



Review article

The bulbospinal network controlling the phrenic motor system: Laterality and course of descending projections



Michael George Zaki Ghali*

Department of Neurobiology & Anatomy, Drexel University College of Medicine, Philadelphia, PA 19129, USA

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ABSTRACT

The respiratory rhythm is generated by the parafacial respiratory group, Bötzing complex, and pre-Bötzing complex and relayed to pre-motor neurons, which in turn project to and control respiratory motor outputs in the brainstem and spinal cord. The phrenic nucleus is one such target, containing phrenic motoneurons (PhMNs), which supply the diaphragm, the primary inspiratory muscle in mammals. While some investigators have demonstrated both ipsi- and contralateral bulbophrenic projections, there exists controversy regarding the relative physiological contribution of each to phasic and tonic drive to PhMNs and at which levels decussations occur. Following C1- or C2 spinal cord hemisection-induced silencing of the ipsilateral phrenic/diaphragm activity, respiratory stressor-induced, as well as spontaneous, recovery of crossed phrenic activity is observed, suggesting an important contribution of pathways crossing below the level of injury in driving phrenic motor output. The precise mechanisms underlying this recovery are debated. In this review, we seek to present a comprehensive discussion of the organization of the bulbospinal network controlling PhMNs, a thorough appreciation of which is necessary for understanding neural respiratory control, accurate interpretation of studies investigating respiratory recovery following spinal cord injury, and targeted development of therapies for respiratory neurorehabilitation in patients sustaining high cervical cord injury.

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* Corresponding author at: Department of Neurobiology and Anatomy, Drexel University College of Medicine, 2900 Queen Lane, Philadelphia, PA 19129, USA.
 E-mail address: mgg26@drexel.edu

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1. Introduction

Near the end of the 19th century, [Porter \(1895\)](#) performed an elegant set of experiments in which he tested the effects of high cervical spinal cord injury on breathing. Following C2 hemisection of the spinal cord in anesthetized spontaneously-breathing animals, movements of the ipsilateral respiratory muscles ceased. In response to contralateral phrenicotomy, hemidiaphragm paresis was observed on that side with reemergence of respiratory movements on the side ipsilateral to the cord injury. This came to be known as the crossed phrenic phenomenon (CPP), wherein a respiratory stressor (e.g., hypoxia, hypercapnia, contralateral phrenicotomy) causes re-emergence of phrenic/diaphragm activity ipsilateral to a cervical cord hemisection above the level of the phrenic nucleus. Over the course of the following century, the CPP was consistently observed in experiments employing either phrenic neurogram or diaphragm electromyogram recordings and postulated to be mediated via increased drive to pathways crossing below the level of hemisection ([Goshgarian, 1979, 1981; Fuller et al., 2003, 2006, 2008](#)).

Over the past several decades, it has been shown that phrenic nerve (PhN) activity ipsilateral to a cord hemisection will recover spontaneously (i.e., absent respiratory stressors) weeks to months following injury (e.g., [Goshgarian, 1979, 1981; O'Hara and Goshgarian, 1991; Castro-Moure and Goshgarian, 1996; Polentes et al., 2004; Fuller et al., 2003, 2008; Doperalski et al., 2008](#)). Recently, we have shown crossed phrenic activity recovers acutely over minutes to hours following a C1 hemisection in the unanesthetized decerebrate adult rat ([Ghali and Marchenko, 2015](#)).

[Porter \(1895\)](#) initially hypothesized crossed phrenic activity to be mediated by phrenic motoneuron (PhMN) dendrites crossing into the contralateral ventral horn receiving contralateral descending bulbospinal drive. While this figure prominently in crossed phrenic activity observed in the neonatal rat (~1/4 of PhMNs in early neonates), the proportion of PhMNs with midline-crossing dendrites diminishes rapidly over development and comes to represent ~3% of the adult PhMN pool ([Allan and Greer, 1997; Song et al., 2000](#)). A more tenable hypothesis explaining crossed phrenic activity in adult animals emerged when [Goshgarian et al. \(1991\)](#) demonstrated the existence of descending bulbophrenic projections from medullary regions subserving phasic drive crossing at cervical cord levels corresponding to the phrenic nucleus in the ventral white commissure.

