Chapter 6

A5 and A6 Noradrenergic Cell Groups: Implications for Cardiorespiratory Control

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Abstract

Central pontine A5 and A6 noradrenergic cell groups are two of the main sources of noradrenaline release at the spinal cord, at the level of the superficial dorsal horn, the motoneuron pools of the ventral horn, lamina X and the thoracic and sacral intermediolateral cell columns. Noradrenergic ascending or descending pathways originating in the A5 or A6 noradrenergic cell groups are highly sensitive to stress and to other high-arousal states. These noradrenergic groups present extensive projections that play a key role in the modulation of all antinociceptive and autonomic responses elicited by painful or threatening situations. Depending on the locations of these projections, different possible roles for each noradrenergic cell groups are suggested. The A6 noradrenergic cell group might have the greatest effect on somatosensory transmission and the A5 group on sympathetic function. Consistent with this, stimulation of central noradrenergic pathways evokes an array of stresslike and antinociceptive effects, including changes in blood pressure, heart rate and respiratory rate. In addition, it also produces an increase in excitability, which leads to a high degree of arousal and a potentiation of cortical and subcortical mechanism generating the necessary cognitive, behavioral and autonomic responses to confront these physical or psychological situations.

Keywords: pontine noradrenergic cell groups, A5 region, locus coeruleus, cardiovascular control, analgesia

1. Introduction

Noradrenergic (NA) central pathways located at the level of the brainstem were initially described by Dahlström and Fuxe in 1964 and contain several clusters or groups of neurons

classified from A1 to A7. These clusters extend rostrocaudally from the lateral pons to the caudal ventrolateral medulla. Afferent and efferent connections are sent and come from very different locations along the central nervous system (CNS) and are implicated in physiological and behavioral functions associated with a wide cascade of processes, such as homeostasis, arousal, memory, learning, autonomic and behavioral responses to stress and pain, among others [1, 2].

NA neurons are characterized by the presence, within the synaptic terminal, of the cytoplasmatic enzymatic machinery, which is necessary to biosynthesize noradrenaline from the amino acid tyrosine through a precise and sequential enzymatic reaction. Tyrosine hydroxylase (TH) is the limiting enzyme. It transforms tyrosine into dihydroxyphenylalanine (L-DOPA), which is converted into dopamine by L-DOPA decarboxylase. Finally, dopamine is used as a substrate by dopamine-β-hydroxylase (DBH), which transforms dopamine into noradrenaline [3]. DBH immunodetection is specific for NA neurons and NA central demand [4]. Although once the noradrenaline is a precursor to adrenaline synthesis, the immunodetection of DBH is not restricted to noradrenergic neurons except in the cases where the referred group is isolated from adrenergic neurons (as A6 and A5). After its release into the synaptic cleft, noradrenaline can bind to the pre- or post-synaptic adrenergic receptors and activates intracellular signaling cascades depending on the specific function of the subtype of the adrenergic receptor activated (facilitatory or inhibitory receptors).

Briefly, in terms of the precise location of the different NA cell groups: the A1 NA cell group is found in the ventrolateral medulla; the A2, located close to the dorsal vagal complex, has an intimate relationship (as part of) with caudal NTS complex, starting in very caudal level of medulla until the open of fourth ventricle; A3 neurons are included within the medullary reticular formation, and neurons of the A4 cell group are situated in the surroundings of the fourth ventricle. The precise location of the most studied NA cell groups, the A5, A6 and A7, is the following: the A5 NA cell group is located in the ventrolateral pons; A6, which represents the locus coeruleus, is located in the lateral floor of the fourth ventricle and, finally, A7 is found in the lateral part of the pons. These last three groups of NA neurons represent the most important NA clusters with projections to the spinal cord [5, 6].

Early studies using retrograde transport of horseradish peroxidase combined with immunostaining for DBH or retrograde transport of anti-DBH antibodies demonstrated that the NA endings of the spinal cord arise from the A5, A6 and A7 cell groups in the pons [7]. The projections from the neurons located in the A5, A6 and A7 cell groups are found throughout the spinal cord, but the highest density of synaptic contacts is established at the level of the superficial dorsal horn, the motoneuron pools of the ventral horn, lamina X and the thoracic and sacral intermediolateral cell columns (IML) [5].

In this chapter, the main focus is centered on the main pontine NA cell groups, which project to the spinal cord (A5 and A6), and their implications for cardiorespiratory control.

2. Spinal projections

The A5 and A6 pontine NA clusters of neurons project widely across the spinal cord [5]. These projections reach the dorsal and ventral horns (laminae I-VII) and the IML of the spinal cord

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at thoracic levels. These descending projections of the NA cell groups are crucial in explaining their functional implications in central cardiorespiratory control and in other important autonomic functions involved in behavioral responses to stress or pain.

