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Locus Coeruleus: From Global Projection System to Adaptive Regulation of Behavior

Gary Aston-Jones¹ and Barry Waterhouse²

Gary Aston-Jones: aston.jones@rutgers.edu; Barry Waterhouse: Waterhouse@DrexelMed.edu

¹Brain Health Institute, Rutgers University/Rutgers Biomedical and Health Sciences, Piscataway, NJ 08854

²Dept Neurobiology & Anatomy, Drexel University College of Medicine, Philadelphia, PA 19129, Barry

Abstract

The brainstem nucleus locus coeruleus (LC) is a major source of norepinephrine (NE) projections throughout the CNS. This important property was masked in very early studies by the inability to visualize endogenous monoamines. The development of monoamine histofluorescence methods by Swedish scientists led to a plethora of studies, including a paper published in *Brain Research* by Loizou in 1969. That paper was highly cited (making it a focal point for the 50th anniversary issue of this journal), and helped to spark a large and continuing set of investigations to further refine our understating of the LC-NE system and its contribution to brain function and behavior. This paper very briefly reviews the ensuing advances in anatomical, physiological and behavioral aspects of the LC-NE system. Although its projections are ubiquitously present throughout the CNS, recent studies find surprising specificity within the organizational and operational domains of LC neurons. These and other findings lead us to expect that future work will unmask additional features of the LC-NE system and its roles in normative and pathological brain and behavioral processes.

Keywords

norepinephrine; noradrenaline; locus coeruleus; neural projections; arousal; attention

History of LC and Brain Norepinephrine

The locus coeruleus (LC) is one of the smallest but most extensively projecting nuclei in brain. It was first recognized in published material by Vicq-d'Azyr in 1786 (Tubbs et al., 2011). Russell notes in his extensive 1955 review (Russell, 1955) that the Wenzel bothers described LC in 1811 as a pigmented set of neurons in the dorsorostral tegmentum of human

Correspondence to: Gary Aston-Jones, aston.jones@rutgers.edu.

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brain. Although unusual in its pigmentation, little else about LC garnered attention until the development of the Falck-Hillarp histofluorescence technique (Falck and Hillarp, 1959). This method allowed unprecedented visualization of tissue monoamines – suddenly, one could see cells, fibers and varicosities of the ubiquitous brain monoamines. Notable among these was the LC system. LC neurons in rat appeared to be nearly entirely aminergic, and a series of lesion and other studies revealed a small population of neurons that provided surprisingly widespread projections throughout the neuraxis. This novel efferent organization was unknown previously because existing methods for tracing fiber projections lacked ability to reveal the fine, unmyelinated fibers of LC neurons. Thus, these histofluorescence results were transformative and ushered in a new structural motif - a broad efferent network emanating from a small brainstem nucleus. This implied a global function for LC neurons as multiple areas with contrasting functions all received inputs from LC.

The 1969 Brain Research paper by Loizou (Loizou, 1969) was an important extension of reports by Swedish researchers on central aminergic systems. By studying the effects of lesions of monoamine fiber pathways (including LC projections) on fluorescence distal and proximal to the lesions (Andén et al., 1966; Dahlström and Fuxe, 1964); they inferred the sources and trajectories of monoamine projections including those from LC. Loizou (Loizou, 1969) extended these findings by making electrolytic lesions of the LC nucleus and examining histofluorescent fibers compared to what the Swedish groups had reported. He found that LC lesions greatly reduced aminergic fluorescent staining in several brain regions, including profound decreases in fibers and terminals in the dorsomotor nucleus of the trigeminal nerve and medullary tractus solitarius, as well as in forebrain regions including amygdala and hippocampus. Thus, his results provided important direct confirmation that LC projections were widespread and apparently diffuse. Often overlooked is his finding that such LC lesions decreased NE fibers in Edinger-Westphal nucleus, consistent with recent reports of relationships between LC neural activity and pupil diameter (Aston-Jones and Cohen, 2005; Gilzenrat et al., 2010; Joshi et al., 2016).

Modern LC Anatomy

Following this seminal work, there was considerable effort devoted to obtaining a more detailed characterization of LC and its circuit connections. This included anterograde and retrograde tract tracing and selective staining of NE neurons and fibers using antibodies directed against the NE synthetic enzyme, dopamine-beta-hydroxylase (DBH). This work confirmed the uniqueness of LC; a compact cluster of NE neurons whose projections distribute broadly throughout the neuraxis, from spinal cord to neocortex (Segal and Landis, 1974a; 1974b; Swanson and Hartman, 1975); reviewed in (Foote et al., 1983).

