HHS Public Access

Author manuscript

Brain Res. Author manuscript; available in PMC 2017 June 15.

Published in final edited form as:

Brain Res. 2016 June 15; 1641(Pt B): 197–206. doi:10.1016/j.brainres.2015.11.022.

Evidence for a specialized role of the locus coeruleus noradrenergic system in cortical circuitries and behavioral operations

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Abstract

The brainstem nucleus locus coeruleus (LC) innervates the entire central nervous system and is the primary source of norepinephrine (NE) to the neocortex. While classically considered a homogenous modulator of forebrain activity by virtue of highly widespread and divergent axons, recent behavioral and pharmacological evidence suggest this nucleus may execute distinct operations within functionally distinct terminal fields. Summarized in this review are the anatomical and physiological properties of the nucleus within a historical context that led to the interpretation of the nucleus as a homogeneous entity with uniform and simultaneous actions throughout its terminal fields. Also included are findings from several laboratories which point to a more nuanced model of LC/NE function that parallels that seen in other forebrain-projecting monoaminergic nuclei. Such compartmentalized models of the nucleus promote the idea that specific LC circuits are involved in discrete behavioral operations, and therefore, by identifying the networks that are engaged by LC, the substrates for these behaviors can be identified and manipulated. Perturbations in the functional anatomy and physiology of this system may be related to neuropsychiatric conditions associated with dysregulation of the LC-noradrenergic system such as attention deficit hyperactivity disorder. Recent findings regarding the organization and operation of the LC/NE system collectively challenge the classical view of the nucleus as a relatively homogenous modulator of forebrain activity and provide the basis for a renewed scientific interest in this region of the brain.

Historical perspectives of the locus coeruleus

The locus coeruleus (LC) is the largest noradrenergic nucleus in the brain, and is the primary source of norepinephrine (NE) to the neocortex. This widespread projection system innervates the entire central nervous system, modulates sensory processing, motor behavior, arousal and cognitive processes (McGaughy and Sarter 1998; Devilbiss and Waterhouse 2000; Berridge and Waterhouse 2003; Devilbiss and Waterhouse 2004; Hurley, Devilbiss et

al. 2004; Devilbiss, Page et al. 2006; Moxon, Devilbiss et al. 2007; McGaughy, Ross et al. 2008; Newman, Darling et al. 2008; Sara 2009; Cain, Wasserman et al. 2011), and is implicated in a wide array of disease states (Berridge and Waterhouse 2003). First described by Johann Christian Reil as a dark band of tissue in human brain in 1809 (Swanson 1976), this bilateral structure sits lateral to the wall of the fourth ventricle and medial to the mesencephalic trigeminal nucleus in the pons and is relatively well conserved across mammalian species (Russell 1955; Foote, Bloom et al. 1983). LC has been most extensively studied in the rat, in which it contains an estimated 1,600 neurons of both multipolar and fusiform morphologies (Swanson 1976; Foote, Bloom et al. 1983). The borders of LC were originally defined on the basis of Nissl staining (Russell 1955) which were later shown to correspond well with the structure of the nucleus as delineated by catecholamine fluorescence (Dahlström and Fuxe 1964). These cells stain intensely for dopamine β hydroxylase (DBH), the enzyme that catalyzes the conversion of dopamine (DA) to NE. The body of LC can be subdivided into three main components: an anterior pole, a compact core which expands dorsoventrally as it progresses caudally, and a posterior pole (Loughlin, Foote et al. 1986). Reports have been made of different zones of this nucleus being occupied by neurons of varying morphology. The anterior pole comprises mainly large multipolar cells which stain intensely for DBH (Grzanna and Molliver 1980; Loughlin, Foote et al. 1986), while the posterior pole has been described to contain mostly fusiform neurons (Olson and Fuxe 1971; Grzanna and Molliver 1980; Loughlin, Foote et al. 1986). The compact core of the nucleus, however, contains both cell types: the more dorsal portion of the compact core has been found to contain primarily densely packed fusiform neurons with smaller somata, while the more ventral portion contains larger multipolar neurons (Swanson 1976; Satoh, Tohyama et al. 1977; Loughlin, Foote et al. 1986; Loughlin, Foote et al. 1986).