2.1. Spinal projections from the A6 (locus coeruleus)

The projections from A6 cells use two main pathways: through the spinal cord in the ventral funiculi and through the dorsal surface of the dorsal horn. The A6 NA cell group supplies the highest concentration of synaptic endings at all levels. It includes all regions of the spinal gray matter, but it is especially dense at the level of the dorsal horn, although it has a small number of axons to the ventral horn and IML [5]. Extensive literature for this exists, not only at an anatomical level [6–12] but also with electrophysiological evidence [13, 14]. Intra and extracellular neuronal recording studies provide the assignment to caudal A6 NA neurons with a role in regulating the excitability of the cell bodies of somatic alpha motoneurons located within the ventral horn of the spinal cord.

2.2. Spinal projections from the A5

It is well established that the spinally projecting axons of the A5 NA group mainly travel through the spinal cord within the lateral funiculi to end at the level of the IML cell column

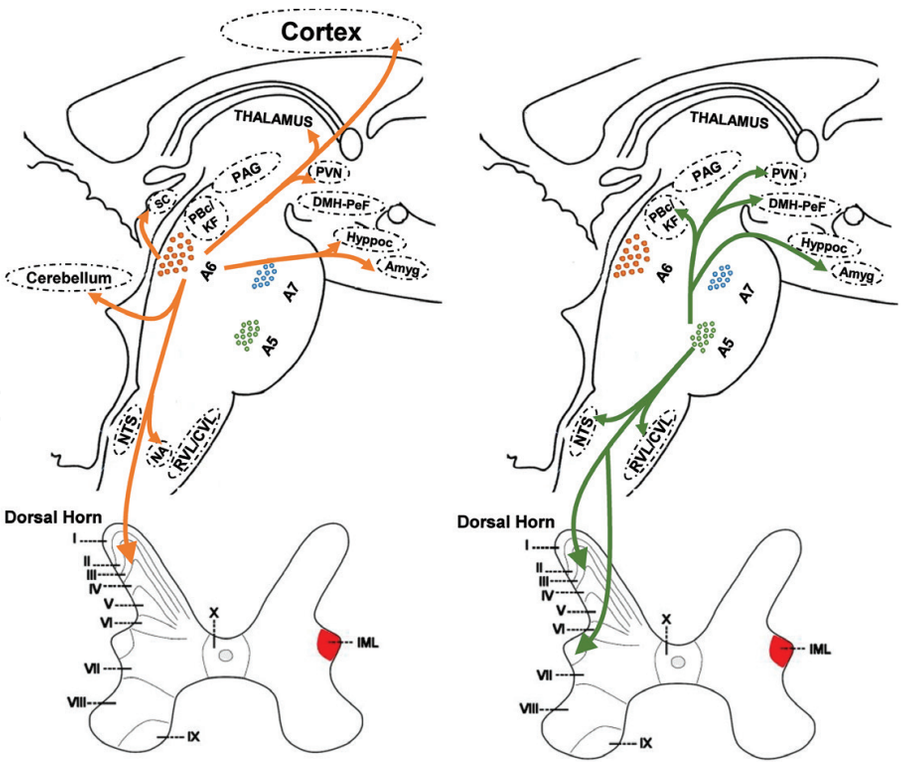

Figure 1. Schematic diagram of a sagittal section of human brain in which the main pontine noradrenergic nuclei (A5 and A6) and their main efferent connections are positioned. (A5) A5 noradrenergic cell group. (A6) A6 noradrenergic cell group, Locus Coeruleus. (Amyg) Amygdala. (CVL) Caudal ventrolateral medulla. (DMH-PeF) Dorsomedial Hypothalamic nucleus and perifornical area. (Hyppoc) Hyppocampus. (IML) Intermedio lateral cell collum of the spinal cord. (KF) Kölliker-Fuse nucleus. (LH) Lateral Hypothalamus. (NTS) Nucleus Tractus Solitarii. (PAG) Periaqueductal gray. (PBc) Parabrachial complex. (PVN) Paraventricular nucleus. (RVL) Rostral ventrolateral medulla.

of the thoracic spinal cord segments [5, 15–17]. There are also projections to the dorsal horn of the spinal cord (laminae IV–VII) [5, 16], where a high density of nociceptive neurons can be observed [18]. The A5 NA cell group contributes only with sparse projections to the dorsal and ventral horns at cervical and lumbosacral levels, but it supplies the thoracic IML with the densest projections, particularly to sympathetic preganglionic neurons [5].

In summary, the projections of A5 and A6 NA cell groups to the spinal cord are distributed in a complementary and topographic way. This suggests a different possible role for each of these cell groups, which depend on the precise location of their projections. Therefore, the A6 NA cell group might have its main effect on somatosensory transmission, and the A5 group on sympathetic autonomic function (**Figure 1**).

3. Functional pathways related to central and spinal projections

Although the previously described spinal projections are enough to explain the roles of each NA cell group, the efferent connections that these nuclei send to other areas of the CNS involved in autonomic control are what reinforce their role in autonomic control and homeostasis.

