Chapter

Central Control of the Larynx in Mammals

Manuel Víctor López-González, Marta González-García, Laura Carrillo-Franco, Amelia Díaz-Casares and Marc Stefan Dawid-Milner

Abstract

Speech is a complex process that requires the coordination of multiple structures of the phonatory system regulated by the central nervous system. Specifically, the larynx is the key point necessary for the vocal folds to come into contact to convert the air that comes out of our lungs into sound. Vocal emission involves the genesis of a precise and prolonged expiration that provides an adequate pressure/air flow component to generate a subglottic pressure compatible with vocalization. The starting point for voluntary vocal production is the laryngeal motor cortex (LMC), a common structure in mammals, although the specific location within the cortex differs in humans. LCM projects to the periaqueductal gray matter (PGM), which leads to pontomedullary structures to locate the generators of laryngeal-respiratory motor patterns, necessary for vocal emission. All these regions present a high expression of FOXP2 transcription factor, necessary for brain and lung development that is closely related to vocalization. These central structures have in common that not only convey cardiorespiratory responses to environmental stress but also support vocalization. At clinical level, recent studies show that central circuits responsible for vocalization present an overactivity in certain speech disorders such as spasmodic dysphonia due to laryngeal dystonia.

Keywords: central nervous system, laryngeal motor cortex, laryngeal motoneurons, periacueductal gray matter, FOXP2, vocal emission, speech, laryngeal dystonia

1. Introduction

Central control of vocalization involves the activation of different interrelated brain structures in complex networks. Vocalization in mammals depends on a network originating in the laryngeal motor cortex, which projects to the mesencephalic Periaqueductal Gray Matter (PAG). The PAG modifies the activity of all pontomedullary structures responsible of generating all the laryngeal-respiratory motor patterns, necessary for vocal emission. These pontomedullary generators control the pattern and intensity of activation of respiratory, laryngeal, oropharyngeal, and craniofacial motor neurons [1].

Vocal emission involves the genesis of a precise and prolonged expiration that provides an adequate pressure/air flow component to generate a subglottic pressure compatible with vocalization. The nucleus ambiguus (nA), where laryngeal motor neurons are concentrated, is mainly responsible for this. All these regions present a high expression of the FOXP2 factor. FOXP2 is a transcription factor necessary for brain and lung development that is closely related to vocalization. Throughout the evolution of the human species, synaptic connectivity and plasticity in the circuits of the basal ganglia were increased, improving motor control and human cognitive and linguistic abilities [2].

Vocal fold abduction and adduction are known to be accomplished by two distinct populations of motor neurons located within the caudal third of the nA. It can be divided into three main parts: the compact formation (with motor neurons that innervate the esophagus), the semi-compact formation (with motor neurons that innervate the pharynx and the cricothyroid muscle of the larynx innervated by the superior laryngeal nerve) and the sparse formation (with motor neurons that innervate the laryngeal muscles except the cricothyroid) [3].

In previous work by our research group, the activity of the laryngeal motor neurons of nA and the reflex mechanisms involved in respiratory laryngeal responses have been characterized, suggesting that the parabrachial complex (PBc) and the A5 region (A5) have a role in modifying the activity of laryngeal motoneurones localized in the nA and accordingly the striated laryngeal muscles of the upper airway [4, 5] (**Figure 1**). Pontomedullary respiratory nuclei: PBc, A5, the nucleus of the solitary tract (NTS), nA and retroambiguous nuclei (nRA), paraambiguous (nPA) and retrofacial (nRF) integrate inputs from central and peripheral receptors and from superior structures to produce changes in the basic respiratory rhythm (eupnea). These changes are a prerequisite for survival (for example, tachypnea associated with the defense reaction, which increases the supply of oxygen preparing to fight or defend, or the response of gasping reset in the event of intense anxiety with respiratory alkalosis). But these changes in respiration are also necessary to maintain a constant
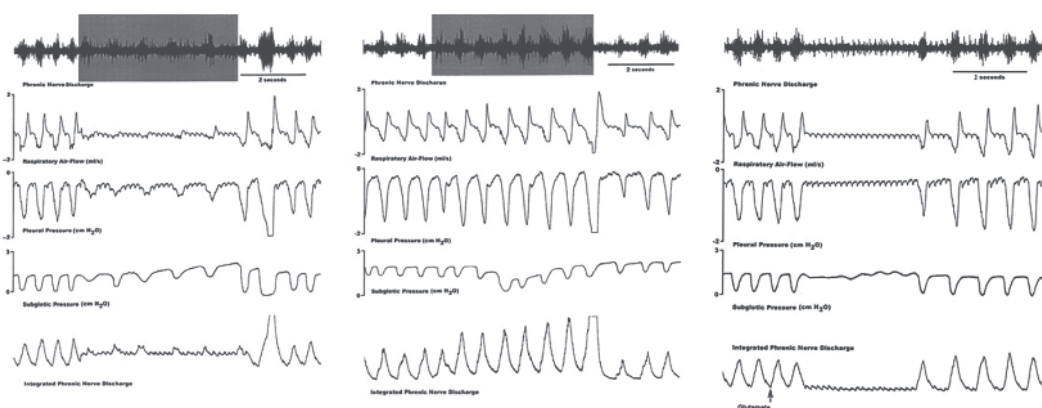

