anatomy
http://dergipark.org.tr/en/pub/anatomy
An International Journal of Experimental and Clinical Anatomy

Review

http://dergipark.org.tr/en/pub/anatomy
Received: August 27, 2024; Accepted: November 28, 2024
doi:10.2399/ana.24.1539427

The locus coeruleus in aging and neurodegenerative diseases

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Abstract

The locus coeruleus (LC), a prominent neuromelanin-containing nucleus, plays a critical role in the central nervous system by serving as the main source of norepinephrine. First described by Félix Vicq d'Azyr in the 18th century and later identified as a noradrenaline-rich region through fluorescence histochemistry in the 1960s, the LC influences various brain functions, including attention, learning, stress responses, pain modulation, memory, and sleep. This review explores the anatomy, morphology, and neurochemistry of LC neurons, emphasizing their projections and interactions with multiple brain regions such as the cortex, hippocampus, and thalamus. Additionally, we examine the involvement of the LC in the pathophysiology of age-related neurodegenerative diseases, including Alzheimer's and Parkinson's diseases, where significant neuronal loss in the LC correlates with cognitive decline and other clinical symptoms. Understanding the anatomical and functional heterogeneity of LC neurons provides insights into their crucial role in neuromodulation and highlights potential therapeutic targets for neurodegenerative disorders.

Keywords: brainstem; locus coeruleus; neurodegenerative diseases; norepinephrine

Anatomy 2024;18(3):106–110

Introduction

The locus coeruleus (LC) (**Figure 1**), often referred to as the "blue spot" due to its neuromelanin content, is a distinct structure visible to the naked eye because of its size and pigmentation. Initially described by the French anatomist Félix Vicq d'Azyr in the late 18th century, the LC's primary composition of monoaminergic neurons was not identified until the development of fluorescence histochemistry in the 1960s.[1] The LC, designated as A6 in the classification by Dahlström and Fuxe, is part of the noradrenergic cell groups extending rostrocaudally from the lateral pons to the caudal ventrolateral medulla, as described by these researchers in 1964.[2] As the principal source of norepinephrine in the central nervous system, the LC projects to numerous brain regions, including the cortex, hippocampus, and thalamus, thereby influencing a wide array of functions such as attention, learning, autonomic and behavioral stress responses, pain modulation, memory, and sleep.[3,4] This review focuses on the LC's anatomy, neuronal morphology and neurochemistry, and its significance in neurodegenerative diseases like Alzheimer's and Parkinson's.

Morphology and Neurochemistry

Mature LC neurons are predominantly medium-sized cells with fusiform and multipolar morphologies and sparse branching. The axons of these neurons, especially those extending to the forebrain, exhibit bifurcations that allow them to innervate multiple regions along the neuroaxis of a single neuron. In humans, LC neurons can be classified into four types based on size and dendritic branching: large multipolar neurons, large elliptical "bipolar" neurons, small multipolar neurons, and small ovoid "bipolar" neurons. Large multipolar neurons have round or multiangular somata with numerous thinly branching dendrites that extend in various directions, enabling them to travel long distances and reach different levels. Large bipolar neurons, similar in size to large multipolar neurons, have dendrites emerging as relatively thicker roots from the soma. Small multipolar neurons

