Chapter 4

Role of the Dorso- and Ventrolateral Pons in Cardiorespiratory Hypothalamic Defense Responses

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Abstract

Stimulation of discrete sites throughout the hypothalamus elicits autonomic and somatic responses. This chapter will stand out the cardiorespiratory changes evoked from stimulation of specific areas within the caudal hypothalamus: the perifornical area and the dorsomedial nucleus. The stimulation of these regions, known as the hypothalamic defense area (HDA), produces a pattern of visceral and somatic changes characteristic of the defense reaction, which includes tachypnea, tachycardia and a pressor response. A close review of the literature demonstrates that the changes observed during this defensive behavioral response are partially mediated by the interactions with pontine regions. These include the parabrachial complex, located in the dorsolateral pons, and the A5 region, located in the ventrolateral pons. Specific glutamatergic stimulation of cell bodies located within the parabrachial complex and A5 region evokes cardiorespiratory responses similar to those observed during stimulation of the HDA. This functional interaction suggests a possible role of glutamate pontine receptors in the modulation of the HDA response. This chapter describes the most important evidences confirming the implication of the dorso- and ventrolateral pons in the control of cardiorespiratory autonomic responses evoked from the perifornical and dorsomedial hypothalamus and the role of glutamate in this interaction.

Keywords: caudal hypothalamus, parabrachial complex, A5 region, cardiorespiratory responses, glutamate receptors, defense response

1. Introduction

Brief alerting stimuli such as an unexpected noise or light will evoke in animals immediate cardiovascular and respiratory responses, including strong cutaneous vasoconstriction and

respiratory activation [1–5]. Consistent with this, alerting stimuli in humans reliably increase cutaneous sympathetic activity [6]. Brief alerting stimuli also evoke variable changes in heart rate due to the fact that there is an activation of cardiac sympathetic and vagal parasympathetic activity [5, 7–10].

The initial response to alerting stimuli is a reflex termed "defense reaction" or "visceral alerting reaction" [11]. It is known that alarming stimuli evoke a characteristic autonomic response that includes tachypnea, accompanied by an increase in heart rate and blood pressure. A vasoconstriction in renal and mesenteric vascular beds with vasodilatation of skeletal muscle vessels is also observed in humans [12–22] and animals [23–27]. These cardiovascular changes are accompanied by a marked increase in total norepinephrine spillover in humans, indicative of an overall increase in sympathetic activity [28]. Research carried out in both, humans and animals, shows that stress elicits a typical pattern of catecholaminergic responses, with significant increases in sympathetic activity to the heart, kidney, skin, adrenal medulla and mesenteric beds and with a variable effect to the skeletal muscle.

Previous studies, using c-Fos expression, have identified several brain regions that are activated during stress. These morphological studies show that most of these regions also play a crucial role in respiratory and cardiovascular sympathetic regulation. These regions include, among others, the dorsomedial hypothalamus (DMH), the perifornical area (PeF), the paraventricular nucleus (PVN), the parabrachial complex (PBc), the periaqueductal gray (PAG), the nucleus tractus solitarius (NTS) and the ventrolateral medulla (VLM) [29–37].

The stimulation of specific areas within the caudal hypothalamus in rat, such as the PeF and DMH, classically known as hypothalamic defense area (HDA) (**Figure 1**), produces a pattern of visceral and somatic changes characteristic of the defense reaction [23]. The cardiorespiratory changes observed during the defense response are partially mediated by a facilitation of the chemoreceptor reflex and an attenuation of baroreceptor [38, 39] and laryngeal reflexes [40, 41] involving a GABAergic mechanism in the NTS [42]. The cardiovascular response is also mediated by direct descending projections from the PVN to sympathetic preganglionic

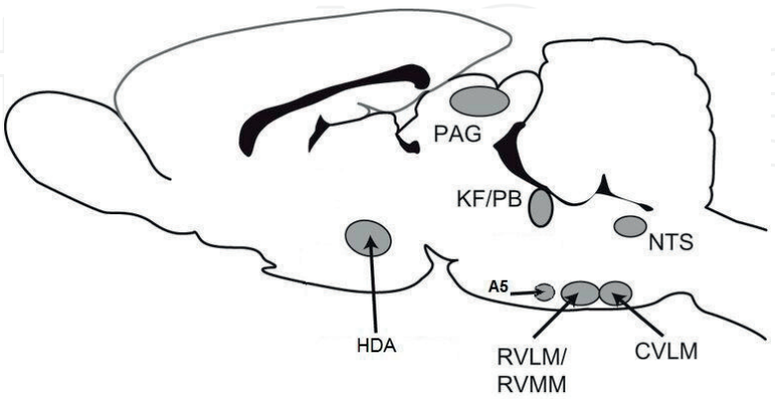

Figure 1. Semischematic line drawing of the parasagittal section through the rat brain showing the location of the hypothalamic defense area (HDA) and periaqueductal gray matter (PAG). The dorso- and ventrolateral pons shows the parabrachial complex (PB), Kölliker-Fuse (KF) and A5 region (A5). In the brainstem, nucleus of the solitary tract (NTS), rostroventrolateral medulla (RVLM), rostroventromedial medulla (RVMM) and caudalventrolateral medulla (CVLM) are shown.

neurons of the intermediate lateral cell column in the thoracic spinal cord (IML) [43], the rostral ventrolateral medulla (RVLM) [44] and the A5 catecholaminergic region of the pons [45].

Several observations clearly demonstrate the critical importance of the DMH in mediating stress-evoked cardiovascular and respiratory responses. The inhibition of neurons within the DMH greatly reduces the pressor response and tachycardia evoked by air jet stress [46, 47]. In addition, activation of somata of the DMH evokes a pattern of autonomic and respiratory effects, including a resetting of the baroreceptor reflex, which are similar to naturally evoked stress responses [48–55].

Interestingly, there are also evidences showing that the cardiovascular effects elicited by the activation of the pontine parabrachial nucleus are partially generated by a similar control of the function of the baroreceptor reflex at the level of the NTS [56–58].

The PBc lies at the junction between the rostral dorsolateral pons and the mesencephalon (**Figure 1**). The PBc contains three main subdivisions: the medial parabrachial nucleus (mPB), the lateral parabrachial nucleus (lPB) and Kölliker-Fuse area (KF) [59]. This region has been considered the site of the "pneumotaxic center" controlling inspiratory duration and is now often referred to as the pontine respiratory group [60]. The PBc modulates respiration in two different ways. Neurons located in the mPB and KF are implicated in the increase of expiratory time observed during bradypnea. On the contrary, somata located within the lPB elicit the classical tachypnea, characterized by a decrease of expiratory duration with an inspiratory facilitation [61–63]. The PBc is also related to a topographical organized regulation of bulbar laryngeal motoneurons regulating subglottic pressure [63]. Moreover, activation of these regions, typically considered as "respiratory areas," also produces cardiovascular changes including an increase of heart rate and arterial blood pressure [63, 64].