Figure 1.
Laryngeal and respiratory responses to electrical stimulation in the medial (a) and lateral (b) parabrachial nucleus and (c) to glutamate microinjection in the A5 region. Phrenic nerve discharge, respiratory airflow, pleural pressure, subglottic pressure and integrated phrenic nerve discharge showing an expiratory facilitatory response with an increase of subglottic pressure during electrical stimulation (20 mA, 0.4-ms pulses, 50 Hz for 5 s) in the medial parabrachial nucleus, an inspiratory facilitatory response with the decrease of subglottic pressure during electrical stimulation (10 mA, 0.4-ms pulses, 50 Hz for 5 s) in the lateral parabrachial nucleus and an expiratory facilitatory response with an increase of subglottic pressure during a glutamate injection (10 nl over 5 s) in the A5 region. The arrow shows the onset of injection.

expiratory flow that allows vocalization. It is known that Periaqueductal Gray Matter (PAG) is a key point in coordinating the efferent activity from limbic, cortico-prefrontal and cingulate afferents, modifying the activity of all these mesencephalic-pontomedullary nuclei [2].

2. PAG as a key point in vocalization

The PAG presents a large number of afferences. The most important have their origin from the prefrontal cortex, amygdala and hypothalamus. Its efferent projections to different pontine nuclei allow it to coordinate different patterns of cardiorespiratory and motor responses depending on the type of stimulus. Other functions of PAG include thermoregulation, participation in wakefulness and sleep mechanisms, or modulation of neuropathic pain or urination. At the clinical level, we know that its activity is modified in different neurodegenerative processes such as Alzheimer's and multisystemic atrophy [6–9].

All these higher structures that project to the PAG integrate visual, auditory and somatosensory information in the context of basic mechanisms for survival, maintaining an efferent tone on the PAG which, in turn, projects on the pontomedullary respiratory nuclei involved in respiratory rhythmogenesis to change from eupnea to a rhythm adapted to vocalization or growling. Specifically, the nRA is the perfect target to convert passive breathing into active breathing to generate motor activities that produce changes in abdominal pressure, in addition to modifying the activity of the motor neurons that are located in the nA and that control the caliber of the pharynx and larynx [10, 11]. Stimulation of PAG and nRA is known to produce vocalization [12] and lesions in PAG cause mutism in animals and humans [13, 14] and vocalization and problems in the production of voice when lesions occur in nRA [15]. However, the electrophysiological influence of PAG on these pontomedullary nuclei has not yet been described.

3. Vocalization in apes: PAG-laryngeal motor cortex connectivity

Regarding the studies of the pathways that participate in voluntary and involuntary vocalizations, there is a model that explains vocal control that includes two hierarchically organized pathways. Involuntary vocalizations are innate and require a different control mechanism than that which dominates voluntary vocalizations or speech [16, 17]. These emotional expressions, such as crying or laughing, are directed by the emotional system, made up of specific pathways that target the brain stem and spinal cord [18, 19]. Specifically, research carried out with the squirrel monkey has determined that the system includes: the cingulate gyrus, the PAG, and various pontine and medullary nuclei [20–24].

