



Physiology of quantal norepinephrine release from somatodendritic sites of neurons in locus coeruleus

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Norepinephrine (NE) released from the nerve terminal of locus coeruleus (LC) neurons contributes to about 70% of the total extracellular NE in primates brain. In addition, LC neurons also release NE from somatodendritic sites. Quantal NE release from soma of LC neurons has the characteristics of long latency, nerve activity-dependency, and autoinhibition by α_2 -adrenergic autoreceptor. The distinct kinetics of stimulus-secretion coupling in somata is regulated by action potential patterns. The physiological significance of soma and dendritic release is to produce negative-feedback and to down-regulate neuronal hyperactivity, which consequently inhibit NE release from axon terminal of LC projecting to many brain areas. Recent discoveries about the LC somatodendritic release may provide new insights into the pathogenesis of clinic disease involving LC-NE system dysfunction, and may help developing remedy targeted to the LC area.

Keywords: norepinephrine, somatodendritic, quantal release, locus coeruleus, α_2A -adrenoceptor

INTRODUCTION

Locus coeruleus (LC) is located in the ventrolateral side of the fourth ventricle in the pons, most of which are noradrenergic neurons projecting to the cortex, cingulate cortex, amygdala nucleus, thalamus, hypothalamus, olfactory tubercles, hippocampus, cerebellum, and spinal cord (Swanson and Hartman, 1975). Norepinephrine (NE) released from the nerve terminal of LC neurons contributes to about 70% of the total extracellular NE in primates brain (Svensson, 1987). It plays important roles not only in arousal, attention, emotion control, and stress (reviewed in Aston-Jones and Cohen, 2005; Berridge and Waterhouse, 2003; Bouret and Sara, 2005; Nieuwenhuis et al., 2005; Sara and Devaugs, 1989; Valentino and Van Bockstaele, 2008), but also in sensory information processing (Svensson, 1987). LC directly modulates the somatosensory information from the peripheral system. Under the stress condition, LC could completely inhibit the input from painful stimuli through the descending projection to the spinal cord (Stahl and Briley, 2004). Dys-regulations of LC neurotransmission have been suggested to be involved in physical painful symptoms, attention deficit hyperactivity disorder (ADHD), sleep/arousal disorder, post-traumatic stress disorder, depression, schizophrenia, and Parkinson's disease (reviewed in Berridge and Waterhouse, 2003; Grimbergen et al., 2009; Mehler and Purpura, 2009).

Although extensive studies are carried out on functions of LC neurons in their targeting areas, accumulating evidences suggest that somatodendritic NE release within the LC nucleus also exerts important functions. The somatodendritic release of LC

was first suspected by an early observation of a NE synthesis enzyme, dopamine β -hydroxylase, in both soma and dendrites of LC neurons (Swanson and Hartman, 1975). Microdialysis, push-pull superfusion and voltammetry are then used to investigate neurotransmitter release in the LC area *in vivo* or in brain slice (reviewed in Singewald and Philippu, 1998). Application of high potassium solution, field stimulation, or systematic drug all induce NE release in the LC nucleus but it is hard to differentiate whether NE is released from the somatodendritic sites or terminals of LC neuron. Recently, we have applied patch-clamp technique on the somata area of the LC neuron while recording its quantal NE release simultaneously by carbon fiber electrode (Huang et al., 2007). Single vesicle release of NE is detected after depolarization of soma of the LC neurons. In this review, we will discuss the physiology and characteristics of NE release from LC somatodendrite.

PHYSIOLOGY OF NE SOMATODENDRITIC RELEASE IN LC NUCLEUS

AUTOINHIBITION OF NE RELEASE IN LC SOMATA

Adrenergic receptors belong to a family of G-protein coupling receptors (GPCRs) which are involved in signal transduction (reviewed in Gilsbach and Hein, 2008). Among them, functional α_{2A} receptors are presented on the somatodendrite of LC neurons (Norenberg et al., 1997). Therefore, somatodendritic release of NE may be regulated by the interaction of released NE and α_{2A} receptor. Using voltammetry analysis, systemic application of α_{2A} receptor antagonist is shown to increase