Afferent regulation and efferent topography of LC

Golgi impregnation and DBH immunostaining have shown that LC neurons possess highly ramified dendritic arbors that extend well beyond the dense core of the nucleus (Swanson and Hartman 1975; Swanson 1976; Foote, Bloom et al. 1983; Shipley, Fu et al. 1996) where it receives afferent information from a multitude of regulatory centers. Anterograde and retrograde tracing, and electron microscopic studies have shown that LC receives input prefrontal cortex (PFC) (Arnsten and Goldman-Rakic 1984), bed nucleus of the stria terminalis (Van Bockstaele, Peoples et al. 1999) hypothalamic nuclei (Peyron, Tighe et al. 1998), raphe nuclei (Pickel, Joh et al. 1977), amygdala (Van Bockstaele, Colago et al. 1998), solitary nucleus (Van Bockstaele, Peoples et al. 1999), nucleus paragigantocellularis and nucleus prepositus hypoglossus (Aston-Jones, Ennis et al. 1986), indicating that it integrates information from the autonomic nervous system, neuroendocrine nuclei, stress and limbic circuitry, as well as higher order cognitive centers. While it is clear that this nucleus is regulated by a number of functionally and neurochemically distinct structures and cell types, the efferent projections of LC innervate virtually all levels of the central nervous system. Unlike more conventional sensory and motor systems which are characterized by a tight point-to-point topography, only crude relationships between anatomical location and morphology of individual neurons with their terminal fields have been described Mason and Fibiger first revealed an efferent topography of the nucleus by injecting the retrograde tracer

horseradish peroxidase into various structures throughout the neuraxis. They found that injections into hippocampus or septal nuclei consistently filled cells located in the dorsal but not ventral portion of the core of the nucleus, whereas injections into motor-related structures such as caudate-putamen and cerebellum labeled both ventral and dorsal portions. Injections into thalamus produced labeling in the posterior pole but not in more rostral portions, whereas hypothalamic injections labeled cells in the anterior pole. Furthermore, injections into amygdala and cortical structures, frontal regions in particular, produced labeling of neurons scattered throughout all three axes of the compact core of the nucleus (Mason and Fibiger 1979; Loughlin, Foote et al. 1986).

These findings were confirmed and explored further by both Satoh, and Loughlin and colleagues, who showed that morphologically distinct cells within the subdivisions of LC have different efferent targets (Satoh, Tohyama et al. 1977; Loughlin, Foote et al. 1986). Several investigators also showed that the projection from LC to cortex is primarily ipsilateral (Jones, Halaris et al. 1977; Mason and Fibiger 1979; Waterhouse, Lin et al. 1983), whereas subcortical structures receive bilateral input from LC (Simpson, Altman et al. 1997). Experiments in which multiple retrograde tracers were injected into different structures in the same brain have shown that LC contains a fairly high proportion of cells which possess divergent axons innervating functionally distinct terminal fields. By pairing injections of different tracers into cortex and cerebellum, Nagai and colleagues (Nagai, Satoh et al. 1981) showed that some LC neurons possess axons innervating both structures, but others project to one area or the other. This was corroborated by others who showed that pairs of injections into cortex and thalamus (Ader, Room et al. 1980) or cortex and cerebellum (Steindler 1981) similarly resulted in distributions of multi labeled neurons innervating multiple structures simultaneously. Loughlin and colleagues likewise showed that injections of paired fluorescent retrograde tracers into various cortical regions yielded high proportions of double labeled LC neurons, especially when injections were made in the same or proximal sagittal planes. They therefore concluded that single LC cells innervate their terminal fields in a geometrically defined manner rather than on a functional basis (Loughlin, Foote et al. 1982). More recently, data from our laboratory has shown that LC neurons innervate functionally related structures along ascending sensory pathways (Simpson, Altman et al. 1997), providing a circuit mechanism for simultaneous modulation of information along the same sensory pathway.

Organization of noradrenergic cortical afferents

DBH immunohistochemical staining has also shown that noradrenergic fibers are present throughout virtually the entire forebrain. Morrison and colleagues reported that DBH fibers innervate the different cortical layers in unique ways, but the laminar variations in geometry and orientation are generally consistent between cortical regions (Morrison, Grzanna et al. 1978). Specifically, DBH fibers in layer I are primarily parallel to the pial surface, layers II and III are innervated by radial fibers orthogonal to the pial surface, layers IV and V contain obliquely oriented fibers, and layer VI DBH fibers are oriented rostrocaudally (Morrison, Grzanna et al. 1978). Morrison and colleagues also later showed through lesion studies that medial cortical regions are innervated by fiber bundles which ascend medially through the septum over the corpus callosum and progress caudally, whereas dorsolateral cortical