The PAG receives projections from the upper limbic regions and from cortical areas such as the anterior cingulate gyrus, insula, and orbitofrontal cortex. In addition, it maintains connections with the caudal part of the nRA. The nRA has direct access to the motor neurons involved in vocalization, that is, it controls the motor neuron groups that innervate the soft palate, pharynx, and larynx, as well as the diaphragm, intercostal, abdominal, and pelvic muscles. Its final objective is to control/modify the intra-abdominal, intrathoracic and subglottic pressure, the control of which is essential to generate vocalization.

In primates, vocalizations, in addition to activation of the PAG, can be produced by electrical stimulation of the hypothalamus [20, 25, 26], amygdala [20], bed nucleus of the stria terminalis [22], orbitofrontal cortex [27] and anterior cingulate gyrus [28], since all these regions have a strong connection with the PAG [29–33]. The only necessary condition is that the PAG was intact [13, 34, 35].

On the contrary, if areas that are not connected with the PAG, such as the motor or premotor cortex, are stimulated, no vocalizations are produced [36, 37]. These results emphasize the essential role of the PAG in the production of vocalization in primates as well as in humans. This coordinating role in the generation of vocalization is also demonstrated by the fact that the activation of the caudal levels of the PAG can generate partial vocalizations through its connection with the nRA [10, 38, 39].

In summary, the input of the stimulus occurs in the primary integrating center of vocalizations (VOC). Next, the superior temporal gyrus, the supplementary motor area and the insula, will be in charge of modulating the stimulus. Once the output from the VOC is produced, the stimulus can be directed to the corticobulbar pathway and cerebellum directly or, on the contrary, it can go from the cingulate gyrus, the PAG, the pons, until reaching the reticular area of the medulla; which has access to the nA ipsilaterally and contralaterally [40]. On the other hand, the voluntary production of voice in human beings consists of a sound modulation of sound. This production depends directly on the laryngeal motor cortex, that is, the production of voluntary vocal emissions in humans, requires the activation of this cortex, located in the dorsal portion of the ventral zone of the primary motor cortex, and its direct connection with the laryngeal motor neurons of the nA, which are in charge of controlling the laryngeal muscles for the emission of learned vocal patterns [41].

However, it has been shown that during speech emissions there is a joint activation of the voluntary and involuntary system [19]. An involuntary activation of the path takes place automatically to give the vocal emissions the appropriate emotional character. Therefore, stimulation of the pathway that originates in the primary motor cortex and runs through the PAG and nRA is required; in addition to the activation of the pathway that goes from the laryngeal motor cortex directly to the corticomedullary fibers, which will activate the motor neurons of the face, mouth, tongue, larynx and pharynx, to control the production of words and phrases.

Finally, vocal control will depend on the primary motor area, a bilateral structure that is responsible for laryngeal control and orofacial musculature [42], in addition to the activation of the superior temporal gyrus to compensate for alterations in the auditory feedback of the tone used during phonation. Likewise, two feedback loops are put into operation that provide the motor cortex with the information necessary to carry out motor commands for phonation. One of these loops includes the basal ganglia, while the other involves the cerebellum. However, these structures seem unnecessary for the production of innate vocal patterns [43, 44].