NE release both from LC nucleus and projecting brain area (Callado and Stamford, 1999, 2000). Consistently, local perfusion of the α_{2A} receptor agonist clonidine decreases NE in the LC, whereas the opposite effect is observed with its antagonist BRL44408 (Pudovkina et al., 2001; Fernandez-Pastor et al., 2005). With combined measurements of amperometry and patch-clamp, a doubly enhanced individual quantal release events from LC somata is achieved upon inhibition of α_{2A} receptor by yohimbine (Huang et al., 2007). Thus, NE released from somatodendrite inhibits the activity of LC neurons through the activation of local α_{2A} receptors (Svensson et al., 1975; Cedarbaum and Aghajanian, 1977) (Figure 1). However, whereas inhibition via an autoreceptor was originally assumed to involve NE released from recurrent collaterals (Cedarbaum and Aghajanian, 1977), our findings identify that TTX blocked $\sim 20\%$ of total secretion induced by depolarization of the soma, indicating $\sim 80\%$ of NE detected in the somatodendrite of LC neuron comes from LC somata.

INHIBITION OF NEUROTRANSMITTER RELEASE IN PROJECTING BRAIN AREA

In addition to autoinhibition of release, activation of α_{2A} receptors by NE also hyperpolarizes LC neurons and reduces the firing rate of LC neurons (Williams et al., 1985). This effect on LC firing should inhibit the terminal NE release of LC neurons. It is shown that local administration of a selective NE transporter inhibitor desipramine (DMI) increases NE concentration in the LC and simultaneously decreases NE level in the cingulate cortex (Mateo et al., 1998; Fernandez-Pastor et al., 2005). Consistently, administration of α_{2A} receptor antagonists into LC increases NE release in the cortex in a concentration-dependent manner (Fernandez-Pastor and Meana, 2002). Thus, NE-induced

α_{2A} receptor activation in the LC cell body exerts inhibitory tonic modulation on NE release in its terminal areas as well as in soma.

It is known that stress factors also activate LC neurons through neurotransmitter receptors located in LC soma, which consequently modulate NE release in projecting brain area. The emerging knowledge of how the LC-NE system is regulated by stressors and determinants of sensitivity of LC neurons to stress-related neurotransmitters is important for understanding and alleviating diverse stress-related psychiatric disorders (Valentino and Van Bockstaele, 2008).

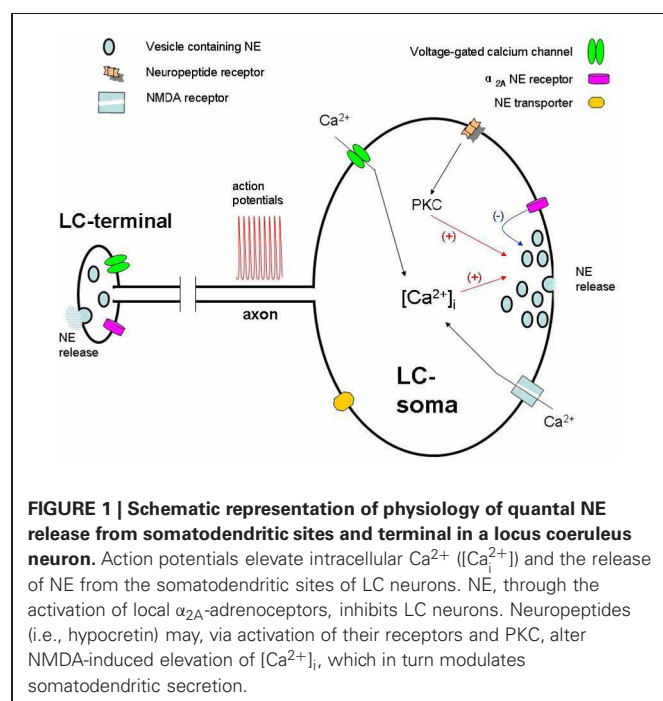
CHARACTERISTICS OF NE RELEASE FROM SOMATODENDRITIC SITES OF NEURONS IN LOCUS COERULEUS

