateral LC innervation that arises only slightly preferentially from the caudal half of LC. These subcortical projections can exhibit an ipsilateral or contralateral bias, depending on the targeted structure [450]. For example, in the case of the rodent trigeminal somatosensory pathway, output from the LC to whisker-related cortical and subcortical sites is organized such that activation of one LC nucleus could selectively bias transmission of sensory information from the contralateral side of the body. This biasing influence could be an essential component of the neural process that enables an animal to orient or direct attention toward novel or task-related environmental stimuli.

Recent evidence also suggests that individual LC neurons innervate functionally related, yet discrete, elements within an ascending sensory pathway [450,470,470, 527,527]. For example, LC neurons that project to trigeminal somatosensory cortex are more likely to co-innervate trigeminal somatosensory thalamus than non-somatosensory thalamic regions (e.g. dorsal lateral geniculate nucleus [450]). Thus, individual LC neurons display a propensity to send axon collaterals to multiple targets that process the same sensory information. These findings provide the basis for the suggestion that the LC is organized according to the functional properties of its efferent targets. Because of their collateral projections, the discharge of some LC neurons would result in an almost simultaneous release of NE at two or possibly more sites along the ascending trigeminal somatosensory path. As a result of this anatomical arrangement, subsets of LC neurons could exert coordinating influences on the transfer of modality-specific information through selected channels in ascending sensory networks.

Together, the rat LC and sub-coeruleus provide noradrenergic innervation to the forebrain, cerebellum and brainstem as well as both dorsal and ventral horns of the spinal cord [103,193,217,268,432,455]. Most of the sub-coeruleus efferent fibers are directed to the brainstem and spinal cord, while the bulk of the LC's output is to forebrain structures. In monkey and rat both LC and subcoeruleus give rise to descending projections to all levels of the spinal cord [561–564]. In rat, rabbit and monkey the LC and sub-coeruleus have prominent projections to the vestibular complex and the nucleus prepositus hypoglossus prompting the suggestion [433] that noradrenergic fibers from these sources modulate vestibulo-ocular and vestibulo-spinal responses during changes in alertness or vigilance. More recent reports using pseudorabies virus transneuronal labeling strategies have identified multi-synaptic connections from the rat LC and sub-coeruleus to the urinary bladder, urethral sphincter and kidney via autonomic (sympathetic and parasympathetic) pathways [313,456,538]. Furthermore, microinjection of CRF into the rat LC and sub-coeruleus stimulated colonic transit and bowel discharge [347] while inhibiting gastric secretion [348]. This latter effect persisted following bilateral vagotomy, indicating mediation via a spinal cord pathway. The above observations provide evidence of functional compartmentalization within the LC nucleus and further suggests the possibility that discrete subsets of LC neurons can regulate separate forebrain, spinal cord and autonomic functions.

2.1.4. Afferent regulation of LC

Initial reports indicated that the LC received inputs from a broad array of CNS structures [83,104]. In contrast, subsequent work demonstrated that the LC nucleus receives a substantially more restricted set of afferents arising from the nucleus paragigantocellularis (PGI) and the nucleus prepositus hypoglossus (PH [29]). Based on these findings it was concluded that a limited set of brainstem afferents are in control of the output of the broadly projecting network of LC–noradrenergic fibers. PGI neurons respond to stimuli that activate the sympathetic nervous system, whereas PH neuronal activity is related to control of eye movements. As such, the information provided by these inputs could indicate a shift to new targets in the visual field or relay an arousal or alarm signal to forebrain circuits via the LC.

More recent studies demonstrated a dense plexus of LC neuronal processes, primarily dendrites, that extend beyond the borders of the nucleus proper [446]. Importantly, this pericoerulear region is the target for a large number of presynaptic fibers from a variety of sources including prefrontal cortex, central nucleus of the amygdala, lateral hypothalamus, bed nucleus of the stria terminalis and dorsal raphe [19,340,383,386,526–530]. Arnsten and Goldman-Rakic [19] and later Jodo et al. [235] provided anatomical and electrophysiological evidence, respectively, that the prefrontal cortex is a major source of afferent drive to the LC. The existence of this connection is particularly important insofar as it links circuits involved in higher cognitive and affective processes with the LC-efferent path. Additional recent work demonstrates inputs from the ventral medulla (PGI) to LC are topographically ordered in rat with respect to ventral and dorsolateral target zones of

the nucleus [525]. These findings suggest the possibility that under certain behavioral or physiological conditions subsets of LC neurons may be subject to selective activation by discrete, functionally organized sets of afferents.

Electrophysiological investigations indicate that LC neurons respond to microiontophoretic or bath application of a variety of neurotransmitters, including glutamate, acetylcholine, serotonin, opiate peptides, and CRF. These results suggest a large array of transmitters that may be utilized by LC input pathways. In some cases, the identity of transmitters utilized by specific afferent pathways is already known. For example, glutamate inputs arise from the PGI [148], GABA inputs arise from PH [149,150] and serotonin inputs arise from the dorsal raphe nucleus [386]. In other cases clarification of the anatomical pathways associated with a given neurotransmitter/neuromodulator remains to be determined.

Evidence suggests corticotropin-releasing hormone (CRH) inputs to LC from PGI and Barrington's nucleus may mediate activation of the LC by physiological stressors, whereas CRF projections from the central nucleus of the amygdala to LC may activate the LC in response to environmental stressors [518–521,524,527,528]. More recently, a direct connection from hypocretin (orexin)-containing neurons in the lateral hypothalamus to LC has been identified [340,383]. Furthermore, hypocretin receptor mRNA is abundant in rat LC and hypocretin increases the discharge of individual LC neurons (for review, see [221,250]). As reviewed below, both CRH and the hypocretins are implicated in stress and arousal-related processes.

The connection between the dorsal raphe and LC is particularly intriguing since efferent projections of these two monoamine systems demonstrate considerable overlap in forebrain circuits. Moreover, in rat visual cortex NE and serotonin exert complementary modulatory actions on single neuron responses to visual stimuli (cf. Figs. 1 and 3, [553]). The prediction from these findings is that the noradrenergic and serotonergic systems up- and down-regulate, respectively, the responsiveness of target sensory neurons to afferent signals. To better understand the combined physiological impact on target cell function, it is important that future studies delineate the precise nature of the communication between these two monoamine nuclei.

2.1.5. Neurochemical composition and organization of LC

Early studies demonstrated that virtually all neurons within the LC nucleus proper of rodent and primate contained dopamine beta-hydroxylase, the enzyme necessary for converting dopamine to NE [194,501]. It is generally accepted that NE is the primary transmitter utilized by the LC efferent pathway. However, the identification of multiple peptides colocalized within LC neurons adds additional complexity to what initially appeared to be a fairly simple system. Vasopressin, somatostatin, neuropeptide Y, enkephalin, neurotensin, CRH and galanin are among the variety of putative peptide transmitters found in LC neurons (for review, see [370]). Galanin is of particular interest since it has been estimated that 80% of LC neurons colocalize galanin and NE [216,335]). Initial investigations using immunohistochemical techniques provided little evidence of galanin-containing fibers in sensory neocortex or sensory relay nuclei of the brainstem and thalamus [335,337,351,453]. Despite these findings, lesions of the anterior noradrenergic fiber bundle decrease cortical galanin concentrations, suggesting LC is, in fact, a source for cortical galanin [180]. Using modified immunohistochemical procedures, recent studies have now demonstrated extensive networks of galanin-positive fibers within rat cortical, hippocampal, thalamic and brainstem sensory circuits [451,576]. The majority of these galanin-containing axonal processes co-contain DBH, the marker enzyme for identification of NE-containing neurons.

Other studies have shown that galanin is differentially expressed in different subsets of LC projection neurons [216]. For instance, following retrograde tracer injection into medial thalamus 30% of retrogradely labeled LC neurons contained galanin. In contrast, infusion of tracer into lateral thalamus and zona incerta resulted in 57% and 76%, respectively, galanin-positive LC neurons [272]. Such an uneven distribution of galanin-positive neurons within different populations of LC projection neurons suggests a selective, perhaps topographic, organization of galanin-containing efferents from LC. In support of this idea, it was recently observed that although 80% of rat LC neurons co-express galanin and NE, only half of the LC neurons that project to either cortical or sub-cortical somatosensory circuits contain galanin [451].

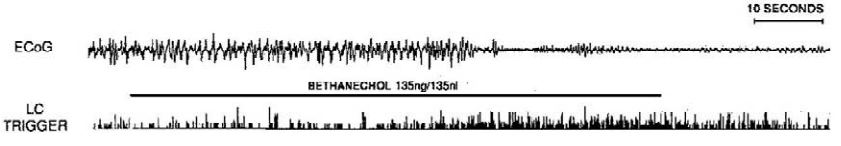

Fig. 1. Relationship of LC activity to cortical EEG (ECoG) before, during and after peri-LC infusions of the cholinergic agonist, bethanechol. Cholinergic agonists exert potent excitatory effects on LC neuronal discharge rates. Bethanechol was infused at a constant rate throughout the interval indicated. EEG activity is shown in the *top trace* and the raw trigger output from LC activity in the *bottom trace*. LC activity is seen to increase during the latter part of the infusion. Several seconds later, reduced amplitude and increased frequency becomes evident in the ECoG. Simultaneous alterations in hippocampal EEG activity were observed with changes in ECoG (data not shown). The EEG activating effect of LC stimulation was prevented by ICV pretreatment with a β-antagonist (data not shown). From [46].

2.1.6. NE-peptide interactions within LC efferent targets

These findings suggest that NE and galanin are co-transmitters or co-modulators of neuronal function. Depending upon neuronal discharge conditions, NE, galanin or a combination of NE plus galanin may be released from LC axon terminals and exert physiological actions on pre- or postsynaptic membranes. Galanin has been demonstrated to influence a variety of cellular processes in a variety of brain regions [244,251,377,388]. Importantly, the net impact of galanin-NE interactions in LC target regions of the brain is currently unknown. Simpson et al. [451] reported striking differences between the density of galanin-immunoreactive fibers across the trigeminal somatosensory thalamic nuclei, posterior medial (POm) and ventral basal (VB, or ventral posterior medial-VPM) nuclei. The POm is considered part of the paralemniscal pathway, which imparts more qualitative, dynamical attributes to stimulus coding. In contrast, VPM of the lemniscal pathway codes stimulus properties with greater spatial and temporal fidelity. The differences in the patterns of galanin innervation of POm and VPM could be related to the functional roles that these nuclei play in trigeminal somatosensory signal processing. Thus, galanin may play a specific role in regulating the cellular processes in primary sensory pathways that underlie sensory perception. Of additional interest are the findings that galanin, but not tyrosine hydroxylase (rate limiting enzyme for NE synthesis), mRNA levels are selectively elevated in rat LC neurons after treadmill exercise training [367] or estrogen-treatment [515]. These observations suggest intrinsic mechanisms for independent, selective regulation of co-localized putative neuromodulatory substances in LC neurons.

A novel functional interaction has been proposed for NE and vasoactive intestinal peptide (VIP) within the cerebral cortex. Magistretti and Morrison [302,354] have shown that axonal processes of VIP-immunoreactive intracortical neurons are oriented perpendicular to NE-containing coeruleo-cortical projection fibers. Furthermore, VIP and NE act synergistically to: (1) increase cyclic AMP levels in cerebral cortical tissue [300,301,304]; and (2) facilitate responses of individual cortical neurons to local application of the putative transmitters GABA and acetylcholine [440]. The proposal is that NE and VIP afferents to cortex may exert convergent influences on neuronal responses to afferent synaptic inputs such that their combined modulatory actions are anatomically focused within the cortex. More specifically, activation of VIP neurons might provide for local amplification of an otherwise global modulatory effect of synaptically released NE.

2.2. Physiology of LC neurons

The compact and homogeneous nature of both the rat and primate LC facilitates the recording of neuronal discharge activity from these neurons. The early availability of this information was relatively unique to this neurotransmitter system and was essential in the formulation of hypotheses concerning potential behavioral functions of the LC–NE system.

2.2.1. Cellular attributes of LC neurons

In both anesthetized and unanesthetized animals, NE-containing LC neurons are characterized electrophysiologically by slow, spontaneous discharge rates (0–5 Hz), broad action potential waveforms (1–2 ms) and burst discharges that are followed by a prolonged period of quiescence or decreased firing. LC neurons are polymodal and have a surprisingly homogeneous response profile throughout the nucleus. Moreover, multi-unit recordings suggest synchronous discharge properties such that the nucleus has been likened to a syncitium of neurons that fires en masse to provide for global release of NE throughout the neuraxis [27,28]. More recent studies in brain slices from adult rats have demonstrated synchronous patterns of discharge for neurons in all regions of the LC nucleus. This synchronous firing is not mediated by transmitter release, is reduced or blocked with agents that disrupt gap junctions or by isolating cell bodies from their pericoerulear dendritic fields and is linked to oscillations in membrane potential [229]. Together, these results suggest that LC neurons in adult animals are electrotonically coupled via interactions between dendrites outside the cell body region. This arrangement provides for a mechanism whereby the majority, if not all, LC neurons can discharge simultaneously in response to afferent input, at least under certain conditions. This synchronous mode of discharge would provide a cellular mechanism for ensemble output from the nucleus.

Antidromic studies have concluded that LC–NE fibers have slow conduction velocities on the order of 0.20–0.86 m/s, characteristic of thin, unmyelinated axons [34]. Moreover, conduction velocity along LC fibers decreases with prolonged trains of activity. On the basis of these studies it has been estimated that the maximal rate at which LC axons can faithfully transmit impulse activity is approximately 20 Hz.

2.2.2. LC neurons display tonic and phasic discharge activity patterns

It is important to note that LC neurons fire in two distinct activity modes: *tonic* and *phasic*. *Tonic* activity is characterized by relatively low-frequency, sustained, and highly regular discharge patterns, as described above. The pioneering work of Hobson and McCarley and colleagues demonstrated that tonic discharge activity is state-dependent: LC neurons display highest discharge rates during waking (quiet waking <2 Hz; active waking >2 Hz), lower rates during slow-wave sleep (<1 Hz), and are virtually silent during REM or paradoxical sleep [167,212]. Of particular interest is the fact that, in general, changes in LC discharge rates anticipate changes in behavioral state

[27,167,212]. Within waking, sustained increases in tonic discharge rates are elicited by environmental stimuli that elicit sustained increases in EEG and behavioral indices of arousal or attentiveness [27,167]. Tonic discharge rates as high as 15 Hz have been reported for limited durations under high-arousal conditions [167]. However, the extent to which these rates are sustained for prolonged periods under high-arousal conditions remains unclear.

Within waking, LC neurons also display *phasic* alterations in discharge rates in response to salient sensory stimuli [28,167]. These phasic responses are observed with a relatively short latency (15–70 ms in rat) and are comprised of a brief burst of 2–3 action potentials followed by a more prolonged period of suppression of discharge activity (approximately 300–700 ms). Phasic responses are observed in association with overt attending to a novel stimulus within a particular environmental location (e.g. an orienting response). Phasic LC responses habituate with repeated stimulus presentation, accompanied by habituation of the orienting response. Additionally, as reviewed below, phasic discharge is closely associated with sustained attention in tests of vigilance using conditioned stimuli [33].

Phasic discharge appears, in part, dependent on tonic activity levels. Thus, phasic responses are less robust under conditions associated with lower tonic discharge levels and lower levels of vigilance, including those associated with sleep, grooming, and eating [28]. Moreover, higher levels of tonic discharge activity associated with higher arousal levels, are also associated with less robust phasic discharge activity. For example, stressors that elevate tonic discharge activity reduce sensory-driven phasic discharge [518,519,523]. A similar reduction in phasic discharge associated with elevated tonic discharge levels has been observed in a vigilance paradigm [408].

The phasic mode of discharge is particularly interesting in light of the co-localization of the neuropeptide galanin and other peptides in NE-containing LC efferent fibers. Studies in hypothalamus have shown that peptide release from peptide-containing fibers occurs with phasic impulse activity but not tonic discharge [56,57,146]. A similar facilitatory effect on peptide release has been described for neurotensin release from dopaminergic neurons [39]. Thus, it is possible that tonic discharge of LC neurons prompts release of NE only from LC efferent fibers, whereas phasic discharge is capable of promoting release of both NE and galanin and/or other peptides.

2.3. Relationship between rates of NE efflux to rates of LC discharge activity

Extracellular (extrasynaptic) levels of NE are linearly related to tonic LC discharge rates across the range of LC firing rates typically observed across the sleep–wake cycle [41,165]. These observations indicate that relatively small fluctuations in absolute LC discharge rates within the range typically observed in normal sleep and waking (i.e. a change from 1.5 to 3.0 Hz) result in pronounced changes in NE efflux. Dopaminergic neurons display a tonic and burst type mode of firing over prolonged periods. The burst mode is associated with greater rates of DA efflux relative to similar frequency tonic discharge activity [39,309]. In contrast to dopaminergic neurons, LC neurons do not display prolonged burst-type firing activity. Instead, LC neurons display quite brief phasic discharge events superimposed upon tonic discharge activity. Importantly, the 2–3 action potential burst comprising phasic discharge are followed by a sustained period (200–500 ms) of suppressed firing. The net effect of 2–3 action potentials followed by a prolonged period of inhibition on synaptic levels of NE remains to be determined. Greater levels of extracellular NE are observed following prolonged (minutes) burst-like LC stimulation compared to tonic stimulation at similar rates [165]. Although intriguing, both the presence of a NE reuptake inhibitor and the fact that the contribution of tonic discharge activity that presumably occurs between burst stimulation epochs was not assessed in these studies, pose potential confounds for unambiguous interpretation of these observations. Future work needs to examine the impact of burst firing (including the post-excitatory LC discharge suppression) on extracellular NE levels using in vivo voltammetry, which has a temporal resolution better suited for this issue.

It is estimated that a large percentage of noradrenergic terminals release NE at sites not closely apposed to post-synaptic junctions (e.g. extrasynaptic release, volume neurotransmission; for review, see [35,583]). It is possible that brief increases in NE release associated with phasic firing has a larger impact on NE levels within the small volume of a traditional synaptic cleft than on extracellular NE levels outside the synaptic cleft. In contrast, via extrasynaptic release, tonic discharge may have a larger influence on NE levels outside the synaptic cleft.

2.4. Sensitivity of the LC–noradrenergic system to stressors

Early electrophysiological studies suggested that LC neuronal activity was driven primarily by aversive stimuli either alarming, threatening or noxious [190,414]. Consistent with these observations, substantial evidence demonstrates stressor-elicited increases in NE release [12,142,145,163,258,364,478,479,512,556–558,582].

These observations suggest a possibly selective role of LC neurons in stress and have led to a number of hypotheses concerning an alarm- or anxiety-related function of these neurons. However, it is important to note that electrophysiological studies in unanesthetized animals demonstrate that phasic responses are elicited by appetitive as well as aversive stimuli, provided that a stimulus is perceived as salient [28,167]. Further, recent microdialysis studies measuring NE efflux demonstrate elevated extracel-

lular NE levels in response to appetitively conditioned stimuli, presumably reflecting elevation in tonic discharge rates [155–157]. Combined, these observations suggest that both tonic and phasic LC discharge activity are more closely related to the overall salience and/or arousing nature of a given stimulus rather than the affective valence of the stimulus. As mentioned, certain stressors have been demonstrated to disrupt LC phasic discharge while elevating tonic discharge discharge [518,519,523]. It remains to be determined whether appetitive stimuli-induced increases in tonic discharge are similarly associated with a disruption on phasic discharge activity.

