The Neuromodulatory Role of the Noradrenergic System

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The noradrenergic system is one of four primary neuromodulatory systems. It plays an important function in altering basic synaptic transmission patterns. The groups of neurons responsible for the delivery of the neuromodulators are known as ascending neuromodulatory systems. Norepinephrine (NE) has classically been viewed as a major mediator of arousal that plays an important role in regulating cognition, perception, and sensory processing.

locus coeruleus noradrenergic system norepinephrine neuromodulation

1. Introduction

The central nervous system performs an incredibly large number of continuous computations, the result of which is to efficiently process the external world and execute a relevant response. In the human brain, an estimated 10^{11} neurons make approximately 1000 average connections to other neurons, forming up to 10^{14} distinct sites for information transmission. That is likely an order of magnitude higher than the total number of cells in the entire human body [1]. Even this staggering number of physical connections understates the complexity of information handling in the brain. Beyond simple neuron-to-neuron connections, multiple subtypes of glial cells are also known to play a role in synaptic transmission [2][3]. This ever-shifting structural background, across which the flow of information proceeds throughout an individual's life, is then capable of giving rise to a diverse array of orchestral melodies through the 100+ endogenous substances that play a role in modulating synaptic transmission [4]. Some of these substances, known as neurotransmitters, can act over varying physical distances through their interaction with a much larger number of receptors.

Since the discovery of the first neurotransmitter, acetylcholine, in 1926 by Otto Loewi, there has been an explosion in the identification and understanding of chemical neurotransmission. Conceptually simplified, information transfer occurs in two modes: electrical propagation within neurons or chemical propagation outside neurons. Neurotransmitters are the chemicals that traverse the physical division between cells connecting the postsynaptic cell with information from the presynaptic cell. This is primarily mediated through an array of specific receptors on the postsynaptic cell. For any given neuron, the combination of presynaptic inputs will determine if a message is electrically transcribed and transmitted. If it is transmitted, an action potential will travel down the length of a neuron, resulting in the release of extracellular neurotransmitter onto the dendrites of postsynaptic cells. The substances released are usually tightly regulated and reuptaken or degraded to limit the action of the substance on its target.

Generally, neurotransmitters may have excitatory, inhibitory, and neuromodulatory effects on neurons through the action of their receptors. Excitatory receptors, when activated by corresponding neurotransmitters, result in a membrane depolarization and the propagation of an action potential. Glutamate is the neurotransmitter that predominately mediates excitatory effects through its receptor, which is nearly ubiquitously expressed in all types of neurons and many types of glial cells [5]. Inhibitory receptors exert an opposing effect, with the binding of corresponding neurotransmitters resulting in a membrane hyperpolarization that limits the ability of a neuron to initiate an action potential. In the mature brain, γ-aminobutyric acid (GABA) is the primary neurotransmitter that exerts inhibitory effects on neurons through GABAergic receptors [6]. The interplay between these two competing systems has been studied in a variety of contexts [7][8][9] and provides the foundation for how neurotransmission is thought to occur in the brain. The summation of excitatory and inhibitory inputs at every connection point in the brain determines the direction and pattern of information propagation in complex networks of neurons. The third type of neurotransmitters, known as neuromodulators, add an additional, but important, complexity to this paradigm by altering the balance of transmission on a micro, meso, or macroscale.

2. Anatomical Overview of the Noradrenergic System

2.1. Sources

Noradrenergic projection to the forebrain is exclusively provided by a single source, the locus coeruleus (LC), which is a small, bilateral nucleus located in the pons [10][11][12][13][14]. A complete review of the LC was provided by Poe et al. in 2020 [15], but a brief description is provided here. Traditional investigations of the LC presumed it to be a broadly acting, primarily homogenous source of norepinephrine (NE) with wide implications [10][11][16][17], but more recent research has shown that the LC is composed of many distinct modules with highly specific functional roles throughout the brain [15]. There are two major, complementary theories on how a diffusely projecting single source of norepinephrine can achieve such disparate functional results. The first is that the function of NE release relies on regional differences in postsynaptic receptor distribution and resulting differences in spatiotemporal NE reuptake [18][19][20]. The second is a corollary to the function of the noradrenergic system in the periphery, in which the sympathetic nervous system has discrete efferent limbs that are organ specific but capable of acting in a unified manner [21][22]. In this theory, the LC provides localized neuromodulation to well-defined target regions and spiking is synchronized in highly specific subsets of LC neurons. For a more complete review, see Totah et al., 2019 [23].