ACTION POTENTIAL PATTERN DEPENDENCE

Intracellular recordings of LC neurons in slices from P8–P26 rats show that in response to stimulation, the spontaneous firing rate increases from (0.3–4 Hz) to (15–20 Hz) (Williams et al., 1987). Interestingly, quantal release events from somatodendritic sites of LC neurons are detected only when the firing rate is high (15–20 Hz) but not low (4 Hz) (Berridge and Waterhouse, 2003; Huang et al., 2007). In contrast, terminal glutamate release of LC neurons, measured by excitatory post synaptic current (EPSC), is not affected by the frequency of action potential (Huang et al., 2007). The high-frequency action potential most likely elevates the level of residual calcium in LC somata which leads to NE release, as shown in chromaffin cells (Duan et al., 2003). LC neuron firing is a premise for NE release from terminal. However, it is not consistent with NE release from soma, because we could not observe quantal release events when the firing frequency is low. Therefore, stress/stimulus-induced LC hyperactivity in firing may trigger somatodendritic NE release, which exerts auto-inhibitory function to alleviate the hyperactivity. This negative-feedback via α_{2A} receptor enables an auto-regulatory mechanism and may play important roles in LC physiological function. If these negative-feedback mechanism is damaged, LC neurons hyperactivity induced by a wide range of stresses would not be inhibited and, therefore, contribute to many disorders such as epilepsy, ADHD, sleep/arousal disorder, post-traumatic stress disorder, main depression disease, schizophrenia, Alzheimer's disease, and Parkinson's disease et al (Svensson, 1987; Valentino and Van Bockstaele, 2008).

TIMING OF QUANTAL NE RELEASE FROM SOMATODENDRITES IN LC

Combined amperometry and patch-clamp study of somatic transmitter secretion from neurons in brain slice preparation allows accurate measurement of the timing of quantal NE release following LC neuron firing or depolarization. Compared with the fast synaptic transmission in the range of milliseconds, the latency of LC somata release is in the range of seconds, which is 100–1000 times slower (Huang et al., 2007). A plausible explanation for the dramatic difference between fast glutamate release at synapse and slow NE release at the somatodendritic region is vesicle positions with respect to calcium channels. As shown in chromaffin cells, the channel-vesicle distance is about 10 nm for the fast release, but > 200 nm for the slow release (Elhamdani et al., 1998). The long latency of NE release from somatodendritic area of LC neurons may contribute to the delayed autoinhibition on LC neurons.



COMPARISON TO OTHER SOMATODENDRITIC EXOCYTOSIS

Amperometry measurements have been used to detect quantal monoamine release in different kinds of cell body, such as chromaffin cell (Chow et al., 1992), leech neuron (Chen et al., 1995), substance nigra neuron (Jaffe et al., 1998), and dorsal raphe nucleus (Benzekroufa et al., 2009). Quantal NE release from somatodendritic sites of neurons in LC is characterized by long latency, high sensitivity to frequency of action potential, calcium-dependence, and low sensitivity to TTX. The quantal size of NE release from soma of LC neuron is 11.9 fC, corresponding to 37,000 NE molecules (Huang et al., 2007). However, the quantal size of NE release from terminal of LC neuron could be 100 times larger. In organotypic rat brainstem slice cultures, >1 pC quantal events occurred at predominantly axonal release sites (Chiti and Teschemacher, 2007).

Other monoamines, such as dopamine and 5-HT, are also released from somatodendritic sites of neurons. Substantia nigra pars compacta (SNc) neurons release dopamine from somatodendrites with charge integrals ranging from a few to several hundred fC, corresponding to about 14,000 dopamine molecules on average (Bjorklund and Lindvall, 1975). The dopamine release in SNc is also Ca²⁺-dependent. A voltage-gated calcium channel blocker, Cd²⁺, blocks the stimulatory effects of glutamate on quantal dopamine secretion in cultured SNc neurons (Kim et al., 2008). Interestingly, somatodendritic dopamine release in the substantia nigra proceeds in a botulinum toxin B resistant pathway, unlike that of terminal release, suggesting different molecular players in somata release (Bergquist et al., 2002). In addition, central 5-HT exocytosis from cell bodies of raphe nuclei is reported with a quantal size of ~34,000 molecules (Benzekroufa et al., 2009), similar to what we observe for NE. Further studies on somata release from various neurons are needed to understand its physiological roles and characteristics.