The extent to which LC neurons display sensitivity to both aversive and appetitive stimuli, across varying species, is currently unclear. For example, cat LC neurons appear to be relatively insensitive to novel non-stressful stimuli [1]. Moreover, the LC–noradrenergic system of the cat appears different than that of either the primate or rodent in a number of additional aspects. For example, in contrast to that of rat and monkey, the cat LC is comprised of both noradrenergic and non-noradrenergic neurons. In addition, during alert waking LC discharge rates of rat and monkey are higher than those observed in cat [1]. Thus, in rat and monkey tonic LC discharge rates up to 5 Hz are typically observed in normal waking [167]. Further, in monkeys, complex sensory stimuli that increase behavioral and EEG indices of arousal elicit brief epochs of tonic discharge rates of approximately 7–15 Hz [167]. This is in contrast to the approximately 1.0 Hz observed in the non-stressed, awake cat [1]. Thus, cat LC neurons appear to differ substantially in a number of aspects from either rat or monkey and thus, extrapolation from information collected in the cat to primate may not be justified.

2.5. Afferent regulation of LC in stress

Currently, little is known regarding the identity of afferents involved in the activation of LC neurons across varying environmental conditions. What little information exists is confined primarily to stressor-induced activation of LC. CRH plays a prominent role in the coordination of autonomic, behavioral, and electrophysiological responses associated with stress [144,257]. CRH-immunoreactive fibers are observed within LC, suggesting that CRH may modulate LC neuronal activity [118,338,505,521]. At least a portion of this CRH arises from the central nucleus of the amygdala, targeting the dorsolateral dendritic field [524,528]. Work by Valentino and colleagues and others demonstrates that ICV [143,271,519,520] or local [123,372,376,457] CRH administration increases LC discharge activity and NE release. Interestingly, the actions of CRH on LC discharge activity are specific to tonic discharge and not sensory-driven phasic firing, resulting in a decrease in the ratio of sensory-evoked to tonic LC discharge rates [519]. The functional significance of alterations in this ratio remains to be determined.

Given the association between CRH and stress, it was hypothesized that CRH may contribute to stressor-induced activation of LC. In support of this hypothesis, hemodynamic-stress (hypotension)-induced activation of LC neurons [122,522] is prevented by local application of a CRH antagonist but not ICV administration of the excitatory amino acid antagonist, kynurenic acid [522]. Further, colonic distension-induced activation of LC was reversed by a CRH-antagonist, but only at low-volume distension and not high-volume distension [273]. In contrast to that observed with hemodynamic stress, ICV, but not local, kynurenic acid prevented colonic distension-induced LC neuronal activation at all distension volumes [375]. Finally, in contrast to either hypotension or colonic distension, bladder distension-induced activation of LC is insensitive to CRH antagonist pretreatment [373], but is blocked by ICV pretreatment with kynurenic acid. Thus, elevation of tonic LC discharge rates associated with varying physiological challenges is dependent on the actions of varying LC afferent systems. Although alterations of stress-related behavior with either CRH or CRH-antagonist infusions into the general region of LC have been observed [71,508], the small size of the nucleus and the close proximity of LC to other brainstem nuclei preclude unambiguous determination of site of action of these treatments. For example, in some cases, evidence has been obtained suggesting a prominent LC modulatory influence of CRH via actions within the adjacent parabrachial nucleus [64].

In summary, it appears that LC activation in stress results from the actions of multiple afferent systems. The extent to which a given system participates in the activation of LC is dependent on the exact nature of the aversive stimulus. Obviously, this makes it difficult to posit a simple unitary mechanism underlying stress-related alterations in LC discharge and/or dysfunction resulting from these stress-related alterations in LC activity. Unexplored to date is the nature of afferents underlying activation of LC under appetitive conditions. Future work needs to identify the complete array of afferents that participate in aversive and appetitive stimulus-induced activation of LC. As part of this work, it will be interesting to determine whether different sets of afferents to LC participate in the activation (both tonic and phasic) of LC neurons associated with aversive and appetitive stimuli. For example, does CRH participate in LC activation associated with appetitive stimuli or are its actions on LC confined to a subset of stressors?

2.6. Plasticity of the LC–noradrenergic system

Central noradrenergic (as well as dopaminergic) systems possess robust compensatory mechanisms that permit adjustment to long-term alterations in activity. These alterations are observed in response to damage as well as environmental (e.g. stress) and pharmacological (e.g. antidepressant) manipulations. This plasticity may well be a

key feature of these systems and likely contributes to at least some of the cognitive and affective effects of both certain environmental conditions and certain classes of psychoactive drugs.

2.6.1. Damage

In general, the net result of perturbation-induced alterations in LC–NE neurotransmission is to keep rates of neurotransmission within a narrower range than would otherwise be the case. A particularly robust example of plasticity within noradrenergic systems is observed following damage to LC or noradrenergic fibers (induced by electrical or neurotoxic lesions). Following such damage, numerous responses are observed that act to minimize the functional consequence of this damage. Most of these occur within 7–10 days of the insult. Compensatory responses are observed at the level of release, post-synaptic receptor number, second-messenger systems, and fiber number [176,200,201,294,454,466]. Microdialysis indices of NE or DA release are not decreased substantially until tissue levels of NE/DA have been reduced by more than 90% from control conditions [4,81,417–419]. Moreover, even in the presence of substantial decreases in extracellular levels of NE, increases in postsynaptic receptor number and/or second messenger responsivity may well be able to compensate for such a reduction in NE levels. Given the robust nature of these compensatory responses, it is not surprising that following substantial, though incomplete, destruction of the LC efferent system evidence for hyperactive, rather than hypoactive, noradrenergic function has been observed [44,135,342]. These latter observations suggest that even in the presence of a significant effect of a noradrenergic lesion on behavioral or physiological processes, care should be taken in the interpretation of these results.

2.6.2. Stress

In contrast to damage-induced upregulation of the LC–NE system, prolonged or repeated exposure to LC-activating stressors such as footshock, cold, or restraint, elicits a decrease in β-receptor-driven accumulation of cAMP [480,481]. The stressor-induced downregulation of the β-dependent cAMP response appears to result largely from a reduction in the α_1-receptor potentiation of the β-receptor cAMP response [484,488,489,492]. Repeated exposure to a stressor also attenuates LC neuronal responsivity and NE release to the same (homotypic) stressor [2,364]. Although repeated presentation of certain stressors results in tolerance to the LC activating actions of those stressors, enhanced responsivity of LC neurons to repeated immobilization stress has been observed [380], indicating that tolerance to a given stressor is not obligatory.

The development of tolerance of the LC–NE system in stress is in contrast to the well-documented ability of both acute and chronic stressors to increase activity and/or quantity of the rate-limiting enzyme in NE biosynthesis, tyrosine hydroxylase (TH; [260,486]). Thus, although chronic/repeated stressors may not result in increased release of NE, they do result in increased capacity of the system to release NE, due to elevated rates of NE synthesis (for review, see [145]). CRH appears to participate in stressor-induced upregulation of TH synthesis within LC neurons, at least under certain conditions [336].

These observations raise the question under what conditions would increased synthetic capacity be utilized? Insight into this issue is provided by the observation that, in contrast to homotypic stressors, repeated/chronic stress results in an increased responsiveness of the LC–noradrenergic system to presentation of a *different* (heterotypic) stressor. For example, following exposure to chronic cold stress, greater increases in extracellular NE levels are observed within hippocampus in response to tail-shock [364] or tail-pinch [163]. Thus, during prolonged exposure to a particular stressor the LC–NE system develops an increased capacity to respond to additional challenges.

The development of tolerance to the LC activating effects of repeated presentation of certain stressors may involve alterations in CRH neurotransmission. For example, acute footshock-stress decreased the sensitivity of LC neurons to CRH as well as to hypotensive challenge [124]. A decrease in the maximum LC response to CRH was observed with prior exposure to swim-stress [125], repeated foot-shock, or repeated auditory stress [112]. Similar to that observed with repeated stress, repeated administration of CRH also decreases LC activation to subsequent CRH administration [112]. Stressor-induced alterations in LC responsivity to afferent input is dependent on the identity of the afferent system driving LC activation. For example, neither acute nor repeated footshock altered phasic LC activation induced by sciatic nerve stimulation, which is dependent on actions of excitatory amino acids and not CRH [148]. Despite the above-described observations, the actions of repeated stress on the sensitivity to CRH are more complicated than a simple down-regulation of LC neuronal responsiveness to this transmitter. Thus, although swim-stress or repeated footshock-stress decreases the maximum response of LC neurons to CRH, this treatment also shifts the dose–response curve for CRH-induced activation of LC to the left, indicating sensitization to lower doses of CRH [124,125].

Combined, these observations suggest that prolonged or repeated stressors result in a complicated array of alterations in rates of LC–NE neurotransmission and responsivity of LC neurons to various afferent transmitters as well as environmental stimuli. Future work will need to better characterize the actions of stressors on the variety of afferent systems known to regulate LC activity. Additionally, similar studies will need to assess the extent to which repeated presentation of appetive stimuli alter LC responsivity to subsequent exposure to both appetitive, as well as aversive, stimuli.

2.6.3. Antidepressants

Interestingly, antidepressants, when administered chronically, decrease the β-receptor-dependent cAMP response [86,499,500,536]. At least in the case of desmethylimipramine, the decreased cAMP response is primarily due to an alteration in the action of β-receptor activation rather than a reduction in the α_1-potentiation of the β-response. Stone has written in-depth on the similarity in the actions of antidepressants and stress on β-receptor-mediated increases in cAMP production (for review see [482,483]). Moreover, the fact that chronic restraint-stress elicits an antidepressant-like action in the swim test [396] further suggests that plasticity within noradrenergic neurotransmission may contribute to the therapeutic actions of at least certain antidepressants.

3. Modulatory actions of LC–noradrenergic efferents on forebrain neuronal and behavioral activity states

3.1. Introduction

Waking is associated with an enhanced ability to detect, process, and respond to information arising from the environment [292,472]. Associated with changes in behavioral state are changes in activity patterns of cortical and thalamic neurons. These changes in neuronal activity are, in turn, reflected in EEG measures [513,534]. For example, during non-REM sleep, cortical EEG is characterized by the presence of large-amplitude, slow-wave activity, reflecting slow, synchronous firing of cortical and thalamic neurons. During alert waking and REM sleep these neurons no longer fire slowly in synchrony, which is reflected in cortical EEG recordings by the presence of high-frequency, low-amplitude activity (desynchronized activity; EEG activation). At the neuronal level, waking and REM sleep are associated with increased excitability of thalamic and neocortical neurons (for review, see [473]). An obvious distinction between REM sleep and waking is the extent to which an animal is aware of and responsive to environmental stimuli. Distinction between quiet and active waking, slow-wave sleep and REM-sleep is made on the basis of combined EEG and electromyographic (EMG) recordings: from REM to active waking, progressively larger amplitude EMG activity is observed, corresponding to progressively greater muscle tone [513].

Within waking, fluctuation in attention to the environment occurs which is associated with changes in cortical/thalamic activity patterns. Thus, animals engaged in self-directed behaviors (such as grooming) display lower frequency, larger amplitude activity in cortical EEG than animals actively attending to the environment (for review, see [534]). In humans, the degree of cortical EEG activation is highly associated with the ability to maintain sustained selective attention (e.g. vigilance), indicating a close association between cortical activity patterns and higher cognitive processes [241,305,306].

The fact that LC neurons increase firing rates in anticipation of waking and waking-associated forebrain activation (as measured by EEG) suggests LC efferents participate in the induction of either the awake state and/or cortical/thalamic activity patterns associated with waking and enhanced arousal. Obviously, an activated forebrain per se is not dependent on LC efferents, given LC neurons are virtually quiescent during REM sleep-associated forebrain activation. Nonetheless noradrenergic efferents may well provide a critical contribution to waking-associated forebrain activation.

The degree to which noradrenergic systems modulate both EEG and behavioral indices of behavioral state has been examined extensively over the past many decades. Despite this effort, the degree to which noradrenergic systems modulate behavioral state remained ambiguous for much of this time (for review, see [534]). Conflicting observations most likely stem from the ill-suited nature of then-available methods for manipulation of rates of noradrenergic neurotransmission, including lesions and pharmacological manipulations, as reviewed below. More recent observations using more selective manipulations indicate a potent role of the LC–NE system in the regulation of the waking state and forebrain neuronal activity states associated with waking and enhanced arousal.

3.2. Noradrenergic modulation of cortical and thalamic neuronal activity state, in vitro

Cortical and thalamic neurons display distinct activity modes during sleeping and waking behavioral states. Thus, during slow-wave sleep, these neurons are hyperpolarized relative to that observed in waking and display a burst-type activity mode. This activity mode is associated with a relative insensitivity to incoming sensory information. In contrast, during waking these neurons display a single-spike mode associated with the efficient and accurate processing of sensory information [139,317,319,359,474]. The above described electrophysiological observations indicate increased rates of NE release during conditions associated with the single-spike mode, suggesting that LC efferents contribute to the induction of this activity state [27,167]. Consistent with this hypothesis, McCormick and colleagues have demonstrated that, in vitro, NE induces a shift in the firing pattern of cortical and thalamic neurons from a burst mode to a single-spike mode [318,326,378]. The ability of NE to induce the single-spike activity mode involves actions of both α_1-receptors and β-receptors [323]. The action of NE on basal activity state of cortical and thalamic neurons is similar to that of other extrathalamic cortical afferents, including cholinergic [318,325], serotonergic [378] and dopaminergic [281] systems. Future work will need to assess the functional significance of the concerted actions of these transmitter

systems on the activity state of cortical and thalamic neurons.

3.3. Effects of manipulation of LC–noradrenergic neurotransmission on EEG and behavioral indices of arousal

In general, lesions of noradrenergic systems have failed to elicit robust and sustained alterations in behavioral and/or EEG indices of arousal [237,288,534]. However, interpretation of these results is confounded by lesion-induced compensatory responses that occur within central noradrenergic systems, as reviewed above. Thus, the general lack of effect of noradrenergic lesions on EEG and behavior may result from a failure to impair noradrenergic neurotransmission to a sufficient degree. Supporting a role of the LC–NE system in behavioral and EEG indices of waking are the well-documented sedative effects of systemic, ICV, or intra-brainstem administration of α_2-agonists, which acutely suppress LC neuronal discharge activity and NE release [127–129,181,555]. In fact, due to their ability to reduce the effective anesthetic dose, α_2-agonists are commonly used as adjuncts to surgical anesthesia [63,247]. These sedative effects of α_2-agonists are opposite those observed following intrabrainstem infusions of an α_2-antagonist [128,129]. Despite the consistency of these observations, interpretation regarding the involvement of LC in these effects is confounded by a lack of anatomical specificity of these manipulations.

The small size of LC, situated in close proximity to a variety of brainstem structures, presents a substantial challenge for the *selective* manipulation of LC neuronal discharge rates. A combined recording/infusion probe was described recently that permits greater degree of anatomical localization of intratissue infusions [5]. Using this approach, Berridge and Foote demonstrated that *unilateral* LC activation, produced by 150 nl infusions of the cholinergic agonist, bethanechol, elicited a robust *bilateral* activation of cortical and hippocampal EEG (see Fig. 1; [46]). A number of observations indicated a causal relationship between LC activation and forebrain EEG activation, including: (1) results from mapping studies; (2) the fact that increased LC neuronal discharge always preceded EEG activation, and; (3) the ability of pretreatment with a β-receptor antagonist to prevent EEG activation typically observed following bethanechol-induced LC activation.

Additional studies demonstrated bilateral suppression of LC neuronal discharge activity via small (35 nl) infusions of an α_2-agonist produced a robust increase in slow-wave activity in cortical and hippocampal EEG. Importantly, even minimal (i.e. 10% of basal levels) neuronal discharge activity unilaterally was sufficient to maintain bilateral forebrain activation [52]. These studies demonstrate that minimal LC neuronal discharge activity within one hemisphere is sufficient to maintain bilateral activation of the forebrain. This observation is consistent with previous observations demonstrating diminished, yet not absent, LC discharge activity in animals that are clearly awake, though engaged in consummatory or grooming behavior [27]. Combined, these observations indicate that LC is a potent modulator of forebrain EEG state, with unilateral LC neuronal discharge activity causally related to the bilateral maintenance of EEG activity patterns associated with arousal.

3.4. Enhanced LC discharge contributes to stress-induced activation of forebrain EEG

As described above, stressors increase LC tonic discharge rates. Given that the state of stress is typically associated with enhanced arousal, it is posited that stressor-induced activation of LC neuronal discharge rates contributes to stressor-induced increases in arousal. Consistent with this hypothesis, hypotension-stress-induced activation of LC is associated with an activation of cortical and hippocampal EEG. Bilateral suppression of LC neuronal activity via peri-LC infusions of an α_2-agonist (clonidine) prevented hypotension-induced EEG activation [374]. These results indicate a dependence of hypotensive stress-induced activation of the forebrain on the LC–NE system.

3.5. NE acts within the basal forebrain to modulate forebrain EEG and behavioral activity states

The above-described studies demonstrate a role of LC neurons in the regulation of forebrain activity state. The complete array of sites within which noradrenergic efferents act to modulate behavioral state remain to be elucidated. Potential sites include cortical and thalamic, basal forebrain, and brainstem regions. Basal forebrain structures implicated in the regulation of cortical and hippocampal activity state include the general region of the basal forebrain encompassing the medial septal area/diagonal band of Broca (MS; [42,47,74,458]), the general region of the anterior hypothalamus, encompassing the medial preoptic area of the hypothalamus, (MPOA; [50,162,308,330,445]), and the substantia innominata (SI; [72,339]). Each of these regions receives a relatively dense noradrenergic innervation and thus could be involved in noradrenergic modulation of forebrain activity state [504,579]. Results of recent studies demonstrate potent EEG activating and wake-promoting actions of NE via actions within MS and MPOA, but not SI. These actions involve both β- and α_1-receptor subtypes.

3.5.1. Medial septal area

MS provides a large source of afferent input to hippocampus and exerts a strong modulatory influence on hippocampal EEG activity patterns [74]. Similarly, the SI widely innervates neocortex and exerts a strong modulatory influence on cortical EEG activity patterns [72,339].

Thus, the modulatory influence of LC on cortical and hippocampal neuronal activity state described above could involve simultaneous actions of NE within MS and SI. To test this hypothesis, infusions of NE or noradrenergic agonists were made into MS and SI in anesthetized animals. Small (150 nl), *unilateral* infusions of a β-agonist into MS elicited a robust and sustained *bilateral* activation of both cortical and hippocampal EEG with a response latency of approximately 3–8 min in the halothane-anesthetized rat [42]. In contrast, bilateral, but not unilateral, infusions of a β-antagonist blocked cortical and hippocampal EEG activation induced by either LC activation [55] or activation that occurs spontaneously in the lightly-anesthetized rat [42]. These EEG modulatory actions of NE within MS are in contrast to that observed following infusions into SI (see below).

