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Frontiers review

The brainstem respiratory network: An overview of a half century of research

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ABSTRACT

This review aims at summarizing the work performed over 40 years by Professor Armand Bianchi and the research team he directed, which was devoted to the study of the central respiratory network. The major steps towards the understanding of this complex network will be presented together with methodological considerations. This includes the sequential progress that was made in the identification and characterization of respiratory neurons as deduced from inferences gleaned from intracellular recordings, which revealed putative synaptic connections within the respiratory network. Also reviewed is a comparison of *in vivo* versus *in vitro* approaches. The search for the "real" respiratory neurons must consider that those neurons are redundantly represented within the brainstem and express a wide variety of patterns. The last part of this review focuses on the concept that the brainstem respiratory circuitry forms part of a multifunctional network subserving both respiration and non-respiratory motor behaviors. Numerous data provide evidence that the respiratory network operates as a dynamic assembly of neurons, some of which can belong to several networks involved in the coordination of respiratory muscles during functions that include coughing, swallowing and vomiting.

1. Introduction

During the second half of the 20th century the concept of a respiratory center has progressively evolved from an undefined respiratory neuronal system as part of the brainstem reticular formation to the modern concept of a central pattern generator (CPG). During this period various respiratory neuronal groups were recognized within the brainstem each of them having a well defined function in producing the respiratory drive to the motor outputs and breathing muscles.

Those looking for the real respiratory neurons within the brainstem might keep in mind that for O_2 up take and CO_2 release, air breathing animals and specifically mammals have developed neuronal groups which must coordinate the activities of two essential parts of the respiratory system: one is devoted to create air aspiration and air expulsion, **the pump muscles**, and the other for regulating air flow, **the valve muscles** (Fig. 1). In addition, they might be aware that the respiratory muscles are involved in several functions other than respiration. In these circumstances the respiratory CPG must adapt to a new behavioral situation quickly and to do this undergo rapid reconfiguration. The CPG can be seen as an dynamic assembly of neurons able to produce a rhythmic discharge that can easily adapted to generate different breathing patterns, and to contribute almost entirely or only partially to non-respiratory behaviors such as coughing, swallowing or vomiting.

2. Discharge activities of the respiratory motor outputs versus spike discharge activities of brainstem respiratory neurons

The sequence of breathing is composed of three essential phases as defined by Diethelm Richter (1982), i.e., inspiration (I), post-inspiration (or early expiration, E1) and late expiration (E2). In eupnea, the main inspiratory pump muscles, the diaphragm, and external intercostal muscles with their respective nerves develop an augmenting inspiratory activity, which is prolonged by a declining activity during early expiration. The expiratory outputs (abdominal muscles and internal intercostal muscles) are active in late expiration, although the phase of expiration can be passive in quiet breathing so that no discharge is observed in these motor outputs (Fig. 1).

It is also important to consider the patterns of activity of the nerves driving the valve muscles since their motoneurons are included within the brainstem together with the respiratory neurons of the CPG (Fig. 1A and C). Their axons are distributed within several cranial nerves. The vagus nerve and its branch the recurrent laryngeal nerve (RLN) contain motoneurons active in inspiration (for abduction of the glottis) and motoneurons active in early expiration (for adduction of the glottis that reduce the airflow at this

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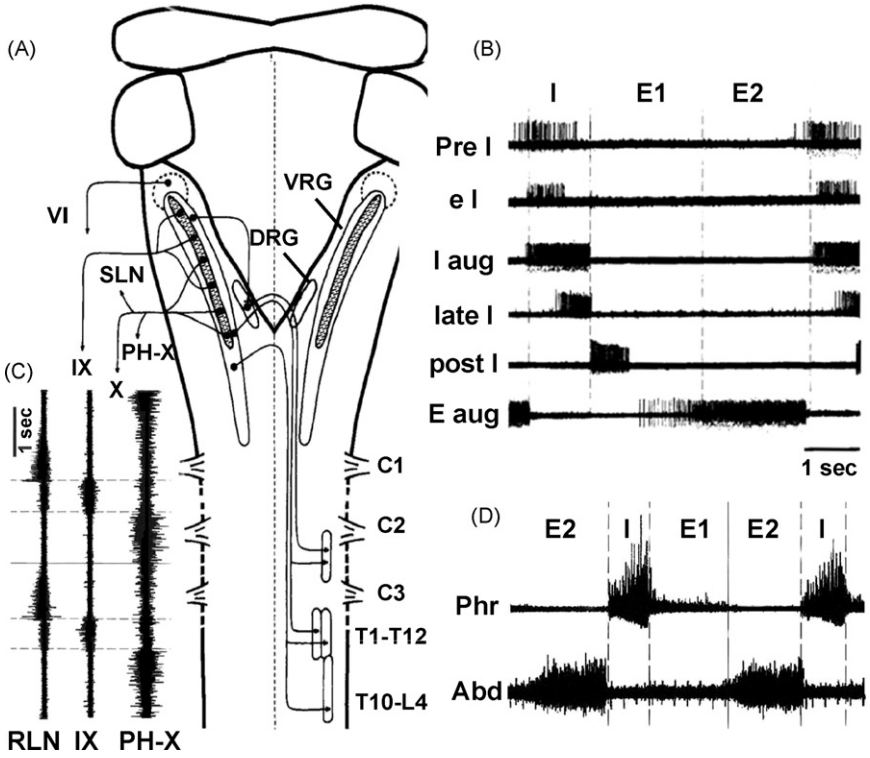