regions are innervated by noradrenergic fibers in the medial forebrain bundle (Morrison, Molliver et al. 1981). In addition to these laminar organizations, Morrison and colleagues also showed that the density of noradrenergic fibers is lower in anterior cingulate cortex (ACC) than in both prelimbic and posterior cingulate cortices (Morrison, Molliver et al. 1979), suggesting that the pattern and density of noradrenergic innervations is not homogeneous throughout the cortical mantle. More recently, our laboratory has used stereological analyses to show that the density of varicosities, the putative sites of neurotransmitter release, along noradrenergic fibers, is highest in frontal cortex versus motor, somatosensory, and piriform cortices. Interestingly, amongst all frontal regions sampled, the highest density of noradrenergic varicosities was found in ACC (Agster, Mejias-Aponte et al. 2013). Although Morrison and colleagues found a low density of fibers in this region, the number of release points per distance of fiber was found to be higher than other terminal fields, possibly accounting for this discrepancy. These data collectively suggest that release of NE from LC terminals is not necessarily consistent throughout the brain, which could promote differential actions of uniform LC activation in distinct cortical circuitries with unique functions. Therefore, NE fibers and varicosities seem to be organized in a manner that would elicit a greater release of NE into PFC regions than other cortical and subcortical structures (Agster, Mejias-Aponte et al. 2013). Intriguingly, despite the longstanding view that LC is the sole source of NE to the cortex (Berridge and Waterhouse 2003) and therefore the source of all of its NE-containing DBH immunoreactive fibers, a recent study by Robertson and colleagues (Robertson, Plummer et al. 2013), shows that insular cortex is innervated by both LC and non-LC derived NE containing fibers. Therefore, NE release in insular cortex may be achieved through activation of LC, or by activation of the functionally and anatomically distinct sub-coeruleus, A1, or A2 cell groups. The differential functions of these various noradrenergic nuclei suggest that NE can be released into insular cortex under unique sensory or environmental circumstances. Furthermore, the finding that insular is the only cortical structure in this study to be innervated by non-LC NE fibers suggests that the transmitter may maintain unique roles in frontal versus non-frontal cortical function.

Noradrenergic regulation of prefrontal cortical operations

Because of the critical role that NE plays in prefrontal cortical function, it is of little surprise that noradrenergic transmission is implicated in a variety of neuropsychiatric and neurodegenerative diseases characterized by deficits in PFC function (Newcorn, Schulz et al. 1998; Leonard 2001; Mehta, Goodyer et al. 2004; Rahman, Robbins et al. 2006; Paloyelis, Mehta et al. 2007; Weinshenker 2008; Poyurovsky, Faragian et al. 2009; Szot, Miguelez et al. 2010). Furthermore, activity in the mammalian PFC is strongly modulated by LC, and noradrenergic manipulations are capable of altering behavioral and physiological measures of PFC function (Arnsten, Mathew et al. 1999; Arnsten 2000; Lapiz and Morilak 2006; Arnsten 2007; McGaughy, Ross et al. 2008; Newman, Darling et al. 2008). It has been demonstrated that manipulations of the NE system in discrete prefrontal subregions are capable of selectively altering discrete aspects of behavioral flexibility. For example, NE specific lesions of medial prefrontal cortex (mPFC) impair extradimensional shifting, a behavior in which animals must reorient their attentional reserves to novel stimuli to obtain

reward, but not reversal learning, an orbitofrontal cortex (OFC) dependent behavior in which animals must reorient attention to familiar but irrelevant stimuli (McGaughy, Ross et al. 2008; Newman, Darling et al. 2008). Moreover, NE has been identified as a potent modulator of various measures of prefrontal function (Arnsten, Mathew et al. 1999; Arnsten 2000; Bouret and Sara 2004; Dalley, Cardinal et al. 2004; Devilbiss and Berridge 2006; Lapiz and Morilak 2006; Arnsten 2007; Ramos and Arnsten 2007; Tait, Brown et al. 2007). Because of the apparently dissociable roles of NE in mPFC and OFC dependent behaviors, we initially hypothesized that these two cortical regions are innervated by distinct subsets of LC neurons. After confirming this hypothesis (Chandler, Lamperski et al. 2013), we next sought to investigate the possibility that LC might independently and asynchronously modulate functionally distinct cortical terminal fields. To achieve this end, we carried out set of experiments in which we assayed the anatomical, molecular, and electrophysiological properties of LC cells projecting to OFC, mPFC, ACC, and primary motor cortex (M1) (Chandler, Lamperski et al. 2013; Chandler, Gao et al. 2014).