To assess the extent to which noradrenergic efferents act within MS to modulate behavioral state, in the absence of anesthesia, the behavioral and EEG/EMG effects of β- and α_1-agonist infusions into MS were examined in the unanesthetized sleeping rat, using methods that permit performance of infusions without disturbing the animal (e.g. remote-controlled infusions; [47]). Under these conditions, infusions of either a β-agonist [47] or an α_1-agonist [48] into MS produced a robust and sustained increase in time spent awake and a near-complete suppression of REM sleep. Behaviorally, β- or α_1-agonist-induced waking resembled spontaneous waking. Additive wake-promoting actions of simultaneous stimulation of β- and α_1-receptors within MS are observed (see Fig. 2 [48]). Similar dose-dependent wake-promoting effects are observed following amphetamine infusions into MS [50], consistent with the NE reuptake blocking actions of amphetamine [261].

MS, as defined here, is an anatomically complex area containing neurons located within the medial septum, the vertical limb of the diagonal band of Broca, the islands of Calleja, and the shell region of the nucleus accumbens. The accumbens shell has anatomical connections to a variety of limbic- and autonomic-related structures and thus might modulate certain aspects of arousal [131,580]. However, results of pharmacological mapping studies suggest that the shell region of the accumbens is not the primary site within which noradrenergic receptors act to modulate EEG/behavioral state [42,47,50]. Further, although the accumbens shell receives a moderately dense noradrenergic innervation [54], LC does not appear to be a major source of noradrenergic efferents to the shell accumbens [130]. Nonetheless, the extent to which noradrenergic receptors located within the accumbens shell modulate behavioral state remains to be determined unambiguously.

Within the limits of the temporal resolution of the EEG measures (approximately 1–2 s), near simultaneous activation of cortical and hippocampal EEG was observed following noradrenergic agonist infusions into MS. A number of possible anatomical substrates could support the coordinated activation of cortical and hippocampal EEG activity, including via MS efferents to other regions involved in regulation of state, such as hypothalamus, thalamus, or midbrain. Such efferents could be either direct projections to these regions [119,334,503] or indirect via hippocampal efferents [226,502,539].

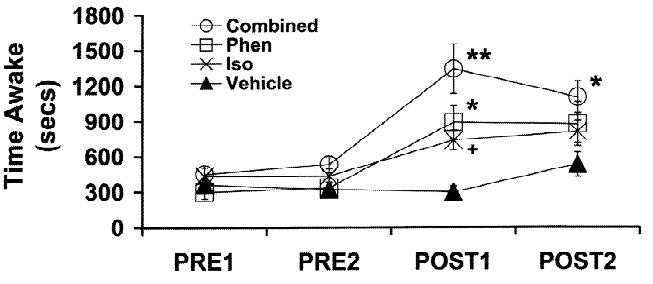

Fig. 2. Additive wake-promoting effects of combined MS α_1- and β-receptor stimulation. Shown are the effects of individual and combined α_1- and β-receptor stimulation within MS on total time spent awake as determined from EEG/EMG measures. Animals received 250 nl infusions unilaterally into MS of either: (1) vehicle; (2) 4 nmol of the β-agonist, isoproterenol (*Iso*); (3) 10 nmol of the α_1-agonist, phenylephrine (*Phen*), or; (4) 4 nmol isoproterenol+10 nmol phenylephrine (*Combined*). Marginally effective doses of isoproterenol and phenylephrine were used to better observe any additive effects of combined receptor stimulation. Symbols represent mean (±S.E.M.) time (seconds) spent in a given behavioral state per 30-min testing epoch. PRE1 and PRE2 represent pre-infusion epochs. POST1 and POST2 represent post-infusion epochs, beginning 15 min following infusion. Prior to infusion, animals spent the majority of time in slow-wave sleep. Combined stimulation of α_1- and β-receptors elicited substantially larger increases in measures of waking than that observed with stimulation of either receptor subtype individually. During POST2, the only significant alteration in time spent awake was observed in the combined-treated animals. Associated with infusion-induced increases in time spent awake was a robust decrease in slow-wave and REM sleep (data not shown). $^{*}P<0.05$, $^{**}P<0.01$ compared with vehicle-treated controls. $^{+}P<0.05$ compared with Combined-treated animals. From [48].

3.5.2. Substantia innominata

To assess the extent to which actions of NE within SI might contribute to LC-dependent modulation of forebrain EEG activity state, the EEG and behavioral effects of NE, α_1- or β-agonist infusions into SI were examined in anesthetized and sleeping, unanesthetized rat. In contrast to that observed with infusions into MS, these infusions failed to alter EEG and/or behavioral indices of arousal, even with infusion volumes substantially larger than those used in the MS studies [42,51]. The only exception to this was observed with the highest dose of NE tested, in which case the magnitude and duration of waking was substantially less than that observed with infusions into the adjacent MPOA (see below). Further, even high doses of amphetamine infused into SI had no effects on EEG and/or behavioral indices of arousal [50]. The general lack of EEG response to noradrenergic agonist infusion into SI is in contrast to the robust EEG activating effects of glutamate infusions into SI [42,339]. Taken together these results suggest that although SI modulates forebrain neuro-

nal activity state, this action is relatively insensitive to noradrenergic neurotransmission.

3.5.3. Medial preoptic area

Substantial evidence indicates a role of MPOA in the regulation of behavioral state. For example, electrical stimulation of MPOA alters sleep–wake patterns [211,475]. Importantly, infusions of either NE, α_1-, or β-agonists into MPOA in unanesthetized animals increases time spent awake [42,47,50,266,308,461,577]. When infused into sleeping rats, the increase in waking observed with these infusions is accompanied by decreases in REM and slow-wave sleep, similar to that observed with infusions into MS [51]. Increased waking is observed when infusion needles are placed throughout the anterior–posterior length of MPOA, but not when infusion needles are placed immediately posterior, or lateral, to MPOA [51]. Similar to that observed for MS, simultaneous stimulation of β- and α_1-receptors within MPOA exert additive wake-promoting effects [48]. Also similar to that observed for MS, dose-dependent wake-promoting effects are observed following amphetamine infusions into, but not outside, MPOA [51].

The wake-promoting actions of intra-MPOA infusions of NE and α_1- and β-receptor agonists are inconsistent with a decrease in waking reported following destruction of MPOA-projecting noradrenergic fibers [267]. Given these lesions disrupted the wake-promoting actions of NE or β-agonist infusions into MPOA [461], it was proposed that the wake-promoting actions of NE infusions into MPOA result from α_2- and β-mediated suppression of NE release. However, this mechanism does not explain the wake-promoting actions of direct acting α_1-agonists infused into MPOA [51]. As predicted by the wake-promoting actions of NE infusions in *intact* animals, infusions of an α_2-agonist or α_2-antagonist into MPOA exert wake-suppressing and wake-promoting effects, respectively [308]. In contrast to these observations, recent studies have observed the opposite pattern of sleep–wake effects following infusions of these drugs into MPOA [409,410]. However, in these latter studies, the α_2-agonist-induced increase in waking (determined by EMG recordings) was accompanied by moderately-slow frequency (but greater than 3–4 Hz) large amplitude cortical EEG activity, consistent with a sedative action of these infusions. The explanation for the discrepancy between these studies and the dissociation between EEG and behavioral indices of arousal is not clear. It is possible that postsynaptic α_2-receptors located within MPOA may also modulate behavioral state. In the prefrontal cortex, postsynaptic α_1- and α_2-receptors exert opposite effects in tests of working memory (see below; [16]). If this occurs within MPOA, the combined actions of both pre- and post-synaptic α_2-receptors in the presence of lesion-induced compensation may contribute to the complicated pattern of effects observed with α_2-agonists and antagonists in these studies.

3.5.4. Summary

The above-described studies demonstrate that NE acts within an extended region of the medial basal forebrain, defined anteriorally by the anterior-most aspect of the MS/diagonal band of Broca and posteriorally by the posterior-most aspect of the MPOA to modulate forebrain and behavioral activity states. The circuitry underlying the wake-promoting actions of NE within MS and MPOA remains to be delineated. The general lack of effect of NE within SI on EEG is somewhat surprising given the prominent EEG modulatory actions of this region [42,72,339] and the previously documented neuromodulatory actions of NE within SI [173]. Combined, these observations indicate that although NE acts within SI to modulate neuronal activity, these actions do not elicit a transition from sleep to waking. This conclusion is in contrast to the wake-promoting actions of high concentrations of NE when infused into SI [79]. Based on the fact that MPOA lies in close proximity to SI and MPOA is sensitive to the arousal-increasing actions of NE, it is postulated that the arousal-increasing effects observed in this one study reflects diffusion outside SI and into MPOA. To date, the behavioral/cognitive functions of NE acting within SI remain to be elucidated. Nonetheless, evidence indicates a role of SI in state-dependent attentional processes (for review, see [425]). Given the state-dependent nature of LC discharge activity, NE may act within SI to modulate state-dependent cognitive processes, such as attention (for review, see [425]).

3.6. Is NE necessary for EEG and behavioral indices of alert waking? Synergistic sedative actions of α_1- and β-receptor blockade

As described above, α_1- or β-receptors exert unique and additive wake-promoting actions, the sum of which contributes to the overall arousal state of the animal. Given this, it might be proposed that combined blockade of α_1- and β-receptors would be necessary to impact noticeably EEG and behavioral indices of arousal. In support of this hypothesis, combined administration of a β-antagonist (timolol, ICV) and an α_1-antagonist (prazosin, IP) results in a profound increase in large-amplitude, slow-wave activity in cortical EEG in animals exposed to an arousal-increasing, brightly-lit novel environment (see Fig. 3; [45]). This increase in slow-wave activity is in contrast to the minimal EEG effects observed following either ICV administration of a β-antagonist or the high-voltage spindles elicited by systemic administration of an α_1-antagonist alone [73]. The extent to which slow-wave activity is observed with combined α_1/β-receptor blockade is dependent on the time spent in the testing apparatus. Thus, although α_1-antagonist-induced high-voltage spindles or α_1/β-antagonist-induced slow-wave activity is usually observed to a small degree during the first 5 min of testing, the magnitude of these responses increases over the

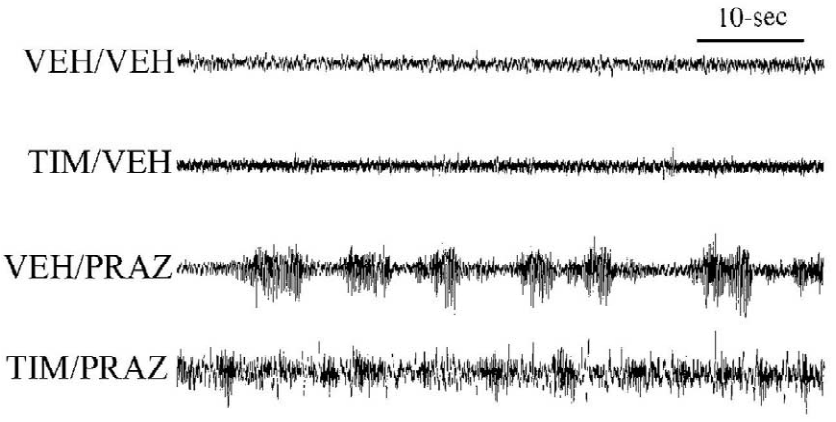

Fig. 3. Effects of α_1-receptor blockade, β-receptor blockade, and combined α_1/β-receptor blockade on cortical EEG activity. The β-antagonist, timolol, was infused into the lateral ventricles (ICV, 150 μg/2 μl) whereas, the α_1-antagonist, prazosin, was administered intraperitonally (IP, 500 μg/kg). Thirty minutes prior to testing, animals were treated with either: (1) ICV vehicle+IP vehicle (VEH/VEH); (2) ICV timolol+IP vehicle (TIM/VEH); (3) ICV vehicle+prazosin (VEH/PRAZ), and; (4) combined timolol+prazosin (TIM/PRAZ). At the time of testing, animals were placed in a brightly-lit novel environment. (A) Shown are approximately 1-min ECoG traces (printed at 5 mm/s) from the second 5-min epoch of testing. Vehicle-treated controls displayed behavioral and ECoG indices of waking throughout much of the recording session. This is reflected in sustained ECoG desynchronization (low-amplitude, high-frequency). Treatment with the β-antagonist, timolol, alone had no effects on ECoG activity. Treatment with the α_1-antagonist alone elicited substantial increases in the frequency, amplitude, and duration of HVS. In contrast to either α_1- or β-receptor blockade alone, combined α_1/β-receptor blockade a substantial increase in large-amplitude, slow-wave activity. From [45].

subsequent testing period. This suggests that although prevention of noradrenergic neurotransmission at β- and α_1-receptors has a profound impact on behavioral state, under certain high-arousal conditions this effect can be minimal. A profound suppression of behavioral activity was also observed following combined α_1- and β_1-receptor blockade, suggesting the involvement of β_1-receptors in the regulation of behavioral state [490].

In contrast to that of the unanesthetized state, in the anesthetized rat, centrally-administered β-antagonist increases cortical and hippocampal EEG indices of sedation [42,46] and blocks amphetamine-induced cortical EEG activation [49]. Thus, in the unanesthetized animal, α_1-receptor blockade more closely mimics the sensitivity of forebrain EEG to noradrenergic β-receptor blockade observed in the anesthetized state. It remains to be determined why β-receptor blockade is sufficient to prevent forebrain activation in the presence of anesthesia but not in the absence of anesthesia. Possible explanations include lower rates of neurotransmission at α_1-receptors during anesthesia compared to waking or lower rates of neurotransmission within other activational systems during anesthesia compared to waking.

3.7. Potential role of the LC–noradrenergic system in Type I and Type II behaviors

The above-described observations demonstrate that via the combined actions of α_1- and β-receptors, noradrenergic systems are an integral component of the neural architecture that supports forebrain activation in alert waking. It is of interest that Vanderwolf and colleagues have suggested that behavior can be divided into two general categories (see [534]). The first, termed Type I, can be referred to as voluntary or purposeful and includes behaviors such as walking, running and isolated movements of the head. These behaviors are always associated with hippocampal EEG activation (e.g. theta activity). Type II behaviors include licking, chewing and grooming and are not associated with hippocampal theta activity. This is of interest in that this general classification of behaviors is similarly correlated with LC neuronal discharge activity [27]. Thus, during automatic-type behaviors such as grooming and eating LC neurons display low discharge rates. However, when the animal moves its head to attend to the environment or engages in other environment-directed behaviors, LC discharge rates increase. Thus, it is possible that the classification of type I and type II behaviors in terms of hippocampal theta might, in part, result from a relationship between LC neuronal activity and type I/II behaviors.

3.8. Summary: arousal-enhancing actions of the LC–noradrenergic system

The above-described observations indicate that the LC–NE system is a potent modulator of forebrain and behavioral activity states. Under low-arousal conditions (e.g. anesthesia, sleeping) unilateral activation of LC neurons or activation of β- or α_1-receptors within either MS or MPOA is sufficient to elicit an activated forebrain and waking. Further, NE appears to be necessary for the maintenance of the alert waking state in that simultaneous blockade of α_1- and β-receptors elicits large-amplitude slow-wave cortical EEG activity and decreases behavioral indices of arousal/attention. At least in part, the wake-promoting actions of NE involve actions within an extend-

ed region of the medial basal forebrain encompassing MS and MPOA. In contrast, NE does not appear to exert robust wake-promoting actions lateral to this region, including within SI, despite the neuromodulatory actions of NE within SI. Currently, the extent to which NE acts in vivo directly within cortex and thalamus to modulate state-dependent neuronal activity patterns remains to be determined.

Systemic administration of the cholinergic antagonist, atropine, elicits a profound suppression of EEG activation [74,534]. As described above, similar effects are observed following combined blockade of noradrenergic α_1- and β-receptors [45] or systemic or brainstem administration of adrenergic α_2-agonists, which act to inhibit LC neuronal activity and NE release [46,113,127,434]. Further, inhibition of serotonergic neurotransmission [533] and blockade of dopaminergic receptors [208,514] decreases EEG indices of arousal. These observations suggest that a variety of ascending neuromodulatory systems exert robust modulatory actions on state-dependent forebrain neuronal activity. It remains for future work to identify both the redundant as well as the unique contribution of these systems to behavioral state and state-dependent processes.

4. Modulatory actions of the LC–noradrenergic system on sensory processing within cortical and thalamic circuits

4.1. Introduction

One of the unique emergent properties of the central nervous system is its ability to extract highly detailed information from the sensory surround. However, in order for an organism to make efficient and appropriate use of the continuous stream of incoming information, it must be able to regulate the sensitivity of this process as well as focus on that fraction of sensory input that is novel or relevant to an ongoing task. Such regulation of sensory processing capabilities represents the essence of an organism's ability to respond and adapt to changing environmental conditions and behavioral contingencies [242]. Although state-dependent regulation of sensory perception can readily be demonstrated in behavioral experiments, neither the cellular basis nor the circuit mechanisms responsible for this dimension of CNS function have been fully elucidated. Studies aimed at characterizing physiological correlates of attention and arousal have examined synaptic efficacy and cortical neuronal responsiveness during various stages of the sleep–waking cycle [153,472]. In general, cortical neuronal response to synaptic input is facilitated during arousal. This facilitation can either take the form of an increase in the number of evoked spikes per stimulus or by an enhancement of evoked response relative to suppression of spontaneous discharge. Additional electrophysiological experiments have investigated the influence of attentive behavior or vigilance on cortical neuronal excitability in awake animals [70,70,224,292,356,384]. In all cases, neuronal responses were facilitated from control situations during behavioral tasks that require selective attention. In many of these reports the authors discuss the possibility that output from the LC–noradrenergic system may be responsible for mediating the observed attention-related increases in cerebrocortical neuronal responsiveness. A major focus of studies on LC function has been elucidation of the cellular actions of NE within noradrenergic terminal fields, particularly thalamic and cortical regions. Investigations conducted in the 1960s and early 1970s viewed NE as a conventional putative neurotransmitter and set out to determine the excitatory or inhibitory actions of NE on target neurons. For the most part, local application of NE by microiontophoresis or stimulation of the input pathway from LC suppressed the spontaneous discharge of neurons in the cerebellum [214,215], cerebral cortex [14,497], and elsewhere in the brain [448]. These depressant responses were mimicked and blocked by adrenoceptor agonists and antagonists, respectively. Taken together, these findings suggested that NE might function primarily as an inhibitory transmitter at central synapses. However, since these earlier studies a variety of observations across multiple terminal fields have revealed a spectrum of noradrenergic actions on target neurons. These more recent observations suggest the term *neuromodulator* is a more accurate descriptor of the actions of NE within noradrenergic terminal fields.

4.2. Modulatory effects of NE on response properties of single sensory neurons

In the mid-1970s, studies in monkey auditory demonstrated a differential depressant effect of microiontophoretically applied NE on single neurons such that the spontaneous firing rate was suppressed to a greater extent than stimulus-evoked discharge in cortex [171]. This effect was interpreted as a net increase in the 'signal-to-noise' ratio. Additional work in cerebellum, hippocampus, and thalamus demonstrated that application of NE to these neurons can likewise reduce spontaneous activity while at the same time preserve or enhance neuronal responses to potent and specific synaptic input [171,343,574].

These initial studies prompted other laboratories to investigate actions of NE in a variety of sensory circuits [97,108,246,310,349,420,421,427,537]. In many cases, local application of NE was found to enhance extracellular responses of individual sensory neurons to synaptic stimuli [97,108,420,421]. In other cases, mixed effects were observed including the suppression of stimulus-evoked discharge [310,349,537]. Thus, while there was general agreement that NE could modulate neuronal responses to non-monoaminergic synaptic inputs, the exact nature of that modulation and the conditions under which it was observed were open to question.