Briefly, phrenic pattern formation can be conceptualized as the net product of (1) tonic excitation (background excitatory drive throughout all phases of respiration rendering PhMNs responsive to phasic inputs by maintaining membrane potential close to action potential threshold), (2) tonic inhibition (background inhibitory drive), (3) phasic excitation (excitatory drive during inspiration) and (4) phasic inhibition (inhibitory drive during expiration). Knowledge of the laterality and course of descending projections mediating each of these contributions to phrenic/respiratory pattern formation enhances our understanding of neural control of breathing in general, as well as mechanisms responsible for respiratory recovery following high cervical cord injury. A comprehensive review of bulbophrenic network organization is presented to serve as a reference in order to thoroughly understand neural control of respiration, permit accurate interpretation of physiologic data generated by high cervical spinal cord injury studies, and aid in the

development of therapeutic strategies for patients suffering from respiratory compromise following high cervical spinal cord injury.

2. Organization of bulbospinal network controlling the phrenic motor system

2.1. Monosynaptic and polysynaptic bulbophrenic pathways

Medullospinal projections to phrenic motoneurons (PhMNs) are predominantly monosynaptic, demonstrated both neuroanatomically, via anterograde and retrograde tracing studies ([Ellenberger et al., 1990a; Dobbins and Feldman, 1994; Lipski et al., 1994](#)), as well as neurophysiologically through cross-correlation analysis performed on simultaneous recordings of rostral ventral respiratory group (rVRG) pre-motor units and PhMNs (e.g., [Tian and Duffin, 1996a,b](#)). Although disynaptic pathways to PhMNs are described, they are less prominent in the native state and assume a more significant role following spinal cord injury ([Lane et al., 2009](#)). This stands in contrast to pre-motor neurons projecting to *intercostal* nuclei, which are predominantly polysynaptic, analogous to corticospinal and reticulospinal tracts supplying non-respiratory motor systems, which likewise project initially to pre-motor propriospinal interneurons in rodents ([Kastner and Gauthier, 2008](#)).

In addition to supraspinal pre-MNs, PhMNs receive inputs from spinal interneurons at different spinal levels ([Lipski et al., 1993, 1994; Tian and Duffin, 1996b; Lane et al., 2008b](#)). For example, in addition to monosynaptic bulbospinal projections to PhMNs, supraspinal pre-motor neurons have been shown terminating in the upper cervical spinal cord ([Tian and Duffin, 1996a](#)), putatively functioning as pre-motor interneurons ([Lipski et al., 1993, 1994; Tian and Duffin, 1996a; Qin et al., 2002; Lu et al., 2004; Lane et al., 2008a,b](#)), acting as a relay to PhMNs from supraspinal centers. Some investigators have argued that upper cervical (used in this work interchangeably with and to indicate C1–C2 levels) pre-phrenic interneurons cannot drive inspiratory activity without medullary projections ([Gauthier et al., 2006; Vinit et al., 2006](#)), in contrast to the locomotor central pattern generator (CPG), wherein homologous pre-motor propriospinal interneurons can generate rhythmicity in the absence of extrinsic drive ([Rossignol et al., 2008](#)). In contradistinction, we, along with other investigators, have provided evidence for the existence of an analogous and latent spinal CPG located in the upper cervical cord capable of producing phasic/rhythmic discharge in respiratory motor outputs independently of rVRG ([Aoki et al., 1980; Ghali and Marchenko, 2016a; Ikeda et al., 2017](#)).

2.2. Projection laterality

Projections from pontomedullary respiratory nuclei to the phrenic nucleus have been shown to be ipsilateral and/or contralateral, with bilateral innervation a common feature in rats ([Fig. 1](#)). Injections of retrograde tracers into the phrenic nerve and nucleus reveals bilateral labeling of rVRG ([Rikard-Bell et al., 1984; Onai et al., 1987; Dobbins and Feldman, 1994; Boulenguez et al., 2007a](#)) and anterograde tracing studies corroboratively demonstrate that each rVRG projects to PhMNs bilaterally ([Feldman et al., 1985; Goshgarian et al., 1991; Lipski et al., 1994](#)). However, whether or not pre-motor neurons decussate at cervical cord levels corresponding to the phrenic nucleus had been debated. [Ellenberger](#)

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