Control of hypoglossal pre-inspiratory discharge

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Abstract
The hypoglossal nerve (XII) innervates muscles mediating excursive movements of the tongue. The population discharge of hypoglossal motoneuronal axons constituting the hypoglossal nerve precedes and extends through the inspiratory epoch. The epoch subtended between the onsets of hypoglossal and phrenic neural discharge constitutes so-called pre-inspiration. Hypoglossal pre-inspiratory neural discharge serendipitously displaces the tongue along a tensor reducing upper airway resistance anticipative of succeeding inspiratory efforts. Hypoglossal motoneurons exhibiting discharge onset during pre-inspiration experience successive hyperpolarization of membrane voltage and attenuation of unitary spiking frequency, although a subset may, paradoxically and state-dependently, exhibit depolarization of membrane voltage and augmentation of neuronal spiking frequency, by dynamic stretch placed upon the alveolar walls and interstitium. Marked static elevation of positive-end expiratory pressure may induce hypoglossal bursting decoupled from phasic rhythmic phrenic discharge. Augmentation of the amplitude and/or duration of hypoglossal inspiratory discharge during successive pre-inspiratory and inspiratory epochs by inhalation of a hypoxic and/or hypercapnic gas mixture remains restrained in the presence of intact vagal inputs and is potentiated by interruptions of vagal continuity. Unravelling the mechanisms underlying the genesis of pre-inspiratory activity will inform our understanding of respiratory rhythm generation and pattern shaping. In the present work, I seek to explore the mechanisms underlying modulation of hypoglossal pre-inspiratory discharge by hypercapnia, hypoxia and static and dynamic lung stretch placed upon hypoglossal pre-inspiratory activity, the mechanisms underlying the generation of hypoglossal pre-inspiratory activity, and the extent of microanatomical and functional overlap between propriobulbar interneuronal microcircuits generating hypoglossal pre-inspiratory activity and propriobulbar interneuronal microcircuit oscillators generating pre-inspiratory activity inaugurally inducing respiratory rhythmic activity and thus use experimental data from previous work and that developed by other investigators to explore the modulatory role of lung vagal afferents and intra-neuraxial and carotid body chemoreceptors upon hypoglossal pre-inspiratory activity.

KEYWORDS
central pattern generation, generation, hypoglossal nerve, initiation, nerve XII, pre-inspiratory propagation, respiratory rhythm, synchrony, vagal modulation

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INTRODUCTION

Julien Legallois (1802) abolished chest wall excursions by transecting through the brainstem, with breathing spared exclusively if medullospinal continuity was preserved. Pierre Flourens (1858) abolished breathing by microsurgical ablation of a ∼1 mm zone within the medulla, la nœud vitale de la respiration. Dittler and Garten (1912) identified respiratory-related fast synchronous oscillations in canine phrenic nerve discharge, successively revealed in spectra of respiratory-related neurons and nerves in cats, rabbits, rats and mice (see Ghali et al., 2013). These oscillations indicate common origins of neural activity and synchronization across disparate brainstem and spinal cord zones generating and conveying the breathing rhythm and pattern to effector musculature. Lumsden (1923a, 1923b) incipiently developed an emergent and progressively nuanced understanding of the respiratory rhythm and pattern by eliciting apneas (prolonged inspirations) by lesioning the metencephalic tegmentum alone or together with interruption of vagal continuity. Richter (1982) characterized triphasic eupnoea, although it is suggested that a pentaphasic pattern might more appropriately characterize neural breathing, constituted by early-inspiratory (I), late-I, post-I, faux mid-expiratory (E) (given that neurons firing exclusively during mid-expiration do not exist) and pre-I, a conceptualization enhancing our understanding of relevant interactions amongst neuronal populations generating the breathing rhythm and pattern (see Ausborn et al., 2018 for an exceptional computational modelling study). Smith and colleagues (1991) abolished rhythmic breathing, decrementing C4 ventral rootlet bursting after transections below the pre-Bötzinger complex (preBötC), more appropriately termed the post-Bötzinger complex according to formal anatomical nomenclature or the Legallois–Flourens–Smith–Marchenko nucleus in honor of those incipiently discovering and neurophysiologically characterizing the neuronal cluster. Spontaneously bursting cells in preBötC, parafacial respiratory group and post-inspiratory complex may constitute auxiliary respiratory oscillators in a dynamic, synaptically and gap junction-coupled network. Marchenko and colleagues (2016) proved that generation of triphasic eupnoea uses fast inhibitory GABA_A and glycine receptor-modulated synaptic neurotransmission. Kölliker–Fuse and medial parabrachial neuronal efferents to Bötzinger complex glycineric decrementing post-inspiratory neurons modulate inspiratory and expiratory phase duration (Navarrete-Opazo et al., 2020; Zuperku et al., 2017). Smith, Rybak, Molkov and Shevtsova have constructed precise mathematical models ontogenically recapitulating the mechanistic interactions of neurophysiologically segregable populations of brainstem neurons generating the respiratory rhythm and pattern (Ausborn et al., 2019; Barnett et al., 2018; Molkov, Rubin, Rybak, & Smith, 2017). Dynamic emergent network synchrony incipiently generates and propagates the respiratory rhythm (Ashhad & Feldman, 2020; Ghali, 2019b). Brainstem propriobulbar microcircuit oscillators generate pentaphasic eupnoea (Ghali, 2019a; Marchenko et al., 2016; Molkov et al., 2017), sympathetic oscillations, cardiovagal premotoneuronal spiking and derivative reflexes (Barman, 2020).

New Findings

What is the topic of this review?

This review explores the modulatory role of lung vagal afferents and intra-neuraxial and carotid body chemoreceptors upon hypoglossal pre-inspiratory activity.

What advances does it highlight?

Pre-inspiratory activity manifesting in hypoglossal neural efferent discharge may be potentiated by mechanical interruption of vagal continuity and challenge with administration of a hypoxic and/or hypercapnic gas mixture and attenuated by static and/or dynamic pulmonary stretch. Differential excitability of, or premotoneuronal volleys exhibiting distinct spatiotemporal patterns of discharge arriving at, motoneurons residing within the hypoglossal motor nucleus may emergently generate phase-spanning pre-inspiratory inspiratory activity of hypoglossal neural efferent discharge manifest at the population level.

Contraction of the genioglossus and the composite activity of the stylo- and hyoglossus muscles act to protrude and retract the tongue (Fregosi and Fuller, 1997; Fuller et al., 1998), the coordinated activity of which expands the conduit constituting the oral cavity. Electromyogram recordings of protrudor and retractor muscles exhibit insiphaphasic (i.e. phreni-phasic) discharge in a coordinated manner (Ghali, 2015; Lee & Fuller, 2010a,b). Coordinated activity of these muscles augments the calibre of the upper airways during inspiration (Fuller, Mateika, & Fregosi, 1998). The interval interposed between successive onsets of hypoglossal and phrenic neural efferent bursting defines the pre-inspiratory epoch identifiable in hypoglossal recordings conducted in the in vivo preparation of the unanaesthetized decerebrate adult rat (Ghali, 2015; Ghali & Marchenko, 2016b) and EMG recordings of tongue muscles conducted in adult individuals (Mateika, Millrood, Kim, Rodriguez, & Samara, 1999). Precession of the onset of hypoglossal, vagal, glossopharyngeal, facial and trigeminal neural discharge with respect to phrenic inspiratory bursting depresses the tongue and expands the lumen of the upper airway to enhance the magnitude of dynamic airflow during immediately successive contractions of the diaphragm (Figure 1). The somatotopically organized hypoglossal (XII) motor nucleus contains motoneurons (MNs) innervating the extrinsic and intrinsic muscles of tongue excursion. Hypoglossal motoneurons receive locoregionally subspecialized axodendritic and/or axosomatic inputs from, among other sources, the medullary raphe, the medullary division of the lateral tegmental field, the nucleus subcoeruleus, the gigantocellular reticular formation and the Kölliker–Fuse and parabrachial nuclei.
Premotoneurons residing within the medullary lateral tegmental field conferring axodendritic and axosomatic inputs upon hypoglossal motoneurons within the medial branch of the hypoglossal nerve may be found situated ventrally and/or ventrolaterally with respect to those projecting to hypoglossal motoneurons that have axons within the lateral branch of the hypoglossal nerve. Motoneurons residing within the hypoglossal nucleus and conveying axons within the medial branch of the hypoglossal nerve distinctly receive axodendritic and axosomatic inputs from the ipsilateral group of parabrachial nuclei and retrotrapezoid nuclei. However, motoneurons residing within the lateral branch of the hypoglossal nerve receive axodendritic and axosomatic inputs from neurons residing within the ventral and medial divisions of the nucleus tractus solitarius (NTS), facial nuclei and spinal trigeminal nucleus (Dobbins & Feldman, 1995).

Hypoglossal pre-inspiratory and inspiratory phases constitute bursting epochs alternately or coordinately generated by fundamentally distinct sets of propriobulbar interneuronal micro-circuit oscillators or rapid time-scale state-dependent reconfiguration of neural microcircuit elements emergently constituting the respiratory rhythm generator and pattern former (Ghali, 2015; Ghali & Marchenko, 2016a). Separability (Lee et al., 2007a) and the deviation of the spectral constitution of hypoglossal pre-inspiratory and inspiratory epochs from identity (Leiter & St-John, 2004) suggest that distinct generators are likely to generate emergently differentially component of the emergently confluent phase-spanning discharge (Ghali & Marchenko, 2016a). Hypoglossal motoneurons possessing maximal, intermediate and minimal excitability exhibit confluent phase-spanning discharge during successive pre-inspiratory and inspiratory epochs, phase-restricted inspiratory activity, or isoelectric neural silence in the presence of preserved vagal continuity and saturation of blood perfusing the arterial tree with normocapnic non-hypoxic alveolar gas (Lee & Fuller, 2010a).

Several fundamental strategies may be exploited in order to confer spatiotemporally disparate activities upon cell bodies residing within the hypoglossal motor nucleus (Figure 2; Ghali, 2019b; Ghali & Marchenko, 2016a). Differential excitability of hypoglossal motoneuronal somatodendritic membranes may gate distribution of pre-inspiratory activity among a subset of the motoneuronal population otherwise coordinate receiving distinct or confluent composite pre-inspiratory and inspiratory premotoneuronal drive (Ghali, 2015; Ghali & Marchenko, 2016a). A set of assumptions predicated upon such a model would demand that relatively smaller motoneurons possessing higher membrane resistance be activated in precession to relatively larger motoneurons possessing lower membrane resistance (Marchenko et al., 2012; Ghali, 2018), respectively, constituting so-called phase-spanning pre-inspiratory/inspiratory and phase-restricted inspiratory neurons residing within the hypoglossal nucleus (Lee & Fuller, 2010a), although the tenet of differential motoneuronal excitability fails to explain phase-restricted pre-inspiratory activity manifesting among a subset ofurons residing within the Kölliker–Fuse nuclei (Dutschmann, Kron, Mörschel, & Gestreau, 2007), lateral zones of the parafacial respiratory group (Onimaru, Kumagawa, & Homma, 2006; Anderson et al., 2006; Anderson and Ramirez, 2017) and the preBötzC (Sun, Goodchild, Chalmers, & Pilowsky, 1998; see Table 1). Distinct subsets of the hypoglossal motoneuronal population (recorded by Lee & Fuller, 2010a) may coordinately or alternately receive axodendritic and/or axosomatic inputs dynamically conveying phase-restricted pre-inspiratory and/or phase-spanning pre-inspiratory/inspiratory drive (see Ghali & Marchenko, 2016a), although we do not exclude the possibility that common phase-spanning pre-inspiratory/inspiratory drive might be conveyed to all hypoglossal motoneurons, with selective inhibition of a subset of hypoglossal motoneurons by a subset of GABAergic interneurons that receive phase-restricted pre-inspiratory drive during the pre-inspiratory epoch, residing within Roller’s nucleus (van Brederode & Berger, 2011; van Brederode et al., 2011; Table 1).

Stated simply, pre-inspiratory synaptic drive may be conveyed to distinct subsets of hypoglossal motoneurons by phase-restricted pre-inspiratory or phase-spanning pre-inspiratory/inspiratory premotoneurons (Ghali & Marchenko, 2016a). GABAergic interneurons residing within the Bötzinger complex and/or Kölliker–Fuse nucleus may project to and tonically may presynaptically prevent the expression of pre-inspiratory activity in respiratory-related spinal motor outputs and state-dependently modulate the expression of pre-inspiratory activity in supraspinal respiratory-related motor outputs (see Sun et al., 1998). In this regard, propriobulbar interneuronal microcircuit oscillators independently forming rhythmic activity successively identified throughout the rhombomyelic axis (Janczewski & Feldman, 2006) may contribute to selective conveyance of pre-inspiratory or phase-spanning pre-inspiratory/inspiratory drive to hypoglossal motoneurons (Saito, Ezure, & Tanaka, 2002), lending credence to differential central genesis originating disparately segregated activities.
FIGURE 2 The potential mechanism underlying central control of pre-inspiratory (pre-I) and inspiratory (I) hypoglossal motoneuronal bursting. Upper panel shows that hypoglossal motoneurons receive the same input drives, and the different bursting type (pre-I/I versus I) reflects differential intrinsic properties (e.g., cell size, membrane resistance) of the output motoneurons. Middle panel shows that pre-inspiratory and inspiratory hypoglossal motoneurons receive differential synaptic inputs. Lower panel shows that pre-I/I XII motoneurons receive distinct pre-I and I synaptic drives contemporarily, whereas inspiratory hypoglossal motoneurons receive exclusively inspiratory synaptic input.