To better characterize the electrophysiological actions of NE, Waterhouse and colleagues conducted an in-depth analysis of the net facilitating effect of NE on synaptic transmission in rat primary somatosensory cortex [547,548,550,554]. In particular, these studies examined the effects of iontophoretically applied NE on excitatory and inhibitory responses of cortical neurons to microiontophoretic application of putative transmitter substances (GABA or glutamate) or afferent pathway stimulation. Importantly, levels of NE that had minimal or no effect on spontaneous discharge activity were used in these studies. Numerous instances were observed where NE increased stimulus-evoked cortical cell discharge well above control levels [547,554]. In other cases, NE application revealed robust cellular responses to otherwise subthreshold synaptic stimuli [552]. Thus, in some cases NE enhanced the 'signal to noise' ratio, whereas in other cases NE acted to elicit an absolute potentiation of neuronal responsiveness to synaptic stimuli independent of changes in background firing. The demonstration of NE-induced facilitation of responses to direct iontophoretic application of GABA or glutamate [547] argues for a postsynaptic site of action. Similar observations were made in cerebellum of anesthetized [343–346] and awake behaving [560] animals. Combined, these observations suggest that a prominent physiological function of central noradrenergic pathways is the enhancement of the efficacy of *both excitatory and inhibitory* synaptic transmission within target neuronal circuits (see Fig. 4; [346]).

Additional studies in cortex and elsewhere determined that noradrenergic enhancement of neuronal responses to excitatory synaptic stimuli were mimicked and blocked by α_1-receptor agonists and antagonists, respectively [314,357,420,546]. By contrast, the augmentation of inhibitory responses to GABA application or afferent pathway stimulation was shown to involve activation of β-receptors

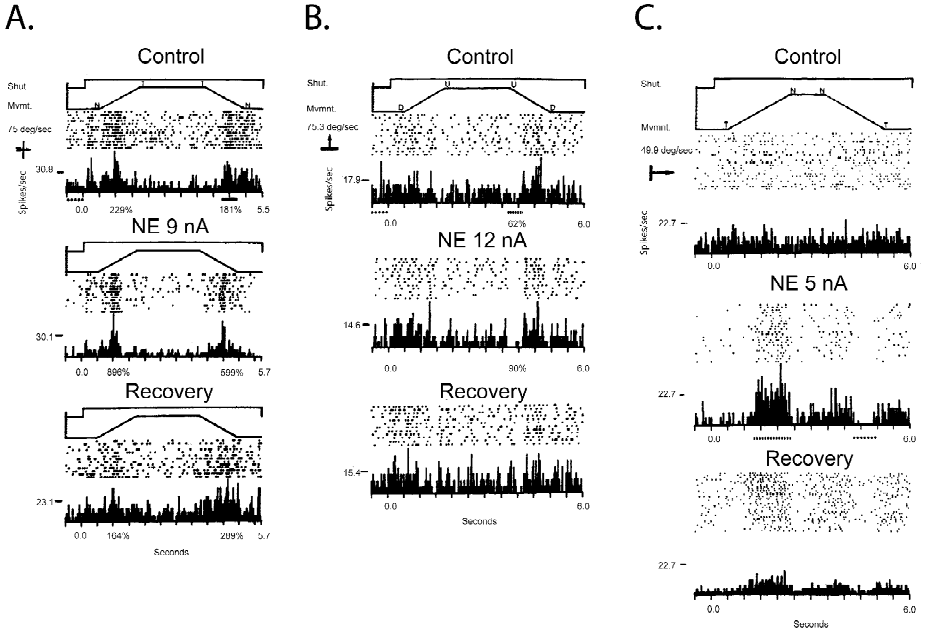

Fig. 4. Effects of NE on visual cortical neuronal responses to receptive field stimulation. Raster and peri-event histogram records illustrate the responses of three neurons in the rat visual cortex to visual stimulus presentation, before, during and after NE microiontophoresis. For each set of records, the uppermost line depicts the opening (step-up) and closing (step-down) of the shutter controlling the stimulus display. The trapezoid waveform indicates the position of the stimulus (bar of light) in visual space as it moves in the temporal (T) to nasal (N) or downward (D) to upward (U) direction and back along the same path in the reverse direction. Time is indicated along the horizontal axis of the histogram, and discharge frequency of the cell is indicated along the vertical axis. Each histogram sums unit activity during an equivalent number of stimulus presentations. Stimulus-bound excitatory or inhibitory components of these complex responses were expressed as a percentage increase or decrease of background firing rate, (dotted line in A and B), respectively. (A) The initial response (top) of this cell was an excitatory discharge as the stimulus moved across the visual field in the N to T direction and a similar period of increased activity as the stimulus traveled in the reverse direction (T to N). Local iontophoretic application of NE at 9nA (middle) suppressed spontaneous discharge to a greater extent than activity during the period of visually evoked excitations, thus yielding a net enhancement of the stimulus-bound excitatory signals. Recovery toward the control pattern of response was observed gradually after cessation of NE application (bottom). (B) For this neuron the control response (top) to movement of a horizontally oriented bar of light was an increase in firing rate preceded by an inhibition as the stimulus moved from a U to D position across the visual field. The inhibitory response (broken bar) was quantitatively expressed as a 62% suppression of spontaneous firing rate. During NE iontophoresis (12 nA, middle) the stimulus-bound inhibition was augmented from the control level (62–90%) with minimal change in background firing rate. Recovery to the control pattern of response was seen after termination of the NE ejection current (bottom). (C) For the third neuron there was no evidence of a stimulus-induced response under control conditions (top). However, during 5 nA NE administration (middle) a robust excitatory discharge (broken bar) became evident as the stimulus moved across the visual field in the T to N direction. Likewise, a prominent inhibitory response (dotted line) was revealed as the stimulus moved across the visual field in reverse direction from the N to T position. During recovery from NE iontophoresis (bottom) the cell again became minimally responsive to visual stimulation.

[435,442,550]. Other studies, particularly those in hippocampus, provided data suggesting the opposite, i.e. NE enhancement of excitatory synaptic transmission was dependent upon β-receptor mechanisms and augmentation of synaptic inhibition was mediated by α_1-receptor mechanisms [202,210,358]. These disparate results have not been reconciled but may reflect unique receptor distributions or second messenger linkages among neurons within different brain regions.

More recent work in cat [331] and rat [543] primary visual cortex has shown that iontophoretically applied NE can alter specific receptive field properties (e.g. direction selectivity, velocity tuning, response threshold) of visually responsive neurons (see Fig. 4). Additional NE-induced alterations in the receptive field structure of sensory neurons have been observed for single neurons in somatosensory and auditory cortices [182,310] and cochlear nuclei [259]. As such, these results go beyond the demonstration of simple monoamine-induced changes in the magnitude of synaptically evoked responses and begin to demonstrate that NE can selectively alter feature extraction properties of individual sensory neurons.

Additional studies demonstrate that, in vitro, the actions of NE on sensory cortical neuronal activity are both dose-dependent and receptor-sensitive [134]. Specifically, the magnitude of cellular response to direct glutamate application was maximally enhanced at a specific level of NE administration, and only moderately or minimally affected by concentrations above and below this level (see Fig. 5). Furthermore, at the highest levels of NE, suppression of neuronal responsiveness to glutamate was observed. Similar results were obtained in both normal and low Ca_2^+–high Mg_2^+ conditions, indicating a postsynaptic site of NE action. The facilitating effects of NE on glutamate-evoked responses were mimicked and blocked by α_1-receptor agonists and antagonists, respectively. Further, the high-dose suppressant effects of NE were blocked by α_1-antagonists. In contrast to these results, the glutamate-evoked discharge of some neighboring neurons in the same preparation were never enhanced at any dose of NE but rather were suppressed from control levels by NE administration. These 'suppression-only' modulatory effects were mimicked by β-receptor activation.

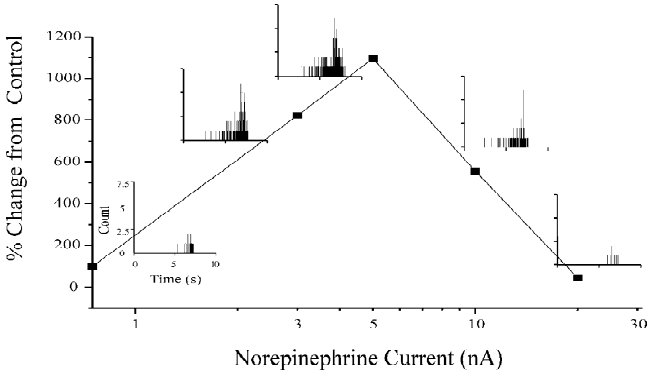

Fig. 5. Biphasic dose–response relationship for NE modulation of glutamate-evoked responses in rat sensory cortical neurons. Each point on the graph and its associated perievent histogram represent the extracellularly recorded response of a single layer V somatosensory cortical neuron (in vitro tissue slice preparation) to uniform iontophoretic pulses (20 nA, 8 s duration, 40 s cycle) of glutamate before (control, at left) and during administration of different tonic levels of iontophoretic NE (1–20 nA). NE increases the glutamate-evoked neuronal response maximally when administered at an intermediate dose. Above and below this concentration, NE does not facilitate glutamate-evoked neuronal responses to a comparable extent. Each histogram sums unit activity during six consecutive glutamate applications. From [549].

These observations indicate that within neocortex an array of noradrenergic modulatory actions are possible depending upon cellular expression of receptors and levels of NE available for interaction with those receptors. This explanation accounts for many of the previously reported mixed electrophysiological effects (both suppression and inhibition within the same terminal field) of local administration of NE [182,246,537] or activation of the LC [248,426]. More importantly, these findings suggest that physiologic activation of LC neurons and synaptic release of NE across narrow ranges might induce a state in which forebrain circuits are tuned according to behavioral demands in order to provide the greatest possible discrimination between optimal and non-optimal inputs. Clearly, such a scheme suggests an important role for the LC/NE system in attentional and other cognitive processes.

4.3. Modulatory effects of NE on response properties of single sensory neurons: intracellular studies

Intracellular studies have revealed multiple actions of NE on intrinsic membrane currents and cellular membrane response properties that could play a role in regulating signal transmission through sensory pathways as a function of behavioral state. In many preparations NE has been shown to produce a small depolarization in resting membrane potential resulting from blockade of a slow potassium current. Madison and Nicoll and others have further shown that noradrenergic blockade of a calcium-dependent potassium current (afterhyperpolarization, AHP) leads to blockade of accommodation and effectively prolongs neuronal discharge in response to membrane depolarizing events [137,166,299,326]. This latter effect is mediated by a β-receptor-linked increase in intracellular cyclic AMP and accompanied by a slight membrane hyperpolarization. Thus, according to these reports, NE can reduce spontaneous firing rates of individual neurons (via a mild hyperpolarization) while enhancing stimulus-evoked discharge (blockade of AHP and accommodation). The net outcome of these actions would be an increase in signal-to-noise ratio of neuronal response to synaptic input.

McCormick and colleagues [318,321] have also postulated that NE's depolarizing action influences a complex interaction between intrinsic membrane currents in

thalamic relay neurons. This interplay moves thalamic neurons back and forth between a non-signal transmitting oscillatory mode during sleep and a single-spike transmission or 'relay' mode during waking [318,321–323,326,378]. According to their hypothesis, reduction of LC activity and NE output during sleep contributes to a reduction in resting membrane potential in thalamic neurons by increasing the leaky potassium membrane current and decreasing an H-current [318,321]. Thus, the net effect of reduced NE outflow during sleep is a tendency for enhanced hyperpolarization of thalamic neurons, followed by activation of a T-current and subsequent generation of thalamic network oscillations. In this mode, thalamic neurons are less likely to respond or transmit afferent information. With increasing NE release, as occurs during waking, thalamic neurons are less hyperpolarized, do not exhibit synchronous membrane oscillations, and are capable of responding with a high degree of fidelity to synaptic inputs.

While it is important to establish the membrane mechanisms responsible for various noradrenergic effects, it is equally important to identify the cell types within a neural network that are capable of expressing different NE actions. Different neuronal populations within the same circuit likely have markedly different membrane properties including resting membrane potential, input resistance, membrane time constant and spike amplitude, duration and threshold [293]. Neurons also vary with respect to their patterns of spiking [110,111,293,320] and expression of membrane receptor subtypes [431]. Hence, the observed actions of NE could vary substantially depending on the constellation of membrane properties of the postsynaptic cell.

Intracellular studies in neocortical tissue slice preparations have shown that in the absence of a direct hyperpolarizing action and under current clamp conditions, bath applied NE (1–30 μM) can increase the probability of cortical neuronal spiking in response to *threshold, perithreshold and subthreshold* activation of afferent synaptic inputs [551]. This effect was reliably mimicked by α_1-receptor activation and was consistently observed in 'regular' spiking but not 'intrinsic burst' type neurons of layer V somatosensory cortex. NE-induced increases in spike probability were observed both with and without concomitant increases in EPSP amplitude. In other neurons, morphologically identified as layer V neurons with projections through the corpus callosum, NE (over the same dose range) consistently suppressed membrane responses to excitatory synaptic inputs.

Finally, in both tissue slice and acutely dissociated cell preparations, NE has been shown to augment GABA-A receptor-mediated increases in chloride conductance [89,441]. Such effects occurred in the absence of any direct effect of NE on membrane conductance and in both instances were mimicked and blocked by β-receptor agonists and antagonists, respectively. In neocortical tissue slices this effect was observed in most, but not all, layer V 'regular' spiking neurons [441].

4.4. Second messenger mediators of NE-induced alterations in synaptic efficacy

There is strong evidence to implicate the β-receptor linked cyclic AMP system in NE-mediated augmentation of GABA-induced inhibition. For example, in vivo, local administration of agents that elevate intracellular levels of cyclic AMP (e.g. β-receptor agonists, 8-bromo-cyclic AMP, forskolin, or a phosphodiesterase inhibitor) mimic or augment NE-mediated enhancement of GABA-induced inhibition of cerebellar Purkinje neurons [442]. In vitro, the membrane response of layer V pyramidal neurons to GABA was also augmented by NE, a β-receptor agonist, and 8-bromo-cyclic AMP [441]. Subsequent studies by Cheun and Yeh [89,90] in acutely dissociated cerebellar Purkinje neurons demonstrated augmentation of GABA membrane currents via intracellular diffusion of 8-bromo-cyclic AMP or the catalytic subunit of protein kinase A. It is important to point out that membrane permeable modulators of the adenylate cyclase system have also been reported to reduce GABA-gated chloride current in cultured spinal cord neurons [207,401] and transfected cell lines [355]. The discrepancies between these results may reflect fundamental differences in the physiological condition of acutely dissociated vs. cultured neurons.

Additional studies have shown that subunits of the GABA-A receptor can be phosphorylated by protein kinase A in its activated state [68,252,471,506]. Thus, the working hypothesis is that upon release NE initiates a cascade of events via postsynaptic β-receptors that results in activation of protein kinase A and phosphorylation of GABA-A receptor subunits. In Purkinje neurons this phosphorylation of the receptor leads to enhanced GABA binding capacity or chloride conductance thus providing for an overall increase in GABA response by the neuron. In hippocampal neurons phosphorylation of GABA-A receptor subunits leads to a reduction in miniature inhibitory postsynaptic currents [398]. In either case, these studies begin to identify the intracellular events that are the basis for LC–noradrenergic influences on neuronal responses to synaptically-mediated, GABAergic inhibition. Moreover, they provide additional opportunities for development of drugs that selectively alter noradrenergic-sensitive neuronal functions that may be associated with cognitive performance.

The intracellular events associated with NE-induced enhancement of stimulus-evoked excitatory discharges have not been identified with as much certainty although studies by several laboratories identify protein kinase A [114,115,191,299,422,540] and protein kinase C [116,285,365] as candidates for mediating transmitter/modulator effects on synaptically-evoked excitation. Elucidation of the intracellular cascade of events and the

accompanying membrane physiological actions that underlie NE-induced enhancement of sensory neuron responsiveness to synaptic inputs are major issues for consideration in future studies.

4.5. Local factors influencing rates of NE neurotransmission in sensory circuits

The primary means of terminating NE action after synaptic release is reuptake into the presynaptic terminal by an active transport mechanism (for review, see [36]). In recent years there has been considerable progress in characterizing the NE transporter (NET) in terms of its synthesis, distribution and physiology. As this information emerges it is well to remember that moment-to-moment regulation or long-term plasticity of the reuptake process would provide a powerful means for local control of NE actions in neural circuits. Evidence from an earlier microdialysis study suggests at least a limited degree of plasticity controlling NE reuptake. In this experiment infusions of a NE reuptake blocker (1.0 μM, desipramine) through a microdialysis probe did not alter basal levels of NE, but did increase K^+-stimulated increases in NE levels, suggesting a possible concentration-sensitive component of the NET [3].

α_2-receptors located on noradrenergic axon terminals are an additional potent mechanism for local regulation of NE release. Binding of NE to these receptors initiates a cascade of events that results in decreased release of NE as new action potentials arrive at synaptic terminals. Thus, in theory, pre-synaptic α_2-receptors provide a local feedback mechanism for counteracting excessive release of NE under conditions of high frequency noradrenergic axon stimulation. An enhanced action of presynaptic autoreceptors at higher rates of impulse activity has been observed for dopamine release in cortex using microdialysis measures [39]. It remains to be determined whether presynaptic α_2-receptors display similar-rate dependent activity.

Although a specific mechanism was not identified, Marrocco et al. [312] showed that NE release in monkey and cat visual cortex was not ubiquitous across the expanse of striate cortical tissue but, rather, was dependent upon visual stimulus-induced activation of ocular dominance columns. In their study it appeared that joint activation of the LC and visual thalamic relay circuitry were required for this selective release of NE to occur. Such local control of NE release and subsequent local expression of noradrenergic modulatory actions would provide a means of focusing the facilitating action of NE on neuronal responsiveness to afferent synaptic inputs. The cortical machinery would thus be able to selectively distinguish and perhaps amplify responses to peripheral stimuli of interest to the organism. As described above, a local amplification of NE action has been proposed as a hypothetical outcome of local interactions between synaptically released vasoactive intestinal peptide (VIP) and NE [301,302,304]. Taken together the results of these studies prompt consideration of novel mechanisms for amplifying or focusing the modulatory actions of the LC–noradrenergic pathway on sensory signal processing, perception and, perhaps, other cognitive processes.

4.6. LC activation and single neuron sensory signal processing: anesthetized studies

As reviewed earlier, LC neurons increase tonic firing rates from sleep to waking [27,167] and, within waking, display alterations in both tonic and phasic discharge activity [28,167]. Furthermore, based upon multi-unit electrophysiological recordings [27,28], it is generally acknowledged that neurons within LC discharge en masse, either tonically or phasically, in response to afferent inputs. Thus, an important step in establishing the physiological significance of the modulatory actions of NE on sensory signal transmission has been to determine the extent to which phasic or tonic activation of the LC–noradrenergic pathway influences stimulus-evoked responses in sensory cortical neurons.

