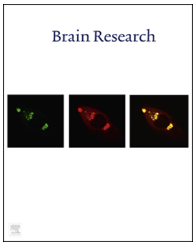
BRAIN RESEARCH 1641 (2016) 320–337

Available online at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/brainres



Review

Regulation of neurological and neuropsychiatric phenotypes by locus coeruleus-derived galanin

David Weinshenker[a,*], *Philip V. Holmes*[b,**]

[a]*Department of Human Genetics, Emory University School of Medicine, 615 Michael St., Whitehead 301, Atlanta, GA 30322, USA*
[b]*Neuroscience Program, Biomedical and Health Sciences Institute and Psychology Department, University of Georgia, Athens, GA 30602, USA*

ARTICLE INFO

Article history:
Accepted 12 November 2015
Available online 20 November 2015

Keywords:
Locus coeruleus
Galanin
Norepinephrine
Alzheimer's disease
Depression
Addiction
Epilepsy
Stress

ABSTRACT

Decades of research confirm that noradrenergic locus coeruleus (LC) neurons are essential for arousal, attention, motivation, and stress responses. While most studies on LC transmission focused unsurprisingly on norepinephrine (NE), adrenergic signaling cannot account for all the consequences of LC activation. Galanin coexists with NE in the vast majority of LC neurons, yet the precise function of this neuropeptide has proved to be surprisingly elusive given our solid understanding of the LC system. To elucidate the contribution of galanin to LC physiology, here we briefly summarize the nature of stimuli that drive LC activity from a neuroanatomical perspective. We go on to describe the LC pathways in which galanin most likely exerts its effects on behavior, with a focus on addiction, depression, epilepsy, stress, and Alzheimer's disease. We propose a model in which LC-derived galanin has two distinct functions: as a neuromodulator, primarily acting via the galanin 1 receptor (GAL1), and as a trophic factor, primarily acting via galanin receptor 2 (GAL2). Finally, we discuss how the recent advances in neuropeptide detection, optogenetics and chemical genetics, and galanin receptor pharmacology can be harnessed to identify the roles of LC-derived galanin definitively.

This article is part of a Special Issue entitled SI: Noradrenergic System.

Contents

1. Introduction 321
2. Overview of LC anatomy 321
3. LC afferents 321
4. LC efferents: focus on prefrontal cortex, hippocampus, and ventral tegmental area 322

---

[*] *Corresponding author.* Fax: +1 404 727 3949.
[**] Corresponding author. Fax: +1 706 542 3275.
E-mail addresses: dweinshenker@genetics.emory.edu (D. Weinshenker), pvholmes@uga.edu (P.V. Holmes).

http://dx.doi.org/10.1016/j.brainres.2015.11.025
0006-8993/

5. Galanin coexistence in LC neurons and galanin receptors in prefrontal cortex, hippocampus, and ventral tegmental area . . . 322
6. Neuromodulatory effects of galanin . . . 323
7. Neurotrophic actions of galanin . . . 323
8. Addiction . . . 324
9. Seizure susceptibility . . . 325
10. Depression . . . 325
11. Stress and anxiety . . . 327
12. Summary . . . 328
13. Future directions . . . 329
Acknowledgments . . . 330
References . . . 330

1. Introduction

The brainstem locus coeruleus (LC) is the major noradrenergic nucleus in the brain and is the sole source of norepinephrine (NE) in many parts of the limbic system and forebrain, such as the hippocampus and frontal cortex. The LC is implicated in many aspects of physiology and behavior, including attention, arousal, motivation, and stress. Although NE is considered the “primary” neurotransmitter employed by the LC, these neurons also synthesize and release a host of neuropeptides, including galanin, neuropeptide Y, cocaine- and amphetamine-related transcript, and brain-derived neurotrophic factor. In particular, galanin is expressed in most LC neurons in rodents and humans. The purpose of this review is to catalog the putative functions and consequences of LC-derived galanin, integrate them into a comprehensive model, and provide a roadmap for the use of new technologies to define how galanin release from LC neurons impacts brain function and disease.

2. Overview of LC anatomy

Electrophysiological evidence consistently shows that LC neurons respond to sensory stimulation of all modalities with a high degree of fidelity to the intensity and temporal pattern of the stimulation. The response of LC neurons to sensory stimuli appears to be more sensitive than the brainstem cholinergic, serotonergic, or dopaminergic systems (Koyama et al., 1994; Strecker and Jacobs, 1985), suggesting the LC plays a primary role amongst these systems in directing attentional resources to a dynamic environment. The responsiveness of LC neuronal discharge to novel and conditioned stimuli that represent salient features of the immediate environment is well established in a variety species under awake, freely behaving conditions (Aston-Jones et al., 1991; Bouret and Sara, 2005; Rasmussen et al., 1986; Sara and Bouret, 2012). An early study of freely behaving cats is particularly informative and demonstrates the wide range and nature of stimuli influencing LC discharge (Rasmussen et al., 1986). These experiments revealed that the treadmill exercise was a potent driver of LC firing, more so than other stimuli, including the presence of rats or other cats. This entrainment to physical activity presumably reflects the high degree of innervation carrying somatosensory, mechanoreceptive, vestibular, and visceral information to the LC, in addition to other sensory inputs.

3. LC afferents

The LC is remarkably sensitive to a range of general and special sensory input from somatic and visceral sources; however, some early tract-tracing studies of LC afferents revealed surprisingly few structures projecting to the LC and identified the nucleus paragigantocellularis (PGi) and nucleus prepositus hypoglossi (NPH) as the major afferent sources (Aston-Jones et al., 1986). In contrast, other, early retrograde tracing studies revealed a much more extensive afferent network involving multiple forebrain and brainstem sources (Cedarbaum and Aghajanian, 1978). As detailed below, recent experiments involving a range of tracing techniques have confirmed a broad convergence of inputs to the LC.

In addition to direct input from the dorsal horn and spinal trigeminal system (Craig, 1992), the nucleus PGi, a structure in the rostral ventrolateral medulla, can account for much of the somatosensory and mechanoreceptor input from the skeletomotor system (Samuels and Szabadi, 2008; Sara and Bouret, 2012). The PGi also carries auditory input via the inferior colliculus (Van Bockstaele et al., 1993). These pathways excite LC neurons primarily via glutamatergic transmission (Aston-Jones et al., 1991; Ennis et al., 1992; Park et al., 2005), though distinct populations of inhibitory, GABAergic neurons arising from the PGi innervate the LC, as well (Sirieix et al., 2012). Sympathetic afferent input to the LC also arises from the PGi, which itself functions as a sympathoregulatory center. Parasympathetic regulation of the LC occurs via projections from the nucleus tractus solitarius (NTS) (Groves et al., 2005; Van Bockstaele et al., 2001). Though known primarily as a brainstem micturition center, Barrington's nucleus projects to both the LC and a range of sympathetic and parasympathetic targets (Guo et al., 2013; Valentino et al., 1995) and may thus coordinate autonomic input to the LC. GABAergic projections from the NPH constitute a major pathway to the LC that regulates the inhibition of REM sleep induction (Kaur et al., 2001; Sirieix et al., 2012). The NPH also integrates vestibular (Seo et al., 2004) and visual information (Korp et al., 1989) and thus may coordinate kinetic, positional, and visual input to the LC.

A wide range of neural systems involved in motivational, emotional, and cognitive functions impact the LC. Hypothalamic innervation of the LC is substantial and includes