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Review

Respiratory related control of hypoglossal motoneurons––Knowing what we do not know

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ABSTRACT

Because tongue position and stiffness help insure that the pharyngeal airspace is sufficiently open during breathing, the respiration-related behavior of the tongue muscles has been studied in detail, particularly during the last two decades. Although eight different muscles act upon the mammal tongue, we know very little about the respiration-related control of the majority of these, and almost nothing about how they work together as a complex electro-mechanical system. Other significant gaps include how hypoglossal motoneuron axons find their appropriate muscle target during development, whether the biophysical properties of hypoglossal motoneurons driving different muscles are the same, and how afferent information from cardiorespiratory reflex systems is transmitted from major brainstem integrating centers to the hypoglossal motoneuron pool. This brief review outlines some of these issues, with the hope that this will spur research in the field, ultimately leading to an improved understanding of the respiration-related control of the mammalian tongue musculature.

1. Introduction

The mammal tongue is mechanically complex, and its shape, stiffness and position in space are controlled by the combined actions of seven different muscles (Fregosi and Fuller, 1997; Smith et al., 2005). Because tongue position and stiffness help insure that the pharyngeal airspace is sufficiently open during breathing (Hoffstein, 1996; Oliven et al., 2007a,b; Remmers et al., 1978), the respiration-related behavior of the tongue muscles has been studied in detail, particularly during the last two decades. The mammal tongue is composed of four extrinsic muscles,[1] which originate on bony structure or connective tissue and insert into the tongue body, and four intrinsic muscles that originate and insert within the tongue body [see Fig. 1, and Fregosi and Fuller (1997) for review]. The tongue has been described as a muscular hydrostat (Smith, 1985), which refers to a cylindrical muscular structure that retains a constant volume. Thus, contraction of the tongue muscles changes the shape and rigidity of the tongue, but not its volume. Another important part of the muscular hydrostat theory is that all tongue muscles participate in all tongue movements (Smith, 1985). Nonetheless, studies of the respiration-related activity of the tongue muscles has focused almost exclusively on the genioglossus muscle; the whole hypoglossal nerve, which contains the axons of up to seven muscles (Fig. 1, and see Footnote 1), or on hypoglossal motoneurons without identification of the neuron's target muscle. The failure to understand the function and interactions among all components of this complex neuromuscular system has left us with a narrow view of the respiration related function of the tongue muscles. The remainder of this section will briefly describe some of the reasons for these deficits, setting the stage for a brief summary of what I perceive as the major unresolved issues regarding the respiration-related control of the tongue musculature.

The advantage of studying human subjects and unanaesthetized animals is that the confounding influence of drugs is avoided, and natural state-dependent changes (e.g., sleep vs. waking, rest vs. exercise, disease vs. health, hypoxia vs. normoxia, etc.) in activity can be investigated. However, recording EMG activity in the tongue is challenging owing to the complex anatomy and accessibility. For example, the complex interdigitation of the intrinsic muscles in the body of the tongue precludes us from knowing which of the muscles is being sampled (Pittman and Bailey, 2009). And although the extralingual portions of the extrinsic muscles allow recordings that are free of contamination from adjacent muscles, accessing the hyoglossus and styloglossus requires invasive procedures that should be done by a qualified physician (Mateika et al., 1999). In contrast, because the extralingual portion of the genioglossus muscle is eas-

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[1] Note that the palatoglossus elevates the tongue dorsum, but because it originates on the palatine aponeurosis and inserts into the posterolateral tongue, it is sometimes considered to be a palatal muscle and sometimes a tongue muscle. Importantly, the motor innervation of palatoglossus is via the pharyngeal plexus, not the hypoglossal motoneuron pool. Accordingly, in the remainder of this review, and including Fig. 1, I exclude the palatoglossus in my descriptions and discussions of the extrinsic tongue muscles.

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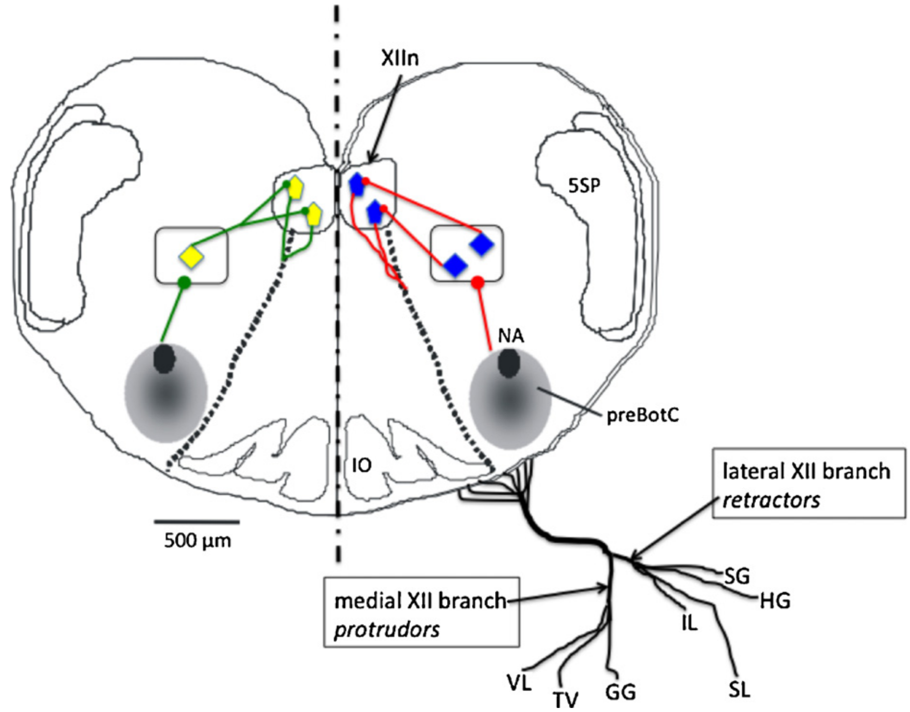