Therefore, we see that emotional emissions in humans require bilateral activation of the laryngeal motor cortex (**Figure 2**) [45]. Furthermore, the system for the production of speech involves a predominant activation of the left hemisphere, including the superior temporal gyrus, the anterior insula, the basal ganglia, and the cerebellum. For this production, the activity of the cingulate gyrus and the PAG is also necessary, in variable degrees, to associate the emotional character with the vocal production.
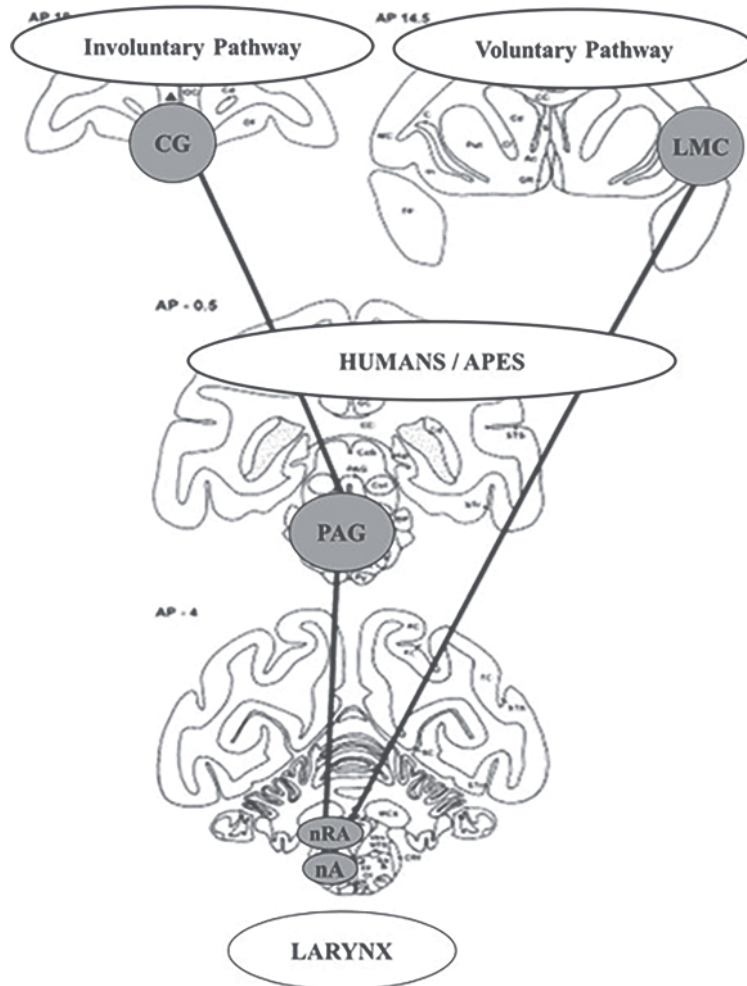
Figure 2.
Scheme of squirrel monkey brain coronal section showing the voluntary and involuntary pathways controlling the larynx.

4. Other structures functionally related to the PAG

Other intermediate structures project both to the laryngeal motor cortex and the nA. One of these structures is PBc, cited above [46]. Neuronal unit recording experiments demonstrate the presence of neuronal activity during vocalization [47], suggesting that this nucleus is involved in laryngeal motor coordination as an intermediate nucleus of proprioceptive information between the cortex and the nA. In addition, recent work has shown that both cPB and PAG have high immunoreactivity to the expression of the FOXP2 gene, demonstrating that both regions are primarily involved in modulating the expiratory flow necessary for the production of the sound and voice [2].

In one of the latest works carried out by our research group, we have demonstrated that the column corresponding to the dorsolateral PAG is involved in the control of defense response [48, 49], which is associated with tachycardia, hypertension and redistribution of blood flow. This sympathetic response is mediated by the rostro-ventrolateral medulla (RVLM), which, in turn, activates sympathetic preganglionic neurons present in the intermediolateral column of the spinal cord. These projections

are ultimately responsible for the sudden increase in blood pressure. It is also known that the increase in blood pressure is produced by indirect activation of the RVLM by other less studied pathways [50–52].

The dorsolateral PAG does not have direct connections with the RVLM but has very dense connections (afferents and efferents), with the hypothalamic area responsible for the activation of the RVLM during the defense response. We know that the cardiorespiratory activity of dorsolateral PAG neurons depends on the activity of these hypothalamic neurons [52, 53]. Likewise, our group has shown that there are functional connections from this hypothalamic area and other pons structures such as the parabrachial complex (cPB) [54, 55] and A5 area [56, 57]. Both regions are rich in FOXP2 expression. Our research group has shown the importance of the interrelation between some of these hypothalamic-midbrain and pontomedullary structures involved in cardiorespiratory control. More specifically, we have focused on the analysis of these interactions by analyzing the defense response evoked from specific areas of the hypothalamus (dorsomedial hypothalamic area and perifornical area (DMH-PeF)) [54–57] and midbrain (PAG) (**Figures 3** and **4**) [48, 49].