Electrical stimulation or microinjections of excitatory amino acids within the PBc [63, 65, 66] show different modulatory respiratory responses depending on the location of PBc-stimulated neurons. At all locations where respiratory responses are elicited by stimulation of PBc somata, a cardiovascular response is also observed. Similar cardiorespiratory effects are observed when glutamate is microinjected within these sites. The response comprises an increase in blood pressure with a small increase in heart rate. The cardiovascular response evoked by the stimulation of cell bodies located within the PBc resembles the response evoked on HDA stimulation [63].

The dorsolateral pontine modulation of the arterial baroreflex primarily originates from ventrolateral regions of the lPB and involves descending projections to both the NTS [56, 67] and the VRLM [67–69]. In the early 1980s, it was established that electrical stimulation of the PBc attenuates baroreflex responses [69]. The functional importance of PBc modulation of baroreflex function has been linked to the simultaneous pressor response and tachycardia evoked during the defense response, which indicates a resetting of the barorreceptor reflex. Chemical lesions of the PBc eliminate the descending modulation of the baroreflex control of heart rate and mean arterial pressure evoked from at least one "brain defense region," the dorsal PAG [70]. Blockade of neurons located in lPB, using bilateral microinjections of muscimol, a $GABA_A$ receptor agonist, or kynurenic acid, an unspecific glutamate receptor antagonist, decreases but not abolishes the attenuation of the cardiac baroreflex response evoked from the

dorsal PAG [71]. These data support the hypothesis that lPB is also a crucial pontine region implicated in the descending modulation of cardiac brainstem baroreflex function during the stress reaction evoked from hypothalamic stimulation.

In addition, the PBc is an important pontine secondary relay from the NTS, because it is involved in the modulation of this arising cardiorespiratory information [72]. The PBc, mainly its lateral part, is reciprocally connected with forebrain structures involved in cardiorespiratory regulation [59]. The activation of neuronal somata of the lPB with glutamate elicits a cardiorespiratory response that includes hypertension, tachycardia and tachypnea, while activation of cell bodies located within the mPB and KF produces a similar cardiovascular response, increase in blood pressure and heart rate, but on the contrary, accompanied with bradypnea [63]. Thus, the integrity of PBc neuronal circuits seems to be essential for the modulation of baroreflex function and appears to represent an important relay between midbrain and medulla for the coordination of autonomic defense responses.

On the other hand, the PBc is connected with another crucial area in cardiovascular control, the A5 region [73]. Electrical stimulation of the mPB or lPB produces an increase of c-Fos-like protein immunoreactivity within the A5 pontine catecholaminergic region [74].

The A5 group of catecholamine-containing neurons is located in the ventrolateral pons, between the root of the facial nerve and the superior caudal olivary nucleus (**Figure 1**). Classically, the A5 has been defined as a catecholaminergic region. It is known to provide the major component of the noradrenergic input to the sympathetic preganglionic neurons of IML [75–77], whereby it is implicated in cardiovascular control [41, 65, 78–82]. It also contains noncatecholaminergic neurons, which are mainly located at the level of the most caudal part of the A5 region [83]. These neurons seem to have properties similar to the respiratory chemoreceptors identified in the rostral medulla oblongata [84]. The A5 region has connections with the NTS, RVLM, caudal ventrolateral medulla (CVLM), caudal pressor area and the retrotrapezoid nucleus in the medulla oblongata; with the mPB, lPB and KF in the pons; and with the PeF, the PVN and the amygdala in the hypothalamus [85–90]. These connections with regions of the central nervous system involved in cardiorespiratory regulation are indicative for a role of the A5 region in the control of both sympathetic activity and cardiorespiratory function [81, 91, 92]. Moreover, A5 neurons are activated during baroreceptor unloading [81] and stimulation of carotid chemoreceptors [93, 94]. Thus, it has been proposed that A5 neurons may play an important role in the carotid sympathetic chemoreflex triggered by hypoxia [95–97]. Furthermore, the A5 region plays an important role in respiratory control, modulating the activity of respiratory neurons [98]. These cells are synaptically connected to phrenic motoneurons [99] and contribute to the respiratory responses evoked by hypoxia and hypercapnia [96, 97, 100–102]. A5 cells also modulate the cardiorespiratory response evoked by activation of the PBc [65], which is a critical component of the brainstem respiratory network required for eupnea [103].

Stimulation of A5 neurons with glutamate produces cardiorespiratory and laryngeal responses similar to those observed with mPB stimulation. That is, an expiratory facilitatory response associated with an increase in blood pressure, heart rate [104] and subglottic pressure [41]. In the same way as with PBc stimulation, the cardiovascular response is similar to that obtained during electrical stimulation of the HDA.

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The similarity of the responses to stimulation of the mPB and the A5 region suggests a possible interaction between these two pontine regions. In fact, studies from the literature demonstrate a role for the A5 region in the cardiorespiratory responses evoked on PBc electrical