4.6.1. Phasic activation of LC

Many studies have reported that either tonic or phasic activation of the LC efferent pathway either suppresses [91,240], facilitates [233,343,344] or has mixed [246,426] effects on neuronal responses to synaptic stimuli. Several of these investigations were conducted in cat where, in contrast to rat, the LC nucleus is not a homogeneous cluster of NE-synthesizing neurons [194,238,399]. Thus, despite pharmacological evidence that observed effects were noradrenergically mediated, the experiments in cat were complicated by the fact that LC stimulation may have caused activation of non-noradrenergic brainstem components.

Recently, it was demonstrated that phasic activation of LC (3–6 pulses, 0.2–0.5 ms pulse duration, 50–350 μA) could enhance both excitatory and inhibitory components of primary somatosensory cortical neuron responses to threshold-level tactile stimulation of peripheral receptive fields in anesthetized rat [423]. Such effects were optimal with condition-test intervals of 100–400 ms and were observed in cells recorded from cerebrocortical layers II through VI. The levels of LC stimulation that enhanced neuronal responsiveness to synaptic inputs were subthreshold for producing direct suppression of cortical unit spontaneous discharge. Furthermore, LC-mediated facilitating actions demonstrated anatomical and pharmacological specificity in that they were only prominent in animals where brainstem stimulation sites were in or near the ipsilateral LC and were minimal, if not absent, in animals with 85% or greater depletion of cortical NE. Overall, these findings support the general hypothesis that a major function of the central LC–noradrenergic efferent system is to facilitate the transfer of information through

sensory circuits following events that phasically activate the LC nucleus.

There are several important issues to consider when interpreting these results. First, phasic activation of LC represents an output mode that is commonly observed in awake rats and monkeys. Under normal conditions LC neuronal tonic discharge fluctuates across the continuum of behaviors associated with various stages of arousal and is periodically interrupted by burst discharges elicited by task-related or novel sensory stimuli. The results of previous studies [28,33,167] predict that phasic bursts of activity along LC efferent fibers should temporally summate at axon terminals and produce a large instantaneous release of NE within target tissue. Second, as reviewed above, evidence from microdialysis studies suggests that phasic stimulation may elicit greater increases in NE efflux than that observed with similar rates of tonic discharge activity [165]. Third, phasic impulse activity along LC axons may also promote galanin release within brain regions that receive LC efferent projections. Finally, because of the broad distribution of LC efferent fibers to brainstem, thalamus and cortex, activation of this noradrenergic pathway may influence signal processing at multiple levels of the somatosensory system [278,279,289,291,353]. Electrophysiological effects of LC manipulations observed within sensory cortex likely reflect the combined influence of NE on signal processing at brainstem, thalamic and cortical levels. The contribution of LC input to signal processing at multiple different levels of a hierarchically organized sensory pathway has not been specifically identified. New experimental strategies using multi-channel, multi-neuron recording in intact animals (see below) may be prove useful in addressing such questions.

4.6.2. Tonic vs. phasic activation of LC

Recent pilot studies conducted in anesthetized rat have examined the effects of phasic vs. tonic activation of the LC efferent path on single sensory thalamic neuronal responses to afferent pathway stimulation (Rutter, Devilbiss and Waterhouse, unpublished observations). In these experiments individual whisker-responsive neurons in the VPM thalamus were recorded during activation of the LC efferent pathway and tactile stimulation of the mystacial vibrissae on the contralateral face. For each cell recorded, the stimulus–response curve for graded mechanical deflections of the primary whisker on the contralateral face was determined before, during, and after phasic and tonic electrical stimulation of the ipsilateral LC. Control responses to whisker movement were recorded first, followed by characterization of responses to the same set of stimuli presented during tonic activation (75 μA at 5 Hz for 10 min) of the ipsilateral LC or with each whisker deflection preceded by phasic burst stimulation (75 μA at 10 Hz for 300 ms) of the ipsilateral LC. The results of a typical experiment utilizing this paradigm are shown in Fig. 6. As indicated by the histogram records (Fig. 6A–D) and the stimulus–response curves (Fig. 6E), tonic LC stimulation produced a relatively uniform increase in the magnitude of the neuronal response to threshold and suprathreshold level whisker deflection, whereas phasic activation of the LC efferent pathway had a more profound facilitating effect on responses to subliminal or perithreshold whisker deflection. A possible implication of these results is that during tonic increases in LC output such as occurs with generalized arousal, responses of sensory neurons to threshold and above threshold stimuli would be amplified. By contrast, phasic burst discharges of LC such as occur in response to novel or salient stimuli have the ability to enhance the detection of low level signals that would otherwise be subthreshold for eliciting a response. The initial interpretation of these findings is that phasic and tonic patterns of LC discharge represent physiologically distinct modes of operation for the LC efferent system. Each of these firing modes likely promotes unique changes in the stimulus–response functions of individual sensory neurons such that the signal processing capabilities of sensory networks are optimized for different behavioral contingencies.

4.7. LC activation and single neuron sensory signal processing: unanesthetized studies

A limitation of the above-described studies is the use of the anesthetized preparation. Recent experiments [133,545] employing multi-channel, many neuron recording strategies in awake rats have examined the impact of LC output on neuronal activity at multiple levels of the trigeminal somatosensory pathway. With this technique it is possible to record simultaneously the spike train activity of many ($n=20$ or more) single neurons from multiple brain regions. In these studies, spontaneous and stimulus-evoked activity of whisker responsive neurons in the VPM thalamus and barrel field cortex was monitored before and during phasic vs. tonic electrical stimulation of the ipsilateral LC nucleus. LC stimulus parameters were chosen so as to mimic the range of impulse activity normally observed in the LC efferent pathway. The trigeminal somatosensory pathway was activated by non-noxious electrical stimulation of the whisker pad through an indwelling subcutaneous electrode. Under quiet rest conditions, both phasic and tonic activation of the LC efferent path enhanced the probability of evoked spiking in both cortical and thalamic neurons according to an inverted-U function. Thus, as shown previously for iontophoretically applied NE, neuronal response to afferent pathway stimulation was increased to a maximum at intermediate levels of LC stimulation and to submaximal levels with LC activation levels above and below this intermediate level of LC stimulation. Although an inverted-U response relationship was observed in all cases, the absolute level of LC activation that resulted in a maximal neuronal response

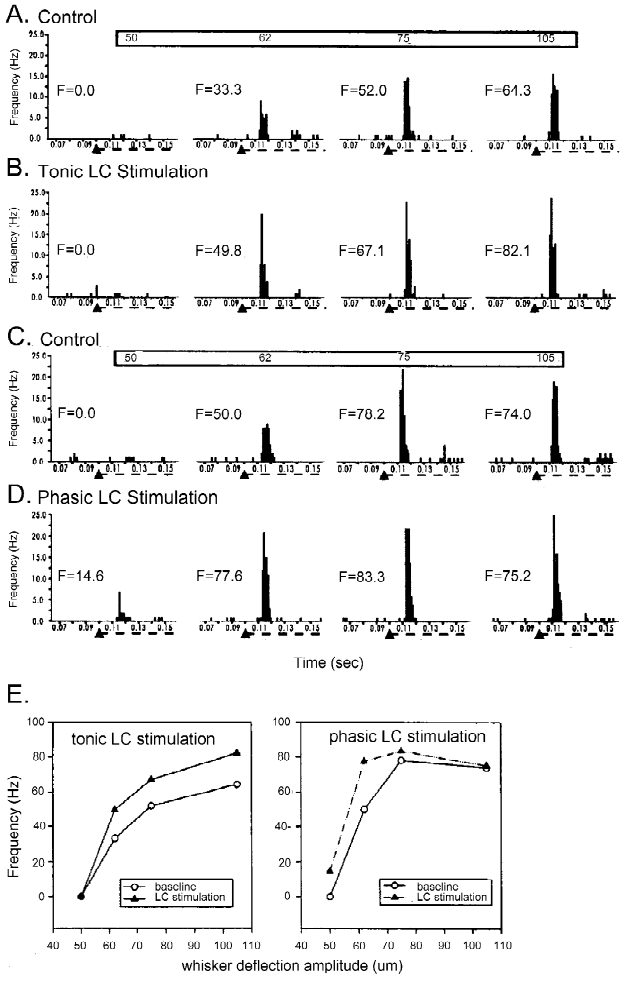

Fig. 6. Tonic and phasic-burst activation of LC produce differential enhancement of VPM thalamic neuron responses to peripheral receptive field stimulation. Poststimulus time histogram records illustrate responses of a single thalamic neuron to graded displacement (at arrowhead—50, 62, 75, 105 μm) of the 'primary' or 'central' whisker on the contralateral face; each histogram sums activity during 40 whisker displacements. Numbers above histograms indicate the frequency of discharge during the excitatory response epoch. Top panels illustrate the VPM neuronal response to graded whisker displacement before (A) and during (B) *tonic* conditioning stimulation (5 Hz for 10 min, 75 μA) of the ipsilateral LC nucleus. Tonic activation of the LC efferent pathway increased the cell's responsiveness to not only perithreshold (62 and 75 μm) but also maximal (105 μm) displacements. Lower panels illustrate the VPM neuronal response to graded whisker displacement before (C) and at fixed time intervals (300 ms) after (D) *phasic* conditioning stimulation (10 Hz for 300 ms, 75 μA) of the ipsilateral LC nucleus. Phasic activation of the LC efferent pathway increased the cell's responsiveness to perithreshold displacements (62 and 75 μm) as well as revealed a response to an otherwise subliminal stimulus (i.e. 50 μm whisker deflection). (E) Graphic representation of the effects shown in A–D. Each plotted point represents the cell's evoked excitatory discharge as a function of stimulus amplitude (i.e. whisker deflection in μm) for baseline (open circles) and LC stimulation (filled triangles) conditions. Note different influences of tonic vs. phasic LC activation on subliminal vs. threshold level stimulation of the peripheral receptive field.

varied from cell to cell. This differential action of LC output on neuronal responsiveness occurs within cortex as well as thalamus.

In some cases, LC stimulation revealed cellular responses to otherwise subthreshold synaptic inputs. This effect was similar to the 'gating' actions observed previously with iontophoretically applied NE. In some cases, activation of the LC also decreased mean response latency and reduced trial-to-trial variability of response latency for both sensory thalamic and cortical neuron responses to whisker pad stimulation. Thus, increased output from the LC (phasic or tonic) was capable of altering the magnitude and timing of cellular responses to repetitive, threshold-level synaptic input. These results are important in so far as they extend observations of LC- and NE-mediated modulatory actions into the waking condition. Further, they show that LC output can simultaneously facilitate stimulus-evoked discharge patterns at multiple levels of an ascending sensory network. It remains for future studies to identify potential differences between the effects of phasic vs. tonic activation of the LC on sensory neurons in the waking condition.

The observed effects of LC stimulation on response threshold, response magnitude and response latency in individual cells suggests that under certain output conditions the LC–noradrenergic system can optimize information processing within sensory circuits (e.g. signal detection and stimulus coding) and provide for a network-wide enhancement of sensory signal transmission. It remains for future studies to determine if the LC-mediated modulatory actions observed at the level of single cells underlie a more global impact on sensory signal representation by ensembles of functionally related neurons.

4.8. Modeling the effects of the LC–NE system on sensory neural networks

Neural modeling studies that rely upon data accumulated from animal experiments support predictions regarding the impact of the LC–noradrenergic system on sensory signal processing and behavioral performance. In the early 1990s Servan-Schreiber et al. [439] developed a 'top–down' neural network model based on experimental observations of NE-induced enhancement of 'signal-to-noise' ratios in sensory neurons. In their model, increases in signal-to-noise ratios at the cellular level improved significantly the signal detection functions of the network in which those cells operated. More recently Moxon et al. (Moxon, Devilbiss and Waterhouse, unpublished observations) have simulated the cellular actions of NE in a model of the rat sensory thalamic network in order to examine the dynamics of noradrenergic modulatory interactions within sensory circuits of the mammalian brain. The parameters used in this model were based on realistic anatomical constraints and biologically-based measurements of membrane currents and NE modulatory actions in thalamic

neurons. The goal was to explore how previously demonstrated small changes in membrane function or synaptic efficacy can sharpen the responses of individual neurons and the network as a whole to afferent input. Simulated interactions between NE and afferent inputs to the network revealed a spectrum of effects on individual neurons including both increases and decreases in response magnitude, reductions in response latency and gating of otherwise sub-threshold inputs to individual neurons. These effects follow an inverted-U function, i.e. increasing to a maximum with increasing NE-induced changes but decreasing from that maximum with further simulated increases in NE action. As such, NE effects observed in the model are in good agreement with experimental findings reviewed above. Importantly, this modeling experiment showed that despite the variety of changes observed at the single cell level, there was clear evidence that the overall function of the thalamic-reticular network could be optimized by NE-like actions. Overall, the model predicts a multitude of different NE-mediated cellular actions in LC terminal fields following activation of the LC efferent path and serves to validate results emerging from ensemble recordings of thalamic and cortical neurons in awake and anesthetized animals (see above).

5. NE-elicits long-term alterations in synaptic efficacy within neuronal ensembles

LC-dependent alterations in responsiveness to afferent information are also observed at the level of large-population neuronal ensembles. For example, potent modulatory actions of NE have been observed in an extensively studied cellular model of memory, long-term potentiation (LTP). LTP refers to a use-dependent, long-lasting increase in synaptic strength or efficacy. Thus, when excitatory synapses are rapidly and repetitively stimulated for brief periods (tetanic stimulation), the postsynaptic neurons generate action potentials more readily upon subsequent stimulation. This effect is manifested as an enhancement of the hippocampal population spike. Three forms of LTP have been described in the hippocampal formation; one involving mossy-fiber input to CA3 of the hippocampus (from the dentate gyrus), one involving the Schaffer collateral input to region CA1 (from the entorhinal cortex), and one involving perforant path input to the dentate gyrus. That LTP is readily observed in a structure critical for memory function has further stimulated interest in LTP as a possible mechanism underlying memory.

NE has been demonstrated repeatedly to influence LTP within CA3 and the dentate gyrus. For example, depletion of NE decreases the population spike observed in dentate gyrus [467], whereas NE application elicits a frequency-dependent enhancement of LTP in the CA3 subfield [218]. These effects appear to be dependent on actions of NE at β-receptors [219].

NE also elicits a long-lasting enhancement of synaptic efficacy in both the dentate gyrus and CA1 region of the hippocampus in vitro in the absence of tetanic stimulation [210,468]. These effects also appear to involve actions of NE at β-receptors [210]. In vivo, a similar facilitation of the population spike is observed in the dentate gyrus following enhanced NE neurotransmission induced by LC activation [203], α_2-antagonist administration [436] or direct application of NE [468]. The potentiating effect of NE in the dentate gyrus involves actions of both β- and α_1-receptors [87].

Importantly, enhancement of synaptic strength within the dentate gyrus is observed following behaviorally-relevant, sensory-driven increases in LC discharge rate. For example, LC neurons display a short duration (approximately 1–2 s) increase in discharge activity when a rat encounters a novel stimulus within the environment [535]. This novelty-induced activation of LC is accompanied by a short duration (approximately 20 s) enhancement in the population spike within the dentate gyrus in response to electrical stimulation of the perforant path which is attenuated by pretreatment with a β-antagonist [254].

Taken together these studies demonstrate substantial and coordinated enhancement of synaptic strength within the hippocampal formation following activation of the LC–NE system. An additional form of NE-dependent plasticity has also been described in neocortex [253]. In these studies, it was observed that NE elicits a long-term synaptic depression (LTD) of the population response recorded from layer III of visual cortex. These actions of NE appear to derive from actions at α_1-receptors and are dependent on neurotransmission at NMDA receptors [253].

Overall, these observations indicate a potentially prominent role of the LC–NE system in mediating long-lasting modifications in neurotransmission within large populations of forebrain neurons. It is particularly intriguing that these actions are observed in structures that support higher-level cognitive processes dependent on neuronal plasticity. The actions of the LC–NE system within these structures may serve an essential role in the ability of these structures to maintain optimal plasticity and, by so doing, optimize cognitive processes.

6. LC–noradrenergic modulation of neuronal energy availability

Neuronal activity is tightly linked to energy utilization. Astrocytes are a repository of stored glucose in the form of glycogen, which appears to be highly metabolically active and linked to neuronal activity [225,385,542]. For example, glycogen levels are increased during slow-wave sleep, suggesting increased glucose utilization during waking [245]. Evidence suggests that NE exerts a robust modulatory effect on astrocytic glycogen levels. Thus, application of NE to cortical slice or astrocyte cultures induces a

rapid-onset glycogenolysis [213,301,303,462]. This action of NE is mimicked by application of either an α_1-agonist or a β-agonist [463]. This initial glycogenolysis is followed by an increase in glycogen synthesis to a point where glycogen levels exceed baseline conditions. This NE-induced resynthesis of glycogen is dependent on actions of β-receptors and permits a more sustained glycogenolysis [463]. Thus, these results of in vitro studies suggest that under conditions of increased LC discharge activity, NE acts within terminal fields to increase glucose availability.

Gold and colleagues have demonstrated a substantial impact of glucose availability on memory processes via actions within multiple LC terminal fields [186,274]. As described below in Section 8, NE exerts robust modulatory actions on certain types of memory and other cognitive processes. Additional observations indicate that glucose-induced modulation of memory appears to involve alterations in rates of NE release via modulation of opiate neurotransmission [228,275]. Combined, these observations suggest: (1) NE-dependent modulation of glucose availability may have a substantial impact on learning and memory and possibly other cognitive and/or affective processes; (2) NE-dependent alterations in glucose availability may, in turn, feedback to modulate rates of NE release.

7. LC–noradrenergic-dependent alterations in transcription rates of immediate–early and other plasticity-related genes

Long-term alterations in CNS function involve, at least in part, alterations in rates of gene transcription and protein production. A set of 'immediate–early genes' (IEGs) has been identified that are activated rapidly by a variety of neuromodulators. The IEG's in this group include *c-fos*, *c-jun*, *Arc*, *nur77*, *tis-1, tis-7*, *tis-21*, *NGFI-A* and *-B*, and *zif-268*. These genes, in part, regulate transcription rates of a variety of genes. Through these actions, IEGs may provide an intervening step through which relatively short-term alterations in neuronal discharge patterns are transduced into long-term biochemical events that underlie plasticity, including learning and memory [140,198,341]. It is interesting that recent work demonstrates a prominent role of the LC–NE system in the regulation of IEGs, suggesting a potentially prominent role of this system in the regulation of long-term plasticity and the behavioral processes dependent on plasticity of forebrain circuits. For example, increased NE release elicited by systemic administration of an α_2-antagonist increases c-fos, nur77, tis-7, zif-268 and tis-21 mRNA [60,195] and protein levels [59] in rat cerebral cortex. Direct infusion of NE into cortex [496] or amygdala [494] elicited a similar increase in c-fos mRNA. Similar effects on IEG expression were observed with exposure of animals to stress [59,60,195]. The activating effects of pharmacologically- or stressor-induced increases in NE neurotransmission on IEG expression were attenuated with pretreatment of either β- or α_1-antagonists [59,60,195,494,496] as well as (in the case of stress) LC lesions [495]. Additional studies implicate the β_1-receptor subtype in β-dependent activation of c-fos [493].