2.2. Inputs

An important step in understanding the regional and modular functionality of the LC was achieved through an in-depth characterization of the afferent and efferent projections to and from the LC. The LC itself consists of a small, dense core, where cell bodies are found, and a peri-LC shell in which LC dendrites reside [24][25][26]. There are prominent afferent inputs to the LC core originating from the paragigantocellularis nucleus and the prepositus hypoglossi nuclei—both structures in the rostral medulla [27]. There are also additional inputs from the insular cortex, central nucleus of the amygdala, preoptic area, and the lateral and paraventricular hypothalamic areas [25]

[28][29]. Cerebellar Purkinje cells and neurons from deep cerebellar nuclei also provide synaptic inputs onto the core of the LC [25].

Although the projections of sensory afferents from the mesencephalic trigeminal sensory nucleus (Me5) [30][31] and the nucleus of tractus solitarius (NTS) [32] to the LC exert influences on cognitive functions [33], an important regulatory component on the core noradrenergic neurons in the LC include the peri-LC afferent innervations. Noradrenergic LC neurons possess long dendrites that pass through the surrounding small nuclei-like regions around the LC, which receive separate inputs from a variety of brain regions, including the prefrontal and infralimbic cortex, the amygdala, and the dorsal raphe nucleus [34]. There are additionally cholinergic, serotonergic, and adrenergic inputs to the peri-LC area, representing potential points of indirect regulation from other neuromodulatory systems [15][29]. The peri-LC zone also gives rise to several GABAergic inputs into the LC [35][36].

2.3. Outputs

The efferent projections from the LC are widespread but nonuniform to the neocortex in both rodents [19] and primates [37][38]. Collateral axons from the LC are distributed in a coordinated fashion to target circuits with a specific function [15][25][39][40][41][42][43]. The efferent projections from the LC travel throughout the brain, providing NE input to the cortex, insula, hippocampus, thalamus, amygdala, and cerebellum. A full review of this system was provided by Schwarz and Luo in 2015 [44]. Though the projections are widespread, the selective activation of specifically patterned noradrenergic neurons is poorly understood and likely involves a complex interplay between inputs into the LC and interacting systems [44]. Nevertheless, it has been shown that genetically distinct groups of noradrenergic neurons project to regionally and functionally specific circuits [45]. Understanding the anatomically distinct efferent circuits underlying specific functional consequences is an ongoing area of research that will likely improve our understanding of the role of the LC in the context of localized function.

As an important aspect of neuromodulation, the LC also directly projects to serotonergic, cholinergic, and dopaminergic nuclei, providing a centralized locus of control over, or feedback with, other neuromodulators [46][47].

3. Role of Norepinephrine in the Brain

3.1. Major Noradrenergic Receptor Subtypes

The noradrenergic system exerts influence over brain function through three receptor classes: α_1, α_2, and β receptors. Each of these receptors has control over specific processes of neurotransmission and sympathetic nervous system regulation. α_1 receptors are members of the adrenoreceptor family, a subset of G-protein coupled receptors [48]. They have been further classified into three distinct subtypes: α_{1A}, α_{1B}, and α_{1D}. Each subreceptor has demonstrated unique quantitative differences in effect [48]. Several experiments have explored the different concentrations of these subtypes throughout the brain. Specifically, it has been shown that α_{1B} was more prominent in the thalamus, lateral amygdaloid nuclei, and cortical laminar areas, while α_{1A} was higher in the entorhinal cortex, amygdala, and general cerebral cortex areas [49]. Furthermore, transgenic mouse experiments

have allowed for specific receptors to be knocked out, uncovering that both α_{1A} and α_{1B} have a similar expression throughout the central nervous system, just with different abundances [50]. Around 55% of the brain was shown to express α_{1A}, 35% α_{1B}, and less than 10% was found to express α_{1D} [51][52][53]. The function of α_1 receptors is implicated in a variety of cognitive processes and synaptic efficacies. Beginning with synaptic involvement, α_1 receptors have been shown to increase the firing frequency of pyramidal and somatosensory neurons of the visual cortex through the protein kinase C signaling (PKC) pathway [54][55]. They have also been implicated in the enhancement of glutamate and acetylcholine release as well as neuronal excitation via PKC pathways, calcium pathways, and excitatory synapses [56][57][58][59][60]. α_1 has also been shown to affect non-neuronal function as well, with the modulation of synaptic transmission through astrocytes and glial cells [61][62][63]. With regards to cognitive functions, α1 receptors have been shown to be implicated in memory, motor and motivational behavior, memory retention, and storage, but most of these are associated with general norepinephrine release in the brain [64].