Originally, the stimulation of these areas evokes a series of cardiorespiratory and autonomic changes that characterize the defense response [58]. The defense response prepares the animal for situations environmental stresses that require a rapid loco-motor response characterized hemodynamically by hypertension, tachycardia and redistribution of blood flow from abdominal and visceral areas to the skeletal muscles of the extremities. Additionally, this response is accompanied by mydriasis, increases in respiratory rate and tidal volume and vocalization [56].

Recent publications propose DMH-PeF as one of the main areas of the hypothalamus that generate the defense response carried by the PAG [59]. Disinhibition of DMH-PeF after microinjection of bicuculin (GABA receptor antagonist) produces an increase in renal sympathetic activity and blood pressure that has been attributed to the activation of neurons in RVLM [60, 61]. The administration of bicuculin also produces an increase in heart rate, which decreases between 30 and 50% due to the inhibition of Rafe Pallidus with muscimol [62–64]. In addition, there is morphological evidence of projections from the DMH to the Rafe Pallidus [65]. The results seem to show that the pressor and tachycardia cardiovascular responses, typical of stress, evoked from this region, including in the DMH-PeF, would present two descending
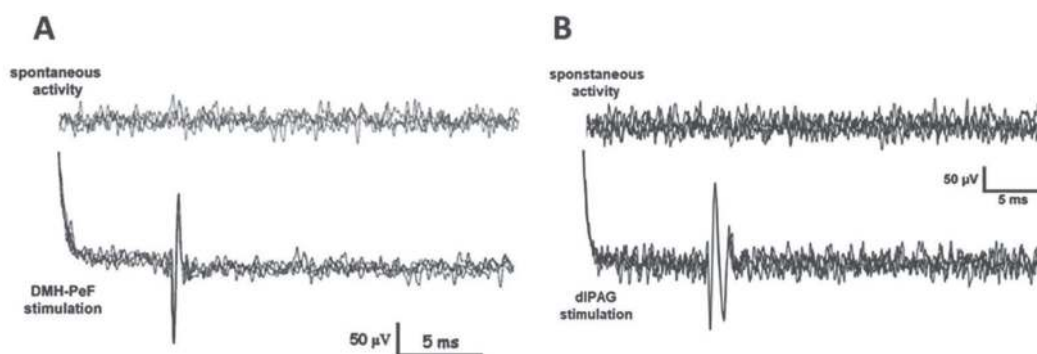