More recent work demonstrates a similar critical role of the LC–NE system in waking-related c-fos and other IEG expression. For example, unilateral LC lesion prevented waking-related increases in Fos and nerve-growth factor-induced A (NGFI-A) as well as levels of phosphorylated cyclic AMP response element-binding protein (p-CREB) in the ipsilateral cortex [98,99]. Other plasticity-related cellular signals that are increased during waking and decreased by LC lesions are Arc and BDNF [100]. In these studies, unilateral lesion of LC did not alter EEG activity patterns associated with waking [98], similar to that described previously [46]. This suggests that the circuitry underlying modulation of forebrain activity state, as measured by EEG, can be dissociated from the direct actions of NE within neocortex on both gene-level plasticity-related events (IEGs) and electrophysiological information processing (see Section 4.0).

In general, the functional impact of NE-depenent rates of IEG transcription has remained unexplored. However, recent observations indicate inhibition of *Arc* protein expression impairs the maintenance phase of hippocampal LTP [197]. Thus, NE dependent alterations in rates of IEG expression likely impacts a variety of physiological systems that support higher cognitive processes, including learning and memory.

8. Actions of the LC–noradrenergic system on state-dependent cognitive processes

The above-described actions of the LC–NE efferent system suggest widespread influences of this monoaminergic pathway on processing of sensory information at both the single neuron and neuronal network levels. Consistent with these observations, additional work indicates that the LC–NE system plays a prominent role in cognitive processes related to the collection, processing, utilization and retention of sensory information. In particular, as reviewed below, experimental evidence suggests a prominent role of NE in both attention and memory processes.

8.1. Relationship between LC electrophysiological activity and vigilance in the non-human primate

Waking is associated with enhanced attention and sensitivity to environmental stimuli. Within this state, the extent to which an animal engages in focused versus scanning attention varies with the environmental configuration. The ability to focus attention on specific environmen-

tal stimuli over sustained periods can be essential for both normal behavior and survival. Vigilance, a measure of sustained attention [298,379,541], is highly correlated with forebrain neuronal activity patterns, as measured by EEG [305]. It is interesting to speculate that this relationship between EEG activity patterns and vigilance may, in part, stem from the modulatory actions of the LC–NE system on forebrain neuronal activity state, as reviewed above.

In support of a role of the LC–NE system in vigilance, Aston-Jones and colleagues have demonstrated a high correlation between *phasic* fluctuations in LC discharge activity and performance on a vigilance task in monkeys [31,32,408]. In this task, animals are required to press a lever when they detect a visual target stimulus embedded in a series of non-target stimuli. Correct behavioral responses are rewarded with delivery of a food reward. Phasic LC responses are elicited preferentially by target stimuli that evoke correct responses from the animal. Importantly, these LC responses precede the behavioral response. When the animal fails to respond behaviorally to the target stimulus, phasic LC responses are absent. Reversal training demonstrates that LC neuronal responses to target stimuli are independent of stimulus attributes and are dependent only on whether a stimulus is a target signal. Thus, in this task, phasic LC discharge is elicited by sensory stimuli that contain information relevant to goal attainment and is associated with focused attention to these stimuli.

The relationship between phasic activity and target detection is dependent on *tonic* discharge activity: phasic responses to correct target detection are observed only when tonic discharge activity falls within a relatively narrow range. At low LC discharge rates, animals appear drowsy and target stimuli fail to elicit phasic discharge. Moderately elevated tonic discharge rates (approximately 2.0 Hz) are associated with optimal target detection and maximal phasic LC response magnitude. In contrast, at somewhat higher tonic discharge levels (3.0 Hz), increased eye movements and decreased ability to foveate on a pretest eye fixation stimulus (e.g. enhanced scanning) are observed, accompanied by more frequent false alarm errors [408]. This increase in false alarms results from a decreased ability to discriminate target from distractor (decreased d') and an increase in non-target responding (decreased β factor; [33,516]).

Combined, these observations indicate a three-way relationship between tonic discharge, phasic discharge, and focused attention (vigilance). As part of this relationship, there is an inverted U-shaped relationship between tonic discharge rates and both phasic discharge and poor performance in a vigilance task: poor performance and minimal phasic discharge are observed at both low and high rates of tonic discharge. These observations suggest a critical role of phasic LC discharge in focused attention. A disruption of phasic LC discharge is also observed with stressor-induced increases in tonic discharge levels [518,519,523]. Thus, phasic discharge appears to be generally disrupted under conditions associated with elevated tonic discharge levels. Given acute stress is most likely associated with tonic discharge levels that approach or exceed 4–5 Hz it is predicted that within this range of tonic discharge activity both phasic discharge and vigilance would be disrupted. The restriction of phasic discharge to a narrow range of tonic discharge rates combined with the association between phasic discharge and focused attention suggests that pharmacological manipulations that act to restrict tonic discharge rates might facilitate focused attention under a wider range of environmental conditions than is normally the case.

Electrotonic coupling of LC neurons [94,95,229] may also play a role in performance of sustained attention tasks. In a computational model examining the relationship between vigilance task performance and tonic and phasic LC discharge rates, Usher et al. [516] demonstrate that increased coupling among LC neurons decreases tonic activity within the nucleus but renders it more likely to respond phasically to the presentation of target stimuli that trigger an appropriate sequence of motor responses. The prediction of the model is that under these conditions monkeys will attain higher accuracy on the vigilance task without sacrificing speed. Experimental results confirm these predictions but further suggest that in order to optimize performance relative to environmental conditions, the LC must transition between high coupling (low tonic discharge) and low coupling (higher tonic discharge) states. In a stable environment where task conditions are predictable, a state of selective responding (high coupling—low tonic discharge) to predictable stimuli is desirable. However, in a changing or unsettled environment multiple potentially relevant stimuli are more abundant and selectivity to predictable events is inappropriate. As such, a more labile attentive state (low coupling—higher tonic discharge) is more desirable to accommodate rapidly changing contingencies. To date, little information exists regarding the functional significance of electrotonic coupling within LC on higher cognitive and affective processes. In addition to the evidence for neuron-to-neuron coupling, recent work by Williams and colleagues [9] has demonstrated heterocellular electrotonic coupling between LC neurons and astrocytes. It remains for future work to determine how this connection between glia and neurons affects LC function and, subsequently, NE release.

8.2. Effects of noradrenergic manipulations on attention

The observations described above suggest a prominent role of the LC–NE system in at least a subset of attentional processes. Additionally, the ability of NE to enhance cortical function by reducing 'noise' and/or facilitating processing of relevant sensory signals suggests that the LC–NE system might enhance cognitive function under 'noisy' conditions where irrelevant stimuli could impair

performance. Results from studies conducted in rodents, monkeys, and humans in which rates of noradrenergic neurotransmission were manipulated largely support these hypotheses. For example, NE depletion produces deficits in the performance of non-aged, otherwise intact animals on a variety of tasks when irrelevant stimuli are presented during testing (for review, see [333]). Thus, the addition of distracting visual stimuli at the choice point in a T-maze produces a greater disruption of performance in NE-depleted rats than in sham-treated animals [369,416]. Similarly, the presentation of irrelevant, auditory stimuli impairs sustained attention in rats with forebrain NE depletion, although these animals perform normally under non-distracting conditions [80]. Further, NE depletion increases conditioned responses to irrelevant stimuli while decreasing responses to relevant stimuli [295,437,438]. Thus, overall, impairment of LC–NE neurotransmission impacts attentional and other cognitive tasks under conditions associated with high-demand and/or increased arousal. These actions are in contrast with the relatively minimal impact of noradrenergic manipulations on tasks requiring simple learning. An exception to this rule is the aged [107,277] or combined LC/nucleus basalis lesioned animal [204], suggesting that NE actions may become significant to simple learning in the compromised brain.

In humans, manipulations of noradrenergic neurotransmission affects attentional and memory processes in a manner similar to that observed in animal studies (for review, see [333]). It has been proposed that tasks affected by these manipulations have in common a sensitivity to fronto-striatal damage, including planning, working memory, sustained attention, and some forms of covert orienting (for review, see [333]). However, it is important to note that not all tasks sensitive to frontal cortex damage appear sensitive to manipulation of noradrenergic neurotransmission, such as attentional-set shifting [117].

Supporting a causal relationship between LC discharge rates and vigilance are preliminary observations indicating that experimenter-induced manipulations of LC neuronal activity rates alter performance in a vigilance task. Thus, in one hyperactive monkey that displayed elevated tonic discharge rates and poor vigilance task performance, pharmacological suppression of tonic LC discharge enhanced phasic discharge and improved task performance. Conversely, when LC neurons were pharmacologically activated in animals performing well, performance was impaired [231].

The LC–NE system may be particularly sensitive to novel environmental stimuli. For example, enhanced LC discharge rates are observed when rats encounter novel stimuli [535]. Further, pharmacological manipulations that enhance NE release increase physical contact/interaction with a novel stimulus located within a familiar environment [132]. In contrast, when examined in a novel environment, enhanced noradrenergic neurotransmission decreases attention to an individual object, possibly reflecting enhanced scanning of the environment [25,43]. These observations indicate that not only is the LC particularly responsive to novelty, but that this system exerts a strong modulatory influence on exploration of and interaction with novel aspects of the environment. Novel stimuli, by their very nature, may be particularly salient given the unknown potential of these stimuli to pose a threat or provide sustenance.

Combined, the above-described evidence suggests a role of the LC–NE system in the attendance to salient environmental stimuli (including novel stimuli), particularly under distracting conditions. Substantial evidence suggests memory modulatory actions of the LC–NE system, although the precise role of this system in memory remains unclear (for review, see [403,584]). Discussion of this complex topic exceeds the scope of this review. However, as reviewed by Sara [424], NE-dependent modulation of attentional systems might impact memory processes indirectly.

8.3. ERPs/P300

The above-described observations suggest the involvement of the LC–NE system in attention-related cognitive processes. Studies on event-related potentials (ERPs) provide additional support for this hypothesis. ERPs are widely-distributed voltage fluctuations time-locked to sensory, motor, or cognitive events that are generated from large populations of neurons and are extracted from EEG recordings using signal averaging techniques. The P300 component of human ERPs is elicited in response to novel and/or task-related stimuli and is thus thought to have particular relevance to attentional or mnemonic processes. P300-like components are also observed in monkeys and have been studied as an animal model of attention. Although the origin of the widely-distributed P300-like potentials has not been determined, evidence suggests that the LC–NE system, with its anatomical and physiological properties, represents a candidate system for the modulation of these potentials [169,170,389,391]. For example, bilateral LC lesion in squirrel monkeys selectively decreases the P300 components of the ERP to infrequent tone pips [390]. Similarly, inhibition of LC firing and NE release with systemic administration of the α_2-agonist, clonidine, also decreases P300 components [507]. These results further suggest an important role of the LC–NE system in the modulation of cortical responsiveness to sensory information and the modulation of attentional processes.

8.4. Working memory

Substantial evidence indicates that NE exerts a potent modulatory influence on working memory via actions within the prefrontal cortex (PFC). In primates, PFC serves a critical role in inhibiting the processing of irrelevant

stimuli [255,573]. In monkeys, this region can be functionally subdivided, with the dorsolateral PFC associated with proper performance of the spatial delayed-response task, a test of spatial working memory. Damage to the catecholaminergic innervation of the PFC impairs performance in tests of working memory [69,109,449]. Although initial evidence suggested a prominent role for dopamine in mediating the effects of these lesions [69], subsequent work clearly demonstrates a substantial role for NE in the modulation of working memory (for review, see [16]).

Experimental evidence collected from nonhuman primates suggests an important, facilitatory role of NE in the proper regulation of PFC-dependent behavior through actions at post-synaptic α_2-noradrenergic receptors. Thus, α_2-agonists, such as clonidine or guanfacine, improve performance in dorsolateral PFC-dependent tasks in monkeys with neurotoxin-induced catecholamine depletion [20,78,430]. The ability of α_2-agonists to improve working memory is most readily observed under conditions that challenge PFC function, such as during the presentation of distracting stimuli [18,232]. Importantly, α_2-agonists do not enhance hippocampal-dependent spatial memory [452], inferior temporal cortex-dependent visual feature discrimination [20,469], parietal cortex-dependent covert visual-spatial attention-shifting ability [572], or perirhinal cortex-dependent visual feature recognition memory [22].

The NE-dependent nature of working-memory may have relevance to age-related changes in cognitive function. For example, aged monkeys, which have a decreased catecholaminergic-innervation of PFC [188], display deficits in tests of working memory [38]. Administration of α_2-agonists to aged monkeys markedly improves performance of the delayed response task [17], especially when irrelevant information is present during the delays [18,232]. These beneficial effects of α_2-agonists are independent of their ability to induce hypotension or sedation [17] and are blocked by α_2-, but not α_1-antagonists [17,21].

The beneficial effects of α_2-agonists on working memory performance involve drug actions directly within the PFC. For example, direct infusion of α_2-antagonist into PFC impairs working memory performance [284], whereas direct infusion of α_2-agonists into PFC improves performance in both young and aged monkey or rat [15,311,509]. Electrophysiological studies reveal comparable actions of α_2-selective compounds within PFC. For example, iontophoresis of the α_2-antagonist, yohimbine, reduces delay-related PFC neuronal activity in a test of working memory [283,428]. In contrast, systemic clonidine increases delay-related PFC neuronal discharge, an effect reversed by iontophoretic application of an α_2-antagonist [283]. Pharmacological studies indicate that enhancement of PFC-related cognitive function results from stimulation of the α_{2A}-subtype which is preferentially distributed postsynaptically [17,18].

In contrast to that of α_2-receptors, α_1-receptor stimulation within PFC exerts a debilitating effect on working memory performance. Thus, infusions of an α_1-receptor agonist into the PFC of rats [24] or monkeys [311] impairs working memory performance, an effect reversed by co-administration of an α_1-antagonist [24]. Further, stress, which is associated with elevated rates of NE release, also impairs working memory [23]. This effect is blocked by infusions of an α_1-antagonist infused directly within PFC [61].

As reviewed by Arnsten [16], these observations suggest that under moderate rates of release associated with quiet, alert waking, NE facilitates working memory performance via actions at α_{2A}-receptors located within PFC. Under conditions associated with low PFC NE levels (e.g. aging), performance is impaired due to insufficient α_{2A}-receptor stimulation of α_{2A}-receptors. α_{2A}-receptors have a higher affinity for NE than do α_1-receptors [368] and thus under normal conditions (moderate arousal levels), minimal α_1-mediated neurotransmission occurs. Under conditions of higher arousal (e.g. stress), associated with increased rates of NE release, stimulation of α_1-receptors impairs working memory. Thus, similar to that observed with NE-modulation of vigilance, there is an inverted-U relationship between rates of NE neurotransmission and performance in tests of working memory. It should be noted that impaired working memory and vigilance associated with higher rates of NE release (stress), is not necessarily detrimental to the animal. Presumably, increased labile attention associated with higher arousal levels, which occurs at the expense of working memory, serves an important survival benefit under appropriate environmental conditions.

The actions of NE within PFC on working memory are similar to those of DA (for review, see [16]). Thus, similar to that observed with thalamic/cortical firing patterns, sensory responsivity, and behavioral state: multiple ascending modulatory systems likely act within PFC to modulate working memory. Although DA and NE systems appear to co-modulate PFC-dependent working memory, there likely exists important distinctions between the actions of these two catecholamines on the modulation of this cognitive process. For example, it has been proposed that in working memory tasks DA primarily participates in the maintenance of on-line information, whereas NE modulates sensitivity to distracting stimuli [101,102,333,415].

8.5. NE modulates the facilitatory effects of emotional arousal on memory via actions within the basolateral amygdala nucleus

Memory strength can be enhanced by emotionally-arousing conditions [92]. Steroid (e.g. glucocorticoids) and catecholamine (e.g. epinephrine) hormones participate in this arousal-induced enhancement of memory [161,187,187,227,249,286]. In the case of epinephrine, circulating epinephrine stimulates release of central NE via

stimulation of β-receptors located on vagal afferents (see [328]). The memory enhancing actions of both arousing stimuli and circulating epinephrine appear to involve enhanced release of NE within the amygdala. For example, epinephrine-induced memory enhancement is blocked by intra-amygdala infusions of a β-antagonist [287,329]. The basolateral nucleus of the amygdala appears to participate in the modulation of a variety of memory processes, including inhibitory avoidance as well as cued and spatial water-maze tasks [328,371]. Recent evidence indicates that this subnucleus of the amygdala is a critical site of action in the memory-modulating effects of NE. Thus, post-training infusions of NE into the basolateral nucleus of the amygdala enhances spatial learning, whereas β-antagonist infusions have an opposite effect on performance in this [209] and an inhibitory avoidance [158] task. Further, glucocorticoid-induced enhancement of performance in an inhibitory avoidance task is blocked by intra-basolateral amygdala infusion of β-antagonists. This effect is observed with either β_1- or β_2-blockade and is not observed when infusions are placed within the central nucleus of the amygdala [404].

Similar to that observed with β-receptor-dependent neurotransmission, α_1-agonists and antagonists also facilitate or impair, respectively, performance in an inhibitory avoidance task when infused directly within basolateral amygdala [160]. This facilitatory action of α_1-receptors on memory appears to result from the α_1-dependent enhancement of β-receptor-mediated cAMP production [159]. For example, β-antagonists block the α_1-agonist-induced enhancement of memory [160]. In contrast, α_1-antagonist infusions into basolateral amygdala shift the dose–response curve for β-agonist-induced memory enhancement to the right [159]. Finally, direct infusion of the cAMP analog, 8-bromo-cAMP, increased retention similar to that observed with β-agonist.

As mentioned above (Section 6), glucose modulates memory performance in the same tasks sensitive to noradrenergic manipulations via modulation of NE release. Evidence indicates that some of the actions of glucose on memory involves actions within both the amygdala [275,332] and the medial septal area [405]. Thus, NE-dependent increases in glucose availability may contribute to memory associated with high-arousal events via glucosed-dependent increases in NE release within the amygdala.

The ability of circulating epinephrine to increase NE release within the amygdala appears to involve an activation of noradrenergic efferents arising from the nucleus of the solitary tract (NTS, A2 noradrenergic neurons), which receives ascending projections from the vagus [243] and which projects to the amygdala [581]. Thus, lidocaine infusions into the NTS block epinephrine-induced increases in NE release within the amygdala [570]. Further, pharmacological manipulations that activate NTS neurons result in an increase in NE release within the amygdala [569]. Finally, reversible inactivation of the NTS attenuates the memory-modulating effects of posttraining epinephrine [567] and performance in a shock-based inhibitory avoidance task [568]. Thus, noradrenergic projections from the NTS play a prominent role in amygdala-dependent memory associated with high-arousal conditions. Nonetheless, the LC provides a moderately dense innervation of the basolateral and central nuclei of the amygdala [154]. Further, NTS projects to LC both directly [350,524,530] and indirectly, via PGI, [531]. Moreover, suppression of excitatory input arising from PGI, via infusion of either lidocaine or a GABA agonist, immediately following training impaired retention of an inhibitory avoidance response [105]. Thus, noradrenergic efferents arising from both NTS and LC provide a modulatory influence on memory associated with high arousal via actions within the basolateral amygdala. Actions of NTS on memory processes could involve direct projections to the amygdala or indirect via the LC.