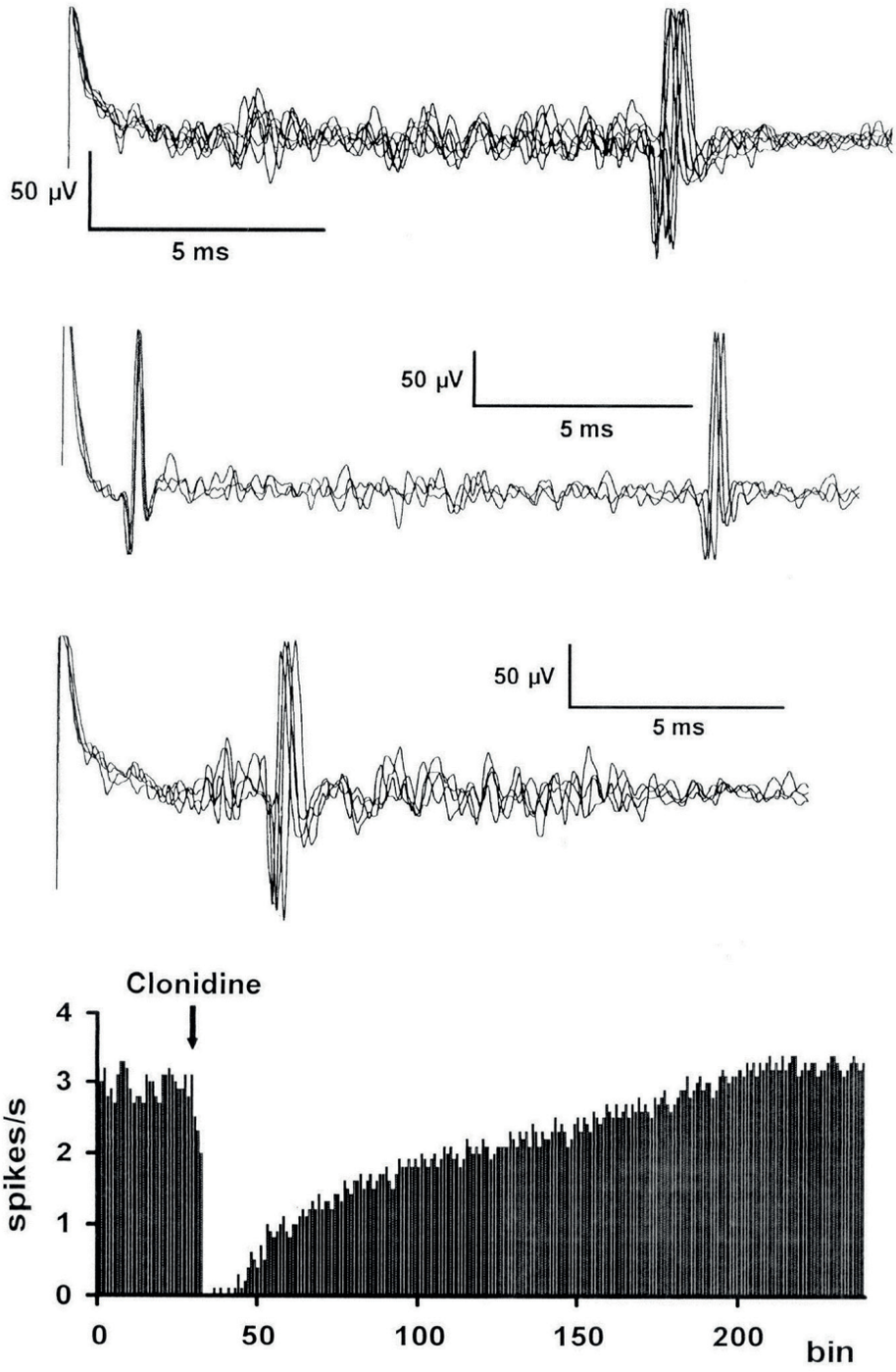

Figure 2. Neurophysiological interactions between PBc and A5. Extracellular recording (superimposed sweeps) of three A5 putative cells activated from the PBc. Effect of clonidine i.v. injection (10 µg/kg) on the discharge rate of a putative A5 neuron. Arrow shows drug injection. Firing rate histogram of a parabrachial-activated A5 putative neuron (bin size 5 s). Authors´ figure modified from Ref. [65].

and chemical stimulation [65]. The microinjection of muscimol or lidocaine within the A5 region modifies the pattern of the cardiorespiratory responses evoked from PBc stimulation [65]. The expiratory facilitatory response elicited from mPB-KF activation is reversed to an inspiratory facilitatory response. Nevertheless, when the lPB is activated, no changes are observed in the inspiratory facilitatory response. The magnitude of the increase of the pressor response and the tachycardia observed during PBc stimulation decreases significantly after A5 blocking microinjections. Moreover, a high number of extracellularly recorded neurons in the A5 region are activated on electrical stimulation within the mPB-KF nuclei [65] (**Figure 2**).

These functional connections suggest a possible interaction between PBc and A5 pontine regions in mediating the defense response evoked from the HDA. This statement will be discussed deeply in the following sections.

2. Dorsolateral pons in cardiorespiratory hypothalamic defense responses: role of the Parabrachial complex

Recent data show that neurons located within the PBc play a role in the cardiorespiratory response evoked from HDA. As previously mentioned, the stimulation of cell bodies located within the PBc resembles the cardiovascular response elicited by HDA stimulation, thus evoking tachycardia and hypertension [63].

Neuropharmacological studies show that the inhibition with muscimol of somata located within the main subdivisions of the PBc, lPB and mPB-KF produces two different patterns of cardiorespiratory responses evoked to HDA stimulation [105].

The inhibition with muscimol of neurons located within the mPB-KF reduces the tachycardia and the pressure response evoked by HDA stimulation [105] (**Figure 3A**). It is known that neuronal activity of the parabrachial nuclei can modify the effectiveness of the baroreflex in rat, rabbit and cat [56, 106] and that the PBc is essential for a full expression of the bradycardia that typically accompanies the initial hypotensive response to blood loss and for the normal rate of blood pressure recovery [107, 108].

The decrease in the cardiovascular response to HDA stimulation seems to be an indication of a resetting of the baroreceptor reflex. The normal cardiovascular response to hypothalamic stimulation, tachycardia and pressor response is due to direct activation of neurons from the RVLM, which send direct projections to sympathetic preganglionic neurons of the IML. The inhibition or the resetting of the baroreceptor reflex is the origin of the tachycardia observed during the activation of the HDA. This inhibition seems to be partially mediated by $GABA_A$ receptors located within the NTS, which produces a hyperpolarization of baroreceptor cells [42, 58].

The reset of the baroreceptor response partially explains the decrease of the tachycardia observed during the stress reaction evoked from the activation of the HDA. It could also explain, through an indirect modulatory pathway, the decrease of the magnitude of the