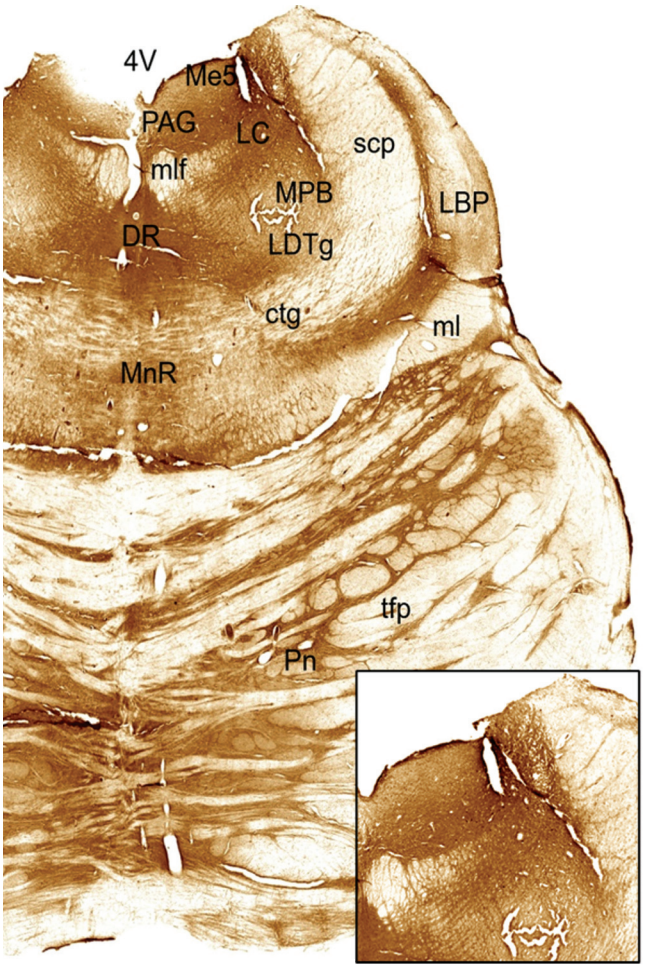

Figure 1. Locus coeruleus localization in the mid-level human pons. **4V:** 4th ventricle; **ctg:** central tegmental tract; **DR:** dorsal raphe nucleus; **LBP:** lateral parabrachial nucleus; **LC:** locus coeruleus; **LDTg:** laterodorsal tegmental nucleus; **Me5:** mesencephalic trigeminal nucleus; **ml:** medial lemniscus; **mlf:** medial longitudinal fasciculus; **MnR:** median raphe nucleus; **MPB:** medial parabrachial nucleus; **PAG:** periaqueductal gray; **Pn:** pontine nuclei; **scp:** superior cerebellar peduncle; **tfp:** transverse fibers of the pons (Unpublished data).

possess round and multiangular somata with dendritic branches arising from all over, but these branches are generally shorter than those of larger neurons. Small bipolar neurons have oval and spindle-shaped somata with dendrites primarily arising from two poles.[5–7]

Besides containing norepinephrine, LC neurons exhibit additional properties that contribute to their diversity. Consistent with their noradrenergic phenotype, LC neurons include the enzymes tyrosine hydroxylase and dopamine beta-hydroxylase involved in norepinephrine production, the norepinephrine transporter,[8] the catabolic enzyme monoamine oxidase,[9] and the α2-adrenoreceptor, which likely functions as an autoreceptor.[10] Furthermore, LC neurons secrete various neuropeptides, including neuropeptide Y,[11] galanin,[12] cholecystokinin, dynorphin A, angiotensin II,[13] and somatostatin.[14]

Anatomy and Projections

The locus coeruleus is situated in the dorsal part of the rostral pons, located in the lateral floor of the fourth ventricle.[15] In a healthy human brain, this nucleus measures about 12 to 17 mm in length and approximately 2.5 mm in width.[16] It is estimated that the bilateral LC neurons in an adult human brain comprise around 45,000 to 50,000 cells.[17]

Understanding the properties of the afferent inputs to the locus coeruleus (LC) is crucial for comprehending the effects of the noradrenergic system on the brain and behavior.[18] The LC is extensively innervated by various nuclei, including the insular cortex, central nucleus of the amygdala, spinal cord dorsal horn and lamina X, ventral tegmental area (VTA), and nucleus of the solitary tract (NST), bed nucleus of the stria terminalis, preoptic region, periaqueductal gray, midbrain pontine reticular formation including the dorsal raphe nucleus, pedunculopontine tegmental nucleus, and cerebellum. LC also receives inputs from area C1 of the ventrolateral medulla[19] and is connected to the dorsal raphe nucleus. Connections to the ventromedial pericoerulear region reported may provide a local circuit interface to LC neurons.[15,19–22] Forebrain afferents include glutamatergic inputs from the prefrontal and anterior cingulate cortices[23] as well as the paragigantocellular nucleus, and perifascicular area of the prepositus hypoglossal nucleus.[21,24] LC neurons receive several afferent inputs and express a wide range of neurotransmitter receptors, indicating multiple levels of cellular regulation. Key neuropeptides include corticotropin-releasing factor, orexin, endogenous opioids, substance P, melanin-concentrating hormone, neuropeptide Y, and somatostatin.[23,25] These neuropeptides regulate LC activity and noradrenaline release, thereby affecting arousal states and related behaviors.[25] Social stress activates specific afferents like CRF from the central amygdalar nucleus and enkephalin from the paragigantocellular nucleus, depending on the individual's coping strategy, with distinct afferents being engaged during short-latency (SL) and long-latency (LL) defeat responses.[26] The LC also receives cholinergic inputs from the basal forebrain, particularly the medial septum, which modulate long-term

potentiation (LTP) in the dentate gyrus via noradrenergic pathways, emphasizing a functional loop involving cholinergic and noradrenergic interactions.[27] Additionally, the LC plays a pivotal role in pain modulation and stress-related disorders, influencing pain perception and emotional responses through its connections with the spinal cord, prefrontal cortex, and amygdala.[27,28] These various afferents to the LC underscore its central role in integrating physiological and emotional signals to regulate arousal, stress responses, and cognitive functions.