The above-described observations indicate a prominent role of NE in the regulation of memory under conditions of high arousal. In support of a role of NE in emotionally-related memory in humans, Cahill et al. [77] demonstrated that β-receptor blockade in human subjects blocks the typically observed enhanced memory for emotionally activating images relative to emotionally-neutral images. Recent work suggests that β-receptors participate in the reconsolidation following reactivation in both appetitively and aversively motivated tasks. Thus, β-receptor blockade attenuates memory following reactivation in either a radial arm maze or passive avoidance paradigms [402]. These results further suggest a prominent role of central noradrenergic systems in the modulation of memory.

9. Noradrenergic modulation of motor function

Currently, much of the information regarding the actions of NE within the brain concerns actions on sensory systems. Less is known about the actions of NE on central motor systems. However, available information suggests, as in sensory neuronal circuits, LC efferent pathway stimulation or NE application enhances motoneuron responsiveness to excitatory synaptic inputs [177,178,412,532,566]. Further, in vitro, locally applied NE increases the excitability of motor cortex pyramidal tract neurons by changes in rheobase and blockade of accommodation [166]. Likewise, an extended series of studies in cerebellum, the area of the brain responsible for coordinating muscular activity and complex movement, has revealed a spectrum of noradrenergic neuromodulatory actions at the level of Purkinje neurons. The actions of NE and LC output on these primary output cells of the cerebellar cortex include augmentation of both excitatory and inhibitory responses to synaptic inputs and direct putative transmitter application [174,343–346]. Finally,

recent work in cat indicates that descending LC efferent pathways exert multiple actions on spinal interneurons, motoneurons, spinal reflex activity and postural mechanisms so as to regulate motor performance [179,400]. Thus, the LC efferent pathway appears to facilitate neuronal function at multiple levels of the motor system. In conjunction with its proposed role in facilitating sensory signal transmission according to the behavioral demands of the organism, LC output may also coordinately regulate the speed and efficiency of motor responses to salient stimuli. As such, an overall outcome of LC activation may be both increased detection and response to stimuli that have survival value for the organism.

10. Noradrenergic participation in the behavioral and electrophysiological effects of amphetamine-like stimulants

Amphetamine (AMPH)-like stimulants, including cocaine, have in common the ability to facilitate dopaminergic and noradrenergic neurotransmission. Some, but not all, of these agents also enhance serotonergic neurotransmission [261,265]. Over the years much insight has been gained regarding the neural mechanisms through which these drugs exert their reinforcing, locomotor-activating, and stereotypy-inducing actions. In each of these behavioral effects, enhanced dopaminergic neurotransmission plays a particularly prominent role. This is in contrast to a relatively minimal participation of NE in these behavioral effects of psychostimulants. However, it should be noted that most studies that attempted to examine the involvement of noradrenergic systems in the behavioral actions of AMPH-like stimulants used either lesions or a single noradrenergic receptor subtype-selective antagonist. As mentioned above, recent observations indicate synergistic actions of α_1- and β-receptors on EEG indices of sedation as well as memory. This raises the possibility that the combined actions of these receptors play a greater role in certain behavioral effects of AMPH than previously identified.

The vast majority of studies that examine the neural bases of the behavioral effects of stimulants have utilized moderate to high doses of these drugs, relevant to addiction and/or schizophrenia. All of the above-listed behavioral actions of stimulants are superimposed on the well-documented arousal-enhancing actions of these drugs, which predominate at low doses. At low doses, AMPH-induced arousal is accompanied by alterations in state-dependent cognitive processes (e.g. attention). Combined, these actions contribute to the widespread use of low-dose stimulants both recreationally and clinically. Moreover, modulation of sensory processing and associative mechanisms may contribute to long-lasting alterations in neural circuits that presumably underlie addiction. Given the widespread use and abuse of AMPH-like stimulants, it is surprising that little is known concerning the neural mechanisms underlying AMPH-induced increases in arousal. As reviewed, substantial evidence indicates that noradrenergic systems modulate a variety of arousal- and attention-related electrophysiological activity and behavior. Based on this evidence, it can be argued that AMPH-induced enhancement of NE release might influence the activity state and information processing ability of neural circuits supporting distinct behavioral states and state-dependent attentional and memory processes. However, for the most part, the extent to which AMPH-induced alterations in arousal and cognitive function are, in fact, dependent on actions of NE remains to be determined.

10.1. Participation of NE in amphetamine-like stimulant-induced arousal

Limited evidence suggests a contribution of NE in the actions of AMPH-like stimulants on behavioral state and state-dependent cognitive processes. For example, Berridge and colleagues demonstrated that AMPH acts within the medial basal forebrain to increase alert waking [50,51]. The pattern of sites where AMPH infusions increase and do not increase waking is identical to that observed with infusions of NE and NE receptor agonists [42,47]. For example, infusions of AMPH into MS and MPOA, but not SI, elicit dose-dependent increases in alert waking. Further support for a role of NE in the arousal-enhancing actions of AMPH is the ability of central pretreatment with a β-antagonist to block intravenous AMPH-induced EEG activation [49]. Finally, it has been demonstrated recently that there exists a close relationship between low-dose AMPH-induced arousal and AMPH-induced increases in extracellular NE levels within PFC [53].

10.2. NE-like actions of amphetamine-like stimulants on sensory neurons

In addition to the above described locomotor activating, rewarding, and arousal-inducing actions of stimulants, individuals who self-administer these drugs report heightened awareness of the sensory surround and an increased capacity for mental and physical work [75,106,164,175,183,184]. In laboratory animals, acute cocaine also increases sensitivity to environmental stimuli [236,269,381,429,571]. Because of their ability to elevate central synaptic levels of NE, 5HT and DA, AMPH-like stimulants possess the ability to impact monoaminergic neurotransmission, and thus sensory processing, via actions at two levels. First, these drugs can reduce the output of monoaminergic nuclei via activation of somatodendritic autoreceptors located on monoamine-containing cell bodies [120,121,147,393–395]. A second potential site of drug action is within monoaminergic terminal fields. Based on studies of low threshold NE actions in cortical and subcortical sensory circuits reviewed above, it is reasonable to

expect that stimulants can exert NE-like modulatory influences within sensory pathways. In this regard, it is interesting that recent studies have revealed an array of actions of cocaine on single sensory neurons that closely resemble the cellular actions of NE in sensory circuits [40,234,423] and cerebellum [553]. Moreover, NE- but not dopamine-containing fibers innervate prominently the sensory pathways of the brain, thus providing further support for a role of NE in the sensory-related effects of stimulants. Consistent with these findings is the report that AMPH-induced (2.5 mg/kg, i.p.) changes in auditory gating are reversed by pretreatment with either noradrenergic α_1- or β-antagonists [476].

10.2.1. Cocaine-induced alterations in receptive field properties and response threshold of somatosensory cortical neurons

Studies by Waterhouse and colleagues demonstrate cocaine-induced alterations in the magnitude and latency of thalamic and cortical somatosensory neuronal responses to perithreshold stimulation of afferent pathways or direct application of putative transmitter substances [40,234,423]. In other work (Bekavac and Waterhouse; Rutter and Waterhouse, unpublished observations), extracellular responses of rat somatosensory cortical neurons to mechanical displacement of 'central' and 'peripheral' whiskers on the contralateral whisker pad were monitored before and after systemic cocaine administration (0.25–2.0 mg/kg, i.v.). Central whisker deflection produced a maximal excitatory response, while equivalent stimulation of a peripheral whisker yielded a lesser response. Cocaine increased or only mildly suppressed responses to central whisker stimulation, whereas neuronal responses to peripheral whisker displacement were progressively reduced, sometimes to the point of complete suppression. These results suggest that a net action of systemically administered cocaine on sensory cortical neurons is to suppress substantially responses evoked from the periphery of the receptive field while preserving or increasing responses to stimulation at the center of the receptive field. The outcome of such actions is that the effective size of a cell's receptive field is reduced. In other experiments cocaine (1.0 mg/kg i.v.) lowered threshold for short latency excitatory neuronal responses. These cocaine-induced and NE-like [543,552] alterations in response threshold and receptive field dimensions of primary somatosensory neurons could lead to changes in the way tactile stimuli are perceived.

10.2.2. Cocaine effects on somatosensory thalamic neurons

Additional studies in rat thalamus have also revealed NE-like modulatory actions of cocaine on single neuron responses to afferent pathway stimulation. For example, cocaine (0.75 mg/kg i.v.) consistently decreased response time and reduced the trial-to-trial variability of response latency in neurons of the VPM thalamic nucleus [423]. In some instances stimuli that were otherwise subthreshold for producing responses in individual VPM neurons, elicited strong discharges following cocaine administration (i.e. NE-like gating effects). In other studies using cumulative dose paradigms (Rutter et al., unpublished observations), cocaine had minimal effect on the magnitude of stimulus-evoked discharge at the lowest dose tested, enhanced stimulus-evoked responses at intermediate doses and caused a decrease in the response to central whisker stimulation at the highest dose tested. Thus, as with NE, cocaine's effect on the magnitude of VPM thalamic neuron responsiveness to synaptic input follows an inverted-U dose response curve. Finally, microdialysis experiments have shown that injection of cocaine at 0.75 mg/kg i.p. increases NE levels in VPM thalamus at times that are coincident with cocaine-induced changes in VPM thalamic neuron responsiveness to afferent synaptic inputs [423].

Overall, these results indicate that acute systemic administration of cocaine causes increases in NE efflux in VPM thalamus and can reduce the latency and increase the magnitude of thalamic sensory neuron response to peripheral receptive field stimulation. Additionally, cocaine can also reduce the threshold of detection for sensory inputs to VPM thalamic neurons. One consequence of these actions may be that cocaine permits lower level sensory signals to gain access to sensory circuit operations and, thus, achieve significance for the organism at the expense of more intense inputs. Combined, these drug-related facilitating actions on VPM thalamic neuron responsiveness could underlie some of the alterations in sensory experience reported by humans following cocaine self-administration.

10.3. Contribution of the LC–NE system to amphetamine-like stimulant abuse

The basis for a role of the LC–noradrenergic system in opiate addiction and, in particular, the withdrawal response to these compounds is now well established and the literature on this topic is extensive (see reviews—[7,93,96,185,196,307,411]; and [6,8,30,206,230,256,413]). However, despite the well-documented ability of AMPH-like stimulants to elevate central levels of NE, the involvement of the LC efferent pathway in the development, maintenance and extinction of patterns of psychostimulant drug abuse is less clear. As emphasized in this review, increased output from the LC is correlated with increased cortical arousal and enhanced transmission of sensory signals, both of which may have a positive impact on cognitive function, i.e. improved clarity of thought, heightened perception of the sensory surround, etc. Such effects may be pleasurable and desirable in social settings and, as such, may in their own right be rewarding and

reinforcing with respect to periodic, recreational use. Harris et al. ([205]) have shown that cocaine produces synchronous oscillations (0.8 Hz) of membrane potential in neurons throughout the LC nucleus. These authors suggest that the resulting synchronous discharge of NE-containing LC cells may augment transmitter release in noradrenergic terminal fields throughout the neuraxis, thus providing a basis for cocaine-mediated arousal.

Persistent use of amphetamines or cocaine elicits long-lasting neuroadaptations as evidenced by cellular/molecular changes in various brain regions [565] and numerous behavioral phenomena including sensitization to drug-induced locomotor effects, drug-related place preference, and drug craving accompanied by high rates of relapse to drug seeking and drug taking. Craving and re-instatement of drug seeking and drug taking behaviors are particularly important dimensions of psychostimulant abuse because of the high incidence of relapse among former, chronic psychostimulant users. Re-instatement of drug seeking and drug taking behaviors can be induced either by conditioned cues, drug priming or environmental stressors, such as footshock. Recently, Stewart and colleagues (see reviews—[151,276,444] have shown that NE is involved in stress-induced, but not cocaine (priming dose)-induced, re-instatement of cocaine seeking. The results of α_2 agonist and 6-hydroxydopamine lesion studies indicate that this effect likely involves ventral noradrenergic bundle projections from NE-containing cell groups in the lateral tegmentum to the central amygdala and bed nucleus of the stria terminalis [443]. Thus, stress-induced re-instatement of drug seeking does not appear to involve the LC–NE efferent pathway. On the other hand Darracq, Blanc et al. ([126,141]) and others ([62,136,459]) have used alpha receptor blocking strategies and α_{1b} receptor knockout mice, respectively, to provide compelling evidence that α_{1b} noradrenergic transmission contributes to the locomotor and rewarding effects of cocaine and amphetamine in rodents. Since these psychostimulant actions involve LC–NE innervated regions of the brain, it is likely that the LC efferent path is involved in these dimensions of cocaine and amphetamine action.

10.4. Summary

The above-described observations indicate that AMPH-like stimulants produce NE-like alterations in sensory neuron responsiveness to synaptic stimulation. Likewise, stimulant effects on arousal and attentional processes likely involve, at least in part, alterations in noradrenergic neurotransmission. Given that stimulants alter both LC neuronal discharge activity and rates of NE release within terminal fields, the arousal-, attention-, and/or sensory perception-modulatory actions of stimulants may involve actions at the level of the noradrenergic cell body and/or within the noradrenergic terminal field.

11. Summary: LC and behavioral processes

An impressive array of information has been collected concerning the electrophysiological and anatomical properties as well as the neural and behavioral actions of the LC–NE system. Alterations in activity of a small number of LC neurons are broadcast globally across functionally diverse regions of the brain, affecting neuronal populations of immense number (excluding basal ganglia). However, within this system there exists a degree of specificity conferred by the pattern of fiber termination, receptor subtype distribution, and second messenger coupling that provides an infrastructure for unique and differential actions across multiple cortical and subcortical terminal fields. One common theme linking the multiplicity of electrophysiological and behavioral observations is the ability of NE to influence processes associated with the collection and processing of sensory information essential for the guidance of subsequent behavior.

From these observations, at least two general levels of action of the LC–NE system can be identified. *First*, LC neurons contribute to the induction of both neuronal and behavioral activity states appropriate for the reception of sensory information (e.g. waking). *Second*, within the awake state, the LC–NE system exerts modulatory actions on a variety of higher cognitive (and affective) processes necessary for the extraction and processing of salient sensory information from an environment filled with a multitude of stimuli, both salient and non-salient. These actions of the LC–NE system involve multiple noradrenergic receptor subtypes located within a variety of cortical and subcortical structures. Importantly, the actions of NE on both cellular and behavioral processes can display complex, non-monotonic dose–response relationships. Thus, qualitatively distinct modulatory actions of the LC–NE system on a given physiological or behavioral process may occur with across varying rates of LC discharge.

Whether at the level of single neurons, neuronal ensembles, or behavior, there exists a high degree of consistency of NE action: NE facilitates responding to relevant stimuli while suppressing responding to irrelevant stimuli. In doing so, NE permits the organism to collect and process information most critical to its survival. The extent to which a stimulus is deemed salient, or necessary, will be dependent on environmental, homeostatic, and experiential factors: water may be highly salient only when in a water-deprived state. Under certain conditions, the collection of salient information may require attending to a single stimulus or set of stimuli for relatively prolonged periods. *Phasic* discharge appears closely linked to focused attention (e.g. vigilance, attendance to novel stimuli). This mode of LC discharge is sensitive to tonic discharge rates, with robust phasic discharge observed only within a relatively narrow range of tonic discharge rates. Under other conditions, typically associated with higher arousal levels (e.g. threat, stress), it may be necessary to scan the

environment for rapid detection of multiple stimuli. Such modulation of attentional resources may well need to occur under both appetitive and threatening conditions. Novelty may be particularly salient, given novel stimuli need to be assessed quickly and efficiently to determine the extent to which they pose a threat or a source of sustenance/pleasure. Threatening stimuli (as opposed to appetitive stimuli) may be particularly salient given that there is often a need to respond quickly in the presence of such stimuli. The actions of NE on energy availability may support neural circuits under conditions associated with increased demand. Moreover, the long-term actions of NE, whether at the level of the gene (IEGs), neural ensembles (LTP/LTD), or behavior (memory) may facilitate rapid and accurate response selection when a stimulus is re-encountered or an environment suggests a particular level of preparedness is warranted (e.g. chronic stress).

The exact relationship between rates of neurotransmission and behavior likely depends on the behavioral process in question. For example, in the case of vigilance, lower rates of NE release are associated with increased sedation and impaired performance in tests of vigilance. In contrast, at higher rates of NE release highly alert animals attend to multiple stimuli in the environment and are less able to focus attention on a specific stimulus (e.g. increased scanning), and thus also display impaired performance in tests of vigilance. This inverted-U relationship between rates of LC discharge and vigilance contrasts with a relatively linear relationship between arousal levels and LC neuronal activity. Combined, the close association between phasic discharge and focused attention (observed both in the context of vigilance and responding to novel stimuli) and the interaction between phasic and tonic discharge suggests that pharmacological manipulations that restrict tonic discharge rates might facilitate focused attention under environmental conditions not typically associated with focused attention.

Over the years, multiple hypotheses have been posited concerning a role of the LC–noradrenergic system in specific cognitive and affective processes, such as anxiety, attention, etc. However, the above-reviewed observations indicate that the LC–NE system may be viewed as a general and global modulator of neural circuits that process specific aspects of sensory information and that guide behavioral action. If this view of a relatively low-level, general function of the LC–NE system is true, is it appropriate to assign highly specialized higher-level functions to this system? The answer is likely both yes and no. The facilitation of *salient* information processing is a general feature of LC efferent pathways, which could explain, on a broad functional level, the actions of this neurotransmitter system across a wide-range of species, whether or not they possess highly developed cortical and limbic systems. On the other hand, in primates and other mammals, NE is found within discrete cortical and limbic neural circuits, which support a finite set of specific high-level affective and cognitive processes. Thus, via actions within these individual circuits, NE is likely to impact highly specific affective and cognitive processes. This conclusion assumes NE-releasing fibers are located within circuits that subserve specific affective and cognitive processes. The complete absence of noradrenergic fibers within the basal ganglia would indicate that the LC–NE system does not modulate directly behavioral processes supported by these structures. The lack of a noradrenergic innervation of the basal ganglia may explain why NE, unlike dopamine, does not appear to contribute to the strong reinforcing and/or motivating actions of AMPH-like stimulants. It remains for future work to determine the actions of the LC–NE system across the variety of LC terminal fields and the consequence of these actions on affect, cognition and behavior.

12. Clinical implications

The LC–NE system impacts widespread neural circuits involved in the collection and processing of sensory information. As such, dysregulation of LC–NE neurotransmission might impact any number of cognitive and affective processes. In keeping with this, multiple cognitive and affective disorders have been posited to involve a dysregulation of noradrenergic neurotransmission. Much of the evidence suggesting a potential role of the LC–NE system in these disorders derives from the therapeutic actions of pharmacological treatments that target noradrenergic neurotransmission. However, it is essential to note that a pharmacological intervention can be therapeutic while not targeting the specific biological deficit causing the symptoms. In most cases, there is very little evidence indicating a direct, causal relationship between dysfunction of noradrenergic neurotransmission and a particular behavioral disorder. This may simply reflect the difficulty of assessing CNS processes in vivo in humans and the limitations of indirect measures that are necessarily used to assess central noradrenergic neurotransmission in humans. Alternatively, this may suggest that a dysregulation of noradrenergic systems is not a primary etiological factor in cognitive and/or affective dysfunction associated with most psychiatric/behavioral disorders. In this latter view, the LC–NE system may well represent an appropriate target for pharmacological intervention because this system modulates a dysfunctional neural circuit, and not because the LC–NE system itself is dysfunctional. The extent to which noradrenergic systems are causally involved in cognitive and affective symptoms associated with a variety of behavioral disorders remains a critical question for future work.