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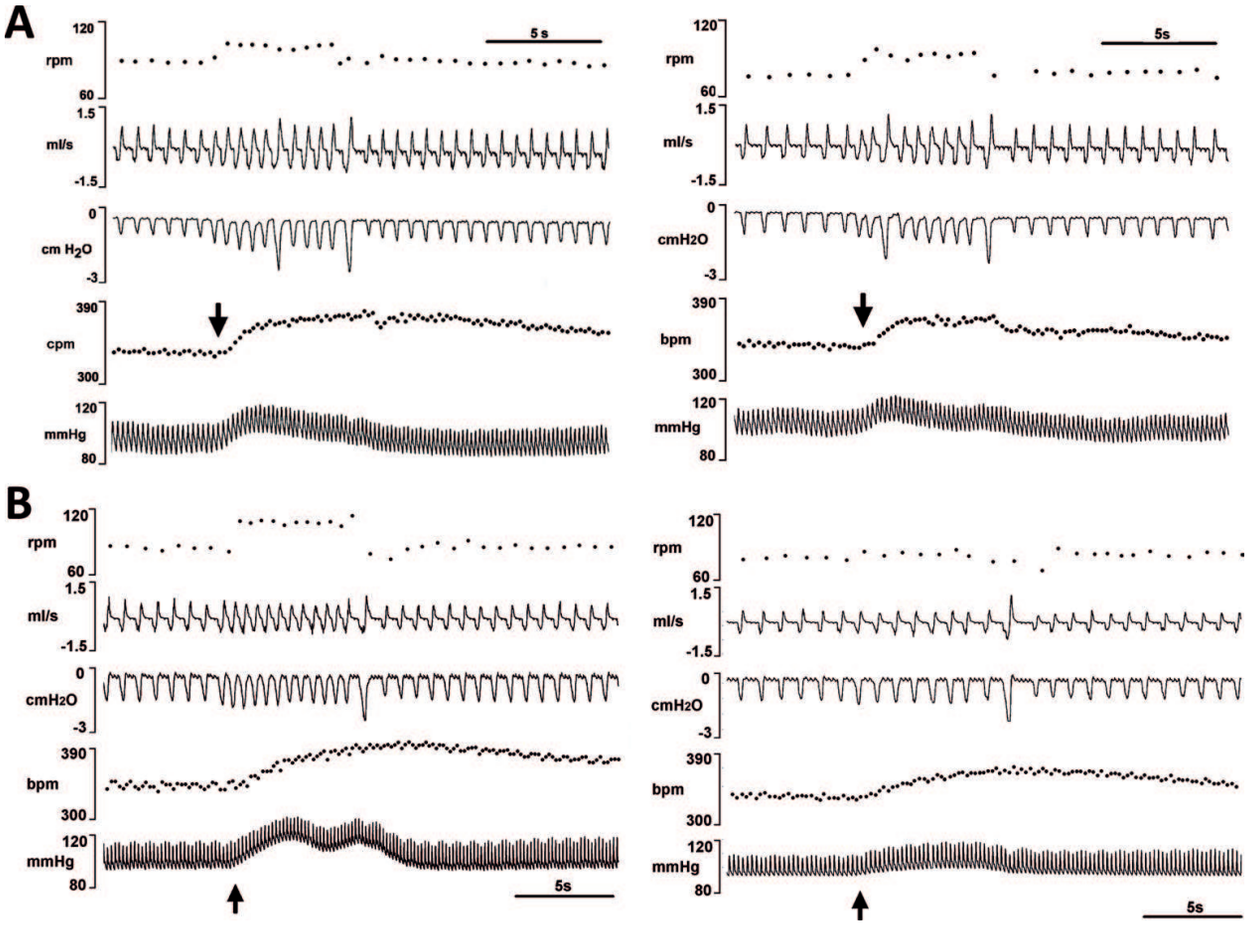

Figure 3. Neuropharmacological interactions between HDA and PBc. From top to bottom, instantaneous respiratory rate (rpm), respiratory flow (ml/s), pleural pressure (cm H_2O), instantaneous heart rate (bpm) and blood pressure (mmHg). Cardiorespiratory response evoked to HDA stimulation before (left) and after (right) muscimol microinjection within the mPB-KF (A) and lPB (B). The arrows show the onset of the HDA electrical stimulation. Authors´ figure modified from Ref. [105].

hypertensive response, although, and probably, the most important factor is the inhibition of the excitatory projections from the PBc to the IML. The most relevant conclusion from this data is the suggestion that the reset of the barorreceptor reflex elicited by HDA activation could be also mediated though a secondary indirect pathway using the PBc of the pons [105].

Therefore, the activity of mPB-KF makes an important contribution to the modulation of the intensity of the cardiovascular response evoked on HDA stimulation through an indirect pathway to both the IML and the NTS.

On the other hand, the inhibition of neurons located within the lPB with muscimol abolishes the respiratory response evoked to HDA stimulation [105]. Similar to mPB-KF inhibition, the increase of blood pressure evoked to HDA stimulation decreases after the microinjection of muscimol within the lPB; however, no significant changes of the heart rate response were observed (**Figure 3B**).

Similar results are observed with PAG stimulation, thus indicating that the PBc is also a critical relay in mediating dorsal PAG-evoked sympathoexcitation and baroreflex modulation [109]. In addition, neurons localized in the lPB are involved in mediating the defense-like behavior response during the stimulation of the dorsal PAG, modulating the arterial baroreflex [71]. This inhibitory effect is more evident from the mPB-KF than from lPB.

Therefore, the pressor response evoked during the stimulation of the HDA and PAG may involve the recruitment of neurons of both the lPB and mPB-KF subdivisions, which, using an indirect pathway, activate the IML.

Morphological studies have confirmed the presence of reciprocal connections between the PBc and different hypothalamic regions [110]. It has been also described that the PBc projects widely to areas of the forebrain involved in cardiovascular regulation and defense reactions [111]. It also projects, via descending fibers, to brainstem nuclei including the A5 region, the NTS and the IML of the spinal cord [112].

It is important to stand out the complete abolishment of the respiratory response to HDA stimulation after the inhibition of lPB somata with muscimol. The lPB is part of the neuronal pathways involved in the sympathoexcitatory component of the chemoreflex [113]. Fos protein expression studies show that the tachypnea evoked on HDA stimulation is produced by activation of carotid chemoreceptors within neurons of the lPB [94]. Moreover, neuronal recordings show that during chemoreflex stimulation, neurons of the lPB are activated and that this increase in firing precedes the classical hypertensive response to chemoreceptor stimulation, thus showing the relevance of lPB neuronal circuits on the central modulation of chemoreceptor inputs and reflex [114].

There are also indications that HDA stimulation may facilitate the chemoreceptor reflex by means of a group of intrinsic excitatory neurons localized within the NTS [115]. These cells are activated or facilitated by HDA-NTS direct excitatory connections. These neurons are also the main targets of excitatory inputs from the lPB [56]. The inhibition of these lPB excitatory projections with muscimol leads to the abolishment of the tachypneustic response evoked on HDA stimulation.

Electrophysiological studies using neuronal recordings support the above. A significant number of mPB-KF and lPB neurons are affected from HDA stimulation, confirming the importance of the functional correlation between the HDA and these pontine regions. The presence of anti-/orthodromic activations, short and long latency excitations, and inhibitions and excitatory/inhibitory activities gives electrophysiological evidence of reciprocal connections between these regions. It is also an index of the complexity of the different types of synaptic interactions between both areas (**Figure 4**) [105].