Sensory signal-processing regions of the brain receive dense innervation from LC.[29] Although LC neurons have sparse dendritic branches, their axons exhibit wide bifurcations, enabling stimulation of many cortical areas.[30] The efferent innervation from the LC includes the cortex, cerebellum, hippocampus, hypothalamus, and spinal cord.[31] This innervation is particularly concentrated in the thalamus, affecting midline, intralaminar, and mediodorsal thalamic nuclei, as well as the lateral posterior complex, periventricular, anteroventral, ventral posterolateral, and reticular nuclei.[32,33] Additionally, the paraventricular and supraoptic nuclei of the hypothalamus are significant targets for LC innervation.[34] Stimulation of LC increases the pupil diameter, indicating LC projections to the parasympathetic Edinger-Westphal nucleus.[22] The LC also projects to the amygdala and medial prefrontal cortex (mPFC), influencing learning and memory functions.[35] Specifically, amygdala-projecting cells are recruited during emotional associative learning, while mPFC-projecting cells are engaged in unexpected situations or when behavioral flexibility is required. Understanding the anatomical and functional heterogeneity of LC neurons is crucial for appreciating their role in the neuromodulatory system.

Involvement in the Pathophysiology of Age-related Neurodegenerative Diseases

The number of neurons in the locus coeruleus (LC) decreases by approximately 30–50% during aging.[5,36,37] This neuronal loss, particularly in those projecting to the forebrain, is linked to functions in arousal, attention, and memory. Several neurodegenerative diseases are associated with age-related LC neuronal loss, including Alzheimer's disease (AD), Down syndrome, Parkinson's disease (PD), dementia with Lewy bodies, progressive supranuclear palsy, corticobasal degeneration, and dementia pugilistica.[38–41] In AD and PD, there can be up to an 80% loss of noradrenergic cells, a reduction greater than the loss of cholinergic neurons in the basal nucleus in AD and dopaminergic neurons in the substantia nigra in PD.[42] Stereological evaluations indicate that in AD, neuronal decline follows a rostrocaudal and dorsoventral pattern, whereas in PD, the loss is concentrated in the more ventral and caudal parts of the LC.[43] Thus, in AD, the LC neuronal loss primarily affects forebrain projections, whereas in PD, the loss impacts spinal cord, brainstem, and cerebellar projections. The reduction in LC neurons is more closely related to the onset and progression of AD than the degeneration of cholinergic neurons in the basal nucleus.[43–45] Recent studies highlight the significance of LC degeneration in the early stages of AD, suggesting that therapies targeting the LC-norepinephrine pathway could be promising for prognosis and treatment, potentially delaying or preventing AD-related pathology.

Conclusion

The LC, a small nucleus with extensive subcortical and cortical projections, is the primary source of norepinephrine innervation in the central nervous system. Due to its broad interaction with various brain regions, the LC significantly influences attention and memory functions in both human and non-human primate brains. In the context of aging and neurodegenerative diseases, the loss of LC neurons can disrupt the integration of sensory, attentional, and cognitive information, leading to age-related memory decline and contributing to the clinical symptoms of various neurodegenerative conditions. Advances in imaging techniques that can visualize the distribution of LC neurons hold promise for future research on the effects of aging and neurodegenerative diseases.

Acknowledgements

We thank the Council of Higher Education of Türkiye for supporting Esra Candar under the 100/2000 CoHE Ph.D. Scholarship Program in the field of "Translational Medicine".

Conflict of Interest

No conflict of interest was declared by the authors.

Author Contributions

GDY: Conceptualization, manuscript writing - original draft. EC: manuscript writing original draft. İD: manuscript writing - original draft. GŞ: onceptualization, supervision, writing, review and editing.

Ethics Approval

No ethical approval was necessary for this review article.

Funding

The authors reported there is no funding associated with the work featured in this article.

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Conflict of interest statement: No conflicts declared.

 How to cite this article: Yaman GD, Candar E, Demirçubuk İ, Şengül G. The locus coeruleus in aging and neurodegenerative diseases. Anatomy 2024;18(3):106–110.