Neurochemical Composition of LC - Further investigation demonstrated that virtually all neurons within rodent and primate LC contained DBH (Grzanna and Molliver, 1980) and therefore NE as LC's primary transmitter. However, later identification of multiple peptides co-localized within LC neurons added new dimensions to what initially appeared to be a conventional one-transmitter system. Vassopressin, somatostatin, neuropeptide Y, enkephalin, neurotensin, corticotropin-releasing factor and galanin are among the variety of

putative peptide transmitters found in LC neurons (reviewed in (Aston-Jones, 2004; Olpe and Steinmann, 1991)).

Efferent Topography of LC - Multiple reports beginning in the late 1970's provided evidence of an efferent topography within LC, i.e., a spatial organization of cells in the LC nucleus with respect to terminal field targets (reviewed in – Berridge and Waterhouse, 2003). For example, cortically-projecting LC neurons are more prominent within the caudal portion of LC and these neurons project in a predominantly ipsilateral (>95%) manner (Waterhouse et al., 1983). By contrast cells projecting to sub-cortical structures exhibit a more pronounced bilateral distribution. Although early retrograde tracing and antidromic activation studies revealed that single LC neurons branch to innervate different brain regions (reviewed in (Aston-Jones, 2004)), other studies (Simpson et al., 1997; Steindler, 1981) indicate that individual LC neurons collateralize to innervate functionally related circuits. For example, LC neurons that project to trigeminal somatosensory cortex are more likely to co-innervate trigeminal somatosensory thalamus than non-somatosensory thalamic regions (Simpson et al., 1997). These findings indicate that LC neurons collateralize according to functional properties of targets.

More recent studies demonstrated segregation among LC neurons that project to primary motor cortex and sub-regions of the prefrontal cortex: anterior cingulate, orbitofrontal, and medial prefrontal (Chandler et al., 2014; 2013). Subsequent examination of the membrane properties and molecular phenotypes of LC-prefrontal and LC-motor cortical projection cells revealed differences in excitability and protein expression between these two groups. Combined, these data indicate that subsets of LC neurons may be capable of asynchronous release of NE in sub-regions of the cortex and distinct roles in executive function versus motor control.

Terminal Field Distribution of NE-containing Fibers - Although early work emphasized the diffuse nature of LC projections throughout the brain, subsequent investigations in monkey and human found substantial regional specificity of noradrenergic fiber distribution across cortical and subcortical structures. Within the primate visual system, NE fibers are more heavily represented in tecto-pulvinar-juxtastriate structures as contrasted with geniculostriate or inferotemporate structures (Foote and Morrison, 1987). On the basis of this distinction Morrison and Foote (Morrison and Foote, 1986) suggested that, within the visual system, NE-LC fibers preferentially innervate regions involved in spatial analysis and visuomotor responses rather than areas involved in feature extraction or 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. Additional selectivity was demonstrated through analysis of DBH immunostained axonal varicosities across rat cortical sub-regions (Agster et al., 2013). These studies showed that the medial prefrontal region exhibits the highest density of NE varicosities of any cortical region examined. These results provide further anatomical evidence that LC-mediated release of NE is not uniform across the cortical mantle.

Synaptic vs Non-synaptic Release of NE – Volume Transmission - The anatomical relationships of varicosities on NE axons – the presumed transmitter release points - have

been controversial (Descarries and Lapierre, 1973; Lapierre et al. 1973; Olschowka et al., 1981; Watkins et al., 1977). Early studies indicated that a high percentage of such varicosities were non-synaptic, leading to a volume transmission theory of NE signaling in the brain (Agnati et al., 1995). However, later work found a greater incidence of conventional synaptic contacts between NE terminals and targets, arguing for more a more specific cell to cell release and action of NE than implied by earlier studies (Olschowka et al., 1981; Papadopoulos and Parnavelas, 1990; Papadopoulos et al., 1987; 1989). It seems possible that both synaptic and non-synaptic modes of NE release occur.

Afferent Regulation of LC - Initial reports indicated that the LC receives inputs from a broad array of CNS structures (Cedarbaum and Aghajanian, 1978). However, subsequent work found that the LC nucleus receives a restricted set of afferents, arising primarily from the ventrolateral and dorsomedial rostral medulla as well as hypothalamus (Aston-Jones et al., 1986). Subsequent studies documented a dense plexus of LC neuronal dendrites that extend far beyond the borders of the nucleus proper into pericoerulear zones (Shipley et al., 1996). Importantly, these pericoerulear regions are targeted by inputs from a variety of sources including prefrontal cortex, amygdala, lateral hypothalamus and dorsal raphe. Recent work using viral-genetic tracing methods confirmed that NE neurons in LC received inputs from a wide array of brain areas, and also exhibited a high divergence in output projections (Schwarz et al., 2015). Jodo and Aston-Jones (Jodo and Aston-Jones, 1997) found that PFC activity activates LC neurons presumably through pericoerulear dendrites, an important connection insofar as it links circuits involved in higher cognitive processes (e.g. working memory) with the LC-efferent path.