Studies related to glutamate receptors suggest that this neurotransmitter plays a crucial role in mediating the functional relation between the PBc and the HDA [116]. Glutamate activates metabotropic and ionotropic (NMDA and non-NMDA) receptors [117]. By employing immunocytochemical and in situ hybridization techniques, studies have demonstrated the presence of both metabotropic and ionotropic receptors in different nuclei of the PBc and KF [118–120]. Activation of vagal afferent fibers releases glutamate within the PBc [121]. An ascending excitatory pathway involving glutamate from the NTS to the PBc has been described [122]. In

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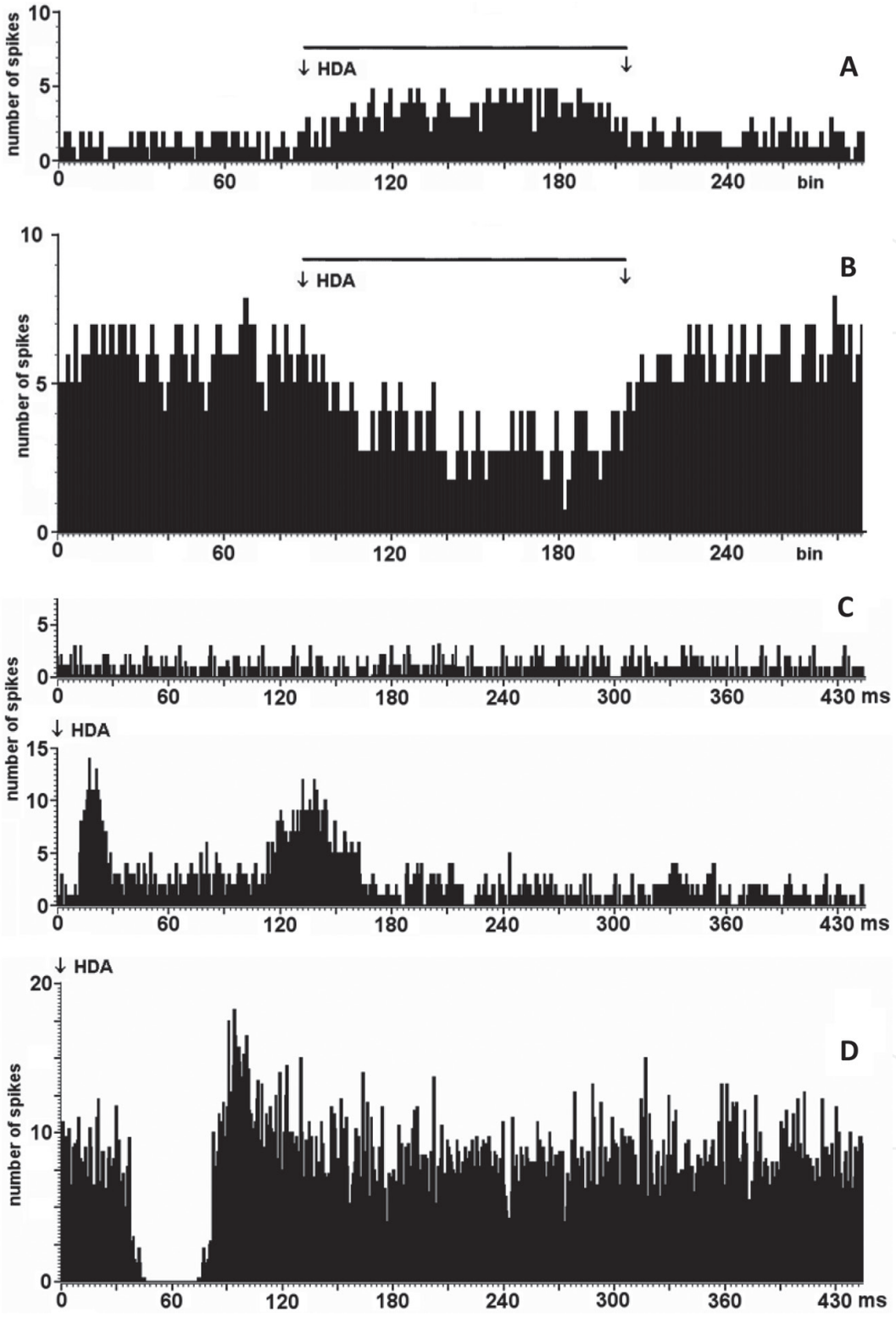

Figure 4. HDA and PBc neurophysiological interactions. (A) Shows a rate histogram (bin size 2 s) representing the firing of an lPB cell not excited nor inhibited during HDA stimulation that increased the activity during HDA stimulation. (B) Shows a rate histogram (bin size 2 s) of an mPB-KF cell not excited nor inhibited during HDA stimulation showing a decrease of activity during HDA stimulation (0.1 ms given at 1 Hz). (C) The poststimulus time histogram shows spontaneous activity of an lPB neuron and double excitation after HDA stimulation. (D) The poststimulus time histogram shows an inhibition of an mPB neuron after HDA stimulation (100 stimuli, 1 Hz). Authors´ figure modified from Ref. [105].

vitro studies also show that glutamate agonists depolarize neurons of the PBc [123], and lPB stimulation causes local glutamate release, which depolarizes lPB neurons through NMDA and non-NMDA receptors [124].

Moreover, the blockade of glutamate receptors and the microinjections of glutamate into the PBc and KF elicit a variety of cardiovascular and respiratory responses indicating that this amino acid is an important neurotransmitter for mediating autonomic functions in these regions [61, 63, 64, 122–127].

The pattern of the cardiorespiratory response evoked from HDA is modified by the microinjection of different glutamate antagonists into the PBc [116]. Kynurenic acid, a nonspecific ionotropic glutamate receptor antagonist, microinjected into the lPB and mPB abolishes the tachycardia and decreased the pressor response to HDA electrical stimulation (**Figure 5A** and **B**). The respiratory response is only abolished when kynurenic acid is microinjected into the lPB (**Figure 5A**) [116]. These results suggest that ionotropic glutamate receptors located within the lPB region are involved in both the respiratory- and the cardiovascular-evoked responses from the HDA, whereas ionotropic glutamate receptors located in mPB seem to be only involved in the modulation of the cardiovascular response.

The effectiveness of the modulation is depending on the distribution of these receptors within the PBc and these findings suggest that lPB appears to exert a more efficient modulation on the cardiovascular response to HDA stimulation compared with mPB. This cardiovascular response seems to be mediated by a direct activation of neurons located within the RVLM, which send direct efferences to sympathetic preganglionic neurons of the IML [128–130]. The activity of the RVLM can be also modulated via indirect projections. The changes in heart rate and blood pressure evoked from "defense" regions of the brain may use separate efferent pathways [51]. The blockade of the PBc attenuates the dorsal PAG-evoked changes in blood pressure [109], thus indicating that the cardiovascular changes observed during the stimulation of the HDA could be partially modulated by "direct" efferences to the RVLM but also by indirect projections, which involve the activation of ionotropic glutamate receptors located in the PBc [116].