2 | DIFFERENTIAL MODULATION OF PRE-INSPIRATORY AND INSPIRATORY ACTIVITY WITHIN THE HYPOGLOSSAL NERVE BY VAGAL AXONS

Axons within the perineurium-invested vagal nerve convey the oscillatory magnitude of tension placed upon alveolar walls to neurons concentrated within the ventrolateral division of the NTS (Widdicombe, 2001), constituting a presumptive mechanism by which hypoglossal motoneurons become dynamically subjected to peripheral modulation (Lee et al., 2007a). In brief, augmentation or attenuation of the amplitude and/or duration of hypoglossal pre-inspiratory activity succeeds bilateral vagal transection (Ghali, 2015; Ghali & Marchenko, 2016a) or static or dynamic amplification of intrapulmonary pressure, respectively, although authors have described illuminative deviations from this general tendency. Authors consequently surmised, in good faith, that mechanical interruption of vagal continuity modulates the amplitude and/or duration of the pre-inspiratory component of hypoglossal neural efferent discharge by severing the influence of pulmonary stretch receptor (PSR) inputs (Fukuda & Honda, 1982; Ghali, 2015; Ghali & Marchenko, 2016a), with investigators yet to reach a consensus preferentially discriminating whether interruption of dynamic or static and slow- or fast-adapting PSRs is the chief mediator of the observed set of experimental effects (see Table 2).

Thus, in order to determine the mechanisms by which mechanical interruption of the vagus and static or dynamic pulmonary inflation or deflation modifies the amplitude and/or frequency of hypoglossal pre-inspiratory discharge, I preface my treatise with a thoughtful consideration of the stereotypic organization and function of PSRs (Widdicombe, 2001).

Pulmonary stretch receptors convey dynamic tension placed upon the alveolar walls (Chen, Marchenko, & Rogers, 2008, 2010, 2011, Cohen & Feldman, 1984; Donoghue, Garcia, Jordan, & Spyer, 1982) via axons travelling within the vagus nerve to neurons residing within the ventrolateral division of the NTS. The discharge of PSRs differentially recruited by inflation or deflation and exhibiting slow (i.e., slowly desensitizing PSRs) and fast (i.e., rapidly desensitizing PSRs) desensitization kinetics conveys oscillatory inputs to neurons residing within the ventrolateral division of the NTS (Bonham & McCrimmon, 1990; Kubin, Alheid, Zuperku, & McCrimmon, 2006; Widdicombe, 2001). Dynamic gradual tension placed upon the alveolar walls during mechanical inspiration (to be distinguished from neural inspiration manifest in phrenic neural discharge) enhances the frequency of slowly desensitizing PSR discharge (Marchenko and Sapru, 2000).

Successive inflations and deflations conducted near the onset and offset of mechanical inspiration elicit the discharge of selectively dedicated groups of rapidly desensitizing PSRs, described as being the most responsive to dynamic rates of pulmonary stretch (Bergren, 2020; Widdicombe, 2001). Intrinsic excitability segregates PSRs into high-threshold units discharging robustly during inspiration and low-threshold units discharging promiscuously during expiration. Dynamic expansion of the alveoli elicits discharge of slowly adapting PSRs,

- **FIGURE 2**
  - The potential mechanism underlying central control of pre-inspiratory (pre-I) and inspiratory (I) hypoglossal motoneuronal bursting. Upper panel shows that hypoglossal motoneurons receive the same input drives, and the different bursting type (pre-I/I versus I) reflects differential intrinsic properties (e.g., cell size, membrane resistance) of the output motoneurons. Middle panel shows that pre-inspiratory and inspiratory hypoglossal motoneurons receive differential synaptic inputs. Lower panel shows that pre-I/I XII motoneurons receive distinct pre-I and I synaptic drives contemporarily, whereas inspiratory hypoglossal motoneurons receive exclusively inspiratory synaptic input.
| Authors(s) | Year | Model | Experimental data and interpretations |
|-----------|------|-------|-------------------------------------|
| Fukuda and Honda | 1982 | Anaesthetized rats | XII pre-I activity is increased by vagal denervation in the anaesthetized state |
| Paton | 1996 | Working heart–brainstem preparation mice | Pre-I neurons depolarized maximally during the E2–inspiratory transition; Chloride-mediated inhibition → late inspiratory inhibition of Pre-I neurons |
| Lee et al. | 2003 | Anaesthetized, VVL, adult rats | Capsaicin, vagus intact; *Low dose → suppression of XII and PhN; reduction in XII pre-I duration; → not surmounted by hypercapnia; *Moderate dose → suppression of XII and PhN activity; reduction in XII pre-I duration; → after vagotomy, moderate capsaicin increased XII and PhN activity (non-X C afferents); *High doses → stimulation of PhN activity; tonic XII activity induced reduction in XII pre-I duration |
| Ezure et al. | 2003 | Decerebrate rats | Moderate PEEP; → induces XII bursts out of phase with PhN inspiratory activity; → induces pre-I activity in XII discharge (preceding PhN-coupled XII I bursting); Maintained lung inflation; → induces pre-I activity; → does not elicited decoupled bursts in the same animal model |
| Onimaru et al. | 2006 | Brainstem–spinal cord en bloc preparation, postnatal day 0–2 | Simultaneous recording of RTN/pFRG pre-I units and VIIN; → VII exhibited pre-I, I, and post-I discharge; Opioid agonist suppressed C4, but not VII neurogram; Transection between pre-Bötzinger complex and parafacial respiratory group (their figure 5B, some of Bötzinger complex spared); *C4 recovered after a brief interval; → inhibited in response to opioid agonist; *VII remained inhibited; → re-emerged in response to opioid agonist (quantal bursting, C4-decoupled) |
| Janczewski and Feldman | 2006 | Decerebrate, ketamine-anaesthetized, spontaneously breathing, juvenile rats; EMG (diaphragm, genioglossus, abdominal muscles) | Fentanyl; *Low dose → quantal breathing (occasional presence of E-AbdN activity without inspiratory efforts); *High-dose → quantal breathing (I-PhN occurs only if E-AbdN activity absent; many E-AbdN bursts without inspiratory efforts); PEEP; *Low (3–5 cmH₂O) → eliminated inspiratory efforts; → increased E-AbdN burst + duration; *High (9 cmH₂O) → eliminated inspiratory efforts; → induced tonic E discharge; Brief lung inflations; → no fentanyl on board → suppressed E-AbdN activity for 40–140 s; → ‘fentanylized’; *inflation started mid-E-AbdN burst → decreased duration of E-AbdN burst; *inflation started at onset of E-AbdN burst → increased frequency of E-AbdN burst; *inflation started between E-AbdN burst → no change or prolongation of inter-E interval; *deflation during E-AbdN → eliminated E-AbdN; induced inspiration; Lung deflation; → increased inspiratory frequency; → no effect or decreased expiratory frequency; Negative pressure → further increase in inspiratory frequency; two inspiratory rhythms seen (one eupnoea locked to E-AbdN and one ectopic/decoupled from E-AbdN); Expiratory bursts abolished by transection caudal to pFRG (but rostral to Bötzinger complex); Dual rhythm generators for inspiration and expiration are uncoupled by fentanyl/inspiratory rhythm generator more potently inhibited by fentanyl; differential control revealed |
| Dutschmann et al. | 2007 | In situ juvenile rat | Orexin B microinjections in Kölliker–Fuse nucleus; *increased XII pre-I activity; *increased respiratory frequency |
### TABLE 1 (Continued)

| Authors(s) | Year | Model | Experimental data and interpretations |
|------------|------|-------|---------------------------------------|
| Lee et al. | 2007a | Urethane-anaesthetized rats, VVL | Mild PEEP<br>→ induces XII pre-I activity<br>→ induces pre-I activity in respiratory-related nerves controlling upper airway<br>*believed to be generated by pre-I/I MNs<br>Increasing PEEP<br>*0–3 cmH₂O<br>→ all ENG frequencies locked (PhN to upper airway neurograms)<br>*from 6 to 9 cmH₂O (constant XII/VII frequency; decreased PhN frequency)<br>*from 9 to 12 cmH₂O (decrease in all ENG frequencies except VII)<br>*when decoupled → turning off ventilator recoupled all ENGs<br>PEEP and pre-I/I MN firing rate during pre-I exhibit direct proportionality<br>PEEP and inspiratory-related motoneuronal firing rate are not related<br>*evidence of differential peripheral modulation (by vagal afferents)<br>*supports differential central genesis of pre-I and I activities (different pre-MN supply generating the pre-I and I activities)<br>Notch between pre-I and I right before level of PEEP that induces decoupling; might indicate separation of pre-I and I (see also notch in Ghali & Marchenko, 2016) |
| Lee et al. | 2007b | Urethane-anaesthetized rats, VVL, pre- and post-vagotomy data | Intrajugular vein capsaicin<br>*PhN<br>– Low dose: transient suppression followed by recovery<br>– Medium dose: transient suppression followed by recovery<br>– High dose: initial suppression followed by transient augmentation<br>*XII<br>– Low dose: persistent suppression followed by recovery<br>– Medium dose: persistent suppression followed by recovery<br>– High dose: persistent suppression followed by recovery<br>*Tonic activity<br>– increased PhN tonic activity (one-third of cases; at medium/high doses)<br>– increased XII tonic activity (all cases, all doses)<br>*Rhythm<br>– prolonged TE<br>– suppressed TE<br>– delayed XII onset (from pre-PhN I to post-PhN I)<br>*Pre-I/I MNs<br>– reduced discharge rate<br>– delayed onset<br>*I MNs<br>– PhN I MNs – suppressed discharge rate in 38%<br>– XII I MNs – complete inhibition in 40%; delayed onset with respect to PhN I<br>*Silent MNs<br>– some activated by capsaicin at 3 (XII-lateral) versus 12% (XII-medial); tonic<br>Vagotomy<br>*induced earlier XII bursting with respect to PhN onset<br>*increased PhN and XII activity<br>*eliminated XII activity (completely) and PhN (augmentation in one breath) responses to capsaicin<br>*prevented capsaicin induced TE prolongation<br>*inhibited capsaicin-induced delay of XII onset (capsaicin-induced elimination of XII pre-I)<br>→ increased tonic medial XII activity<br>*Low dose → reduction of inspiratory activity<br>*High dose → potentiation of inspiratory activity |
| Lee et al. | 2008 | Anaesthetized, VVL, adult rats | PEEP → decoupled VII bursts<br>*stimulation of pre-I and EI neurons during E<br>*inhibition of EI neurons during I<br>Capsaicin → vagal C fibre activation → inhibits pre-I and EI neurons → prevents PEEP-induced decoupled VII bursting |
| Authors(s)       | Year  | Model                                      | Experimental data and interpretations                                                                                                                                                                                                 |
|-----------------|-------|--------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Lee and Fuller  | 2010a | Urethane-anaesthetized, VVL, vagotomized, adult rats | Hypoxia
* increases XII pre-I more than XII I activity; both more than PhN I activity

* XII MNs
  * pre-I/I MNs → increasing firing frequency (more during E than I phase (negligible), increase not immediate)
  * I MNs → increased firing frequency; left-shifting of onset
  * silent MNs → awakening from quiescence, then firing into pre-I phase

STP present in inspiratory-exclusive outputs (XII I, PhN I); not in XII pre-I/I MNs
Differential effect of hypoxia on pre-I versus I — might indicate differential origin of activities |

| Lee and Fuller  | 2010b | Urethane-anaesthetized, vagotomized, VL, adult rats | Hypoxia → increased phrenic I and VII pre-I (present in five of nine animals pre-hypoxia), I, and tonic activity

Hypoxia termination
* I activity remained increased (plasticity)
* VII pre-I and tonic activity returned to baseline (pre-I duration was reduced from pre- to post-hypoxia, from 20 to 7 ms) |

| Lee et al.      | 2012  | Urethane-anaesthetized rats                 | End-expiratory occlusion → increased tongue movements

* onset before diaphragm EMG → thus reflects XII pre-I activity

Intrajugular vein capsaicin (stimulates vagal C fibres) delivery during tracheal occlusion
* delayed onset of tongue activity relative to diaphragm EMG onset
* reflects abolition of XII pre-I activity

Vagal C fibres
* mediate inhibitory control of XII pre-I and total XII motor output
* have negligible control over phrenic motor system |

| Ghali          | 2015  | In vivo, unanaesthetized, decerebrate, adult rat; VVL, ET CO₂ at 5–5.5% | Vagotomy increases XII pre-I activity and duration in the unanaesthetized state |

| Ghali and Marchenko | 2016 | In vivo, unanaesthetized decerebrate, adult rat; VVL, ET CO₂ at 5–5.5% | Vagotomy increases XII pre-I activity and duration

Hypercapnia increases XII pre-I activity and duration
* in the vagotomized state
* not in the vagus-intact state

Hypercapnia increases XII I more than PhN I activity
* in the vagus-intact state
* not in the vagotomized state

XII pre-I is under tonic inhibition from vagal afferents

XII pre-I is potentiated by ventilation with a hypercapnic gas mixture

The potential for hypercapnia to increase XII pre-I is under vagal inhibitory control |

**TABLE 2** Types of pulmonary stretch receptors

| Afferent classification                                      | |
|--------------------------------------------------------------|---|
| Low-threshold slowly desensitizing pulmonary stretch receptors| |
| High-threshold slowly desensitizing pulmonary stretch receptors| |
| Low-threshold rapidly desensitizing pulmonary stretch receptors| |
| High-threshold rapidly desensitizing pulmonary stretch receptors| |
| Tonically discharging unmyelinated C fibres                 | |

which dynamically increases in direct proportion to the magnitude of lung inflation during the inspiratory epoch (Bartoli et al., 1975; Davenport, Frazier, & Zechman, 1981; Paintal, 1973), coordinately augmenting expiratory-related and attenuating inspiratory-related propriobulbar interneuronal, premotoneuronal and motoneuronal discharge frequency (Breuer, 1868; Cohen & Feldman, 1984; Cross, Jones, & Guz, 1980; Hering, 1868). Mechanically ventilated animals possessing preserved vagal continuity exhibit an onset and offset of inspiratory-related neuronal activity in phrenic and hypoglossal neurograms during successive nadirs and peaks of the contemporaneously recorded tracheal pressure curve, respectively, supporting the contention that cyclical PSR loading and unloading underlies mechanical ventilatory entrainment of respiratory-related neuronal discharge in preparations preserving vagal continuity (Cohen, 1979) and coordinately informing, albeit perhaps misguided, a new set of hypotheses explaining vagal modulation of hypoglossal pre-inspiratory and inspiratory discharge (Ghali & Marchenko, 2016a).