3.1. A6

The pontine A6 NA cell group, also called "locus coeruleus," is the most exhaustively studied NA nucleus in the brain. This NA region, which projects mainly to the dorsal horn of the spinal cord, has been linked with antinociception or modulation of pain together with the A7 NA cell group in Harlan Sprague-Dawley and Wistar rats [2, 19–23].

Neurons of the A6 region, as other catecholaminergic nuclei, are known to be immunoreactive for TH and DBH, the two enzymes critically involved in noradrenaline biosynthesis. A6 NA neurons also express a wide selection of neuropeptides including neuropeptide Y, somatostatin and cholecystokinin [24]. Most of the A6 NA neurons have different neurochemical characteristics and morphologies, presenting predominantly a medium size with fusiform and polar morphology, and three or four long thin dendrites [25].

A6 NA neurons send axons with extensive bifurcations, which travel long distances and establish connections even with cortical domains [26]. In addition, neurons located in the rostral part of the A6 NA region have widely branched axons that innervate forebrain areas, providing the main source of noradrenalin to the neocortex, hippocampus, amygdala, thalamus and cerebellum [27, 28]. Specifically, at the level of the hypothalamus, the A6 region makes contact with the paraventricular and supraoptic nuclei [29]. Other projections from the A6 NA neurons target the superior colliculus [30]. An activation of all these superior structures enhances arousal, vigilance and attention to sensory stimuli [31]. It has been reported that electrical stimulation of the A6 region also elicits a pressor response [32]. Furthermore, pharmacological inhibitions or activations of the activity of the A6 NA neurons also evoke changes in blood pressure [33].

With regard to these multiple ascending pathways, it is known that the A6 NA region has a critical role in stress responses, autonomic function, emotional memory, attention and the control modulation of motor and sensory functions. Furthermore, it has been shown that noradrenalin exerts potent neuromodulatory actions, reducing neuronal baseline activity and increasing the responsiveness of target cells to novel synaptic stimuli. Within the neocortex, hippocampus, amygdala and cerebellum, noradrenaline also facilitates synaptic plasticity, including long-term potentiation [34–36].

Tracing and immunocytochemical studies clearly describe all the descending projections from the A6 NA neurons to the brainstem and spinal cord [37]. These studies show the differences between the projections that originate from the subcoeruleus and coeruleus regions. However, the A6 NA neurons primarily project to the parasympathetic neurons of the dorsal motor nucleus of the vagus, nucleus ambiguus and sacral spinal cord, and subcoeruleus neurons send their projections to sympathetic preganglionic neurons and somatic cranial nerve nuclei. Both pathways have widespread projections to the brainstem reticular formation and dorsal horn of the spinal cord [38], and to the region surrounding the central canal and the ventral horn [37, 38].

Finally, A6 NA neurons also play a major role in behavioral and autonomic responses to stress [39]. A6 NA cells orexin 1 receptors are activated by stress-related orexin axons projecting from neuronal cell bodies located in the perifornical hypothalamus [40]. Furthermore, A6 noradrenergic neurons also modulate the interaction between the amygdala and hippocampus, thus promoting emotional memory [41], which involves an activation of β receptors within the basolateral amygdala [39]. In a recent report [42], it has been shown that A6 noradrenergic neurons participate in the tachycardia evoked during autonomic responses to stress and also are recognized as central chemoreceptors [43, 44].

3.2. A5

Multiple reports demonstrate that A5 neurons provide the major component of NA input to sympathetic preganglionic neurons of the IML of the spinal cord. Once there, they branch and establish buttons along the cell bodies and proximal dendrites of cholinergic preganglionic neurons, thus sustaining the earlier anatomical [5, 17] and physiological studies [45–50], which indicate a role for the A5 region in regulating sympathetic function.

The A5 region contains NA and non-NA neurons. The non-NA cells are mainly located at the level of the most caudal part of the A5 region [51]. These neurons seem to have similar properties to respiratory chemoreceptors cells previously identified in the rostral medulla oblongata [52]. By employing immunocytochemical and in situ hybridization techniques, neurons of the A5 region are shown to express ionotropic and metabotropic glutamate receptors. Ionotropic NMDA receptors show NR1-NR2D subunits [53], while the non-NMDA types are both AMPA and kainate [54]. The A5 metabotropic receptors observed within the A5 region are mGluR I, II and III [55].

Focusing on the descending connections from the A5 region, there is a dense connectivity with several medullary nuclei. These include the nucleus tractus solitarius (NTS), caudal ventrolateral medulla (CVLM), rostral ventrolateral medulla (RVLM), the caudal pressor area and the retrotrapezoid nucleus. There is also significant ascending connectivity, showing reciprocal

projections with the Kölliker-Fuse, medial and lateral parabrachial nuclei in the pons, the perifornical area and the paraventricular nucleus in the hypothalamus and with the amygdala [15, 56–60]. The location and connectivity of A5 region cells, the so-called ventrolateral pons, with an entire network of ascending and descending connections with other regions of the CNS involved in cardiorespiratory regulation, supports the idea that these neurons are the perfect candidates to drive and modulate the control of both sympathetic activity and cardiorespiratory function (**Figure 1**) [15, 45, 56, 58, 59, 61–63].