It is known that the PBc is crucial mediating the changes of heart rate appearing during baroreceptor reflex activation [105]. The fall in the magnitude of the cardiovascular changes to HDA stimulation observed after the microinjection of kynurenic acid could indicate that neurons of the lPB and mPB exert an inhibition of tonic excitatory inputs, at the level of the NTS, on inhibitory mechanism of the baroreceptor reflex [40]. This hypothesis is also supported by the observation that the blood pressure response also tends to disappear with the decrease and/or the abolishment of tachycardia.

Another fact that could explain the more efficient modulation exerted from lPB on the cardiovascular response elicited by HDA stimulation is the specific expression of glutamate subtype receptors located within this region. A very different profile is observed when compared with the mPB or with other subnuclei of the PBc. GluR4 non-NMDA receptor subunits predominate in the internal lPB [118]. These subunits are characterized by a high sensitivity for glutamate. There is also evidence that the external and internal lPB express specific subunits of NMDA receptors, which are different to that of the mPB [119]. NMDA receptors can be quite different with respect to their physiological and pharmacological channel properties, such as differences in glutamate affinity and glycine sensitivity, crucial coagonist for glutamate

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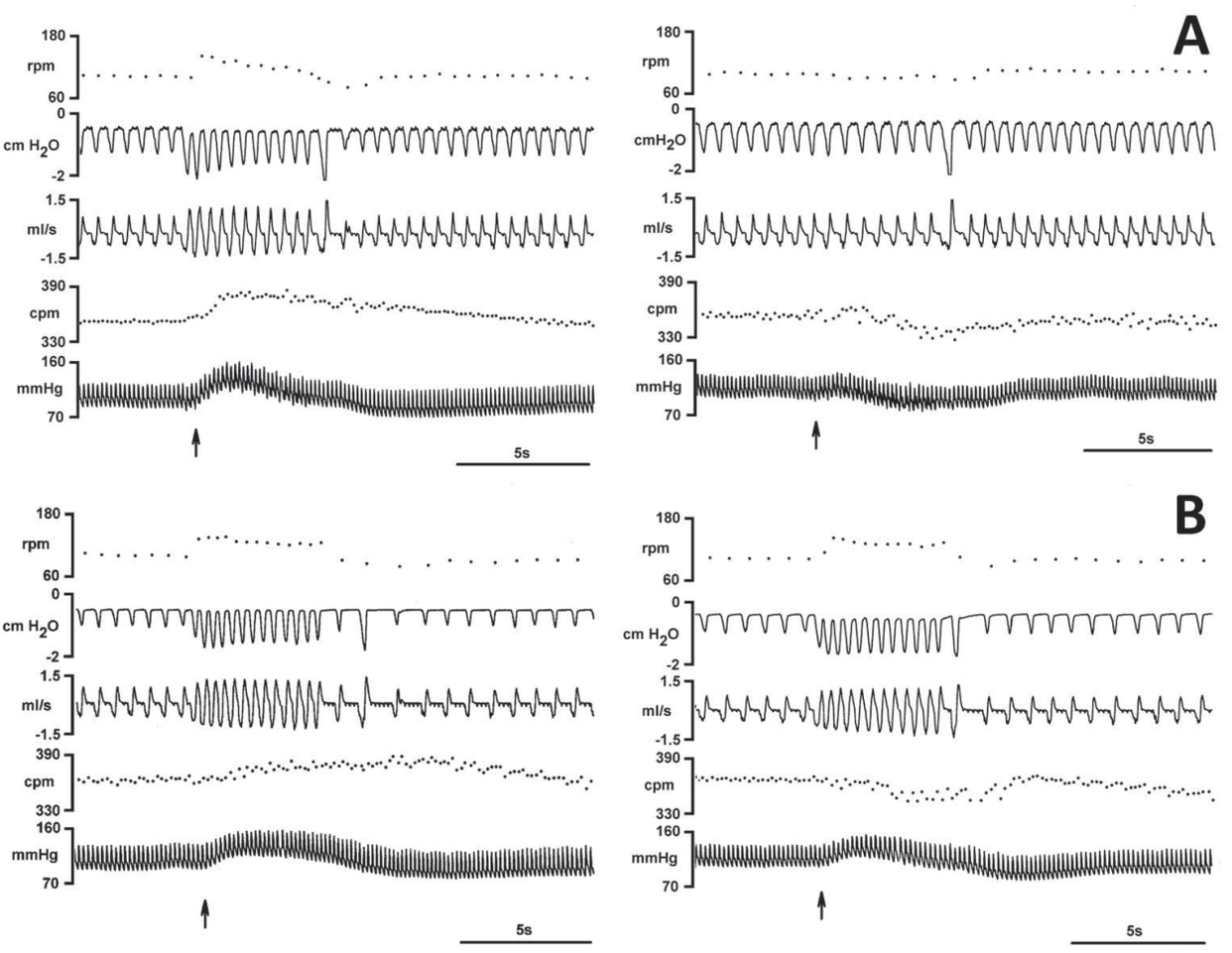

Figure 5. Neuropharmacological interactions between HDA and PBc, role of glutamate. From top to bottom, instantaneous respiratory rate (rpm), respiratory flow (ml/s), pleural pressure (cm H_2O), instantaneous heart rate (bpm) and blood pressure (mmHg). The cardiorespiratory responses evoked on HDA stimulation before (left) and after (right) kynurenic acid microinjection within the lPB (A) and mPB-KF (B) are shown. The arrows show the onset of the HDA electrical stimulation. Authors´ figure modified from Ref. [116].

efficacy [131], in calcium currents and deactivation kinetics as well as other single channel characteristics [132]. NMDA receptors of lPB are composed of NR2A and NR2B subunits, which are characterized by high affinity for glutamate and long mean open time. NMDA receptors located within the mPB are composed of NR2D subunits, which exhibit low affinity for glutamate [119, 132].

In summary, the arterial blood pressor response observed during HDA stimulation could be mediated by the activation of neuronal glutamate ionotropic receptors located in both lPB and mPB somata, which exert an indirect excitation to sympathetic preganglionic neurons at the level of the IML. The inhibitory mechanism of the baroreceptor reflex seems to depend more on the activation of lPB glutamate ionotropic receptors than mPB receptors, because tachycardia associated to the pressor response is only suppressed after lPB microinjections [116].

With respect to the changes of respiratory rate observed during the stimulation of the HDA, we have to highlight that are only abolished when the microinjection of kynurenic acid is delivered within the lPB (**Figure 5A**). Nevertheless, the respiratory response remains unchanged when

kynurenic acid is microinjected into the mPB (**Figure 5B**) [116]. The result suggests that only glutamate receptors of the lPB modulate the respiratory response to HDA stimulation.

It has been shown that the lPB is an important part of the neuronal pathways for the modulation of the respiratory response evoked on HDA stimulation. Muscimol microinjections within the lPB have similar effects to kynurenic microinjections [105]; tachypnea observed during HDA stimulation is abolished. This observation gives a role for the described lPB afferent connections from several hypothalamic nuclei involved in the defense reaction [110].