Pre-inspiratory and inspiratory activity within hypoglossal neural efferent discharge are subject to differential modulation by non-selective or selective manipulation of vagal inputs by mechanical interruption (Ghali, 2015; Ghali & Marchenko, 2016a), typically achieved by transection of the vagus nerve immediately caudal to the origin of the superior laryngeal nerve using iridectomy scissors under microscopic magnification to spare fibres innervating the baroreceptors, dynamic or static lung inflation and deflation (Marchenko & Sapru, 2000), varying the magnitude of pressure delivered at the nadir of lung volume (Lee et al., 2007a), and I.V. administration of capsaicin and/or phenylbiguanidine to stimulate vagal C fibre afferents (Lee, Fuller, & Hwang, 2012; Lee, Fuller, Lu, Ku, & Hwang, 2008; Lee, Fuller, Lu, Lin, & Hwang, 2007b; Lee, Lu, Ku, Lin, & Hwang, 2003). The derivative complement of effects elicited by these experimental provocations indirectly provides information on the mechanisms underlying differential central genesis of temporally distinct components emergently generating confluent hypoglossal neural efferent discharge (Ghali & Marchenko, 2016a; Lee & Fuller, 2010a,b). Apparently paradoxical effects elicited by interrogating the influence of pulmonary stretch inputs upon hypoglossal pre-inspiratory neural discharge have revealed emergent enigmatic complexity and fortuitously and serendipitously motivated an attempt at interpretively resolving these differences to the end of inspiring fruitful hypotheses and mechanistic conjectures (Ghali, 2019b; Lee et al., 2007a). Differential influences of tonically active (Lee et al., 2003, 2007b, 2008, 2012) and mechanical alveolar tension-inducible slow- and fast-adapting PSRs (Lee et al., 2007a) upon hypoglossal motoneurons might explain the apparently paradoxical attenuation of hypoglossal pre-inspiratory activity by gradual dynamic lung inflation and phase advance of bursting in hypoglossal neural discharge immediately preceding the onset of inspiratory-related activity in the phrenic neurogram (Ghali & Marchenko, 2016b).

Although significant headway has been made into illumining the effects of, and mechanisms underlying, vagal modulation of inspiratory-related activity within hypoglossal neural discharge (Ghali & Marchenko, 2016a), the mechanisms by which tonic and phasic resting and provoked vagal influences modulate the biophysical properties of premotoneurons conveying pre-inspiratory axodendritic and axosomatic inputs to hypoglossal motoneurons remain to be elucidated more precisely (for discussion, see Lee & Fuller, 2010a). In the presence of preserved vagal continuity and normoxic or hyperoxic eucapnia, the hypoglossal neurogram fails to manifest pre-inspiratory activity in anaesthetized rats (Fukuda & Honda, 1982), but it reveals diminutive pre-inspiratory activity in supracollicular decerebrated rats that have undergone successful weaning from the influences of potent inhalational anaesthesia (Fukuda & Honda, 1982; Ghali, 2015; Ghali & Marchenko, 2016a; Lee & Fuller, 2010a,b). Vagotomy removes the full set of dynamic or static tonic or phasic influences travelling within the vagus nerve upon hypoglossal and extra-hypoglossal pre-inspiratory neural discharge and amplifies the amplitude and/or duration of hypoglossal pre-inspiratory activity (Fukuda & Honda, 1982; Ghali, 2015; Ghali & Marchenko, 2016a; Lee, Fuller, Lu, Lin, & Hwang, 2007b), although this might constitute a logical non sequitur naturally leading to my possibly imprecise, hasty and haphazard presumption 5 years before writing of the present review that interruption of slowly adapting PSRs constitutes the main mechanism for augmenting pre-inspiratory activity in hypoglossal neural discharge.

Mechanical transection of the vagal nerves bilaterally in the cervical region elicits greater augmentation of amplitude and/or duration of the pre-inspiratory, compared with the inspiratory, component of hypoglossal neural efferent activity (Ghali & Marchenko, 2016a), suggesting that fibres coursing within the vagi tonically restrict pre-inspiratory, to a greater extent than inspiratory, axodendritic and axosomatic inputs conveyed to the hypoglossal motoneurons (see Lee et al., 2003, 2007b, 2008, 2012). A greater magnitude of tonic inhibitory modulation of hypoglossal compared with phrenic neural efferent activity in the presence of vagal continuity might also explain the larger responses elicited by hypercapnia by the former compared with the latter (Ghali & Marchenko, 2016a). Removal of tonic inhibitory modulation of hypoglossal motoneurons imposed by tonically discharging C fibres after vagal transection putatively liberates the population discharge to approach the near-maximal permissible magnitude in the presence and absence of hypercapnic challenge (Ghali & Marchenko, 2016a). Differential augmentation of the amplitude and duration of hypoglossal compared with phrenic neural efferent discharge after vagal transection by administration of a hypoxic gas mixture (Lee et al., 2007a) contrasts with non-differential augmentation of these disparate activities by hypercapnia in unanaesthetized decerebrate models undergoing mechanical interruption of vagal continuity (Ghali & Marchenko, 2016a). Vagal C fibres with preserved continuity are likely to continue to attenuate pre-inspiratory activity robustly in conditions of high respiratory drive (Lee et al., 2003). Intratracheal administration of a hypercapnic gas mixture fails to augment pre-inspiratory activity in hypoglossal neural efferent discharge in the presence of vagal continuity in unanaesthetized decerebrated rats (Ghali & Marchenko, 2016a) and insufficiently overcomes inhibitory modulation of pre-inspiratory activity in hypoglossal neural efferent discharge promoted by I.V. administration of capsaicin (see Lee et al., 2003). Abrogation of stimulation of pre-inspiratory activity in hypoglossal neural efferent discharge corroborates the presumptive conjecture that unmyelinated C fibres within the vagus nerve exhibiting continuous tonic discharge might contribute to pre-synaptically gaitingly restricting the distribution of pre-inspiratory activity to hypoglossal motoneurons, attenuate distinct subsets of premotoneurons axodendritically and axosomatically conferring pre-inspiratory discharge upon hypoglossal motoneurons, or inhibit distinct subsets of hypoglossal motoneurons exhibiting pre-inspiratory inspiratory phase-spanning discharge in preparations preserving vagal continuity (Ghali & Marchenko, 2016a). Paradoxical enhancement of phrenic inspiratory activity by treatment with high doses of capsaicin constitutes a phenomenon the attempted explanation of which will enhance our understanding of mechanisms contributing to incipient
respiratory rhythmogenesis and pattern shaping (see Lee et al., 2003, 2007b).

Unmyelinated C fibres exhibiting a continuous discharge unrestricted to specific respiratory-related subepochs, present within the perineurium-invested vagus nerve, might constitute the mechanism by which pre-inspiratory discharge in hypoglossal neural efferent activity remains restricted in the presence of vagal continuity (Kardon, Peterson, & Bishop, 1975; Lee & Pisarri, 2001; Thorén, Mancia, & Shepherd, 1975). Noxious stimuli and i.v. administration of phentolamine or capsaicin coordinately enhance the discharge of these unmyelinated C fibres within the vagus nerve and differentially modulate the amplitude and/or duration of the pre-inspiratory and inspiratory components of hypoglossal neural efferent discharge and the inspiratory component of phrenic neural efferent discharge in anaesthetized, mechanically ventilated Sprague–Dawley rats with preserved vagal continuity (Lee et al., 2003, 2008). In the same preparation, intrajugular administration of capsaicin augments tonic (extra-phasic) and attenuates inspiratory-related firing evident in hypoglossal neural efferent discharge, irrespective of the dose. Conversely, intrajugular administration of capsaicin at 0.625 or 1.25 μg·kg⁻¹ attenuates the pre-inspiratory and inspiratory components of hypoglossal and phrenic neural efferent discharge and phase delays the onset of bursting activity in hypoglossal discharge beyond that of phrenic neural inspiration (see Lee et al., 2003, 2007b), although administration of capsaicin at 1.875 μg·kg⁻¹ paradoxically and selectively augments inspiratory-related activity in phrenic neural discharge. These effects of i.v. administration of capsaicin upon breathing are consistent with Bezold–Jarisch reflex-related apnoea, suggesting that late-recruited high-threshold medullary lateral tegmental field units modulate propriobulbar interneuronal microcircuit oscillators constituting the respiratory rhythm generator (Lee et al., 2003, 2007b, 2008, 2012). These differential effects upon heterologous motor outputs might be explained by intrajugular administration of capsaicin recruiting distinct sets of neural circuits alternately promoting or attenuating inspiratory-related discharge in hypoglossal neural efferent activity in parallel. Intrajugular administration of capsaicin delays the onset of tongue muscle contraction relative to that of diaphragm EMG discharge, but has diminutive effect updiaphragm activity (Lee, Fuller, & Hwang, 2012). Treatment with capsaicin reduces the frequency and delays the onset of firing of hypoglossal motoneurons exhibiting a discharge during the pre-inspiratory and inspiratory-related epochs. Preferential suppression of hypoglossal relative to phrenic motoneurons by treatment with capsaicin indicates that vagal C fibres differentially modulate supraspinal and spinal cord respiratory-related motoneuronal pools (Lee et al., 2007b). Vagotomy completely abolishes the responses to treatment with capsaicin, preventing the capsaicin-induced prolongation of the expiratory epoch and the capsaicin-induced delay of onset of bursting in the hypoglossal neurogram. Cross-modal modulation amongst static and dynamic pulmonary stretch may powerfully modulate propriobulbar interneuronal microcircuit oscillators, constituting the respiratory rhythm generator and pattern shaper.

In the heat of scientific passion, I presumed prematurely that the mechanical interruption of the influences of slowly adapting PSRs might be chiefly responsible for disinhibiting hypoglossal pre-inspiratory activity after vagotomy in a paper published in Respiratory Physiology & Neurobiology (Ghali, 2015), but further discussion with Professor Dr med. V. Marchenko led me to entertain the more reasonable hypothesis that transaction of tonically active vagal C fibres (unmyelinated axons conducting at 10–12 m·s⁻¹) effects augmentation of hypoglossal pre-inspiratory activity after vagal denervation, a hypothesis presented in a work investigating cross-modal modulation of vagal interruption upon effects of hypercapnia upon phrenic and hypoglossal neural efferent discharge published in the same journal 1 year later (Ghali & Marchenko, 2016a). However, concurrent discharge of slowly desensitizing PSRs that overlaps exclusively with inflation of the lungs (i.e. mechanical inspiration) excludes the hypothesis mechanical interruption of oscillatory inputs deriving there from disinhibits discharge during the pre-inspiratory epoch of hypoglossal bursting with a reasonable degree of certainty (see Ghali & Marchenko, 2016a; Widdicombe, 2001). In contrast and more reasonably, elimination of oscillatory inputs from low-threshold, slowly desensitizing PSRs exhibiting extra-phasic firing during late expiration might explain the augmentation of the amplitude and/or duration of the pre-inspiratory component of hypoglossal neural efferent discharge after mechanical interruption of the vagus nerve (see Ghali & Marchenko, 2016a; Widdicombe, 2001). Thus, late-expiratory discharge of low-threshold, slowly adapting PSRs and C fibres exhibiting continuous non-phasic discharge restrict pre-inspiratory activity from distributing to hypoglossal motoneuronal somatodendritic membranes, successively undergoing integration across space and time at axon hillocks and propagating along axons from pre-inspiratory neurons residing within the Kölliker–Fuse nucleus, parafacial respiratory group and preBötzC (Ghali & Marchenko, 2016a). Propriobulbar GABAergic interneurons sensitive to slowly desensitizing PSRs conveying axodendritic and axosomatic drive to chemosensitive units residing within the retrotrapezoid nucleus and receiving PSRs and/or vagal C fibres exhibiting non-phasic continuous discharge independent of cyclical changes in pulmonary stretch (Takakura et al., 2007) might tonically restrict hypoglossal pre-inspiratory discharge by hyperpolarizing central chemoreceptors conveying tonic excitatory drive to hypoglossal motoneurons (personal communication, Proffesour Dr med. V. Marchenko). In a similar vein, elimination of late-expiratory extra-phasic neural discharge of rapidly adapting PSRs by vagal transection might remove excitatory axodendritic and axosomatic drive conveyed to GABAergic interneurons residing within Roller’s nucleus (see van Brederode & Berger, 2011) and might tonically restrict the distribution of pre-inspiratory activity by promotoneuronal pre-inspiratory and/or pre-inspiratory/inspiratory propriobulbar interneuronal microcircuit oscillators to hypoglossal motoneurons requisite to generate discharge preceding the inspiratory epoch (Ghali & Marchenko, 2016a). Consequently, vagal denervation disinhibits and ‘dis-disfacilitates’ the manifestation of pre-inspiratory activity in hypoglossal neural efferent discharge and hypercapnia-induced...
4 MODULATION OF PRE-INSPIRATORY ACTIVITY WITHIN HYPOGLOSSAL NEURAL EFFERENT DISCHARGE BY AUGMENTING MECHANICAL ALVEOLAR TENSION NEAR THE END OF THE EXPIRATORY EPOCH