Transcriptional properties of LC-cortical projection neurons

By combining retrograde tracing with laser capture microdissection of labeled cells and quantitative PCR, we found that a small number of mRNAs were differentially expressed between cells projecting to M1 and the various PFC terminal fields. Interestingly, all of these mRNAs are related to synaptic excitability and transmission. Specifically, cells innervating both OFC and mPFC contained elevated levels of mRNAs coding for subunits of both AMPA and NMDA receptors (GluR1 and NR1, respectively), as well as vesicular monoamine transporter (VMAT2). Importantly, the mRNA for the voltage gated sodium channel subunit $Na_v\beta3$ was the only transcript that was enriched in mPFC but not OFC projection cells. We interpreted this as being indicative of greater absolute numbers or density of voltage gated sodium channels on LC cells projecting to mPFC than to other regions. As action potential generation requires a high density of voltage gated sodium channels at the axon initial segment, (Kole, Ilschner et al. 2008), we hypothesized that cells projecting to mPFC are capable of maintaining sustained periods of high frequency firing. This is in general agreement with the finding that VMAT2 is enriched in the same population, as a high rate of firing would also require a greater capacity to package NE into vesicles for synaptic release. This is further corroborated by the increased levels of NR1 and GluR1 mRNAs we found in OFC and mPFC projection cells, as increased glutamatergic transmission at these cells might also require an increased capacity for packaging NE into vesicles for synaptic release. Collectively, these findings suggested to us that LC-mPFC projection neurons might be more electrically active and excitable, and subject to greater glutamatergic presynaptic drive than LC-M1 projection neurons.

Although the relative quantification of RNA we describe here did not allow us to make direct ratios of different mRNAs (i.e., two molecules of VMAT2 mRNA for every one molecule of NET mRNA), it is intriguing that some regulators of NE transmission did vary between populations while others did not. For example, relative to M1 projection cells, those projecting to mPFC and OFC contained greater quantities of VMAT2 transcripts, but NET mRNA expression was consistent between groups. As such, it may be the case that this type of organization results in more rapid and efficient packaging and release of NE into OFC

and mPFC than M1, but equal clearance of the transmitter from the synapse. This could result in a greater basal NE concentration as well as a more lasting effect of phasic LC discharge in these prefrontal terminal fields, as there is not as much transporter in those areas relative to NE released. As such, NE would have more time to interact with its receptors before being taken back up, potentially producing distinct network properties in one area versus another.

Electrophysiological variability among LC neurons

We next tested the hypothesis that LC cells projecting to PFC are electrophysiologically distinct from those projecting to M1 by combining retrograde tracing with whole cell patch clamp in a slice preparation. The electrophysiological properties of LC neurons have previously been well characterized by a number of intracellular and extracellular recording studies (Williams and North 1984; Williams, North et al. 1984; Ennis and Aston-Jones 1988; Valentino and Foote 1988; Williams, North et al. 1988; Ennis and Aston-Jones 1989; Ennis and Aston-Jones 1989; Aston-Jones, Akaoka et al. 1991; Ishimatsu and Williams 1996; Curtis, Lechner et al. 1997; Lechner, Curtis et al. 1997; Curtis, Pavcovich et al. 1999; Curtis, Bello et al. 2001; Alvarez, Chow et al. 2002; Devilbiss and Berridge 2006; Devilbiss, Page et al. 2006). Specifically, LC neurons display a spontaneous firing rate in the range of 0.5–5 Hz (Williams and North 1984; Williams, North et al. 1984; Alreja and Aghajanian 1995; Ishimatsu and Williams 1996; Alvarez, Chow et al. 2002) and in young animals, oscillate synchronously by gap junctional coupling (Williams, North et al. 1984; Ishimatsu and Williams 1996) that diminishes with age (Alvarez, Chow et al. 2002). Some in vitro intracellular brain slice recordings from LC have demonstrated that there is an inherent degree of variability in several electrophysiological parameters between cells, including spontaneous firing rate and resting membrane potential (Williams, North et al. 1984). The results of our experiments showed that several electrophysiological properties of LC neurons do in fact vary as a function of their terminal fields. Specifically, LC-mPFC projection cells discharge spontaneously and in response to current injection at a significantly greater rate than those that project to M1. Additionally, the magnitude of the afterhyperpolarization (AHP) of mPFC projection cells was significantly smaller than those projecting to M1, which may contribute to their increased discharge. Glutamatergic neurotransmission at mPFC projection cells was found to be elevated as well. These observations support our data which showed increased expression of mRNAs related to neuronal excitability and synaptic transmission in LC-mPFC projection cells. Therefore, LC comprises neurons which vary in their electrophysiological properties according to their terminal fields. In this context, the fact that other investigators have previously reported that certain membrane properties varied between cells such as spontaneous firing frequency and resting membrane potential may be explained in part by differences in terminal field. One particularly intriguing observation we made is that LC cells projecting to mPFC sustained the greatest increase in firing rate at all levels of current injection, suggesting that they are capable of maintaining elevated levels of discharge. This may be related to the increased levels of $Na_V\beta3$ we also described. Collectively, these observations suggest that mPFC projection cells may fire a greater number of spikes in a shorter period of time during stimulus driven phasic discharge of the nucleus, thereby promoting greater NE efflux in mPFC than M1.