NEUROPEPTIDE REGULATION OF NE RELEASE IN LC

LC activity is finely tuned by the convergence of afferent fibers. Many neurotransmitter receptors are expressed on the cell membrane of LC soma which may control LC functions via regulating LC firing or somatodendritic NE release (Valentino and Van Bockstaele, 2008). Two of the neuropeptides, orexin and tachykinins, are shown to regulate NE release in the LC. In general, neuropeptides play important roles in many essential physiological functions and behaviors. The success in recording NE release from LC neurons in brain slices provides a unique opportunity to investigate the modulation of NE release by neuropeptides at high temporal and spatial resolutions.

HYPOCRETIN (OREXIN)

Hypocretins are neuropeptides in the lateral hypothalamus that regulate sleep/wake states, feeding behavior, and reward processes (Ganjavi and Shapiro, 2007). Hypocretin applied in the LC area depolarizes LC neurons and increases firing rate (Hagan et al., 1999). At cellular level, high level (1 μM) of hypocretin directly produces dose-dependent somatodendritic NE release, while low level (0.1 μM) of hypocretin notably potentiates NMDA receptor-mediated somatodendritic release (Chen et al., 2008). This potentiation is blocked by SB 334867, a selective hypocretin receptor 1 antagonist, or bisindolylmaleimide, a specific protein kinase C

(PKC) inhibitor, indicating the involvement of hypocretin receptor 1 and PKC. Consistently, phorbol 12-myristate 13-acetate, a PKC activator, mimics the hypocretin-induced potentiation. In addition, hypocretin enhances NMDA-induced intracellular Ca²⁺ elevation via activation of hypocretin receptor 1 and PKC, which mediate hypocretin-potentiated somatodendritic secretion. Thus, hypocretin not only induces NE release in LC somata at high concentrations, but also potentiates NMDA receptor-mediated NE release at low concentrations.

TACHYKININS

Tachykinin neuropeptides [substance P (SP), neurokinin A, neurokinin B] and their receptors (NK1, NK2, NK3) are involved in stress-mechanisms, mood/anxiety regulation, and emotion-processing (reviewed in Ebner and Singewald, 2007). In freely moving animals, exposure to forced swimming considerably enhances the release of both SP and NE in the LC (Ebner and Singewald, 2007). Administration of a selective NK1R antagonist into the LC nucleus potentiates the NE response within LC nucleus but abolishes the stress-induced increase in terminal NE release in the medial prefrontal cortex. The NE transmission in the LC and in the medial prefrontal cortex are also affected in neurokinin-1-receptor gene knockout (NK1R^{-/-}) mice (Fisher et al., 2007). The extracellular NE in the frontal cortex of NK1R^{-/-} mice is two to fourfold greater than that of NK1R^{+/+} mice. All these data demonstrate an active interaction between SP and NE system in the LC.

Several other neuropeptides also affect the firing of LC neurons. Corticotropin-releasing factor increases both the activity of LC-noradrenergic neurons and the release of NE in a LC terminal region (Page and Abercrombie, 1999). Opioids inhibit firing by hyperpolarizing LC neurons via μ-opioid receptors (Williams et al., 1987). Neuropeptide Y and galanin also inhibit firing in LC neurons (Pieribone et al., 1995; Xu et al., 2005). It remains to be investigated whether these neuropeptides regulate NE release in LC neurons.

FUTURE STUDY

The molecular mechanism of LC somatodendritic exocytosis (or any somatodendritic exocytosis in general) remains largely elusive. Compared with synaptic exocytosis, soma-exocytosis may be regulated differently in terms of calcium sensitivity, vesicle pools, and exocytosis machinery. The autoinhibition mediated by α_{2A} receptor also begs for further investigation. As a GPCR, α_{2A} receptor may modulate vesicle fusion through G_{βγ} pathway as shown in chromaffin cells (Chen et al., 2005). It is well-known that the LC-NE system is affected by stress and behavior state. Since NE release from somata inhibits LC neuron activity, it may serve as a drug target to modulate LC activity and function. A better understanding of LC somata release may prove useful for drug development in targeting to LC somatodendrite area specifically.

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