The effects of successive elevations activity in stepwise fashion of positive end-expiratory pressure (PEEP) upon hypoglossal pre-inspiratory discharge in urethane-anesthetized rats provide clues about the microcircuit organization of the NTS, hypoglossal motor nucleus and the respiratory rhythm generator and pattern shaper (Lee & Fuller, 2010a). Initially, I will describe the most extreme of outlier experimental perturbations. Dynamically raising end-expiratory pressure to a static level of 15 cmH2O, which is likely to correlate in a non-linear manner with the force density (i.e. pressure) exerted upon the epithelium-lined interstitium demarcating successive alveolar units (i.e. alveolar walls), abolishes phasic inspiratory-related and extra-inspiratory discharge in hypoglossal, facial and phrenic efferent neural activity, presumably by successive enhancement of the frequency of neuronal spiking by slowly desensitizing PSRs and pump cells residing within the ventrolateral division of the NTS (Lee et al., 2007a). Likewise, administration of fentanyl annihilates vagal C fibres exhibiting non-phasic firing, tonically restricting hypoglossal pre-inspiratory-related activity and hypoglossal bursting in decerebrate, spontaneously breathing juvenile rats under the influence of ketamine (Janczewski & Feldman, 2006). Although progressive stepwise elevation of the pressure delivered during end-expiration through moderate levels attenuates the amplitude and duration of the pre-inspiratory component of hypoglossal neural discharge, completely abolishing extraneous pressure delivered at the end of mechanical expiration (0 cmH2O) yields diminutive hypoglossal pre-inspiratory discharge (Lee et al., 2007a). Delivery of 3 cmH2O PEEP to maintain alveolar distension at the end of the mechanical expiratory epoch appears to strike a happy medium, optimally maximizing the amplitude and duration of the pre-inspiratory component of hypoglossal neural discharge, perhaps by incrementally attenuating the discharge of unmyelinated vagal C fibres exhibiting non-phasic firing, tonically restricting hypoglossal pre-inspiratory activity (Lee et al., 2007a). A PEEP of 3–5 or 6–9 cmH2O delivered to maintain alveolar distension towards the conclusion of lung deflation amplifies phasic expiratory-related and extra-expiratory erratic tonic spiking in abdominal neural (AbdN) discharge, respectively (Janczewski & Feldman, 2006). Suddenly raising PEEP from 6 to 9 cmH2O reduced the frequency of bursting in the phrenic neuralgram, but not the discharge in the hypoglossal or facial neuralgram (Lee et al., 2007a). Progressive elevations of PEEP successively reduced the frequency of inspiratory-related bursting in the phrenic and hypoglossal neuralgram, but not the facial neuralgram (Lee et al., 2007a), providing evidence for the caudorostral progression of inhibitory modulation of respiratory-related neural discharge by vagal afferents from the lung, which sparsely relay dynamic pulmonary stretch, then induced hypoglossal bursting decoupled from inspiratory-related bursting in phrenic nerve discharge in unanaesthetized decerebrate rats and conferring pre-I activity upon phrenic inspiratory-coupled hypoglossal bursting (Lee et al., 2007a; Figure 3) and decoupled bursts in the facial neurogram (Lee, Fuller, Lu, Ku, & Hwang, 2008). Maintenance of lung inflation coordinately induces hypoglossal pre-inspiratory activity in unanaesthetized decerebrate rats, but fails to decouple bursts in heterologous neurograms, in contrast to PEEP (Ezure, Tanaka, & Saito, 2003). The data would seem to indicate that distinct sets of proprio-bulbar interneuronal microcircuit oscillators emergently generate hypoglossal pre-inspiratory-related activity and hypoglossal bursting decoupled from the inspiratory-related discharge in the phrenic motor output (Ezure et al., 2003).

Gradual elevation of the pressure delivered to the alveoli during the last part of the end-expiratory epoch has yielded findings that would lead the neurophysiologist having absorbed a commonplace working fund of knowledge to generate apparently paradoxical interpretations (Ezure et al., 2003; Lee et al., 2007a). Elevating the expiratory pressure delivered to the alveoli to 15 cmH2O abolishes the discharge in hypoglossal phase-spanning pre-inspiratory/inspiratory and facial pre-I motoneurons (Lee et al., 2007a). Hypoglossal motoneurons otherwise exhibiting firing that spans the pre-inspiratory and inspiratory phases exhibit diminutive or no discharge during the pre-inspiratory epoch in the absence of end-expiratory pressure in the alveoli exceeding nilility (Lee et al., 2007a). Moderately elevating the pressure delivered to the alveoli towards the end of mechanical expiration to 6 cmH2O derestricts phase-spanning hypoglossal

![FIGURE 3 Decoupled hypoglossal (XII) activity induced by increasing positive end-expiratory pressure in a mechanically ventilated, anaesthetized adult rat with preserved vagal continuity. Rhythmic bursting of phrenic and hypoglossal neural efferent discharge was synchronized during the baseline. Increased positive end-expiratory pressure reduced phrenic bursting frequency and induced several decoupled hypoglossal bursts (indicated by arrowheads). Abbreviation: TP, tracheal pressure.](image-url)
pre-inspiratory/inspiratory motoneurons to exhibit the naturally extant pre-inspiratory component and augments hypoglossal pre-inspiratory/inspiratory motoneuronal spiking frequency, presumably by disfacilitating a subtype of rapidly desensitizing receptors, the discharge of which proves subject to recruitment upon deflation (i.e. deflation-recruited rapidly desensitizing PSRs). Elevation of end-expiratory pressure from 9 to 12 cmH2O decoupled firing by previously phase-spanning hypoglossal pre-I/I motoneurons from phrenic nerve discharge, and 15 cmH2O abolished the spiking evident in putatively individual hypoglossal motoneuronal recordings (Lee et al., 2007a). Recordings made using isotonic fluid-filled micropipettes in continuity with monopolar electrodes, presumably with tips situated external with respect to somatoaxonal membranes of hypoglossal motoneurons, may incidentally pick up pre-inspiratory discharge exhibited by neighbouring units residing within Roller’s nucleus, exhibiting glutamatergic, GABAergic, glycineric or peptidergic neurochemical phenotypes (Lee et al., 2007a; see van Brederode & Berger, 2011a,b). Sudden elevation of the water column to deliver an end-expiratory alveolar pressure from 0 to 6 cmH2O in a stepwise fashion augmented the frequency of two distinct motoneurons exhibiting phase-restricted pre-inspiratory discharge residing within the facial motor nucleus (Lee et al., 2007a). Successive moderate incremental elevations of PEEP dichotomously induced bursting in phase-spanning pre-inspiratory-inspiratory-related neurons residing within the hypoglossal motor nucleus and pre-inspiratory-inspiratory-related motoneurons residing within the facial motor nucleus (Lee et al., 2007a).

Elevating end-expiratory pressure to a magnitude sufficient to abolish inspiratory-related neural discharge in phrenic nerve activity occasionally failed to abolish rhythmic bursting in neurons exhibiting pre-inspiratory neural discharge residing within the facial motor nucleus (Lee et al., 2007a). Curiously, inspiratory-related motoneurons conveying axons travelling within respiratory-related nerves innervating the muscles dilating the upper airway upon contraction never exhibited bursting decoupled from inspiratory-related discharge manifest in the phrenic neuronogram, indicating motoneurons exhibiting discharge spanning the pre-inspiratory and inspiratory epochs proper or precedent premotoneuronal inputs differentially express manifest constituent components of spatiotemporally-disparate firing in amalgam generating an apparently composite activity (Lee et al., 2007a). A direct variably linear relationship between the magnitude of positive-end expiratory pressure and pre-inspiratory-inspiratory motoneuronal firing rate during the pre-inspiratory, though not during the inspiratory epoch, betrays end-expiratory pulmonary pressure more powerfully and specifically modulate hypoglossal neuronal spiking occurring in precession, compared to that antecedent, the onset of phrenic neural inspiration (Lee et al., 2007a). In a similar vein, magnitude of expiratory pressure delivered to the alveoli apparently fails to correlate whatsoever with frequency of spiking by motoneurons residing within the hypoglossal nuclear exhibiting phase-restricted discharge during inspiration, betraying a commensurate sentiment (Lee et al., 2007a). The composite data indicate the discharge of slowly-desensitizing PSRs differentially modulate pre-inspiratory and inspiratory components of hypoglossal motoneuronal discharge (Lee et al., 2007a). Differential peripheral modulation, in turn, would seem to support a model whereby the individual constituent pre-inspiratory and inspiratory components of hypoglossal motor discharge may be generated by distinct, though putatively overlapping, propriobulbar interneuronal microcircuit oscillators (Lee et al., 2007a). Thus, gradual stepwise elevations of static end-expiratory pulmonary pressure facilitates pre-inspiratory-related discharge manifest in recordings of hypoglossal motoneuronal relative to unloaded alveoli and maximal levels abolish hypoglossal pre-inspiratory by extending to modify dynamic pulmonary stretch during the early component of successive inspiratory epochs (Lee et al., 2007a). The pre-inspiratory component of population hypoglossal neural efferent activity reflects discharge by motoneurons exhibiting firing spanning pre-inspiration and inspiration (Lee et al., 2007a). In this regard, authors have yet to reveal the existence of hypoglossal motoneurons exhibiting phase-restricted discharge during the terminal component of late-expiration (Lee & Fuller, 2010a). Though it may be reasonable to presume ‘motor neuron’ constitutes the identity of the majority of electrically-excitatory cells exhibiting respirophasic modulation residing within respiratory-related motor nuclei, antidromic activation or spiked-triggered averaging must be conducted in order to eliminate doubts regarding the true identity of homologously-recorded units.

5 | MECHANISMS UNDERLYING MODULATION OF HYPOGLOSSAL PRE-INSPIRATORY ACTIVITY AND INDUCTION OF BURSTING DECOUPLED FROM PHRENIC INSPIRATIONS BY STATIC AUGMENTATION OF END-EXPIRATORY ALVEOLAR PRESSURE

Mechanisms underlying initial successive augmentation, intermediate attenuation, and final abolition of amplitude and/or duration of the pre-inspiratory component of hypoglossal neural efferent activity or recruitment of pre-I/I phase-spanning motoneurons residing within the hypoglossal motor nucleus by stepwise static inflation of end-expiratory tension placed upon the alveoli (Lee et al., 2007a; see Ezure et al., 2003) may collectively conspire to successively augment the frequency of discharge of a distinct population of late-expiratory neurons conveying glutamatergic excitatory axodendritic and axosomatic drive upon hypoglossal pre-inspiratory-inspiratory motoneurons and putatively differentially cross-modally potentiating the discharge of vagal C fibres exhibiting continuous discharge spanning the pre-inspiratory and inspiratory epochs (see Lee et al., 2003, 2007b, 2008, 2012). Conversely, augmenting hypoglossal pre-inspiratory activity and inducing bursting in hypoglossal neural discharge decoupled from successive onsets and offsets of the phrenic inspiratory epoch (Lee et al., 2007a) may involve differential activation and disfacilitation of distinct segregable classes of PSRs preferentially sensitive to static versus dynamic lung stretch and differentially exhibiting slow versus fast desensitization kinetics (see
Ghali & Marchenko, 2016a). The literature has altogether failed to consider the putative existence of subpopulations of higher-order neurons residing within the ventrolateral division of the NTS which could paradoxically and coordinately enhance frequency of discharge of propriobulbar inspiratory-related, and attenuate propriobulbar expiratory-related, microcircuit oscillators. In this regard, statically elevating end-expiratory pressure delivered to the alveoli would enhance hypoglossal pre-inspiratory discharge (see Lee et al., 2007a) by simply exciting a population of temporally-precedent expiratory-related neurons exhibiting discharge subphase-restricted to late pre-inspiration, contrasted with induction of hypoglossal bursting decoupled from phrenic inspiration (Lee et al., 2007a), which could reflect phase-advance of pre-inspiratory and inspiratory components of hypoglossal neural efferent activity (a hypothesis developed by Prof. Dr. med. K.Z. Lee and Prof Dr. med. D.D. Fuller; see Lee & Fuller, 2010a).