Currently there is ample reason to believe that noradrenergic systems either play a contributory role, or are appropriate targets for pharmacological intervention, in a number of cognitive and affective disorders. A comprehen-

sive review of this topic exceeds the scope of the current review. Nonetheless, it may be useful to survey a subset of these disorders within the context of the above-reviewed information concerning the arousal and state-dependent cognitive functions of the LC–NE system (see Fig. 7).

12.1. Attention deficit hyperactivity disorder (ADHD)

As discussed above, considerable evidence suggests that the LC–NE system modulates both attention and arousal-related processes. One disorder where, based on this information, it can be proposed that noradrenergic systems might participate either in the etiology or in the pharmacological treatment of this disorder is that of attention deficit hyperactivity disorder (ADHD). ADHD is a childhood cognitive disorder originally reported in 1902 [477]. Although the definition of the core features of ADHD has evolved with time, a primary disability associated with ADHD appears to be in the volitional control of attention and impulsive behavior (for review, see [460]). It is of interest, given the above described impact of NE on PFC-dependent processes (e.g. working memory), that many of the features of ADHD resemble those associated with PFC dysfunction (for review, see [16,82]).

Currently, pharmacological treatment is the most effective form of treatment, with low-dose AMPH-like stimulants being the most widely prescribed pharmacological treatment for ADHD (for review, see [192]). These drugs ameliorate the core symptoms of inattentiveness, hyperactivity and impulsivity in 75–95% of ADHD individuals

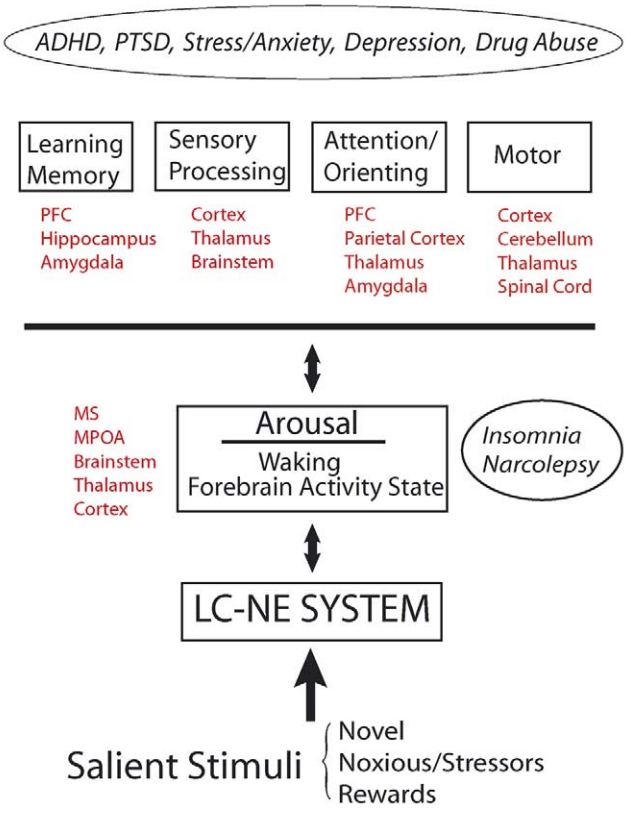

Fig. 7. Relationship between basic physiological processes modulated by the LC–noradrenergic system (Rectangles) and potential clinical relevance of these actions (Ovals). A variety of appetitive and aversive stimuli elicit increases in tonic and/or phasic LC discharge activity. These stimuli have in common being perceived as salient to the animal. NE released from LC efferents modulates a large array of behavioral and physiological processes. These include behavioral and forebrain neuronal activity state. Dysregulation of the LC–NE system at this level of action may be reflected in the dysregulation of arousal level associated with either insomnia or narcolepsy. Additionally, dysregulation at this level may be reflected in the dysregulation of a large array of state-dependent cognitive and affective processes. Within the waking state, the LC–NE system acts directly within sensory, attentional, memory, and motor circuits. Together these actions facilitate the effective interaction with an ever-changing environment. Dysregulation of LC–NE neurotransmission at these levels of action could be associated with a variety of affective and cognitive disorders including attentional disorders (ADHD), affective disorders including stress- and/or anxiety-related (PTSD, Depression), as well as drug abuse. Independent of an eitiological role in these disorders, manipulations of noradrenergic neurotransmission may by clinically efficacious via the neuromodulatory actions of NE within dysregulated cortical and subcortical circuits that give rise to specific cognitive and affective deficits associated with these disorder. Potential LC terminal fields associated with each basic process are listed adjacent to the specific physiological process (Red Text). Direct or indirect descending projections from cortical and subcortical forebrain structures associated with behavioral state could provide additional modulation, either inhibitory or feed-forward, of LC discharge (indicated by the bidirectional arrows). Dysregulation of these pathways could contribute to dysregulation of the LC–NE system in certain clinical disorders.

(for review, see [460]). At the dose-range used in the treatment of these disorders, currently available evidence indicates that these drugs primarily result in increased extracellular levels of NE and dopamine, but not serotonin [265]. Given the above-reviewed evidence linking noradrenergic systems in the regulation of attention, arousal, and PFC-dependent cognitive function, it appears reasonable to propose that therapeutic actions of these drugs in the treatment of this disorder involves, at least in part, enhanced noradrenergic neurotransmission. Additional support for this hypothesis is that other drugs that target noradrenergic neurotransmission exert therapeutic actions in the treatment of ADHD. These include noradrenergic α_2-agonists, particularly post-synaptic selective agonists, such as guanfacine [26,84,220,222,223], as well as NE-selective reuptake inhibitors (for review, see [58,397]).

If the LC–NE system is a target of pharmacological manipulations used in the treatment of ADHD, the neural mechanisms underlying the therapeutic actions of these treatments remains unclear. Work by Arnsten and colleagues suggests that post-synaptic α_2-receptors located within PFC may facilitate focused, goal-directed behavior as assessed in tests of working memory. Thus, increased stimulation of these receptors may contribute to therapeutic actions of drugs used in the treatment of ADHD. Alternatively, at higher doses than those used clinically, stimulants have been demonstrated to decrease *tonic* LC discharge activity. This is of interest because Aston-Jones and colleagues have observed that increased tonic discharge above a certain level is associated with less robust phasic discharge and diminished focused attention and increased impulsivity (e.g. poor target detection accompanied by high false alarm responding). These results suggest the possibility that ADHD is associated with increases in tonic LC discharge activity. If true, low-dose stimulants (and other pharmacological treatments) may result in a moderate suppression of tonic discharge activity into a range that is associated with optimal phasic discharge and optimal focused attention. Available evidence indicates that this suppression of tonic discharge would be accompanied by enhanced release of NE within noradrenergic terminal fields. The net effect of lowered tonic discharge rates, increased levels of NE and enhanced phasic discharge on cortical function remains to be determined. Multiple actions of stimulants and other drugs used in the treatment of ADHD at both the levels of the LC nucleus and LC terminal fields may contribute to the therapeutic efficacy of pharmacological treatments used in ADHD.

Given the relatively common use of AMPH-like stimulants for the treatment of ADHD, it is surprising that currently we lack information regarding neural mechanisms underlying the therapeutic actions of these drugs in this disorder. The vast majority of work on the neurobiology of these drugs has been conducted with doses that exceed greatly those used clinically. This is important because these compounds display profound dose- and drug-dependent neurochemical actions. For example, although relatively high doses of AMPH increase extracellular levels of serotonin, at lower doses AMPH has very little impact on extracellular levels of serotonin, suggesting serotonin is not necessary for the beneficial actions of these drugs in this disorder [265]. Consistent with this conclusion, even relatively high doses of methylphenidate do not increase extracellular serotonin levels [262]. Recent studies by Kuczenski and colleagues demonstrate that at low doses, which likely mimic doses used clinically, methylphenidate enhances extracellular levels of hippocampal NE while having little impact on nucleus accumbens dopamine levels [263,264]. It remains to be determined whether this reflects a differential sensitivity across monoamines or terminal fields to low-dose methylphenidate. Future work needs to characterize more completely the NE and DA responses to clinically-relevant doses of methylphenidate and other AMPH-like stimulants within cortical and subcortical NE and DA terminal fields.

12.2. Sleep/arousal disorders

The fact that noradrenergic neurotransmission can initiate and maintain sustained periods of alert waking suggests that noradrenergic systems may participate in, and are appropriate potential targets in the treatment of, sleep and arousal disorders. This includes both disorders of excessive arousal (insomnia) and excessive sedation (narcolepsy).

12.2.1. Insomnia

The above described studies demonstrate unambiguously that enhanced rates of NE neurotransmission are sufficient to elicit the awake state [47]. These studies demonstrate that rates of NE neurotransmission above a certain level appear incompatible with the sleeping state. This suggests that inappropriate LC discharge activity could contribute to one or more forms of insomnia. Given the PFC and amygdala project to LC, it is feasible that activity in either of these, or other structures associated with higher cognitive and affective function, could lead to inappropriate LC neuronal discharge activity and thus interference with sleep.

12.2.2. Narcolepsy

NE exerts a robust modulatory action on normal waking. Given the actions of AMPH-like stimulants on NE neurotransmission, it is of interest that these drugs are commonly used in the treatment of narcolepsy. As mentioned above, hypocretin neurons provide a relatively dense innervation of LC. Evidence indicates that hypocretin has robust wake-promoting actions [65,152,199,392]. Combined, these observations suggest that hypocretin regulates

wakefulness in part through modulatory actions within LC. Recent work implicates a dysregulation of hypocretin neurotransmission in narcolepsy. For example, studies of genetically-linked narcolepsy in dogs [290] and hypocretin knock-out mice [88] demonstrate a clear relationship between reduced hypocretin function and this sleep/arousal disorder. Further, postmortem examination of tissue from human narcoleptics has revealed a major reduction (>90%) of hypocretin-containing neurons in the brains of these individuals [382,511]. This suggests that a degeneration of hypocretin-producing neurons and the subsequent decrease in hypocretin release within LC contributes to at least a subset of the symptoms of narcolepsy. Despite these observations, it is unlikely that actions of hypocretin within LC are the sole mechanism underlying the arousal and cognitive deficits associated with this disorder. For example, hypocretin also acts within the same basal forebrain region within which NE acts to exert wake-promoting actions [152,510]. Further, when infused into the fourth ventricle, immediately adjacent to LC, substantially weaker wake-promoting actions of hypocretin were observed than those observed following infusions into the lateral ventricle immediately adjacent to the medial septal area [152].

In addition to excessive sleepiness and impaired cognitive function, narcolepsy is associated with episodes of cataplexy. Work of Siegel and colleagues demonstrates that LC neurons cease firing during cataplectic episodes in a canine model of narcolepsy [575]. This observation suggests that cessation of LC neuronal discharge activity may contribute to cataplexy. Interestingly, cataplectic episodes that occur in narcolepsy are not associated with sedation. This observation is in apparent contradiction to the conclusion that noradrenergic neurotransmission is essential for alert waking. However, it is important to note that complete cataplectic episodes typically last in the range of 10 s to a few minutes [575]. Previous pharmacological studies demonstrate that the onset of EEG and behavioral indices of sedation can take minutes following acute impairment of noradrenergic neurotransmission [42,45,47,52]. This is in contrast to that seen with LC activation in the anesthetized rat, in which an activated forebrain is observed within seconds of increased LC discharge rate. Thus, the forebrain activating effects of increased LC discharge appears to have a shorter latency than the sedating effects of suppression of noradrenergic neurotransmission. This could reflect inertia in second messenger systems and/or actions of other neurotransmitter systems involved in the maintenance of an activated forebrain.

In conclusion, it appears that the LC–NE system may well be dysregulated in narcolepsy, in part, due to a dysregulation of hypocretin neurotransmission within LC. Further, due to the wake-promoting and cognitive-enhancing actions, the LC–NE system appears to represent an appropriate target for pharmacological treatment of this disorder.

12.3. Panic and post-traumatic stress disorders

Much has been written about the potential involvement of noradrenergic systems in a variety of mood and anxiety-related disorders (for review, see [11,464,498]). Discussion of this broad and complicated topic exceeds the scope of the current review. However, it is worth noting that much of the original impetus behind speculation of an anxiogenic action of NE was the observation that stressors were particularly potent at activating the LC–NE system. As reviewed above, recent work demonstrates a similar sensitivity/responsivity of LC neurons to appetitive stimuli. These observations indicate that enhanced rates of NE release per se are not sufficient to induce a state of anxiety. Thus, rather than conveying aversive content, the LC–NE system may convey more general information regarding stimulus attributes, such as salience. Further, although the terms stress and anxiety are frequently used interchangeably, the exact definition of these terms and the relationship between stress and anxiety are poorly understood. Most animal work involving noradrenergic systems examines stress-related processes rather than anxiety per se. Stress is operationally defined as the presence of certain, readily measureable physiological responses. Emotional state is less easily measured. As such, it is difficult to make definitive conclusions regarding the role of noradrenergic systems in anxiety and other affective processes on the basis of results obtained in animal studies. In fact, it has been suggested that in contrast to an anxiogenic action, the LC–NE system might serve an anxiolytic function under stressful conditions [559]. Studies in humans indicate increased anxiety following peripheral manipulations that increase NE neurotransmission [85]. However, it is likely that these manipulations impact autonomic processes as well as overall arousal state. The relationship between generalized arousal and anxiety has not been fully explored in humans. Thus, there remains a certain level of ambiguity regarding the extent to which these results indicate direct actions of noradrenergic systems on anxiety-related circuits.

Among stress-related disorders, substantial evidence indicates a hyperreactivity of noradrenergic systems in panic disorder as well as post-traumatic stress disorder (PTSD; see [464]). This is consistent with the above-described ability of prolonged or intense stressors to sensitize noradrenergic systems to heterotypic stressors in animals. Excessive reactivity of noradrenergic systems in PTSD suggests a causal relationship between NE release and panic in patients suffering from these disorders. In support of this hypothesis is the ability of increased noradrenergic neurotransmission via systemic administration of α_2-antagonists to elicit episodes of panic in these patient populations, but not normal controls [67,465]. In the case of PTSD, panic attacks can be associated with memories of traumatic events (see [464]). As reviewed above, NE modulates both strongly emotional memory via

actions within the amygdala and synaptic strength of neuronal ensembles in hippocampus and neocortex (see [464]). These actions could provide the neural substrates for intrusive memories associated with PTSD.

Aside from a possible contributory role of NE to panic/anxiety associated with these disorders, excessive reactivity of central noradrenergic systems in these patient populations could lead to dysregulation of arousal and state-dependent memory and/or attentional processes also associated with these disorders.

13. Summary

In conclusion, results from a variety of investigations of LC and/or NE function reveal a surprising degree of cohesion: whether at the level of the single cell, populations of neurons, or behavior, NE increases the organism's ability to process relevant or salient stimuli while suppressing responses to irrelevant stimuli. This involves two basic categories of action. First, the system contributes to the initiation of behavioral and forebrain neuronal activity states appropriate for the collection of sensory information (e.g. waking). Second, within waking the LC–NE system modulates sensory information processing, as well as attention and memory processes. NE-dependent modulation of long-term changes in synaptic strength, gene transcription and other processes suggest a potentially critical role of this system in experience-dependent alterations in neural function and behavior. These actions appear independent of affective valence (e.g. appetitive vs. aversive) and are dependent on only whether a stimulus is salient (relevant) to ongoing and/or future behavioral action. Whether a given stimulus is deemed salient may well differ with environmental and/or experiential conditions. Many of the neural actions of NE display a non-monotonic, dose-dependent nature, with both low and high levels of NE release associated with diminished information processing (single-cell level) or diminished attention or memory capacity (behavioral level). The actions of the LC–NE system on sensory information acquisition and processing likely occur in conjunction with facilitatory actions on motor responses.

Combined, these observations suggest that the LC–NE system is a critical component of the neural architecture supporting interaction with, and navigation through, a complex world. As such, it appears reasonable to propose that dysregulation of this system might contribute to dysregulation of a variety of attention and/or arousal-related processes, including those associated with ADHD, sleep and arousal disorders, as well as a variety of affective disorders, including PTSD. Independent of whether noradrenergic systems contribute to the etiology of these disorders, noradrenergic systems may well be an appropriate target for pharmacological intervention in the treatment of specific attention, memory and/or arousal dysfunction associated with these disorders. Consistent with this, limited evidence suggests that AMPH-like stimulants, those drugs currently used in the treatment of ADHD and narcolepsy, impact attention and arousal-related processes, at least in part, through alterations in noradrenergic neurotransmission. It remains for future research to delineate completely the multiplicity of cognitive and affective actions of noradrenergic systems and identify the terminal fields and receptor subtypes associated with these actions. The better understanding of the wide range of behavioral actions of this neural system may well provide insight into the development of better pharmacological treatments of a variety of cognitive and affective disorders.

It is important to note that noradrenergic systems do not act in isolation to regulate behavioral state and cognitive functions. NE is one of a number of neuromodulatory neurotransmitters that arise from small brainstem nuclei and widely innervate the CNS. These include dopaminergic, serotonergic, histaminergic, cholinergic and hypocretin systems. To varying degree, these systems share a number of additional features, including state-dependent discharge rates, responsivity to sensory stimuli independent of affective valence, and actions on behavioral/neuronal activity state and information processing. Importantly, these systems appear to be highly interconnected suggesting coordination of activity across these systems. Future research will need to determine the extent to which there is communication between these modulatory systems and the functional consequence of the combined actions of these neurotransmitters on forebrain neuronal activity and higher cognitive and affective processes.

Finally, it should be noted that much of the work on the neural and behavioral functions of the LC–NE system has necessarily focused on rather crude manipulations and measures of function. The nature of the measures used requires a relatively large effect size to conclude an impact of NE neurotransmission on a particular system/process. In contrast, normal human behavior is likely highly sensitive to slight alterations in activity rate and activity patterns of neural systems which are difficult to measure with available methodology. Consider, for example, the impact of a poor night of sleep on daytime function. The affected individual may feel mentally fatigued, inefficient, easily distracted, etc. The day may seem particularly long and difficult. Were the person asked, they would indicate that cognitive and affective processes were impaired. Moreover, if presented with an unexpected challenge; i.e. an emergency situation requiring immediate and decisive action, they might not respond optimally. Yet, to an observer, overt behavior appears unaltered. The person wakes up on time (sleep wake schedule is not altered), drives to work without apparent effort (perception, spatial memory, and motor function appear normal), speaks normally, remembers the names of all family members and co-workers (declarative memory appears normal), and

conducts business as needed (cognitive function appears normal). In short, the person appears to function normally using any number of variables typically collected in behavioral studies. An observer of overt behavior would conclude that poor sleep has no impact on behavior and behaviorally relevant cognitive and affective processes. Such a conclusion would clearly miss the mark. The challenge for future studies on the actions of the LC–NE system will be to delineate the more subtle cognitive and affective consequences of: (1) relatively minor, though highly physiologically-significant, alterations in noradrenergic neurotransmission; (2) relatively minor NE-induced alterations of neuronal activity within NE terminal fields. This may well be particularly important when considering the role of this system in clinical disorders and the behavioral significance of the combined actions of the multiple ascending modulatory systems.

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