The pericoerulear zone also contains a dense collection of GABA neurons co-mingled with peri-LC dendrites (Aston-Jones et al., 2004). This region receives inputs from many brain regions, and resembles a pool of inhibitory interneurons that provide either feed-forward or feedback inhibition of LC-NE neurons. Increasing work is revealing additional transmitter-defined inputs to LC, including hypocretin/orexin, CRF, glutamate, and others (for review, see (Aston-Jones, 2004).

In addition, the transsynaptic retrograde tracer pseudorabies virus (PRV) has revealed circuit-level inputs to LC with functional implications. Studies using this tracer have connected the suprachiasmatic nucleus with the LC via relays in the hypothalamic dorsomedial nucleus including hypocretin neurons (Aston-Jones et al., 2001; Gompf and Aston-Jones, 2008). This was the first circuit identified in the brain for circadian regulation of arousal.

Effects of NE on target neurons

In early studies, application of NE by microiontophoresis, or stimulation of the LC, suppressed spontaneous neural activity in cerebellum (Bloom et al., 1971; Hoffer et al., 1971; 1973; Siggins et al., 1971a; 1971b), cerebral cortex (Armstrong-James and Fox, 1983; Stone, 1973), and elsewhere in brain (Segal and Bloom, 1974a; 1974b; Siggins and Gruol, 1986). These studies, many of which were published in *Brain Research*, were compelling in so far as they provided anatomical, biochemical, electrophysiological, and pharmacological

evidence establishing NE as a putative inhibitory neurotransmitter at central synapses. Moreover, these investigations provided the foundation for more than 40 years of ensuing work leading to modern theories of the role of the LC-NE system in brain function and behavior.

Modulatory Effects of NE on Cells and Circuits - In the late 1970's pioneering studies in monkey auditory cortex (Foote et al., 1975), hippocampus (Segal and Bloom, 1976) and cerebellum (Freedman et al., 1977) demonstrated a modulatory effect of NE, such that the spontaneous firing rates of cells were suppressed to a greater extent than stimulus-evoked discharge, thus yielding a net increase in "signal to noise" ratio. At levels of NE which had minimal or no effect on baseline firing, Woodward and colleagues found that stimulus-evoked excitation and inhibition in cerebellum and somatosensory cortex were increased above control levels during iontophoretic NE or LC stimulation (reviewed in (Berridge and Waterhouse, 2003)). These findings supported the idea that a prominent physiological function of central NE might be to enhance the efficacy of both excitatory and inhibitory synaptic transmission rather than directly suppress cell firing (Woodward et al., 1979). Additional work showed that such actions can lead to selective alteration of the feature extraction properties of individual sensory neurons (Ciombor et al., 1999; Doucette et al., 2007; Kasamatsu and Heggelund, 1982; McLean and Waterhouse, 1994). Subsequent multi-neuron recordings showed that LC output can simultaneously modulate neurons at multiple sites along sensory pathways (Devilbiss et al., 2006; Devilbiss and Waterhouse, 2011).

Activity of LC Neurons and LC Function

Early recordings found that LC neurons were most active during waking and decreased activity in sleep (Aston-Jones and Bloom, 1981a; Hobson et al., 1975). Subsequent work showed that LC neurons also phasically respond to salient stimuli that produce behavioral responses (Aston-Jones and Bloom, 1981b; Foote et al., 1980). More recent studies found that the tonic and phasic patterns of LC activity interact, such that LC neurons fire tonically at a moderate rate but are phasically activated by task-relevant cues during periods of focused attention. In contrast, high tonic LC activity without phasic responses occurs during periods of low utility when task attentiveness wanes. These and other results led to the Adaptive Gain Theory (Aston-Jones and Cohen, 2005), which proposes that LC neurons are phasically activated in response to decision outcome, helping to execute adaptive behavioral responses. In contrast, high tonic LC discharge in this model serves to disrupt low utility behavior and increase behavioral flexibility so that more adaptive strategies can be pursued.

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Synopsis

Overall, much has been learned since Loizou's initial observations about the extent of projections from LC-NE neurons. Subsequent studies have shown that multiple inputs differentially engage the LC nuclear core and dendritic shell so as to increase NE transmission across broad expanses of CNS tissue in a selective manner. Experimental evidence and theoretical constructs argue that such NE release serves to facilitate neural network functions and optimize behavioral outcomes across a range of contingencies that require focused versus flexible attention (Aston-Jones and Cohen, 2005; Bouret and Sara, 2005).