Potentiation of the discharge of pre-inspiratory subphase-restricted premotoneuronal drive conveyed to hypoglossal motoneurons by dynamic pulmonary stretch phase advances a subset of hypoglossal motoneuron population possessing intrinsically lower recruitment threshold (Lee & Fuller, 2010a). Alternatively, potent activation of slowly desensitizing PSRs elicits escape discharge by a subpopulation of neurons residing within the hypoglossal motor nucleus (Lee & Fuller, 2010a).

Hypoglossal bursting decoupled from the phrenic rhythm could putatively represent segregation of pre-inspiratory and inspiratory activities via yet to be determined mechanisms substantiated by the presence of a caudally apical notch in the time constant (usually 0.01–0.05 s) integrated activity demarcating the transition between successive pre-inspiratory and inspiratory epochs in the setting of a static pulmonary stretch of 9 cmH2O occurring immediately before successive decoupling of hypoglossal bursting into distinct components (see Lee et al., 2007a: figures 3B and 6Ab). Alternately, bursting in hypoglossal neural discharge decoupled from phrenic inspiration might simply represent attempts of propriobulbar interneuronal micro-oscillators to overcome vagally mediated entrainment of the ventilator; a phenomenon exhibiting a lower threshold in phrenic compared with hypoglossal motor networks (see Lee et al., 2007a). Analogously, should hetero-presynaptic GABAergic gating state-dependently prevent distribution of pre-inspiratory activity to hypoglossal and phrenic motoneuronal pools, interruption of the mechanism proves distinctly possible and impossible in the former and latter, respectively. Further studies are necessary in order to provide data supporting the conjecture that hypoglossal motoneurons might receive modulation by GABAergic units residing within the Kölliker–Fuse nucleus and other zones within the brainstem (Peever, Matelka, & Duffin, 2001). My intuition naturally leads me to suggest that differential synaptic inputs, prejudiced by differential somatodendritic membrane excitability (resulting from the spatiotemporally differential density of voltage-gated sodium channels), are responsible for generating categorical heterogeneity of the discharge properties of hypoglossal motoneurons. Studies interrogating the microanatomy, neurophysiology and neurochemistry of the relevant propriobulbar interneuronal microcircuit oscillators responsible for generating manifest discharge, modelled in the style of studies conducted by Lipski and colleagues (1994, 1996) and my research group, will elucidate these details more precisely. The neuroanatomical substrate and neurophysiological mechanisms underlying emergent generation of disparate activities constituting the hypoglossal neural discharge remain unknown, presented in section five.

At the precise onset of the inspiratory epoch, the discharge of rapidly desensitizing PSRs conveyed to neurons residing within the NTS via lightly myelinated Aδ axons within the vagus nerve serves to promote propriobulbar inspiratory-related neural activity and attenuate expiratory-related neural activity, whereas the discharge of slowly adapting PSRs conducts the precise inverse (Chen et al., 2008, 2010, 2011; Widdicombe, 2001). A yet to be determined interaction amongst the presynaptic terminals of these Aδ axons targeting postsynaptic somatodendritic membranes of neurons residing within the ventrolateral division of the NTS may exhibit complex patterns of pre-distal cross-modal gating and, in some manner, differentially prejudice differential attenuation versus facilitation of pre-inspiratory activity manifesting in hypoglossal neural discharge by successive differential augmentation of static and/or dynamic pulmonary stretch (Ghali & Marchenko, 2016a). Pronounced elevations of pseudo-static pulmonary stretch might segregate variable locoregional extents of the population of hypoglossal motoneurons neurophysiologically and thus functionally cut them off from the influence of core propriobulbar interneuronal microcircuit oscillators underlying emergent genesis of the respiratory rhythm and serendipitously promote inputs from the so-called pontine respiratory rhythm generator residing within the dorsolateral metencephalic tegmentum to entrain a rhythm in the hypoglossal neural efferent discharge decoupled from phrenic neural inspiration (Lee et al., 2007a). Electron microscopic evaluation of neurons residing within the ventrolateral division of the NTS to identify the organization and differential prevalence of Golgi type I and II synapses will permit us to develop a more intimate and nuanced appreciation of the functional heterogeneity and stereotypic modulation of respiratory rhythm generation and pattern formation by dynamic pulmonary stretch (Izzo, Sykes, & Spyer, 1992). Tonically discharging vagal C fibres putatively exerting an inhibitory influence upon pre-inspiratory activity might synergistically contribute cross-modally to this functional segregation of hypoglossal motoneurons from the influences of the preBötzC and subject them to unhindered monosynaptic and polysynaptic modulation by distinct sets of proprio-bulbar interneuronal pre-I oscillators residing within the lateral zones of the parafacial respiratory group (Lee et al., 2003). Concurrent excitation of late-expiratory discharge and attenuation of late-inspiratory discharge by dynamic pulmonary stretch might thus conspire to successively attenuate pre-inspiratory discharge in hypoglossal neural efferent activity and idiosyncratically and suddenly elicit phrenic-decoupled hypoglossal bursting (Ghali & Marchenko, 2016a). End-expiratory occlusion (lasting for 25 s) enhances the amplitude of tongue movements by disinhibiting hypoglossal motor networks from inspiratory inhibition by vagal afferents relaying lung stretch and activating peripheral/central chemoreceptors in urethane-anaesthetized, spontaneously breathing rats with preserved vagal...
GHALI (2008a,b) to generate a pattern of respiratory-related neural network stepwise successive augmentation of the pre-inspiratory component in hypoglossal and phrenic neural efferent activity, it fails to induce eliciting short-term potentiation in the inspiratory-related discharge configuration that state-dependently enhances the pre-inspiratory phase-spanning pre-inspiratory/inspiratory-related activity residing within the lateral zone of the parafacial respiratory group and/or duration of the pre-inspiratory component of hypoglossal neural efferent activity. Hypoxia might enhance the distribution of pre-inspiratory activity to hypoglossal motoneurons by indirectly encouraging chiefly glycinergic interneurons exhibiting discharge restricted to the post-inspiratory epoch to attenuate recruitment of augmenting late-expiratory units putatively mediating tonic inhibition of pre-inspiratory units (Fortuna, West, Stornetta, & Gueneyet, 2008) and/or by eliciting discharge by a subset of rubrobulbar units driving expiratory-related subphase specificity (Gluckman & Johnston, 1987; Haji, Remmers, Connelly, & Takeda, 1990). Biphasic expiratory activity in the abdominal nerve in the in situ artificially perfused preparation of the unanesthetized decerebrate juvenile rat elicited by hypoxia might be mediated by recruitment of biphasic pre-l bursting nidi residing within the lateral zone of the parafacial respiratory group (Abdala, Rybak, Smith, & Paton, 2009).

Administration of a hypercapnic gas mixture enhances hypoglossal pre-inspiratory amplitude and duration and preferentially augments the amplitude of pre-inspiratory activity in hypoglossal neural efferent activity compared with inspiratory-related activity in hypoglossal or phrenic neural efferent activities, in unanaesthetized decerebrate rats undergoing mechanical interruption of the vagi bilaterally (Ghali & Marchenko, 2016a). In contrast, hypercarbia elicits negligible augmentation of pre-inspiratory discharge in the hypoglossal neurogram in the presence of intact vagus nerves, indicating that propriobulbar neuronal clusters heterologously generating the pre-inspiratory and inspiratory components of hypoglossal neural efferent discharge exhibit differential sensitivity in response to chemostimulation, consistent with a model whereby segregated generation and control of distinct propriobulbar interneuronal microcircuit oscillators underlie the generation of disparate components of discharge manifest in hypoglossal neural efferent activity (Ghali & Marchenko, 2016a). Stimulation of chemosensitive neurons residing within the lateral zone of the parafacial respiratory group may activate a neighbouring subset of neurons exhibiting pre-inspiratory discharge residing within the lateral zone of the parafacial respiratory group and may mediate hypercapnia-induced augmentation of hypoglossal pre-inspiratory discharge (Guyenet, 2008). A subset of GABAergic propriobulbar interneurons receiving inputs from slowly adapting PSRs via axons within the vagus nerve termed pump cells residing within the ventrolateral division of the NTS convey axodendritic and axosomatic inputs to chemosensitive neurons residing within the lateral zone of the parafacial respiratory group that might restrict augmentation of the pre-inspiratory component of hypoglossal neural efferent activity by hypercapnia (Takakura et al., 2007). There are data to suggest that cells sensitive to dynamic pulmonary stretch exhibiting slow desensitization coordinate attenuate spiking frequency by augmentation of the carbon dioxide tension, constituting a substrate permitting bidirectional interaction of, and cross-modal modulation amongst, chemosensory and mechanopulmonary afferent activity (Matsumoto, Okamura, Suzuki, Sugai, & Shimizu, 1996).

Abolition of pre-inspiratory activity in the abdominal nerve by transection caudal to the retrotrapezoid nucleus and parafacial respiratory group indicates that this might constitute the origin of pre-inspiratory activity in AbdN discharge (Abdala et al., 2009). A dedicated subset
of neurons within the Kölliker–Fuse nucleus polysynaptically relaying inputs from chemosensitive neurons within the retrotrapezoid nucleus could putatively constitute, or directly stimulate, a subset of premotoneurons conveying axodendritic and axosomatic drive to pre-inspiratory/inspiratory-related motoneurons within the hypoglossal nucleus (for analogy, see Dutschmann et al., 2007). Hypoxia might alternatively enhance the amplitude and/or duration of pre-inspiratory activity manifest in hypoglossal neural efferent discharge chiefly by stimulation of glomus cells within the carotid bodies, but also by increasing the acidity of the interstitial milieu of the retrotrapezoid nucleus and lateral zone of the parafacial respiratory group and directly potentiating the discharge of bulbar hypoxia-sensitive neurons within the preBötzC and cerebellar fastigial nucleus (demonstrated in goats; Solomon, Edelman, & Neubauer, 2000). Potentiating hypoglossal pre-inspiratory activity by synergistic non-linear augmentation of the CO₂ tension (Ghali & Marchenko, 2016a) and reduction of the O₂ tension (Lee & Fuller, 2010a) may augment the mechanical gain of successive chest wall expansions recruited by augmented eupnoic, transitional and gasping bursts that occur during sleep in patients experiencing somnolent hypopnoeic or apnoeic episodes or mechanical compression of the cervical soft tissues dynamically occluding the lumina of the common carotid artery and internal jugular veins, thus restricting blood supply conveyed to the bulb and diverting venous egress from the intracranium towards the vertebral venous plexus, causing successive bulbar venous congestion and microcirculatory ischaemia of the propriobulbar interneuronal microcircuit oscillators constituting the respiratory rhythm and pattern generator. A subset of individuals undergoing execution by strangulation succumb to vagally mediated abolition of pre-inspiratory and inspiratory discharge in respiratory-related neural activity and/or vagally induced activation of the Bezold–Jarisch reflex (Karsowska, 1956). Oxygen deprivation by propriobulbar interneuronal microcircuit oscillators may functionally eliminate GABAergic and/or glycinergic inhibitory interneurons conveying inhibitory modulation upon neurons liberating dopamine, endorphins, encephalins and anandamide and induce anoxic depolarization of the last set of units directly, resulting in the euphoric pleasure that accompanies the masochistic autoerotic, non-masochistic autoerotic, sadistic alloerotic and non-sadistic alloerotic asphyxiation subjectively described by a cohort of daring individuals (Ha, Lee, & Kim, 2017).

7 | PROPRIOBULBAR INTERNEURONAL MICROCIRCUIT OSCILLATORS CONVEYING PREMOTONEURONAL PRE-INSPIRATORY DISCHARGE UPON HYPOGLOSSAL MOTONEURONS

Neurons exhibiting pre-inspiratory discharge that reside within the preBötzC (Morgado-Valle & Beltran-Parrazal, 2017), parafacial respiratory group (Onimaru & Homma, 2003; Onimaru et al., 2006) and Kölliker–Fuse nucleus (Dutschmann et al., 2007) constitute kernels incipiently generating the respiratory rhythm, conveying pre-inspiratory activity upon hypoglossal motoneurons via subphase-specific premotoneurons and gating pre-inspiratory activity from expression in inspiratory-related discharge in the phrenic motor output, respectively (Table 3; Ghali, 2019a). The discovery by Smith, Ellenberger, Ballanyi, Richter, and Feldman (1991) that transection immediately caudal to the preBötzC elicits a rapid and sudden reduction of respiratory bursting frequency in the in vitro preparation of neonatal rat brainstem nourished by superfusion with a nutrient-saturated solution constituted the impetus encouraging great celebration amongst respiratory neurobiologists. In a series of elegant yet surprisingly simple experiments, Smith et al. (1991) appeared to have demonstrated a zone necessary to maintain respiratory rhythm generation and pattern formation. Precedent discovery of zones corresponding to the preBötzC contains units exhibiting onset occurring immediately preceding the inspiratory epoch and those exhibiting onset spanning the pre-inspiratory and inspiratory epochs possessing intrinsic bursting properties retrospectively identifies that these cells might constitute the chief elements incipiently initiating, maintaining and generating respiratory-related rhythmicity. Neurons that exhibit pre-inspiratory discharge residing within the preBötzC might drive the respiratory rhythm by underlying the genesis of pre-inspiratory activity in motoneuronal outputs (see Ghali & Marchenko, 2016a), a mechanism remaining debatable. The presence of neurons exhibiting pre-inspiratory discharge residing within the region of the retrotrapezoid nucleus and parafacial respiratory group was identified by Onimaru et al. (1988), and they were subsequently localized to the lateral zone of the parafacial respiratory group (Anderson & Ramirez, 2017), causing a similar degree of excitement by the respective investigators, and perhaps a degree of tacit chagrin by authors taking premature solace in the putative identification of the kernel of inspiratory rhythm generation.

