Please cite this article in press as: Llorca-Torralba M et al. Noradrenergic Locus Coeruleus pathways in pain modulation. Neuroscience (2016), http://dx.doi.org/10.1016/j.neuroscience.2016.05.057

Neuroscience xxx (2016) xxx–xxx

REVIEW

NORADRENERGIC LOCUS COERULEUS PATHWAYS IN PAIN MODULATION

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Abstract—The noradrenergic system is crucial for several activities in the body, including the modulation of pain. As the major producer of noradrenaline (NA) in the central nervous system (CNS), the Locus Coeruleus (LC) is a nucleus that has been studied in several pain conditions, mostly due to its strategic location. Indeed, apart from a well-known descending LC-spinal pathway that is important for pain control, an ascending pathway passing through this nucleus may be responsible for the noradrenergic inputs to higher centers of the pain processing, such as the limbic system and frontal cortices. Thus, the noradrenergic system appears to modulate different components of the pain experience and accordingly, its manipulation has distinct behavioral outcomes. The main goal of this review is to bring together the data available regarding the noradrenergic system in relation to pain, particularly focusing on the ascending and descending LC projections in different conditions. How such findings influence our understanding of these conditions is also discussed.

This article is part of a Special Issue entitled: Pain. **© 2016 Published by Elsevier Ltd on behalf of IBRO.**

Key words: Locus Coeruleus, noradrenaline, norepinephrine, pain, neuropathic pain, inflammatory pain.

Contents

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Abbreviations: ACC, anterior cingulate cortex; AMY, amygdala; APS, Air-puff stimulation; AVV, adenoviral vector; CCI, chronic constriction injury; CFA, complete Freund's adjuvant; CNS, central nervous system; CNQX, 6-cyano-7-nitroquinoxaline-2,3-dione; CRF, corticotropin-releasing factor; DBH, dopamine β-hydroxylase; DLPT, dorsolateral pontine tegmentum; DSP-4, N-2-chloroethyl-N-ethyl-2-bromobenzylamine; eGFP, enhanced green fluorescent protein; fMRI, functional magnetic resonance imaging; GABA, γ-aminobutyric acid; GDNF, Glial cell line-derived neurotrophic factor; icv, Intracerebroventricular; IL-2, interleukin-2; LC, Locus Coeruleus; L-DOPA, dihydroxyphenylalanine; NA, noradrenaline; NAT, noradrenaline transporter; NMDA, N-methyl-D-aspartic acid; pERK1/2, phosphorylated extracellular signal-regulated kinases 1/2; PFC, prefrontal cortex; PGi, Paragigantocellularis nucleus; PVN, paraventricular nucleus of the hypothalamus; PrH, Prepositus Hypoglossi nucleus; TH, tyrosine hydroxylase; SC, subcoeruleus; SNI, spared nerve injury; SNL, spinal nerve ligation; SP, substance P.

http://dx.doi.org/10.1016/j.neuroscience.2016.05.057
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INTRODUCTION

Noradrenaline (NA) was first discovered in the brain more than 60 years ago (Von Euler, 1951). Since then, data have accumulated to establish the noradrenergic system as a vital circuit driven by NA interacting with different adrenergic receptors located throughout the nervous system. Pain is one of the sensations regulated by the noradrenergic system and its central structure, the Locus Coeruleus (LC). The noradrenergic modulation of pain has already been discussed in two comprehensive reviews (Pertovaara, 2006, 2013). Hence, here we aim to focus on the latest findings regarding the particular involvement of the LC in the ascending and descending noradrenergic network associated with acute and chronic pain processing, introducing recent innovations in the field.

The central noradrenergic system

In the central nervous system (CNS), noradrenergic neurons are organized in seven clusters or groups, classified from A_1 to A_7, and they are located in the brainstem (Dahlstrom and Fuxe, 1964; Pertovaara, 2006). This organization is common to rats and primates, including humans (Bogerts, 1981). Very briefly, the A_1 group is located near to the area prostrema, while the A_2 is found along the dorsal vagal complex. The A_3 neurons form part of the medullary reticular formation, those of A_4 surround the fourth ventricle, while the A_5 (located in the ventrolateral pons) and A_7 (in the lateral part of the pons) neurons send projections to the spinal cord (Proudfit and Clark, 1991). The A_6 (which represents de LC) is located in the lateral floor of the fourth ventricle, it innervates almost the entire forebrain and represents the most important noradrenergic projection to the spinal cord (Proudfit and Clark, 1991; Howorth et al., 2009). This population contains almost 50% of all the noradrenergic neurons. Although small amounts of other substances are also produced in the LC (e.g., vasopressin, neurotensin and galanin: Olpe and Steinmann, 1991; Singewald and Philippu, 1998) NA is the major and the most important neurotransmitter synthesized by these neurons, exerting its action on specific adrenergic receptors.