Hayward et al. obtained similar results with the blockade of glutamate receptors with the microinjection of kynurenic acid into the lPB during the dorsal PAG stimulation, one of the so-called secondary brain defense regions, confirming the importance of lPB in the integration of tachypneic responses from supraencephalic regions [133].

There are indications that HDA stimulation may facilitate the chemoreceptor reflex at specific cells located within the NTS [115]. These neurons are activated by HDA-NTS direct excitatory connections and are also the main targets of excitatory inputs from the lPB [56]. Glutamate seems to activate these excitatory inputs. The inhibition of the activation of these lPB projections with kynurenic acid leads to the abolishment of tachypnea evoked on HDA stimulation [116].

According to these observations, the cardiovascular component of the response to HDA stimulation seems to be modulated by glutamatergic neurons located in both the lPB and the mPB, whereas the respiratory component seems to be only mediated by glutamate receptors of the mPB. Moreover, different subnuclei within the lPB are involved in this cardiorespiratory modulation, which includes the crescent, ventral, central and external subnuclei. It is interesting to note that microinjections into the internal subnucleus of the lPB have no effects on this cardiorespiratory response. This result is an indication of the specificity and complexity of this region. Nearby areas, separated only by microns, such as the external and internal subnuclei of the lPB, show very different effects in the cardiorespiratory response to HDA stimulation. In contrast, all mPB microinjections, including external mPB, have an effect. These results give us clear evidence that glutamatergic neurons of the PBc are essential intermediaries for the modulation of the descending pathways for cardiovascular sympathetic and respiratory control mechanisms [116]. The impact of these projections on overall cardiorespiratory function is highly dependent on convergent inputs from specific subnuclei of the lPB region and from alternate pathways outside the PBc. Direct projections to the RVLM are also involved in HDA-evoked changes in arterial pressure [128–130], thus supporting those changes in heart rate and blood pressure evoked from "defense" regions of the brain that may travel via separate pathways [51].

3. Ventrolateral pons in cardiorespiratory hypothalamic defense responses: role of the A5 region

As previously mentioned, there are data suggesting the functional connections between the HDA and the A5 region. Fos protein expression studies, neuronal recording and neuropharmacological experiments confirm this hypothesis [23, 65, 104].

Some studies in rats have used HDA electrical stimulation to map methodically populations of neurons within the brainstem and other areas, which are excitated by changes in arterial blood pressure [134, 135]. In the A5 region, blood pressure changes cause a specific and consistent pattern of c-Fos expression.

A c-Fos-ir expression is induced during HDA stimulation in both A5 noncatecholaminergic (TH-negative) and A5 catecholaminergic (TH-positive) cells of the pons [136]. This increase in c-Fos expression is higher in noncatecholaminergic than in catecholaminergic neurons [136]. In addition, in both populations of neurons of the A5 region, this activation seems probably to be due to a direct activation from the HDA and not due to a secondary activation to the pressure response elicited during stimulation of the HDA.

This result is further confirmed with neuronal recordings. It is described as the possible role of A5 neurons in respiratory modulation [65, 93]. Moreover, there are electrophysiological evidences of interactions between HDA and A5 catecholaminergic neurons. The importance of the connections between both regions is confirmed with the observation that a significant number of these A5 neurons are activated from HDA stimulation [136]. In the same way as with PBc, antidromic and orthodromic activation are observed in A5 neurons. Cells that are antidromically activated are spontaneously active, while cells orthodromically activated are silent, indicating the origin of the somata (**Figure 6**). After clonidine, A5 cells are active and decrease their frequency of discharge while, in all cases, hypothalamic fibers are silent [136]. The presence of activations or facilitations indicates the existence of polysynaptic pathways acting on the A5 region. The complexity of the different types of synaptic connections is illustrated by the association of these activations with inhibitions or disfacilitations.

On the other hand, as previously mentioned, the stimulation of cell bodies located within the A5 region resembles the cardiovascular response elicited by HDA electrical stimulation, thus eliciting an increase in heart rate and blood pressure [104] and suggesting the possible interaction between both cardiorespiratory regions. In order to evaluate this possible modulation, microinjection of muscimol also has been made into the A5 region [136].

Muscimol microinjection within the A5 region does not produce changes in the respiratory response to HDA electrical stimulation; however, a clear decrease is observed in the cardiovascular response (**Figure 7**). The increase in heart rate and the hypertension evoked to HDA activation involve a direct excitation of neurons located in the RVLM, which send direct projections to the preganglionic neurons of the IML that are responsible for the acute pressor response [137]. Also, the release of adrenaline by a direct activation of the adrenal medulla provides a secondary increase of blood pressure contributing to the hypertensive response.

Indirect forebrain projections can also modulate the activity of the RVLM. Furthermore, HDA stimulation activates the chemoreceptor reflex by means of the excitation or facilitation of chemoreceptor neurons located in the NTS, in a parallel circuit to the activation of the RVLM and the preganglionic neurons in the IML [38]. An inhibition of the baroreceptor