Putative selective stimulation of C fibres exhibiting continuous discharge unrestricted by respiratory subphase by bath application or i.v. administration of phenylbiguanide coordinately elicited depolarization of the membrane voltage of decrementing post-inspiratory neurons and attenuated discharge by inspiratory-related neurons, but failed to abolish the rhythmic firing exhibited by pre-inspiratory neurons within the preBötzC, revealed by individual intracellular unit recordings conducted in situ and in vivo in mice (Paton, 1997). Administration of capsaicin, presumably selectively enhancing the discharge of unmyelinated vagal C fibres, attenuates pre-inspiratory activity in hypoglossal neural efferent discharge (Lee

| TABLE 3 | Candidate propriobulbar interneuronal microcircuit oscillators conveying pre-inspiratory premotoneuronal drive to hypoglossal motoneurons |
|----------|-----------------------------------------------------------------------------------------------------------------------------------|
| Pre-Bötzinger complex | | |
| Retrotrapezoid nucleus | | |
| Parafacial respiratory group | | |
| Kölliker–Fuse nucleus | | |
et al., 2003, 2007b), but fails to modify appreciably the pre-inspiratory activity of preBötzC propriobulbar interneurons (Paton, 1997). Thus, pre-inspiratory activity generated by neurons within the preBötzC cannot be the source of pre-inspiratory activity manifesting within hypoglossal neural efferent discharge heterosynaptically modulated by the activation of vagal C fibres, indicating that the chief source of pre-I activity manifesting in hypoglossal neural efferent discharge must be distinct from the preBötzC. Pre-Bötzinger complex pre-I cells continue to fire rhythmically after the elimination of all synaptic drive. Superfusion of specimens retaining the preBötzC with a solution containing a low concentration of dissolved divalent calcium cations attenuates the discharge of inspiratory-related units, but fails to abolish the discharge of locally extant units exhibiting pre-inspiratory neuronal discharge. Pacemaker, intrinsic bursting and low-threshold properties exhibited by pre- inspiratory units residing within the preBötzC arms the neural respiratory network with the capacity to restore the oxygen supply to GABAergic and glycinergic inhibitory interneurons mediating eupnoea. We relegate generation of the respiratory rhythm to constitute the chief role of pre-inspiratory and phase-spanning pre-inspiratory/inspiratory units residing within the preBötzC, unlikely to constitute a premotoneuronal source of pre-inspiratory activity conferred upon hypoglossal motoneurons.

Researchers have since investigated neurons exhibiting preinspiratory discharge residing within the lateral zone of the parafacial respiratory group, which might contribute to respiratory rhythmogenesis, and attempted to characterize putative interactions between these units and preBötzC pre-inspiratory units. Researchers have successively revealed the coordinate existence of neurons exhibiting pre-inspiratory discharge residing within the facial nucleus (Onimaru et al., 2006) and the retrotrapezoid nucleus and parafacial respiratory group (Onimaru & Homma, 2003; Onimaru et al., 2006). Parenteral administration of fentanyl attenuates discharge in C4 rootlets but not facial nerve discharge and attenuates the inhibitory influence by neurons residing within the Bötzinger complex upon pre-inspiratory units residing within the lateral zone of the parafacial respiratory group, although the latter remained natively resistant (Janczewski & Feldman, 2006). The discharge of pre-inspiratory neurons residing within the parafacial respiratory group, but not within the preBötzC, remains uniquely recalcitrant to the influence of parenterally administered opioids, the former thus constituting a candidate chief source of premotoneuronal drive conveyed to the latter and neurons exhibiting expiratory discharge residing within the caudal ventral respiratory group and conveying bulbospinal premotoneuronal inputs to abdominal motoneurons (Janczewski, Onimaru, Homma, & Feldman, 2002). Re-emergence of quantal bursting in the facial nerve decoupled from the C4 nerve is consistent with a model whereby propriobulbar interneuronal microcircuit oscillators residing within the preBötzC and rostral tip of the rostral ventral respiratory group chiefly drive the discharge of motoneurons residing within the facial motor nucleus. Mechanical transection through rostral zones of the Bötzinger complex, retaining integrity of the retrotrapezoid nucleus and parafacial respiratory group, transiently abolishes the discharge in neurogram recordings of the facial nerve and ventral rootlets emanating from C4 segments of the cervical spinal cord, with interval recovery of the latter and persistent silence of the former (Onimaru et al., 2006: figure 5B). Midline sectioning through the medulla in brainstem–spinal cord preparations eliminates phasic discharge within C4 ventral rootlets and hypoglossal neural efferent activity and decouples pre-inspiratory activity generated by neurons residing within the medulla (Onimaru, Tsuzawa, Nakazono, & Janczewski, 2015). These data suggest that any influence by propriobulbar interneuronal microcircuit oscillators exhibiting pre-inspiratory discharge residing within the retrotrapezoid nucleus and lateral zone of the parafacial respiratory group upon facial motor output must be indirect, through the preBötzC.

Investigators generally concur that inspiratory-related premotoneurons residing within the Kölliker–Fuse nucleus contribute to emergently generating inspiratory activity within hypoglossal neural efferent discharge (Ezure & Tanaka, 2006; Ezure et al., 2003; Gestreau, Dutschmann, Obled, & Bianchi, 2005; Ghali & Marchenko, 2016a). Bilateral excitation or inhibition of the hypoglossal nerve activity, or ipsilateral excitation and contralateral inhibition of hypoglossal nerve activity, is observed in response to administration of glutamate microbolus via micropipette tips introduced within the architectonic confines of the Kölliker–Fuse nucleus in hopeful proximity to inspiratory-related premotoneurons and elicits augmentation of hypoglossal neural efferent activity bilaterally or paradoxically amplified of ipsilateral and attenuation of contralateral inspiratory-related activity in hypoglossal neural efferent discharge (Kuna & Remmers, 1999). Neurons exhibiting pre-inspiratory and phase-spanning pre-inspiratory/inspiratory discharge residing within the Kölliker–Fuse nucleus within the dorsolateral metencephalic tegmentum conveying axons entering the hypoglossal nucleus, and putatively making synaptic contacts with hypoglossal motoneurons or interposed premotoneuronal interneurons, exhibit respirophasic discharge concordant with that evident in population hypoglossal neural efferent activity and prove commensurately subject to static inflation of alveolar units (Ezure & Tanaka, 2006; Ezure et al., 2003). Orexin B receptor-modulated inputs to neurons residing within the Kölliker–Fuse nucleus deriving from neurons residing within the lateral hypothalamus bear unique functional significance in the maintenance of upper airway tone during sleep (Dutschmann et al., 2007). Pan, Cabral, Ashley, and Perez (2017) have implicated perturbations of orexin signalling and insufficient recruitment of hypoglossal pre-inspiratory activity by hypoxia and hypercapnia in patients developing obstructive sleep apnoea. Hypoxia paradoxically attenuates the discharge of orexin neurons residing within the lateral hypothalamus in rats (Dergacheva, Yamanaka, Schwartz, Polotsky, & Mendelowitz, 2016), an effect that might presumptively reduce hypothalamic orexinergic drive conveyed to pre-inspiratory neurons residing within the Kölliker–Fuse nucleus driving hypoglossal pre-I activity. Pressure exceeding the barometric atmospheric level applied to maintain patency of the alveoli during sleep via a custom-designed mask fitted to the perihral–perioral facial contour in patients experiencing nocturnal desaturations of arterial haemoglobin determined by oximetry prevents hypopnoeic events, effectively
maintaining normoxia and eucapnia and successively preventing hypoxia-mediated inhibition of lateral hypothalamic orexinergic neurons, effectively maintaining premotoneuronal drive conveyed to hypoglossal pre-inspiratory/inspiratory phase-spanning neurons by neurons residing within the Kölliker–Fuse nucleus (Dutschmann et al., 2007).

Evaluation of the literature and consideration of homeobox patterning of successive rhombomeric segments leads to the conjecture that the lateral zone of the parafacial respiratory group constitutes the chief source of pre-inspiratory activity conveyed to motoneurons and propriobulbar interneurons residing within the hypoglossal, vagal, glossopharyngeal, facial and trigeminal motor nuclei (Lee et al., 2003). Congruently, the preBötzC might constitute a source of pre-inspiratory activity putatively conveyed to motoneurons and propriobulbar interneurons residing within external and innermost intercostal and phrenic motor nuclei, presumably gated presynaptically by pathways relaying through the medullary division of the brainstem reticular formation, which slightly hyperpolarizes the membrane voltage in immediately before neural inspiration, constituting a mechanism that generates common sensitivity amongst somatodendritic membranes to successively incoming inspiratory-related volleys, permitting emergent generation of the extremely high coherence amongst high-frequency phrenic motoneurons (Ghali, 2018; see Marchenko et al., 2012: figure 4). Likewise, phrenic motoneurons may be chiefly driven by rhythmically discharging pre-phrenic interneurons residing within the C1 and C2 spinal segments of the upper cervical spinal preceding maturation of the neural respiratory network. The exclusive presence of pre-inspiratory activity in respiratory-related neural discharge emanating from the bulb (Lee & Fuller, 2010a,b; Lee et al., 2007a,b) and abdominal motoneurons (Abdala et al., 2009) provoked by hypercapnia constitutes a most interesting curiosity. The behaviour would seem to indicate that pre-inspiratory activity originating within the preBötzC (see Morgado-Valle & Beltran-Parrazal, 2017; lateral zone of Anderson & Ramirez, 2017), the parafacial respiratory group (see Onimaru et al., 2015) and/or Kölliker–Fuse nucleus (see Dutschmann et al., 2007) might distribute exclusively to respiratory-related motor outputs residing within the brainstem. Alternately, pre-inspiratory activity might distribute commonly to respiratory-related motor outputs above and below the level of the medullocervical confluence, with dedicated pathways presynaptically gating expression of pre-inspiratory activity in inspiratory-related spinal motor outputs tonically (see Song, Li, & Shao, 2000) and respiratory-related brainstem motor outputs state-dependently (see Lee et al., 2003). GABAergic propriobulbar interneurons exhibiting pre-inspiratory activity residing within the Kölliker–Fuse nucleus and/or Bötzinger complex might presynaptically gate pre-inspiratory volleys from reaching a subset of hypoglossal motoneurons or postsynaptically reduce hypoglossal motoneuronal excitability via shunting inhibition, with Peever et al. (2001) having presented data that would seem to indicate hypoglossal motoneurons fail to receive experimentally identifiable inhibition from Bötzinger complex expiratory-related interneurons conveying axodendritic and axosomatic inhibitory modulation of phrenic motoneurons. Pre-inspiratory activity distributing to bulbospinal projection neurons residing within the medullary division of the reticular formation might presynaptically gate its own expression in respiratory-related spinal motor outputs through monosynaptic projections emanating from the gigantocellular depressor area or polysynaptic projections successively relaying through nucleus paragigantocellularis and glycinergic interneurons surrounding the myelic canal (see Brownstone & Chopek, 2018). Analogously, GABAergic axodendritic and axosomatic inputs conveyed to phrenic motoneurons from projection neurons residing within the Kölliker–Fuse and Bötzinger complex might gate pre-inspiratory activity from synthetically distributing to hypoglossal motoneurons, a hypothesis developed in conversations between myself and V. Marchenko. Differential hypoglossal motoneuronal excitability, spatiotemporally phase-restricted synaptic inputs and highly presumptive GABAergic inhibitory gating of pre-inspiratory activity conspire to emergently generate spatiotemporal heterogeneity manifest in pools of units conveying premotoneuronal drive to hypoglossal motoneurons (Ghali & Marchenko, 2016a; Lee & Fuller, 2010a).