LC as a regulator of behavioral output

This is of particular interest due to the possibility that NE promotes distinct actions within these cortical terminal fields. Previous studies have shown that LC output and NE concentration alter behavior and neuronal responsiveness according to an inverted-U dose-response function (Devilbiss and Waterhouse 2002; Devilbiss and Berridge 2006; Devilbiss, Page et al. 2006). Due to the higher basal discharge rate of LC neurons projecting to PFC, uniform input to the nucleus may push actions of NE in PFC to the right-hand side of the inverted-U curve before M1, thereby limiting prefrontal operations and instead engaging motor circuitries. Thus, varying levels of NE between mPFC and M1 on the basis of unique firing patterns and properties of neurons which project there might provide a mechanism for promoting distinct cellular and circuit-level actions in each region. This is of particular interest in the context of the model of noradrenergic function put forward by Arnsten and colleagues (Arnsten 2000; Ramos and Arnsten 2007; Arnsten 2009). This model suggests that shifts between low and high stress states coincide with shifts between prefrontal and posterior cortically guided behaviors, respectively. These shifts are achieved by using differential actio of NE in these regions as a “neurochemical switch”. Specifically, during periods of low stress, moderate levels of tonic LC discharge enhance PFC function through α_{2A} receptor activation, permitting PFC to guide behavior. Then, during stress, which is characterized by elevated LC discharge, the binding of NE to lower affinity receptors impairs PFC function and enhances that of more posterior cortical and subcortical structures, pushing the brain into a “survival” model with little regulation of behavior by executive functions maintained by PFC. The existence of these discrete anatomical pathways from LC to M1 and PFC provide independent channels by which LC discharge could differentially regulate the various structures involved in this switch. Based upon our data, LC projections to PFC would always be in a more active state than those projecting to M1. Increasing LC discharge over the normal physiologic range would lead to the engagement of lower affinity NE receptors, which impairs PFC function while simultaneously improving more posterior and primitive cortical function to limit prefrontal inhibition of sensory processes and motor impulses necessary for survival. Very high levels of LC output, however, may inhibit both prefrontal and motor cortical functions. It has in fact been shown that very high levels of optogenetic stimulation of LC in vivo produce reversible behavioral arrests (Carter, Yizhar et al. 2010).

Our observations also match well with the theoretical construct of LC output and function put forward by Aston-Jones and Cohen (Aston-Jones and Cohen 2005; Aston-Jones and Cohen 2005). According to this more compartmentalized model, the mode of LC firing is determined by, and helps determine, behavioral output. During optimal task performance, LC cells show a low tonic discharge rate and fire phasically in response to behaviorally relevant but not irrelevant stimuli. Then, when a rule changes and the previous strategy used by the animal to predict reward is no longer useful, LC output switches to a higher tonic mode of output. High tonic discharge of LC has been shown to increase terminal field concentration of NE according to a linear function (Berridge and Abercrombie 1999; Devilbiss, Page et al. 2006). This shift in firing mode by LC cells with different terminal fields may facilitate the shift in behavioral strategy: during good behavioral performance

characterized by low tonic output punctuated by stimulus-bound phasic bursts, LC may modulate PFC such that it can facilitate detection of the task relevant stimulus while ignoring others, while simultaneously maintaining M1 network properties necessary to execute a fine-tuned motor act required to retrieve reward. Then, following a rule change, the previously rewarded stimulus becomes irrelevant, LC output to PFC increases to a high tonic mode of firing, causing the animal to lose focus on the original reward predictor by decreasing the signal to noise ratio for that stimulus, and instead scan for alternative behaviorally relevant stimuli, while increased actions of NE in M1 may fine-tune the execution of novel motor acts necessary to retrieve reward.