We have studied the functional relations between this sympathetic NA region and other hypothalamic, pontine and medullary regions involved in cardiorespiratory control. We first demonstrated that the stimulation of A5 NA cell bodies with glutamate mainly produces an increase in both blood pressure and heart rate [47] (**Figure 2**). It is known that the simultaneous increase of sympathetic vasomotor activity, arterial blood pressure and heart rate implies a reset of the baroreceptor reflex but without attenuation in the sensitivity of the reflex [64]. Furthermore, A5 neurons are activated during baroreceptor unloading [45] and carotid chemoreceptors stimulation [65]. Thus, it has been proposed that A5 neurons may play an important role in the carotid sympathetic chemoreflex triggered by hypoxia [66–68].

However, not only do A5 NA neurons have a cardiovascular role, but they also play an important role in respiratory control, modulating the activity of respiratory neurons [69]. A5 neurons are also synaptically connected to phrenic motoneurons [70] and contribute to the

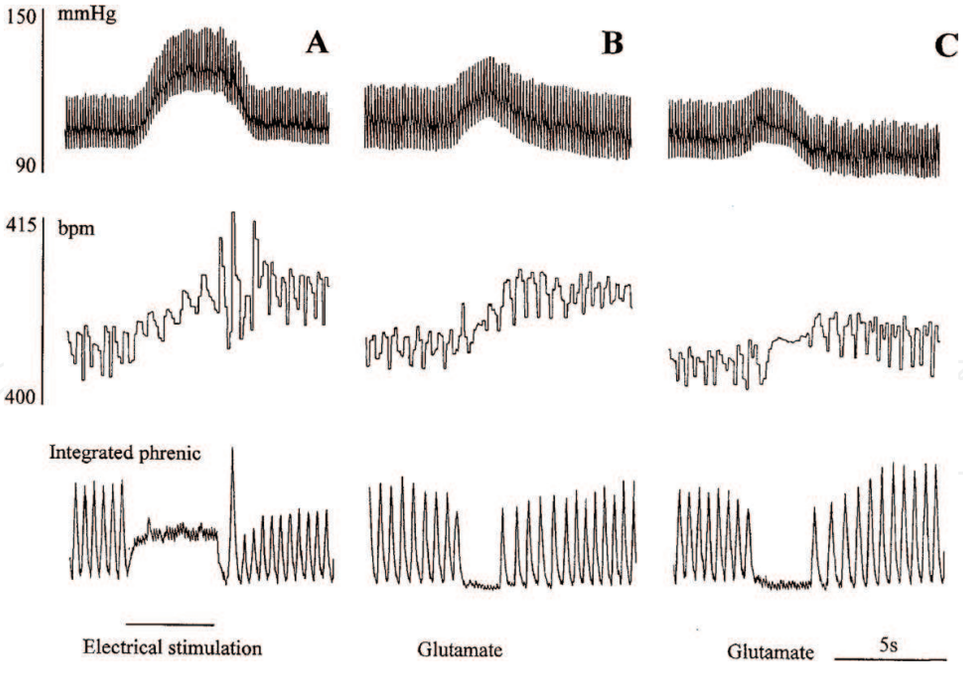

Figure 2. (A), (B), (C). Cardiorespiratory responses to A5 region stimulation in spontaneously breathing animals. Blood pressure (upper traces), heart rate (middle traces) and integrated phrenic activity (lower traces) during (A) electrical stimulation (10 μA, 0.4 ms, 50 Hz for 5 s) and (B) glutamate injection (1.5 nmol, 15 nl, over 5 s) in the same animal showing a decrease in respiratory rate with an increase in blood pressure and heart rate. (C) The response of another animal to glutamate injection (2.5 nmol, 25 nl, over 5 s), in which the respiratory response is similar to (B), but the cardiovascular response is bi-phasic and the increase in heart rate smaller.

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respiratory responses evoked by hypoxia and hypercapnia [66, 68, 71]. We have also demonstrated that the A5 region and medial Parabrachial and Kölliker Fuse nuclei have a role in modifying the activity of laryngeal motoneurons localized in the nucleus ambiguus, producing laryngeal constriction and increasing subglottic pressure (**Figure 3**) [50]. Finally, A5 NA neurons also participate in the cardiorespiratory response elicited by the activation of the parabrachial complex (**Figure 4**) [46], which is a critical component of the brainstem respiratory network required for eupnoea [72].