Figure 3.
Extracellular recordings of two putative cells were recorded from the A5 region. (A) Silent neuron (upper trace, 4 superimposed sweeps) with constant-latency responses to HDA stimulation (lower trace). The cell was demonstrated to be orthodromically activated from the HDA. (B) Silent neuron (upper trace, 4 superimposed sweeps). The lower trace shows constant latency responses (4 superimposed sweeps) to the dlPAG stimulation.
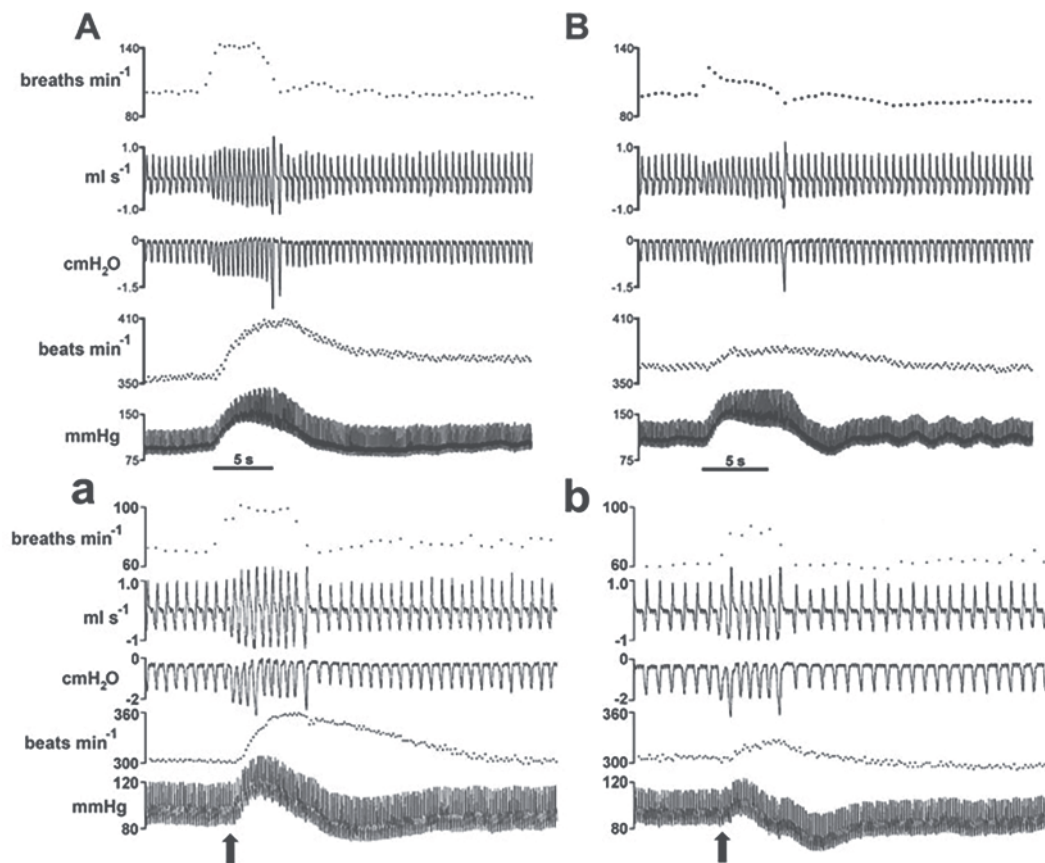
Figure 4.
Instantaneous respiratory rate (upper trace), respiratory flow, pleural pressure, instantaneous heart rate and blood pressure in a spontaneously breathing rat, showing the cardiorespiratory response evoked on PAG (upper figures) or HDA (lower figures) stimulation before [A, a] and after [B, b] the microinjection of muscimol (50 nl over 5 s) in the A5 region. The arrows indicate show the onset of the HDA/PAG electrical stimulation.

routes, one responsible for the increase in blood pressure, via RVLM, and the other responsible for the increase in heart rate, via Pale Rallidus. Both responses use the PAG as an intermediate station [60].

5. Preliminary results

In previous studies, we have characterized the activity of laryngeal nA motor neurons and the reflex mechanisms involved in respiratory laryngeal responses. We have also described the existence of a network of hypothalamic-midbrain-pontomedullary nuclei that modulate the cardiorespiratory responses produced to certain types of stress. Bearing this in mind and knowing that many of these structures express FOXP2 and participate in vocalization processes, the limited number of existing publications that study the electrophysiological relationships between the neural circuits involved in the control of laryngeal activity is striking.

Recently, we have been able to carry out a series of preliminary experiments with the techniques that we had been using for years and that we are taking up again. The results of this previous approach include the "in vivo" recording of laryngeal motor neurons and the recording of subglottic pressure and laryngeal resistance using the technique of "isolated glottis in situ" and the analysis of the changes that occur in

these parameters. During electrical stimulation of the study areas. These works have led to two publications in international congress proceedings; [66] in Proc Physiol Soc 43, PC208 and [67] in J Physiol Biochem, 74 (Suppl 1) and two communications presented at the SENC Congress in Santiago de Compostela (2019), concluding that not also PAG but CnF seem to modify the activity of laryngeal motoneurons.

6. Clinical implications

Therefore, all these central structures described have in common the fact that they convey cardiorespiratory responses to environmental stress and support vocalization. Recent studies show that the laryngeal microstructure and its innervation undergo the same changes during development in rodents and humans [68] and that the central circuits responsible for vocalization present an overactivity in certain speech disorders of central origin such as spasmodic dysphonia due to laryngeal dystonia [69].

Laryngeal respiratory apnea is frequently a particularly serious clinical manifestation, as occurs in newborn apnea or central sleep apneas, caused by immaturity or abnormalities of central respiratory control in these individuals, causing an exaggerated response of the respiratory system, the laryngeal adduction reflex [70].