It is important to note however that some authors have not reported a phasic to tonic shift in LC firing during changing task contingencies (Kalwani, Joshi et al. 2014). Others have identified task related phasic LC responses in both rat and monkey (Bouret and Sara 2004; Bouret and Richmond 2009), particularly during rule changes. Bouret and Sara have therefore suggested that task-related phasic LC activation may serve as a sort of “network rest”, in which NE release in cognitive circuits interrupts ongoing neural network activity and behavior to allow novel and adaptive sensorimotor responses to changing behavioral contingencies (Bouret and Sara 2005). Such a mode of operation might be particularly relevant to data from our laboratory which suggest that LC neurons are minimally divergent and discretely innervate functionally distinct terminal fields: Phasic firing in response to changing environmental features and behavioral contingencies in single LC neurons that project to PFC might allow for reset of networks that help guide cognitive behaviors and decision making without affecting network properties of primary sensory or motor cortices.

Functional organization of the LC-NE efferent system

In general, our observations in LC cells terminating in OFC and mPFC fire faster and are more sensitive to glutamate than those projecting to M1 may be reflective of a greater demand for NE by cortical circuitries related to cognition. It has been shown that executive function is impaired by manipulations which limit noradrenergic transmission in prefrontal cortex (Lapiz and Morilak 2006; McGaughy, Ross et al. 2008; Newman, Darling et al. 2008), and that symptoms of various psychiatric diseases are partially alleviated with drugs that promote noradrenergic actions in the synapse (Mehta, Goodyer et al. 2004; Devilbiss and Berridge 2006; McGaughy, Newman et al. 2008; Arnsten 2009; Poyurovsky, Faragian et al. 2009; Seu, Lang et al. 2009). Interestingly, a recent publication by Robertson and colleagues (Robertson, Plummer et al. 2013) also challenges the notion that LC is the sole source of NE to cortex by demonstrating that both insular and orbital cortices contains NE fibers derived from non-LC sources, including sub-coeruleus and A1 and A2 cell groups. The fact that these non-LC noradrenergic nuclei project to this area but not other cortical regions aligns with our working hypothesis that NE maintains unique and specific roles in prefrontal versus non-prefrontal cortical function. Their observations indicate that NE release may occur in these cortical terminal fields in response to activation of LC, but also in response to stimuli and during behavioral states that activate these other noradrenergic nuclei as well.

It is important to consider that while we have identified segregated channels by which information from LC can travel independently to functionally distinct cortical regions, LC contains a limited number of cells. Therefore, it is highly unlikely that each functionally defined region of the brain and spinal cord receives noradrenergic input from its own respective subset of LC cells: as there are approximately only 1600 cells are present in each side of the nucleus in the rat (Berridge and Waterhouse 2003), there must be some degree of collateralization by LC cells to ensure that the entire central nervous system can be innervated by this structure. As we have shown that functionally distinct cortical regions each receive input from their own subset of LC neurons, it may be the case that this collateralization occurs in a functionally defined manner. Indeed, previous findings from our laboratory have shown that individual LC cells innervate multiple structures along the same sensory pathway (Simpson, Altman et al. 1997). As such, it stands to reason that the cells projecting to various structures in PFC may also send collaterals to other limbic or higher order associative cortical structures. For example, as mPFC is innervated by the mediodorsal thalamic nuclei, LC neurons that project to mPFC may also therefore innervate this region of the thalamus, to facilitate simultaneous modulation of information along this limbic circuit. Experiments are currently underway in our laboratory to investigate this possibility.