Dysfunction of motoneuronal sources of pre-inspiratory activity conveyed to the tongue and upper airway musculature in individuals suffering from various respiratory-related disorders inspire an evaluation of the putative relationship between hypoglossal pre-inspiratory activity, obstructive sleep apnoea and the objective experience of subjectively reported dyspnoea (Wasserman & Casaburi, 1988). Chen and colleagues (1991, 1992) propose that medullary propriobulbar interneuronal microcircuit oscillators, when subjected to enhanced excitatory drive conveyed to somatodendritic membranes of constituent neurons by chemosensory stimulation relays an efference replica of the phrenic motoneuronal population motor output to dedicated mesencephalic zones , which conveys this patterned rhythmic discharge to respiratory-related neurons residing within the thalamus (Ogundele, Lee, & Francis, 2017) and cerebral cortex (Antal, 1984), explaining the development of dyspnoea and setting the conceptual precedence for a model whereby differential phase delays among and mismatches within intra-neuraxial circuits conveying efferent commands from the pontomedullary respiratory rhythm and pattern generator to inspiratory- and expiratory-related brainstem and spinal motor outputs with ascending phrenicoreticular inputs informing the brainstem of the magnitude of spatiotemporally dynamic motor output underlies the objective experience of subjectively endorsed dyspnea. It is suggested that neurons exhibiting discharge before the onset of inspiration residing within the lateralmost zones of the parafacial respiratory group constitute the chief sources of pre-inspiratory activity manifesting in hypoglossal neural discharge; capsaicin coordinately abolishes pre-inspiratory activity manifest in the hypoglossal neurogram, but not that manifest by individual neurons residing within the preBötzC (see Lee et al., 2003). Biphasic units residing within the parafacial respiratory group exhibiting successive biphasic discharge during pre-inspiration and discharge spanning the late-inspiratory and early post-inspiratory...
subepochs separated by an interregnum pause in neuronal spiking during early inspiration (Janczewski & Feldman, 2006) might constitute a conditional expiratory oscillator and/or a source of pre-inspiratory drive conveyed to hypoglossal motoneurons, with post-inspiratory activity seldom, but occasionally evident in hypoglossal neural efferent discharge in animals subjected to marked hypercapnic or hypoxic stress (Connelly, Ellenberger, & Feldman, 1990; Fregosi & Fuller, 1997).

8 | THE EXPIRATORY OFF-SWITCH

The described behaviour illuminates a new theory whereby the successive discharge of augmenting pre-inspiratory and decrementing early-inspiratory units mediates expiratory off switching in a manner ontogenically recapitulating inspiratory off switching mediated by successive activity of plateau late-inspiratory and decrementing post-inspiratory neurons (Richter, Ballantyne, & Remmers, 1986). Akin to medullary late-inspiratory and post-inspiratory discharge mediating so-called inspiratory off switching (Dutschmann & Herbert, 2006), I maintain within the realm of plausible possibility successive discharge of augmenting pre-inspiratory (Lee & Fuller, 2010a) and decrementing early-inspiratory units (Morgado-Valle & Beltran-Parrazal, 2017) residing within the preBötzC might mediate so-called expiratory off switching; augmenting and decrementing activities may discharge in precession and immediate succession on borders demarcating successive respiratory-related subepochs. Thus, I suggest that hypoglossal pre-inspiratory activity might originate from the confluent influence of pre-inspiratory units, residing within the lateral parafacial respiratory group, negatively modulated by a subset of GABAergic pulmonary stretch-sensitive units residing within the ventrolateral division of the NTS conveying inhibitory inputs to neighbouring chemosensitive units residing within the retrotrapezoid nucleus (see Takakura et al., 2007) and putatively coordinately subjected to restriction by tonically discharging vagal C fibres (see Lee et al., 2003) and a distinct population of neurons exhibiting pre-inspiratory and/or pre-inspiratory/inspiratory phase-spanning discharge residing within the Kölliker–Fuse nucleus (see Dutschmann et al., 2007) and conveying homologous premotoneuronal drive to hypoglossal pre-inspiratory inspiratory phase-spanning motoneurons polysynaptically subjected to dynamic pulmonary stretch and restriction by capsaicin-sensitive tonic unmyelinated vagal C fibres (see Lee et al., 2003). Administration of microboli of the slow peptide neuromodulator orexin B into the Kölliker–Fuse nucleus selectively enhances pre-inspiratory activity to the exclusion of inspiratory activity by hypoglossal premotoneurons (Dutschmann et al., 2007). Hypoglossal pre-inspiratory activity originating from a subpopulation of pre-inspiratory neurons residing within the lateral zone of the retrotrapezoid nucleus and/or parafacial respiratory group might prove subject to modulation by dynamic pulmonary stretch (see Lee et al., 2007a) and heterologous negative cross-modal modulation of excitatory chemosensitive inputs (see Ghali & Marchenko, 2016a; Takakura et al., 2007) upon propriobulbar interneuronal microcircuit oscillators, constituting the respiratory rhythm generator.

Hypoglossal pre-inspiratory activity originating in a coordinated manner from a subpopulation of pre-inspiratory units residing within the Kölliker–Fuse nucleus (see Dutschmann et al., 2007) might also prove subject to negative modulation by dynamic pulmonary stretch and restriction by capsaicin-sensitive tonically discharging unmyelinated vagal C fibres (see Lee et al., 2003). Cross-correlogram analysis will distinguish effectively amongst excitatory and inhibitory interactions amongst presumably linked pre-inspiratory propriobulbar interneuronal pairs (see Morris et al., 2010). Subsequent Pontamine Sky Blue labelling of pre-inspiratory units recorded via micropipettes placed immediately external to neurolemmal membranes in proximity to the axon hillock or axonal fibres and immunolabelling with primary and secondary antibodies targeting vesicular glutamate transporter types I and II, glutamate decarboxylase, glycine transporter type II, choline acetyltransferase, tyrosine hydroxylase, phenylethanolamine N-methyltransferase and 5-hydroxytryptophan decarboxylase will neurochemically phenotype cells with neurophysiologically signed interactions. Several circuits originating in the hypothalamus (Horiuchi et al., 2009) and/or dorsal periaqueductal grey matter (Subramanian et al., 2008a,b) may reconfigure to generate pre-inspiratory activity state-dependently in hypoglossal neural efferent activity. Sequential activity of decrementing post-inspiratory and supposedly extant mid-expiratory neurons may constitute a so-called post-inspiratory off switch, complementary to the well-described inspiratory off switching mediated by Bötzinger glycinergic decrementing post-inspiratory neurons (see Smith et al., 2009, 2013). Neurons exhibiting tonic discharge residing within the Kölliker–Fuse nucleus might prevent augmenting late-expiratory discharge from phase restricting hypoglossal premotoneuronal pre-inspiratory, or hypoglossal pre-inspiratory microcircuit oscillators proper, by stimulating the discharge of Bötzinger complex glycinergic decrementing post-inspiratory neurons (see Smith et al., 2009, 2013). Thus, abolition of hypoglossal pre-inspiratory activity by mechanical transection separating the metencephalon from the myelencephalon (Abdala et al., 2009) might indicate that the principal source conveying premotoneuronal pre-inspiratory activity to neurons residing within the hypoglossal motor nucleus must reside within the metencephalon or that loss of excitatory drive conveyed to Bötzinger complex glycinergic decrementing post-inspiratory neurons by Kölliker–Fuse and medial parabrachial nuclei undercuts the capacity of propriobulbar interneuronal microcircuit oscillators to generate segmentation of the expiratory epoch into post-inspiratory and late-expiratory epochs and successive segmentation of the late-expiratory subepoch into early late-E (i.e. ‘pre-pre-I’) and late late-E (i.e. pre-I) sub-subepochs (Smith et al., 2009, 2013). Neurophysiological characterization of these so-called mid-expiratory neurons, constituting the tongue-in-cheek ‘Higgs boson’ of mechanisms underlying respiratory pattern formation, would validate a model of respiratory pattern shaping predicated upon successive segmentations of larger epochs into successively smaller sub-epochs.
Before delving into a declarative and novice discourse evaluating the general hypotheses offered to explain generation of the breathing rhythm and pattern, the reader should bear in mind that it is necessary to consider separately the mechanisms initiating and propagating synchronous and regularly rhythmic activity among neurons constituting the respiratory-related neural network (Ghali, 2019a). Rudimentary monophasic and biphasic respiratory rhythms may be generated without the influence of inhibitory neuronal interactions (Ghali, 2019a). In the faithful attempts of investigators to characterize phenotypically the subpopulations residing within the preBötzC and thus identify specific neuronal clusters that may nascently and incipiently drive the breathing rhythm, researchers have characterized pre-I and pre-I neurons alternately or coordinately expressing membrane ion channels conveying persistent sodium or calcium-activated non-selective cation currents (Morgado-Valle & Beltran Parrazal, 2017), the transcription factor Dbx1 and somatostatin, most recently investigated expertly in a wonderfully conducted study by Ashhad and Feldman (2020) in seeking to explain the mechanisms underlying the initiation and propagation of emergently rhythmic activity in the preBötzC. It is proposed that incentive initiation of respiratory-related rhythmicity commences with the initially chaotic spiking of intrinsic bursting preBötzC and parafacial respiratory group cells spontaneously depolarizing via current flowing through persistent sodium and/or calcium non-selective cationic membrane channels possessing the lowest discharge threshold (Ghali, 2019a). Neuronal spiking by one unit excitedly recruits a monosynaptically coupled set of cells to discharge, most appropriately termed ‘incipient kindling of respiratory rhythmogenesis’ (for presumptive corollary behaviour in phrenic motoneurons, see Marchenko et al., 2012: figure 6), propagating through local surrounding neuronal micro-clusters. Progressive recruitment of units exhibiting the lowest threshold generates dynamic emergent subnetwork and network synchrony, effectively aligning neuronal spiking of propriobulbar microcircuit oscillators (Ghali, 2019b), quantally, synchronously and pseudo-continuously propagating centrifugally in ellipsoid surfaces. Dynamic emergent network synchrony, initially mediated by fast excitatory neurochemical transmission, eventually recruits fast inhibitory synaptic neurotransmission (Bongianni, Mutolo, Cinelli, & Pantaleo, 2010; Ghali, 2019a), concurrently and independently in preBötzC (Smith et al., 1991) and parafacial respiratory group (Onimaru and Homma, 2003; Onimaru et al., 2006; 2012, 2015) pre-I and pre-I/I phase-spanning units. Progressive resurrection of units from a quiescent state to active spiking across respiratory-related oscillators generates dynamic emergent network synchrony exhibiting exponential or sigmoidally shaped integrative quantal pseudo-continuous kinetics within local propriobulbar interneuronal microcircuit oscillators (Ghali, 2019b). The behaviour thus far characterized might generate respiratory rhythmicity (Smith et al., 1991: figures 2, 5C,D1–D3, 6–9), but proves independently insufficient to generate a respiratory pattern (see Smith et al., 2009, 2013). Fast excitatory glutamatergic, slow excitatory peptidergic, fast inhibitory GABAergic and glycinergic and slow inhibitory GABAergic neurosynaptic interactions synchronize and organize the spiking of intrinsic bursting cells collectively constituting a network of diffusely distributed oscillators in the bulb, including the preBötzC, parafacial respiratory group and post-inspiratory complex (Ghali, 2019a,b). Inspiratory epoch termination and generation of post-inspiratory activity characterizing normal triphasic eupnoeic breathing, consisting of inspiratory, post-inspiratory and late-expiratory phases, crucially requires modulatory drive by Bötzinger complex glycinergic decrementing post-inspiratory units upon neurons collectively constituting respiratory pacemaker oscillators and the ventral respiratory group (Smith et al., 2009, 2013). These cells receive spatiotemporally dynamic tonic excitatory drive from Kölliker–Fuse and medial parabrachial nuclei in preparations preserving pontomedullary continuity (see Ghali, 2019a; Smith et al., 2009, 2013).

In brief, a respiratory pattern emerges from activity of pre-BötzC pre-I and pre-I/I microcircuit oscillators providing phasic excitatory neurosynaptic influences upon neural nets of rostral ventral respiratory group augmenting inspiratory units. Bötzinger complex glycinergic decrementing post-inspiratory-modulated propriobulbar interneurons and GABAergic augmenting expiratory propriobulbar interneurons constituting inhibitory microcircuits convey inhibitory synaptic influences upon preBötzC pre-I and post-inspiratory microcircuit oscillators, the former pair of which exhibit mutual and reciprocal inhibition, segmenting the expiratory epoch into post-inspiratory and late expiratory phases (Marchenko et al., 2016). Neuronal clusters of intrinsically bursting and excitatory units are mutually coupled within and across brainstem nuclei through inhibitory neurosynaptic interactions (Ghali, 2019a; Marchenko et al., 2016). I guide the reader into a more instinctive appreciation of interactions occurring amongst the neural nodes and variabilities generating emergent rhythmic and patterned activity in respiratory-related propriobulbar interneuronal microcircuit oscillators (Ghali, 2019b). I consider the incipient generation of the respiratory-related rhythm emerging from a few neurons erratically and chaotically discharging, each of which monosynaptically recruits a set of effereent neurons, a behaviour that quantally and pseudo-continuously generates dynamic emergent synchrony within, amongst and between microcircuit entities (Ghali, 2019b). Centrifugal propagation of these waves and subsequent interactions amongst microcircuit oscillators exhibiting differential respiratory-related phase preference emergently generates patterned neural activity (Bongianni et al., 2010). I present an introductory convention describing the propagation of centrifugal waves of recruitment of neurons residing in the preBötzC. Time-variant wave amplitude at any given coordinates with respect to an origin at (0,0,0) may be given...
by the relationship:

\[
\zeta_r(\psi, \phi, \tau) = [Y [\sin (2\pi \psi) + \sin (2\pi \phi)]] [\sin (2\pi \gamma \tau)]
\]

where \(\psi\) and \(\phi\) represent the position along the \(\psi\) and \(\phi\) axes, respectively, and \(\tau\) represents time. At any given time, \(\tau = \kappa\), the surface integral of the vector field subtended by \(\zeta_r(\psi, \phi)\) may be determined accordingly:

\[
\mathcal{S} \left[ \zeta_r(\psi, \phi) \right] = \int_{\Sigma} \zeta_r(\psi, \phi) \left( \frac{\partial \psi}{\partial \sigma} \times \frac{\partial \phi}{\partial \sigma} \right) d\sigma d\phi
\]

where \(\psi(\sigma, \phi)\) represents the parametrization of the surface into rectangles with dimensions \(d\sigma \times d\phi\), and \(\| \frac{\partial \psi}{\partial \sigma} \times \frac{\partial \phi}{\partial \sigma} \|\) represents the magnitude of the cross-product of \(\frac{\partial \psi}{\partial \sigma}\) with \(\frac{\partial \phi}{\partial \sigma}\). I determine the energy of waves propagating through the preBötzC by considering that energy varies according to the product of Planck’s value, \(\hbar\), and frequency, \(\nu\), such that energy varies with respect to frequency, \(\xi(\nu)\), \(\xi(\nu) = h\nu\), and the neurolemmal membrane experiences oscillations of constant frequency \(\gamma\) in the determinism:

\[
\xi(S) = \mathcal{S} \left[ \zeta_r(\psi, \phi) \right] \times h = h \times \int_{\Sigma} \zeta_r(\psi, \phi) \left( \frac{\partial \psi}{\partial \sigma} \times \frac{\partial \phi}{\partial \sigma} \right) d\sigma d\phi
\]