α_2 receptors are also a type of G-protein coupled adrenoreceptor, classified into three subtypes: α_{2A}, α_{2B}, and α_{2C}. Specifically, α_2 receptors have been implicated in orchestrating the presynaptic inhibition of norepinephrine in the central and peripheral nervous system [65][66][67]. This inhibition is critical for regulation of normal involuntary processes including physiological functions of the heart, vision, and gastrointestinal systems. Using pharmacological agents such as prazosin or oxymetazoline, α_{2A} and α_{2B} receptors have been shown to have significant control over sympathetic outflow and blood pressure [67]. Several other studies have shown α_{2A} receptor agonists enhance both serotonin and norepinephrine release [67]. Interestingly, the abundance of α_2 receptor subtypes is much more localized than α_1. While literature here is limited, studies have shown that α_{2B} receptors are found almost exclusively in the thalamus, while α_{2C} receptors are found in the olfactory bulb, cerebral cortex, hippocampal formation, and dorsal root ganglia [68].

The final type of noradrenergic receptors, classified as β, are also a G-protein coupled receptor, divided into three subtypes: β_1, β_2, β_3 [67]. There have been studies linking β receptors to synaptic plasticity, with norepinephrine acting on β receptors to dictate synaptic strength in hippocampal neurons, as well as NE released from the locus coeruleus enhancing LTD-related memory processing [69].

3.2. Noradrenergic Involvement in Learning and Decision Making

The noradrenergic system has been implicated in a variety of decision-making paradigms as well as throughout the learning process. Studies using optogenetics, pharmacological agents, and lesioning have brought to light the effect norepinephrine has on cognition and higher-order thought processes. One theory regarding the role of NE in decision making involves the idea of network reset, acting as an “internal interrupt” signal [70][71]. Here, it is explained that the phasic activation of locus coeruleus noradrenergic neurons causes an increase of NE throughout the cortex, invoking cognitive shifts and the potential reorganization of neural networks [72]. This shifted brain state is hypothesized to be better equipped for rapid behavioral adaptation and enhanced decision making [72]. Other theories point out how stimulus-induced firing patterns of the LC are closely attuned to behavioral performance, hypothesized from LC primate recordings in visual discrimination tasks [73]. Similar phasic activation in primates has shown how the LC can respond to specific task-related decisions, modulating NE release and

adapting future task-relevant decisions [74], as well as showcasing coordinated activity patterns in cortical networks derived from ascending NE projections [75]. Studies invoking NE release through an agonist have shown enhancements in sensory stimulation, allowing more rapid synaptic plasticity and faster behavioral responses [76].

Several pharmacological experiments have investigated the specific role that α_2 receptors play in the decision-making process. Studies using NE antagonists have shown α_{2A} receptor knockout leading to more risk-on behavior, with rats exhibiting greedier decisions [77]. α_{2A} agonists have been proven to enhance the efficiency of working memory and reduce impulsivity in primates [78]. This increased receptor uptake in the prefrontal cortex seems to be part of the shifted network brain state described earlier. The agonist guanfacine, another α_{2A} agent, was also shown to improve visual object discrimination performance during a reversal learning paradigm in primates [79].

3.3. Noradrenergic Involvement in Attention

The noradrenergic modulation of attention has been studied for several decades [80][81][82]. Studies have established the theory that the LC-NE system regulates the efficacy of information processing during neural coding of sensory signals [83][84][85]. During behavioral tasks, selective attention enhances neuronal responsiveness to sensory cues [86][87]. The firing rates of LC neurons are correlated with attentive behavior in an odd-ball task [80], in which either high or low tonic firing rates correspond to inattentive states and medium firing rates are associated with animals' best performance. In a novel environment where more adaptive behaviors are required, changes in electrotonic coupling among LC neurons regulate goal-directed exploration and preserve attentional selectivity [73]. In addition, some studies have investigated the effects of NE agonists. It is shown that in a cued target detection task (CTD), the application of α_2 receptor agonists clonidine or guanfacine significantly impaired alerting behavior, and the effect was dose-dependent [88], while the effect was blocked by the α_2 antagonists idazoxan or yohimbine.

Most recent studies also show an association between the NE system and impulsivity control [89][90][91]. It was observed from the superior frontal theta band activity that the NE system dynamically gains and loses relevance to regulate inhibitory control under different responding modes [91]. This work has led to the use of the NE-specific reuptake inhibitor atomoxetine as a treatment of pediatric attention-deficit/hyperactivity disorder (ADHD) [89]. Furthermore, it is demonstrated that ADHD patients have a higher positron emission tomography (PET)-measured NET availability in comparison to healthy individuals, suggesting that there are underlying genetic and epigenetic mechanisms.

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