One recent publication employed a viral genetic approach to identify collaterals and afferents of LC neurons that project a one known starting terminal field (Schwarz, Miyamichi et al. 2015). In this work, the authors report that the majority of mouse LC neurons receive input from common afferents, regardless of their terminal field. Somewhat surprisingly, the authors reported a novel source of monosynaptic afferent input to LC arising from Purkinje cells in the cerebellar cortex that bypasses the deep cerebellar nuclei. They also suggest that LC neurons are in fact highly collateralized, and retrograde transfection of LC neurons projecting to any one region results in fluorescent fiber labeling through the majority of the brain (Schwarz, Miyamichi et al. 2015). While these observations are in contrast with our own, they nonetheless lay an important groundwork for viral-genetic investigations of the anatomical and functional properties of the noradrenergic nuclei. However, due to the previously unrecognized pathway arising in the cerebellar cortex and terminating in LC, some comparison between these novel techniques and conventional tracing methodology is necessary in the future.

Towards an updated model of LC and its role in CNS function

While the results of our recent work are compelling and challenge the conventional view of LC, they are not without caveat. First, although we have identified anatomically distinct pathways from LC to functionally defined regions of cortex, the actual impact of these distributions on their respective terminal fields, and whether or not they are in fact capable of producing distinct effects in these targets in vivo, remains to be seen. Because electrophysiological and ultrastructural studies have provided evidence for electrotonic coupling between LC neurons, at least in young animals, (Ishimatsu and Williams 1996; Ballantyne, Andrzejewski et al. 2004; Rash, Olson et al. 2007), one must at least consider that these assemblies of neurons are in fact capable of resulting in simultaneous release of NE throughout vast expanses of cortex. However, computational modeling studies suggest that LC may be capable of switching in and out of electrotonically coupled states depending

on afferent drive to the nucleus (Alvarez, Chow et al. 2002; Aston-Jones and Cohen 2005). Furthermore, even if these cells are in fact electrotonically coupled at times, the amount of NE released per action potential could promote differential actions in distinct termimal fields by activation of different receptor subtypes. This may be the case as we have shown here that cells innervating OFC and mPFC contain elevated levels of VMAT2 mRNA and therefore may package more NE more efficiently into vesicles for release. Microdialysis or fast scan cyclic voltammetry studies could address this issue by electrically or optogenetically stimulating the nucleus and measuring whether or not NE concentration is consistent between prefrontal and non-prefrontal terminal fields. Additionally, microarray or RNA sequencing experiments may reveal many other molecular differences between populations that impart some of their unique electrophysiological properties, such as differences in the expression of various types of ion channels, or protein kinase A and its associated proteins, which contribute to spontaneous activation of LC neurons (Alreja and Aghajanian 1995).

It is also interesting to note that mPFC and M1 projection cells differed in the size and frequency of their EPSCs. Because mPFC projection cells had larger AMPA sEPSCs, it may be the case that their dendritic arbor does not extend as far into the pericoerulear space as those that project to M1, and the difference in amplitude is an artifact of the differential distance EPSCs must travel from the synapse to reach the recording site in each population due to their graded nature. However, such spatial segregation could instead indicate the existence of functionally and/or neurochemically distinct input to these populations so that certain types of information or behavioral circumstances drive these populations differentially. Such an organization may be revealed using optogenetic techniques: for example, by transfecting the central nucleus of the amygdala with a channelrhodopsin driven by the CamKIIa promoter, one could selectively stimulate its glutamatergic terminals in LC while using whole-cell patch clamp to record evoked changes in the different populations of cortical neurons to determine if they are differentially sensitive to its activation. Such experiments may reveal an even more functionally organized LC than we propose here and open the door to the possibility that LC in fact contains discrete populations of cells that are unique in both their inputs and outputs as has been shown recently for the dopamine system (Lammel, Hetzel et al. 2008; Lammel, Lim et al. 2012). We are currently exploring this possibility in our laboratory using viral approaches and hope to elucidate circuit-level function of the LC cells identified in the present studies to identify whether distinct neuroanatomical and neurochemical pathways provide segregated input to these groups of neurons, thus forming unique input/output circuits that selectively regulate cognitive versus motor or other functions.

It will also be of value for future experiments to compare the anatomical distribution and phenotypic properties of LC neurons innervating various terminal fields in animal models of neuropsychiatric and neurodegenerative disease states. For example, evidence suggests that in Alzheimers's and Parkinson's diseases, some LC neurons degenerate selectively (Gesi, Soldani et al. 2000; Grimm, Mueller et al. 2004; Weinshenker 2008; Szot, Miguelez et al. 2010; McMillan, White et al. 2011; Miguelez, Grandoso et al. 2011). Such degeneration preferentially targets LC-PFC projection neurons that play a role in the cognitive decline associated with these diseases. Furthermore, studies investigating the molecular and