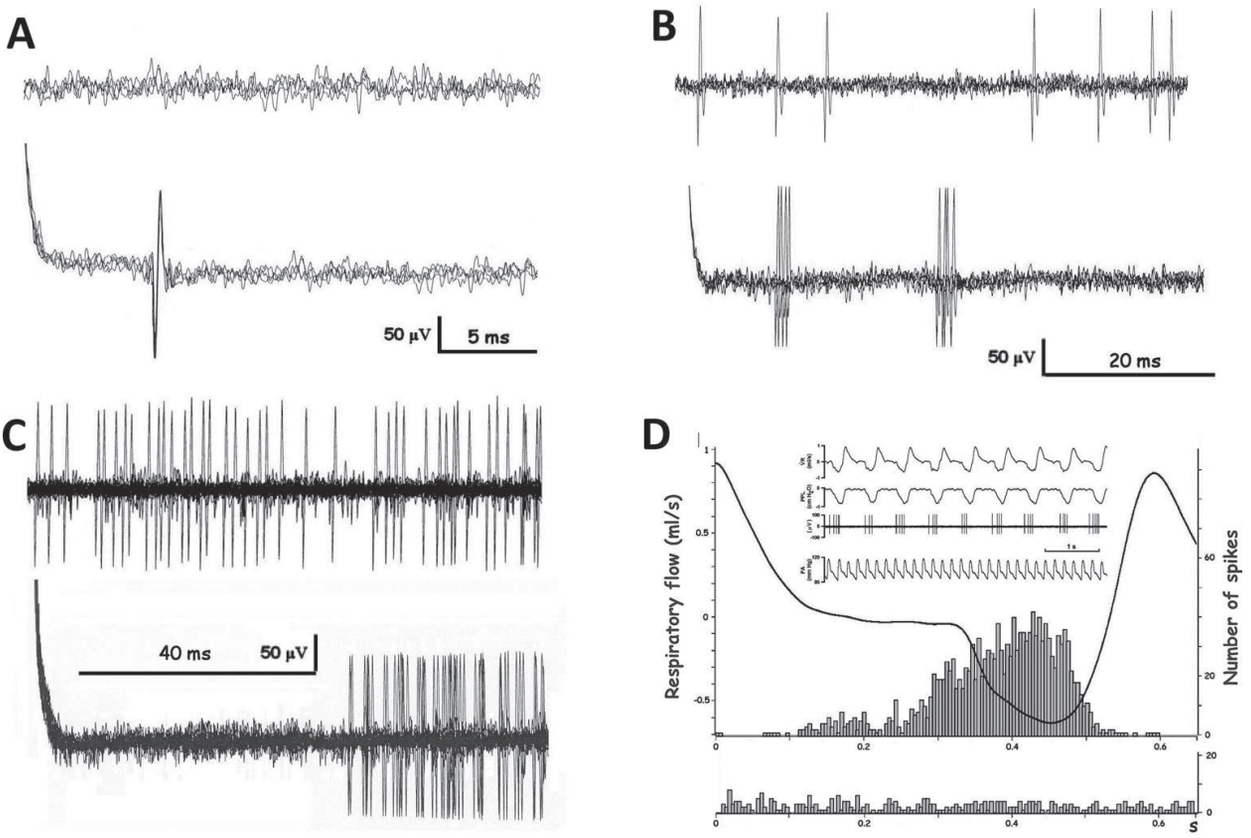

Figure 6. HDA and A5 neurophysiological interactions. Extracellular recordings (superimposed sweeps) of four putative cells recorded form the A5 region. (A) Silent neuron (upper trace) with constant latency responses to the HDA (lower trace). The cell was demonstrated to be orthodromically activated from the HDA. (B) Spontaneously active cell (upper trace) excitated with short and long latency responses from HDA stimulation (lower trace). (C) Spontaneously active cell (upper trace) inhibited from HDA stimulation (lower trace). (D) Recording of respiratory flow, pleural pressure, neuronal activity and blood pressure of a putative respiratory-modulated A5 cell with respiratory flow (ml/s, inspiration downwards) and HDA-triggered histograms (lower trace). This respiratory putative A5 neuron shows no modulation from the HDA. Authors′ figure from Ref. [136].

response is also produced, in another parallel pathway, by the inhibition or disfacilitation of baroreceptor neurons located within the NTS [42, 58], inhibition that seems to be mediated through GABAergic interneurons in the NTS [42].

In conscious rats, stress produces tachycardia and hypertension together with a resetting, rather than an inhibition, of the baroreceptor reflex. Thus, heart rate control is reset to higher levels of blood pressure without decrease in the gain of the reflex [54, 138].

The activation of A5 somata with glutamate also produces tachycardia and hypertension [104]. The increase in heart rate, blood pressure and sympathetic vasomotor activity at the same time indicates a baroreceptor reflex reset but without reduction in sensitivity of the reflex.

http://dx.doi.org/10.5772/intechopen.72625

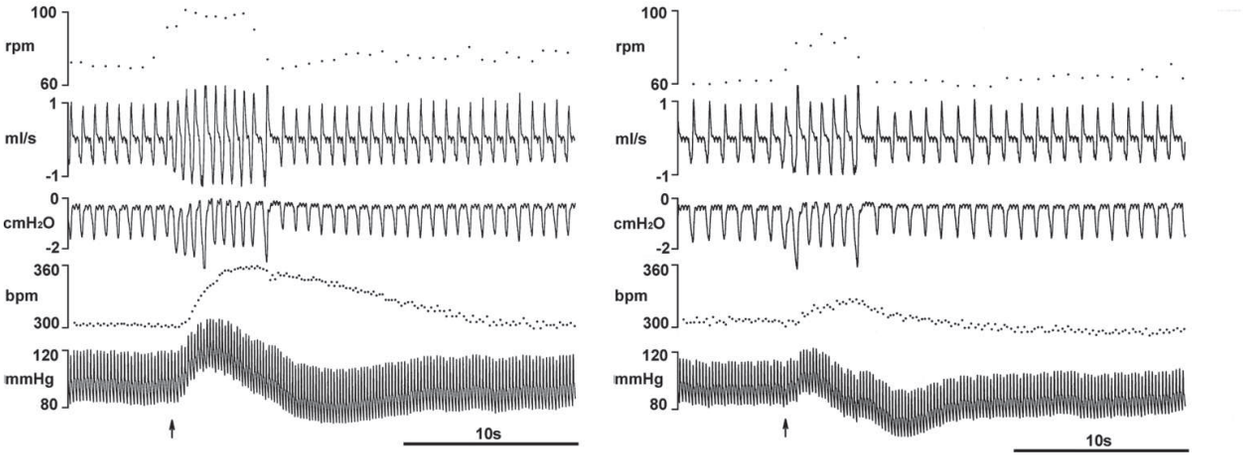

Figure 7. Neuropharmacological interactions between HDA and A5 region. Instantaneous respiratory rate (upper trace, rpm), respiratory flow (ml/s), pleural pressure (cm H_2O), instantaneous heart rate (bpm) and blood pressure (mmHg) showing the cardiorespiratory response evoked on HDA stimulation before (left) and after (right) the microinjection of muscimol in the A5 region. Authors´ figure from Ref. [136].

The inhibition of A5 neurons with muscimol microinjections attenuates the cardiovascular response elicited by the stimulation of the HDA (**Figure 7**) [136]. This attenuation can be an indication of an incomplete resetting of the baroreceptor reflex. This effect can explain the decrease in the magnitude of the tachycardia and the hypertension, through an indirect pathway. But the most relevant aspect of this response is probably the inhibition of the excitatory projections from the A5 region to the IML. These findings suggest that an indirect pathway through the A5 region could also mediate the resetting of the baroreceptor reflex evoked by HDA stimulation. The activity of neurons of the A5 region modulates the intensity of the cardiovascular response evoked on HDA stimulation through an indirect pathway to both the IML and the NTS.

In summary, the A5 region seems to be an important component of those brainstem pathways known to be involved in mediating autonomic changes associated with the defense response elicited from the PeF and the DMH. This response involves also the integrity of the circuits located within the PBc. It is not possible to separate the activity of the PBc and the A5 region; thus, dorso- and ventrolateral pons act together to mediate the cardiorespiratory response evoked on HDA stimulation.

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