Similarly to A6 NA neurons, the A5 region is also involved in the control of stress-related responses. The terms "defense region" or "defense response" have been classically used in the

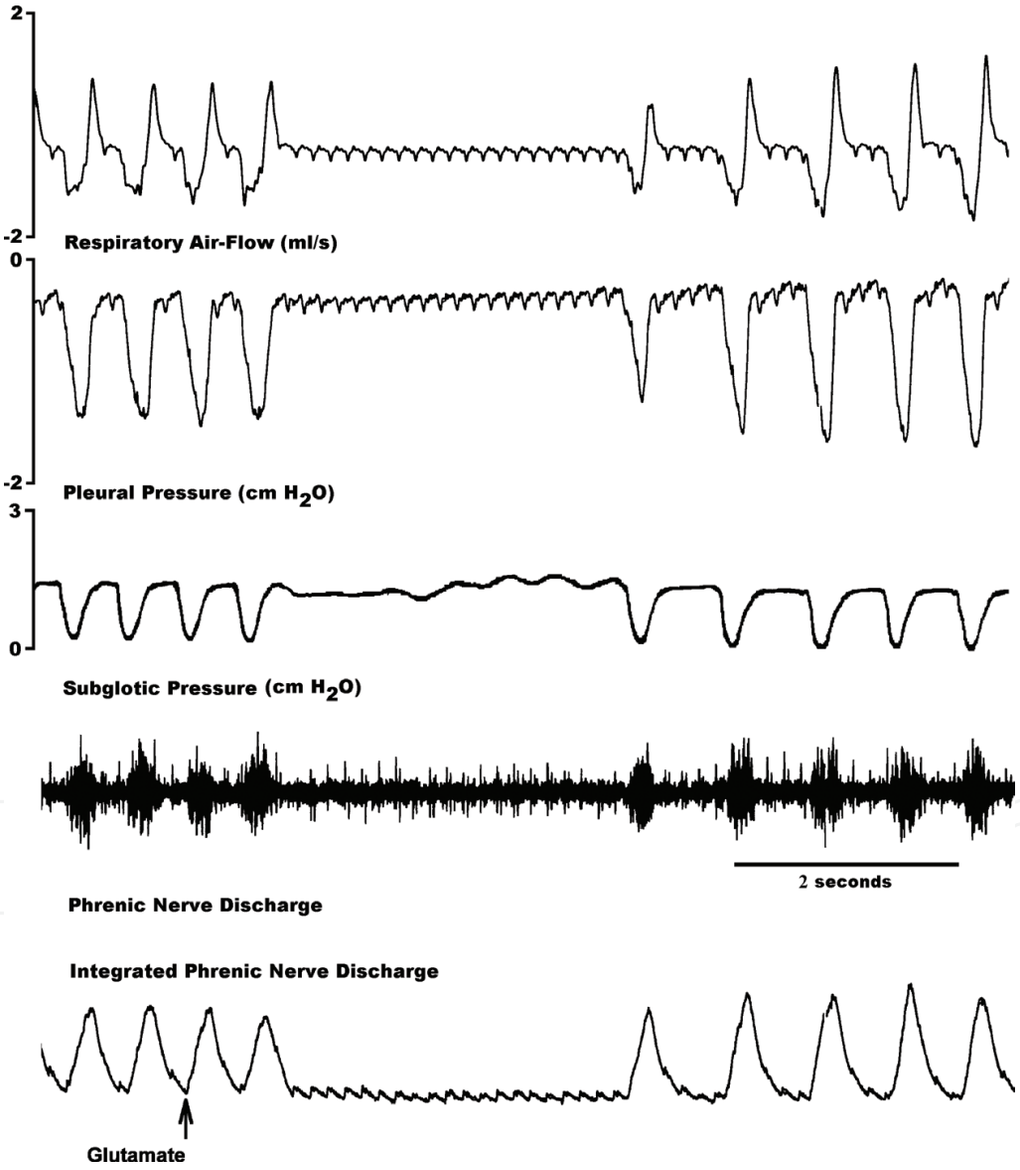

Figure 3. Laryngeal and respiratory responses to glutamate microinjection in the A5 region. Respiratory airflow, pleural pressure, subglottic pressure, phrenic nerve discharge and integrated phrenic nerve discharge, showing a expiratory facilitatory response with increase of subglottic pressure during a glutamate injection (10 nl over 5 s) in the A5 region. The arrows shows the onset of injection.