electrophysiological impacts of such changes to LC cells could potentially reveal mechanisms to counteract these pathological conditions for both experimental and therapeutic purposes. These types of experiments are of critical importance due to the fact that neuroplastic adaptations in LC may occur in response to stress, genetic, epigenetic, or environmental conditions. Additionally, preliminary unpublished data from our laboratory have shown that LC cells innervating mPFC in the spontaneously hypertensive rat (SHR), an animal model for ADHD, fire spontaneously and in response to current injection even faster than they do in the Sprague Dawley, whereas cells innervating M1 show a very high degree of variability in their spontaneous firing frequency. Such observations lend support to our working hypothesis that the characteristics of LC-cortical projection cells identified in this study contribute to the behavioral output, and deviations from this functional organization may relate to the generation hyperactive and impulsive behavior. Future studies should therefore focus on identifying the mechanism underlying this hyperexcitability of LC-mPFC projection cells and attempt to counteract this deficiency both in vitro and in vivo and demonstrate both physiological and behavioral changes.

Conclusions

The results of our studies challenge the longstanding view of LC as a highly divergent and homogeneous nucleus with broad and uniform actions throughout cortex (Fallon and Loughlin 1982; Loughlin, Foote et al. 1982; Waterhouse, Lin et al. 1983; Loughlin, Foote et al. 1986; Loughlin, Foote et al. 1986; Waterhouse, Border et al. 1993). Furthermore, these findings are in general agreement with more recent theories of compartmentalized LC function as proposed by Aston-Jones & Cohen (Aston-Jones and Cohen 2005) and Arnsten and colleagues (Arnsten 2000; Arnsten 2009). We conclude that LC comprises minimally divergent cortical projection neurons whose molecular phenotypes and physiological profiles are matched to the operation of their particular terminal fields. More specifically, LC is organized so as to elicit asynchronous and greater release of NE in PFC versus M1 sub-regions under normal conditions to promote optimization of prefrontal cortical dependent cognitive and executive functions, i.e., behaviors under top-down control. Deviations in the anatomical, molecular, or physiological properties within these subsets of LC-cortical projection cells may favor optimization of motor function while executive function is sub-optimal, and drive an animal towards maladaptive motor hyperactivity and impulsivity. Circumstances that promote such deviations in a more chronic fashion may therefore impair optimal prefrontal driven behavior and manifest as symptoms and behavioral markers associated with various psychiatric disease states.

Identification of specific afferents to LC cells with specified outputs will further the collective understanding of the role of LC in maintaining discrete behavioral operations rather than acting as a homogeneous and uniform modulator of the entire central nervous system. While this topic has been touched upon by Schwarz and colleagues, their results align more with the conventional model of LC organization and function (Schwarz, Miyamichi et al. 2015). Optogenetic, transgenic, and viral approaches may provide a means of elucidating neurochemically, anatomically and functionally distinct pathways into and out of LC that maintain distinct roles and demonstrate that NE release is capable of producing distinct effects in distinct terminal fields under distinct circumstances; however, these

approaches must be carefully validated by comparing results with those obtained using conventional methodology. The recent demonstration by Robertson and colleagues (Robertson, Plummer et al. 2013) that insular cortex is innervated by non-LC NE containing fibers supports this view: specificically, activation of the source nuclei for these fibers (sub-coeruleus, A1, A2) would result in NE release in insular, but not other cortical terminal fields. Such an organization would therefore induce changes in insular cortical physiology without affecting properties of other terminal fields and argues that NE discretely modulates anatomically and functionally distinct terminal networks. The results of the current studies and the growing body of evidence that LC is far more heterogeneous than previously recognized provide a framework for better understanding acquired or genetically transmitted abnormalities of the LC-NE system that result in maladaptive behaviors expressed in a multitude of disease states. Moreover, in light of these new findings, interest in the scientific study of this part of the brain and its relevance to various motivated behaviors, neuropsychiatric, neurodegenerative and developmental disorders, may be renewed.

Acknowledgments

Funded by NIDA DA017960 and NIMH MH087921

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Highlights

- The current, possibly outdated, model of the locus coeruleus noradrenergic system presents the nucleus as a homogeneous entity
- Recent evidence suggests locus coeruleus neurons differ in their molecular and physiological properties
- Locus coeruleus neurons with distinct afferent and efferent connections may have unique roles in discrete behavioral operations
- Dysfunction and plasticity of this system may have an impact on forebrain-dependent behaviors