Fig. 1. (**A**) Dorsal view of the brainstem showing locations of respiratory neurons in dorsal respiratory group (DRG) and ventral respiratory column (VRC), their axonal projections, and cranial nerves to the valve muscles. Respiratory cycle progresses in three phases: I inspiration; E1 post-inspiration or early expiration; E2 late expiration. (**B**) Six basic patterns of action potentials recorded in brainstem DRG and VRC. Discharge activities in cranial outputs (**C**) and spinal respiratory outputs (**D**). The data were obtained from several decerebrate cats. Time duration of respiratory cycles has been matched using computer software. *Abbreviations*: Pre-I, pre-inspiratory; e-I; early inspiratory; I aug, inspiratory augmenting; Late I, late inspiratory; Post I, post-inspiratory; E aug, expiratory augmenting; Phr, phrenic nerve; Abd, L1 lumbar nerve branch; RLN, recurrent laryngeal nerve; SLN, superior laryngeal nerve; VII, facial nerve; IX, glossopharyngeal nerve; X, vagus nerve; PH-X: pharyngeal branch of the X.

period). These changes in upper airway resistance associated with the respiratory cycle are determinant for ventilation. Indeed, the negative pressure generated by contraction of diaphragm and external intercostal muscles in inspiration must be counteracted by a decrease in upper airway resistance to prevent the risk of obstructive apnea. Conversely, an increase in upper airway resistance in early expiration allows a smooth transition between inspiration and expiration. It decreases the speed of the expiratory airflow, preventing therefore alveolar collapse.

Other brainstem motoneurons innervating the oro-pharyngeal region and their respective nerves are active during the respiratory cycle. The glossopharyngeal nerve (IX) is responsible for pharyngeal dilatation in inspiration, the pharyngeal branch of the vagus nerve (PH-X) for pharyngeal constriction in expiration, and the hypoglossal nerve (XII) for tongue protrusion in inspiration (mainly via contraction of the genioglossus muscle) (Fig. 1A and C). Both pharyngeal dilatator and tongue protrusor muscles contribute to upper airway patency, i.e. they maintain an open airspace for effective breathing and prevent obstructive apneas (Chan et al., 2006). However, recordings of genioglossus muscle activity or XII activity in conscious awake rats reported little phasic respiratory-related tongue movements or XII discharges as compared with sleep states or anesthesia (Jelev et al., 2001; Roda et al., 2004; Chan et al., 2006; Besnard et al., 2007). By contrast, robust inspiratory-related XII discharges are more often observed in decerebrate or anesthetized animals with vagotomy (Grélot et al., 1989; Kubin et al., 1992) than when the vagi are left intact (for example Gestreau et al., 1996, 2000). These observations suggest that changes in arterial P_{CO_2} and/or vagal afferent inputs contribute significantly to phasic respiratory activity of tongue muscles. Many other oro-pharyngeal muscles also active during respiration are innervated by the facial nerve and branches of the fifth nerve (not shown in Fig. 1).

Extracellular unitary recordings from the respiratory neurons in the brainstem were largely developed during the second half of the 20th century. In most studies of this type, the major concerns were the description of the discharge patterns of the respiratory neurons and their anatomical location (Batsel, 1964). The identification of neurons was performed by comparison of their patterns of discharge with those recorded from the peripheral nerves, i.e., augmenting or decrementing discharge as in phrenic or laryngeal nerves, respectively (Fig. 1B–D).

On this basis, an important contribution was made by Morton Cohen (1970). He induced changes in respiratory rhythmicity and compared the changes in activity of individual respiratory brainstem neurons with the changes of the overall respiratory cycle, as indicated by the phrenic nerve discharge. He used three major experimental variables, CO_2 tension, lung inflation and brainstem stimulation. Based on the responses of the various classes of neurons, the functional role of such neurons within the central respiratory network could be hypothesized.

3. Antidromic stimulation: a tool for functional identification of brainstem respiratory neurons

Another step was reached when additional characterization of the respiratory neurons was obtained by using antidromic stimulation of their axonal pathway. In the mid sixties such a method of identification was used to identify the spinal axons of inspiratory neurons located in the nucleus of the solitary tract (NTS; Nakayama and Baumgarten, 1964). Subsequent studies identified the spinal axons of respiratory neurons of the ventro-lateral medulla (Merrill, 1970).

Extensive extracellular recording studies of brainstem respiratory neurons during systematic microstimulation of the either the