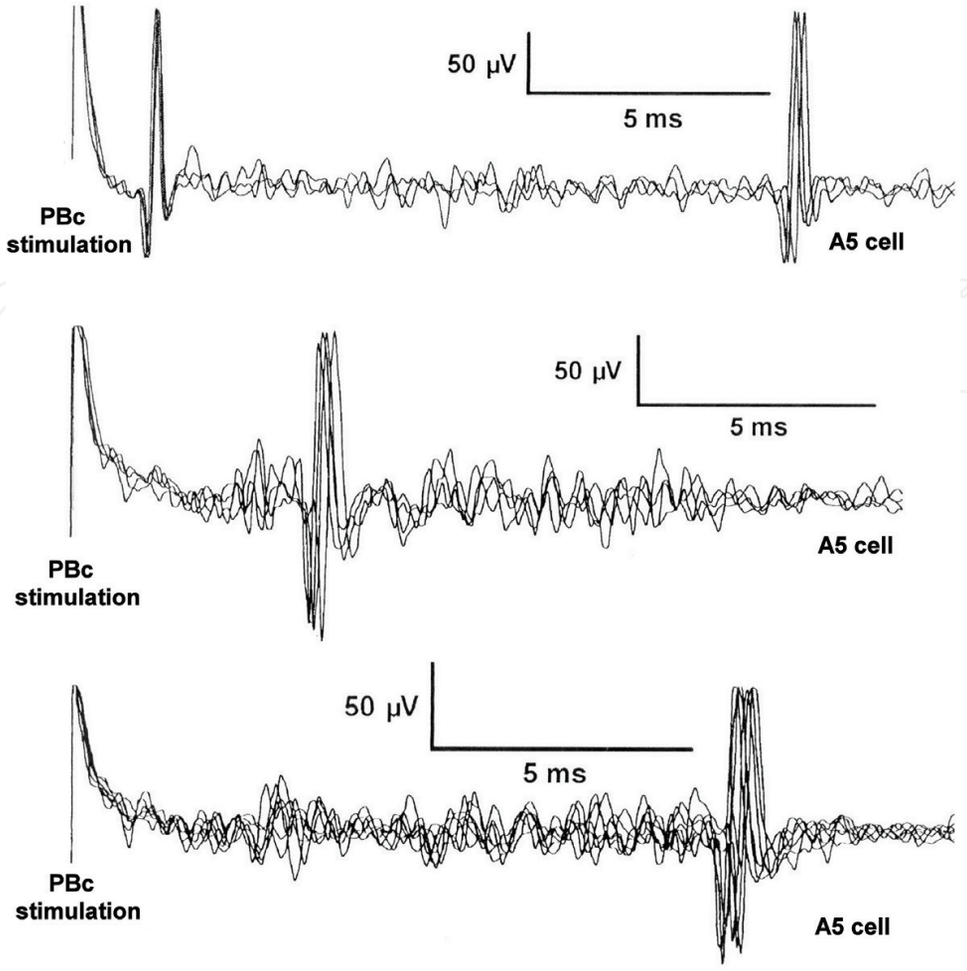

Figure 4. Extracellular recordings of three cells (superimposed sweeps) from the A5 region showing electrophysiological relations between the Parabrachial complex and the A5 region.

literature to describe the areas of the CNS from which we can evoke a pattern of autonomic and behavioral changes that are typically observed when an animal is confronted with threatening stimuli from different types of stressors [73–75]. The complexity of defensive behavior requests different interconnected regions, which plays specific roles according to the origin of the stressor agent or source of fear. It has been reported that there are two important regions from which this "defense response" can be elicited: the dorsomedial hypothalamic and perifornical area (DMH-PeF) in the hypothalamus, and the dorsolateral periaqueductal gray (dlPAG) in the midbrain [76]. The DMH-PeF and the dlPAG are part of an extensive network that coordinates defensive behavior.

The defense response is characterized by hypertension, tachycardia and tachypnea. As previously described, the simultaneous increase of arterial blood pressure, heart rate and sympathetic vasomotor activity implies that the baroreceptor reflex is reset to higher levels of arterial pressure, but without attenuation in the sensitivity of the reflex. A potentiation of the chemoreceptor reflex is known to be involved in this effect [77], as well as an activation of GABAergic mechanisms at the level of the NTS [78, 79].

With electrophysiological and neuropharmacological techniques, we have demonstrated the functional and anatomical interrelations between the Parabrachial complex and the A5 NA region in modulating the cardiorespiratory response evoked from DMH-PeF [80, 81]

(**Figures 5** and **6**) and that glutamate is a possible neurotransmitter candidate involved in these interactions [81, 82]. In unpublished observations, we have obtained similar results with the interactions between the dlPAG and the A5 region [83].

We have also shown that the tachycardia evoked from these defense regions is decreased when the A5 region is pharmacologically blocked with the GABA agonist muscimol. For this reason, we propose the existence of two different pathways that subserve the tachycardia and the pressor response elicited from the stimulation of these defense regions [81, 84]. The tachycardia and the hypertension evoked during defense stimulation involve a direct activation of the neurons of the RVLM. These neurons send direct projections to preganglionic neurons of the IML that are ultimately responsible for the abrupt increase in blood pressure [85]. In addition, a direct activation of the adrenal medulla contributes to a secondary increase in blood pressure due to the liberation of adrenaline. Furthermore, in a parallel pathway to the activation of the RVLM and the preganglionic neurons in the IML, the stimulation of defense regions increases the intensity of the chemoreceptor reflex by means of an excitation or facilitation of chemoreceptor neurons in the NTS [77]. In a parallel circuit, an inhibition of the response to baroreceptor inputs is produced by disfacilitation or inhibition of baroreceptor neurons at the level of the NTS [78, 86]. This inhibition seems to be mediated by GABAergic interneurons in the NTS [78].