Furthermore, it is also known that spasmodic dysphonia, a focal form of dystonia, is a neurological alteration of the voice that manifests with involuntary "spasms" of the vocal cords, which result in speech interruptions and affect the quality of the voice. The two recognized types of spasmodic dysphonia are adductor spasmodic dysphonia (intermittent excessive closure of the vocal cords) and abductor spasmodic dysphonia (prolonged opening of the vocal cords). The cause of spasmodic dysphonia is unknown, although there is some consensus that behind it there is an alteration of the central nervous system, especially at the level of motor control. Specifically, alterations have been described in the circuit of the ganglia of the base, cerebellum and sensorimotor cortex, and structural alterations in the corticobulbar and corticospinal tracts, which are the nerve tracts that come into contact with the bulbar neurons responsible for phonation [69]. A better description and knowledge of the individual contribution of each of the nuclei that make up this hypothalamic-midbrain network on the central control of laryngeal motor neurons, would allow a better understanding not only of normal phonatory control, but would also contribute to a better understanding of the central alterations produced in this type of dystonia as well as in other disorders at the vocal level.

Paradoxical laryngeal adduction movements are characterized by adduction or approximation of the vocal cords during the respiratory cycle (especially during the inspiratory phase), which causes airway obstruction at the laryngeal level. The resulting dyspnoea and stridor are frequently confused with asthma, but do not respond to treatment with steroids and bronchodilators, since the glottic narrowing is independent of the caliber of the bronchial lumen. The origin of this intermittent interruption of transglottic airflow due to paradoxical laryngeal adduction remains to be elucidated. It has been linked to laryngeal irritation from agents such as gastroesophageal reflux or acute severe stress [71].

On the other hand, the pressor response and tachycardia associated with the stimulation of the DMH-PeF and PAG, mediated by the cPB nuclei and A5 Area, are of immediate interest for the knowledge of certain types of hypertensions classified clinically as "essential". We believe that knowledge of the mechanisms involved in the

inhibition of the baroreceptor reflex, which could mediate this type of hypertension, will allow us to provide new data that will contribute to better explaining the mechanisms of neuronal interactions between the hypothalamic-midbrain regions and the pontomedullary cardiorespiratory and laryngeal control centers implicated in this type of pathology.

7. Summary and perspectives

During the last two decades, Health Sciences research has evolved from a purely biological perspective towards a biopsychosocial model of health and disease. As a result, it has been found that there is a relationship between voice disorders and neuro-vegetative responses associated with emotional responses, mainly those related to anxiety and stress. These responses are generated by the activation of the hypothalamic defense areas and are carried by the PAG and pontomedullary structures such as the PBc and A5. The emotional response intervenes, along with other psychological factors, on the tone of the laryngeal muscles causing spasmodic dysphonia or laryngeal dysphonia. This occurs because the laryngeal muscles appear to be extremely sensitive to emotional stress generated by anxiety, anger, irritability, impatience, frustration, and depression, which can lead to spasmodic dysphonia or laryngeal dystonia [69]. Along these lines, Demmink-Geertman et al. [72] confirmed that, due to the characteristics of the higher pitch of the female voice, this effect is greater in women of all ages and that, above all, it affects professionals who use the voice as a means of work. This fundamentally affects women involved in teaching tasks. Only in Andalusia, the number of teachers is 132,985, and in Spain, they exceed 750,000, of which 71.9% are women. The percentage is particularly relevant in early childhood (97.6%), special (81.7%) and primary (81.4%) education. At least 21% have vocal involvement and 15.8% of sick leave is due to voice problems (FETE-UGT 2019 teaching report). Knowing the pathophysiology of the mechanisms by which stress produces alterations in the functionality of the vocal cords would allow the development of adequate treatments for these pathological processes.

Therefore, new contributions are needed to add new perspectives to a series of pathologies that are related to mechanisms that have their origin in these hypothalamic-midbrain regions, such as the so-called central apneas associated with hypertension [70], apneas associated with sudden death infantile syndrome [73], paradoxical laryngeal adduction movements [71] and muscular tension dysphonia secondary to stress [74].

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Conflict of interest

The authors declare that they have no conflict of interest.

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