Noradrenaline synthesis and degradation

NA is a neurotransmitter biosynthesized from the amino acid tyrosine through sequential enzymatic reactions. The first step in this cascade is the conversion of tyrosine into dihydroxyphenylalanine (L-DOPA) through the enzymatic action of tyrosine hydroxylase (TH). Subsequently, L-DOPA is converted into dopamine through the action of the aromatic L-amino acid, decarboxylase, and only in noradrenergic neurons is dopamine then converted into NA by dopamine β-hydroxylase (DBH: Fig. 1). The step catalyzed by TH is the rate-limiting step, as it directly influences the availability of dopamine and NA in the body. Thus, the immunodetection of TH expression is often used as a marker of dopaminergic and/or noradrenergic neurons, and it may be considered indicative of the demand for neurotransmitter synthesis, whereas DBH immunodetection is specific for noradrenergic neurons and NA demand (Bacopoulos and Bhatnagar, 1977). After its synthesis, NA is stored in vesicles in the synaptic terminal of the axon. These vesicles attach to the neuronal membrane through the vesicular monoamine transporter and in response to specific electrical input, their content is released into the synaptic cleft. As a result, NA can bind to post-synaptic adrenergic receptors and activate intracellular signaling cascades specifically in function of the type of adrenergic receptor activated (facilitatory or inhibitory receptors). After transducing their specific signals, NA molecules follow one of two different pathways: they either undergo reuptake by the presynaptic NA transporters to be recycled or they are degraded by enzymes in the synaptic cleft and at the nerve terminal (Fig. 1).

Adrenergic receptors

A large part of the structures implicated in pain modulation express distinct adrenergic receptors (MacDonald and Scheinin, 1995). Consequently, the noradrenergic system may act directly or indirectly through different receptors when dealing with pain. Adrenergic receptors are divided into two main categories: the α- and β-adrenoceptors. Several subtypes of each type are recognized and thus, the α-adrenoceptors can be found as α1A, α1B, α1D, α2A, α2B, α2C and α2D (Bylund et al., 1994). However, in the case of the α2-adrenoceptors, the majority of mammals only have three genes encoding the α2B, α2C and α2A or α2D, and the latter two classes of adrenoceptors (α2A or α2D) are usually simply referred to as α2A. In general, the action of the adrenoceptors is mediated by guanine nucleotide-binding regulatory proteins (G proteins). As such, the α2-adrenoceptors are able to dampen intracellular adenylcyclase activity through the G_i protein or directly modify the activity of certain ion channels, thereby inhibiting signal transduction. By contrast, α1-adrenoceptors are coupled either to phospholipase C through the G_q protein or directly to calcium influx (Summers and McMartin, 1993), thereby stimulating signal transduction. It is important to highlight the importance of α2-adrenoceptor activation as auto-receptors, which inhibits impulse discharge and the further inhibition of NA release from adrenergic terminals. However, α2-adrenoceptors are also found in non-adrenergic cells, acting as heteroreceptors and contributing to the regulation of other neurotransmission systems (Gyires et al., 2009).

The α1A, α1B, α2A and α2B subtypes of adrenoceptors are the best studied to date. Briefly, α1A-, α2A- and α2B-adrenoceptors are found extensively in the supraspinal areas, mostly coinciding with the wide distribution of ascending pain pathways (Tavares et al., 1996; Day et al., 1997). By contrast, the α1B subtype is more restricted and it is generally found in the thalamus, amygdala (AMY), and dorsal and median raphe nuclei (Day et al., 1997). A large proportion of α2A-adrenoceptors are present in the LC (Tavares et al., 1996) and this adrenoceptor is found in the synaptic and non-synaptic plasma membrane of dendrites and peri-

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