Other groups have also suggested the existence of these separates pathways [76]. It has been hypothesized that cardiorespiratory sympathoexcitatory changes evoked during defense stimulation are produced via indirect polysynaptic projections from the dlPAG to the medulla through connections with the DMH-PeF, Parabrachial complex and cuneiform nucleus. Our results suggest that the A5 region is one of the best candidates to mediate in these cardiorespiratory descending pathways because of its excitatory direct connections with the IML and the inhibitory direct projections with the CVLM, which are a source of inhibition to the RVLM [59]. Therefore, the stimulation of both defense regions, DMH-PeF and dlPAG, results in an activation of the A5 region. Thus, this activation will reinforce the pressor response, supporting the hypothesis that neurons within the A5 region are involved in the decrease of the sensitivity of the baroreceptor reflex at the level of the NTS, after the activation of the so-called defense regions, DMH-PeF and dlPAG.

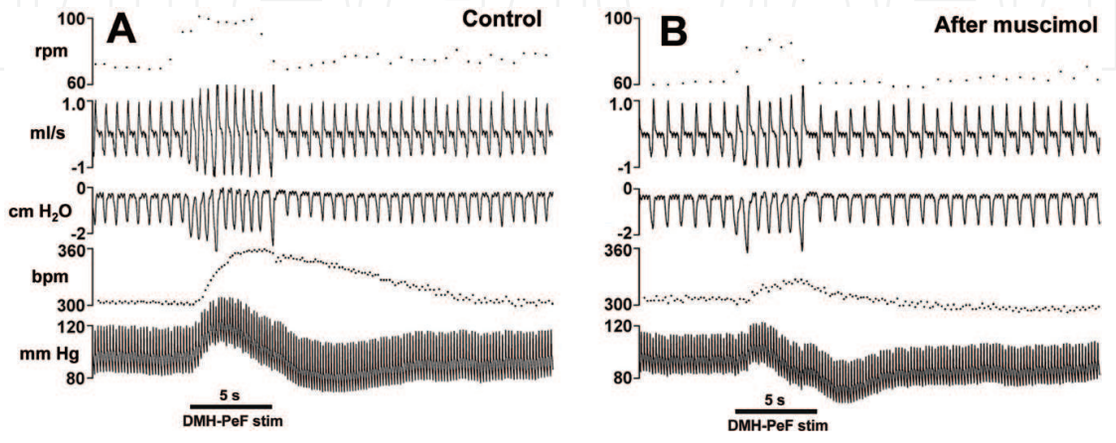

Figure 5. Instantaneous respiratory rate (upper trace), respiratory flow, pleural pressure, instantaneous heart rate and blood pressure in a spontaneously breathing rat, showing the cardiorespiratory response evoked on DMH-PeF stimulation before (A) and after the microinjection of muscimol (50 nl over 5 s) in the A5 region (B) The segment shows the duration (5 s) of the DMH-PeF electrical stimulation.