Fig. 1. Schematic diagram showing the preBotzinger complex (preBotC), the hypoglossal motor nucleus (XIIn, blue and yellow pentagons) and the "premotor" interneuron population (blue and yellow diamonds within the rectangles) that conveys synaptic input from the preBotzinger complex to the motoneuron pool. The diagram also shows the nerve supply to the seven tongue muscles innervated by hypoglossal motoneurons in the mammal (please see Footnote 1), with the medial hypoglossal nerve branch activating extrinsic and intrinsic protrudor muscles, and the lateral branch intrinsic and extrinsic retractor muscles. The left-hand half of the diagram shows divergent input from a single interneuron to two hypoglossal motoneurons. The right half shows unique input from interneurons to motoneurons (see text for detailed explanation). VL, intrinsic verticalis muscle; TV, intrinsic transversus muscle; GG, extrinsic genioglossus muscle; IL, intrinsic inferior longitudinalis muscle; SL, intrinsic superior longitudinalis muscle; HG, extrinsic hyoglossus muscle; SG, extrinsic styloglosssus muscle. 5SP, spinal trigeminal tract.

ily accessed, most available data comes from EMG recordings of this muscle, which protrudes and depresses the tongue. Because of this, there has been an inclination to consider the genioglossus as "the most important" tongue muscle for normal breathing, though we have no idea if this is so. Indeed, the single study that recorded the EMG activity of both genioglossus and hyoglossus muscles in healthy human subjects showed clearly that the respiration-related behavior of these muscles is virtually indistinguishable (Mateika et al., 1999). On the other hand, although anesthetized and decerebrate animal models allow access to all of the tongue muscles, the influence of drugs precludes the study of natural state changes on the respiratory drive to the motoneuron pool. Moreover, studies are typically done in tracheotomized animals, allowing airflow to bypass the upper airway, which greatly disturbs not only the natural function of the upper airway, but presumably the neural drive to the hypoglossal motoneuron pool (Berry et al., 2003; Chamberlin et al., 2007; Doherty et al., 2008; Eckert et al., 2007; Horner et al., 1991; Leiter and Daubenspeck, 1990; Malhotra et al., 2002; Mathew et al., 1982; van Lunteren et al., 1984).

Although modern electrophysiological techniques have allowed detailed *in vitro* study of hypoglossal motoneuron biophysical properties and synaptic transmission, there are several caveats that have slowed our understanding of the respiration related control of hypoglossal motoneurons. First, most studies are done in the rhythmic brainstem slice which provides an intact but very rudimentary respiratory control network, consisting of the preBotzinger complex, interneurons in the intermediate reticular formation and the hypoglossal motoneuron pool (Fig. 1). But this preparation must be prepared from the neonatal brainstem, because in adult brains the thickness needed to capture the entire network results in anoxia within the tissue core (Ballanyi and Ruangkittisakul, 2009; Morawietz et al., 1995; Wilken et al., 2000). As a result, we know a considerable amount about neonatal hypoglossal motoneurons, but whether or not the adult system functions in the same manner or instead changes with development is unknown. More importantly, *in vitro* studies consider the hypoglossal motoneuron pool as a homogenous and assume that the properties of all hypoglossal motoneurons are identical. As a result, understanding how respiration-related drive targets motoneurons of individual tongue muscles within the hypoglossal motor nucleus is a complete mystery.

The remainder of the review focuses on some key unresolved issues pertaining to the motor supply of the tongue musculature; the respiration related motor drive to hypoglossal motoneurons; and the distribution of afferent inputs to the pool. Since we know very little about each of these topics, the review of these issues is designed to identify the major gaps and perhaps guide future work on the respiration-related control of this important motoneuron pool.

2. What we do not know about motor supply to the tongue muscles

Fig. 1 demonstrates how the axons of hypoglossal motoneurons are distributed to the tongue muscles of the rat. The axons emerge from their cell bodies, pass ventrally through the medulla and emerge as six or seven separate branches (10–15 branches in humans), roughly between the pyramid and the olive. The branches then join together to form the main hypoglossal nerve trunk which then separates distally into distinct medial and lateral branches. As shown in Fig. 1, the lateral branch supplies the retractor muscles (the extrinsic hyoglossus and styloglossus, and the intrinsic inferior and superior longitudinal muscles), while the medial branch supplies the protrudor muscles (the extrinsic genioglossus, and the