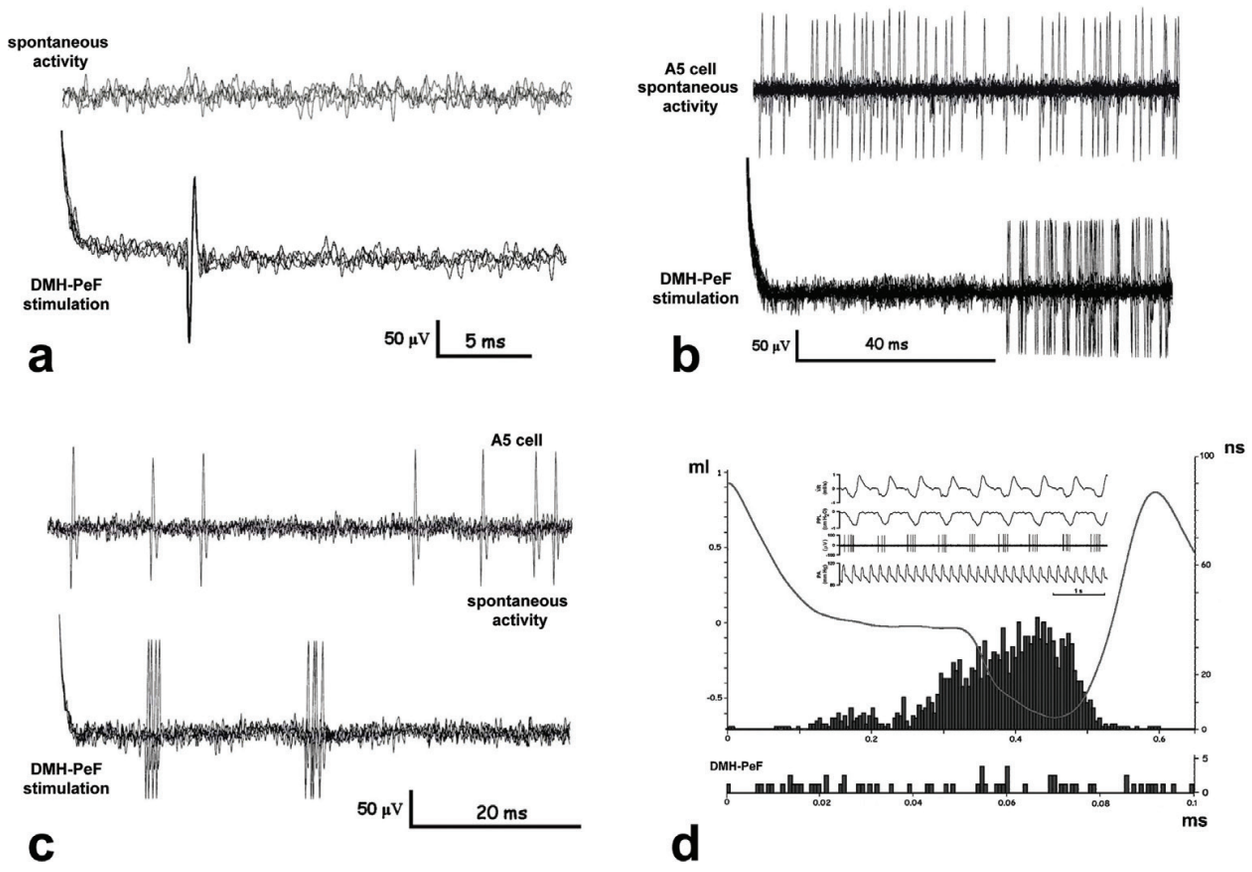

Figure 6. Extracellular recordings (superimposed sweeps) from the A5 region showing electrophysiological relations between the DMH-PeF and the A5 region: (a) Silent axon (upper trace) with constant-latency responses to DMH-PeF stimulation (lower trace). (b) Spontaneously active A5 cell (upper trace) inhibited by DMH-PeF stimulation (lower trace). (c) Spontaneously active A5 cell (upper trace) excited with double short- and long-latency responses to DMH-PeF stimulation (lower trace). (d) Inset shows recording of respiratory flow, pleural pressure, neuronal activity of a putative respiratory-modulated A5 cell and blood pressure. Main graph shows respiratory flow (inspiration downwards), and neuronal activity, while lower trace shows DMH-PeF-triggered histograms. This recordings show the complexity of the neuronal interactions between A5 and DMH-Pef.

4. Clinical implications

The A5 region is also involved in the impairment of sympathetic cardiovascular and respiratory control observed in multiple system atrophy (MSA) [87] and in syndromes such as Sudden Infant Death Syndrome, Rett syndrome, Ondine's syndrome and other genetic failures related to Phox2a, Ret, Mecp2, BDNF and Phox2b mutations [88].

Growing evidence supports the presence of earlier noradrenaline deficiency in neurodegenerative disorders including Parkinson disease (PD). PD dysautonomic symptoms are common, especially in cardiovascular, gastrointestinal and genitourinary systems. Most patients with PD have imaging evidence of cardiac sympathetic denervation. Selective degeneration of the noradrenergic neurons of the A6 NA cell group precedes that of dopaminergic neurons of the substantia nigra pars compacta and has been increasingly recognized as a potential

major contributor to cognitive manifestations in early PD, particularly impaired attention. This makes the A6 NA system a major contributor to the pathophysiology and potential target for therapy of PD [19, 89, 90].

5. Summary and perspectives

This chapter focuses on the different spinal projections and main modulatory actions of the two main NA pontine cell groups derived from this connectivity. Among these NA modulatory actions, a high variety of physiological and behavioral processes can be found that involve multiple cortical and subcortical structures. The diversity of anatomical, morphological, pharmacological and electrophysiological studies carried out in these NA cell groups has demonstrated that A5 and A6 NA pontine cell groups seem to be the best neuronal substrate to articulate the necessary responses to a wide range of psychological and physical stressors. A6 NA neurons present the necessary projections to modulate analgesic responses, while the A5 NA region seems to modulate all of the necessary autonomic responses needed to confront threatening stimuli or situations.

Regarding pain, bidirectional NA modulatory actions of spinal nociceptive processing depends on the type of pain. Moreover, this modulation is not only referred to by the type of nociceptive stimulus but, in addition, is affected by other CNS structures that are involved in emotional, motivational or attentional states. As has been previously explained, A6 and A5 NA cell groups may be the key centers for all modulatory actions exerted from superior structures within the CNS, which inhibit nociceptive transmission at the level of the spinal dorsal horn acting via presynaptic alpha2 receptors.

This chapter has laid the groundwork for further investigations on the topic and numerous unanswered questions remain. For example, how do these noradrenergic nuclei respond when functional or structural diseases caused by genetic or epigenetic factors appear? Are all these centers and their connections equally affected under these different pathological states? Are NA cells of these nuclei affected in the same manner by different external stressors or do they have different functional responses depending on their location within each nucleus or their projections? Does the selective degeneration that occurs in A5 and A6 neurons in diseases, such as MSA and PD, have a relationship with the evolution of the dysautonomia or the cognitive alterations observed in these patients?

Further basic and clinical studies are needed to assess the role of the NA pontine cell groups on physiology and pathophysiology based on these questions.

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