The total energy of tensorized local surface patches is expressed accordingly:

\[
\xi = \Pi \times h \cdot \xi_r \in \left\{ \begin{array}{l}
\psi = \psi_0 \pm q \\
\phi = \phi_0 \pm r \\
\zeta_r = \zeta_{\gamma_0} \pm s
\end{array} \right.
\]

where \(\psi\), \(\phi\) and \(\zeta_r\) represent the Euclidean coordinate overlap of tensor \(\Pi\), \(\psi_0 \pm q\), \(\phi_0 \pm q\) and \(\zeta_{\gamma_0} \pm s\) represent membrane boundaries. Given that energy varies according to quantum number, \(\eta\), such that \(\xi(\eta) = \frac{\hbar^2}{2m} \cdot \gamma\), it is possible to conceptualize the energy of waves propagating through tensorized preBötzC to be expressible accordingly:

\[
\xi(M) = \Pi \times h^2 \eta^2 \left( \omega = \omega_0 \pm q \right) \left( \rho = \rho_0 \pm r \right) \left( \zeta_r = \zeta_{\gamma_0} \pm s \right)
\]

where \(h\) is Planck’s value, \(\eta\) is the quantum number, \(m\) is the total mass of the membrane, and \(\Sigma\) represents the membrane surface integral across \(\omega_0 \pm q, \rho_0 \pm r, \zeta_{\gamma_0} \pm s\). Thus, the energy generated by the arteriolar oscillations propagating through the neurolemmal membrane generates discretized energy directly correlating with the quantum number, \(\eta\). Waves propagating through a neurolemmal membrane of finite particles may only generate energy varying in discretized units. It is presumed that similar perturbations are conferred upon the biophysical properties of the axonal compartment of the neuron in response to perturbations by the arteriolar oscillations (Kandel, Schwartz, & Jessell, 2000). I conform the tensorized surface expressing wave propagation through the preBötzC. It is now possible to model centrifugal propagation of waves of incipient neuronal spiking through the preBötzC using spherical, ellipsoid or variably shaped volumes conforming accordingly:

\[
\sum_{\mu = 1}^{M} \lambda_{\delta}(\sigma) \xi^2 = \lambda_{\alpha}(\sigma) \psi^2(\tau) + \lambda_{\delta}(\sigma) \phi^2(\tau) + \lambda_{\lambda}(\sigma) \zeta^2(\tau)
\]

where \(\lambda_{\delta}(\sigma)\xi^2\) represent the radial distance of incipiently generated waves propagating throughout the preBötzC from the point of origin, \(\lambda_{\alpha}(\sigma)\psi^2(\tau)\) represents an eigenfunction modification of the square of the time-variant function expressing the spatial coordinate \(\psi\), \(\lambda_{\delta}(\sigma)\phi^2(\tau)\) represents an eigenfunction modification of the square of the time-variant function expressing the spatial coordinate \(\phi\), and \(\lambda_{\lambda}(\sigma)\zeta^2(\tau)\) represents an eigenfunction modification of the square of the time-variant function expressing the spatial coordinate \(\zeta_r\). Oscillations are modelled as follows:

\[
\sum_{\mu = 1}^{M} \lambda_{\delta}(\sigma) \xi^2(\psi, \phi, \tau) = \lambda_{\alpha}(\sigma) \left\{ \lambda_{b_\delta}(\tau) \psi^2(\tau) \sin (2\pi \tau) \right\} + \lambda_{\delta}(\sigma) \left\{ \lambda_{b_\delta}(\tau) \phi^2(\tau) \sin (2\pi \tau) \right\} + \lambda_{\lambda}(\sigma) \left\{ \lambda_{b_\lambda}(\tau) \zeta^2(\tau) \right\}
\]

Alternatively:

\[
\sum_{\mu = 1}^{M} \lambda_{\delta}(\sigma) \xi^2(\psi, \phi, \tau) = \lambda_{\alpha}(\sigma) \left\{ \lambda_{b_\delta}(\tau) e^{(2\pi \psi^2 + \frac{1}{\tau^2})} + \psi^2(\tau) \right\} + \lambda_{\delta}(\sigma) \left\{ \lambda_{b_\delta}(\tau) e^{(2\pi \phi^2 + \frac{1}{\tau^2})} + \phi^2(\tau) \right\} + \lambda_{\lambda}(\sigma) \left\{ \lambda_{b_\lambda}(\tau) e^{(2\pi \zeta^2 + \frac{1}{\tau^2})} + \zeta^2(\tau) \right\}
\]

The squared value of each spatial coordinate in tridimensional Euclidean space oscillates about a central tendency equivalent to the squared value of the radial distance from the centre of the preBötzC, with a frequency \(\gamma\), and a half-amplitude of \(\psi^2(\tau), \phi^2(\tau), \zeta^2(\tau)\) scaled by the product of the eigenfunctions or eigenvalues \(\lambda_{\alpha}(\sigma), \lambda_{\delta}(\sigma)\) and \(\lambda_{\lambda}(\sigma)\) with \(\lambda_{b_\delta}\), \(\lambda_{b_\delta}\) and \(\lambda_{b_\lambda}\), respectively. This model contemporaneously explains progressive degradation of respiratory-related neural patterns into successively regular rhythmic, pseudo-regularly rhythmic and chaotically irregular spiking activity and emergent restitution of chaotic irregular spiking activity into retrosuccessively pseudo-regular, regularly rhythmic and patterned activity (Ashhad & Feldman, 2020; Ghali, 2019b). The formalism may be extended to describing pre-I oscillations generated by neurons residing within the parafacial respiratory group and the Kölliker-Fuse nucleus. It is believed any local micro-cluster of propriobulbar interneurons coupling premotoneurons or motoneurons in brainstem or propriospinal interneurons coupling motoneurons within the spinal cord might be capable of emergently generating rhythm-like activity, although the oscillators exhibit differential thresholds. The
lowest threshold microcircuit oscillators dynamically and emergently
drive and synchronize microcircuit oscillators with progressively
increasing thresholds, generating emergent rhythmic activity within
and across physiologically coupled neural networks (Ghali, 2019a).
Piecemeal and stepwise incorporation of inhibitory neuronal synaptic
interactions generates emergent patterned neural activity (Ghali,
2019b). Inspiratory decrementing bursting manifest in phrenic neural
efferent discharge in C1-transected unanaesthetized decerebrate
rats elicited by asphyxic elimination of oxygen supply provided to
propriospinal interneuronal microcircuit oscillators and respiratory-
related rhythmic activity manifest in phrenic nerve discharge elicited
disinhibiting C1-C2 pre-phrenic interneurons through topical
application of a cocktail of GABA-zine and strychnine onto C1–
C2 cervical spinal cord segments (Ghali & Marchenko, 2013) bear
striking resemblance to supraspinally generated ‘gasping-like’ rhythms
in vivo (Marchenko & Rogers, 2007) and in vitro (Smith et al., 1991).
It is suggested that decrementing patterns of inspiratory bursting
represent nascent attempts of naively organized respiratory oscillators
to generate fictive regularly rhythmic breathing-like activity (Ghali &
Marchenko, 2013; Marchenko & Rogers, 2007; Smith et al., 1991).

The controversies and debates extant and raging across the peer-
reviewed literature and Society for Neuroscience forums regarding
the mechanisms contributing to respiratory rhythmogenesis and
pattern formation chiefly derive from deficits in forming appropriate
definitions of the terms ‘rhythm’ versus ‘pattern’, a thoughtful
decomposition of these elementary concepts into elementary
sub-concepts, and inter-experimental differences arising from the
use of different preparation types and experimental conditions
(Feldman & Janczewski, 2006). Signatures specifically and emergently
characterizing a respiratory pattern include neural triphasic eupnoea
possessing post-inspiratory discharge (Ghali & Marchenko, 2016a)
and high-frequency oscillations in recordings of brainstem and
spinal neuronal and population neural efferent activity (Ghali &
Marchenko, 2013; Marchenko & Rogers, 2007; Marchenko et al.,
2012), an augmenting pattern of inspiratory-related discharge (Ghali
et al., 2014; Marchenko et al., 2012), and high coherence between
phrenic motoneuronal spiking and the high frequency band of phrenic
nerve discharge during early inspiration (Marchenko et al., 2012).
Progressive degradation of the respiratory pattern into a featureless
respiratory rhythm, and successive reciprocal restitution of bursting
activity into pseudo-regularly rhythmic and regularly rhythmic activity
corresponds to progressive diminution of these features: reduction of
peak frequency of high-frequency oscillations, reduction of individual-
population motoneuron coherence, dispersion of spectral bandwidth,
and sequential attenuation of inspiratory burst shape from augmenting
to bell shaped to decrementing (attenuation of inspiratory burst slope)
(Ghali & Marchenko, 2013; Marchenko & Rogers, 2006a,b). Features
characterizing a respiratory rhythm include regular or pseudo-regular
monophasic bursting activity without neuronal spiking during epochs
interposed between successive inspiratory bursts and exclusively
monophasic bursting with decrementing spatiotemporal dynamics
(i.e. patternless rhythmic activity) (Ghali & Marchenko, 2016a; Ghali &
Marchenko, 2013; Marchenko et al., 2012).

The full development and evolution of our understanding of
these mechanisms might benefit from spatiotemporally exceptionally
resolved optical imaging of respiratory-related propriobulbar and
propriospinal oscillators and neural network microcircuits conducted
in vivo in order to characterize the incipient initiation, propagation
and emergent network synchrony amongst disparate nodes of the
neural respiratory network (Ghali, 2019b; Ghali & Marchenko, 2016).
The studies might be conducted on individual nodes with ultra-high
resolution and combined in order to generate an emergent operant
understanding of the behaviour. I believe that a synthesis of concepts
emergently developed herein might collectively evolve a more intuitive
and supra-logical understanding of respiratory rhythm generation and
pattern formation conforming to the truth (Ashhad & Feldman, 2020;
Ghali & Marchenko, 2016a; Rybak et al., 2014; Smith et al., 1991, 2009,
2013).

10 | CONCLUSIONS

Pre-inspiratory activity manifests state-dependently in hypoglossal
nerve efferent discharge, promoted by vagal denervation, relative
pulmonary deflation from high mechanoreceptor loading, hyper-
capnia and/or hypoxia. Hypoglossal pre-inspiratory activity becomes
disinhibited by mechanical interruption of tonically discharging
C-type fibres coursing within the vagus nerve and attenuated by
augmentation of alveolar stretch towards the end of expiration.
The exclusive existence of hypoglossal motoneurons alternately
exhibiting inspiratory or phase-spanning pre-inspiratory/inspiratory
activity indicates that the pre-inspiratory component might become
manifest in hypoglossal neural efferent discharge through differential
motoneuronal excitability and/or differential excitatory and/or
inhibitory axodendritic and axosomatic inputs. Premotoneuronal pre-
inspiratory drive might be conveyed upon hypoglossal motoneurons by
volleys from pre-inspiratory and/or pre-inspiratory/inspiratory phase-
spanning units. Pre-inspiratory drive might alternately distribute
to all hypoglossal motoneurons commensurately with GABAergic
interneurons residing within the Bötzinger complex and/or Kölliker–
Fuse nucleus, selectively presynaptically gating action potential
preceding inspiratory onset from manifesting in individual ‘neuro-
nograms’. Distinct oscillators are likely to generate the pre-inspiratory
and inspiratory components of hypoglossal neural efferent activity.
Abrogation of pre-inspiratory activity generated by neurons residing
within the hypoglossal motor nucleus, but not that generated by the
preBötzC, by potentiating the discharge of vagal C fibres exhibiting
tonic discharge by I.V. administration of capsaicin by deductive
exclusion indicates that the lateral zone of the parafacial respiratory
group or Kölliker–Fuse nucleus constitutes the chief source of
hypoglossal pre-inspiratory activity.

In considering differential mechanisms giving rise to pre-inspiratory
activity mediating incipient genesis of the respiratory rhythm and
that manifesting in hypoglossal pre-inspiratory motor outputs,
we develop a successively increasingly intimate understanding of
mechanisms generating the respiratory rhythm and pattern. Severe
hypoxia compromises fast inhibitory synaptic transmission to an extent abolishing pre-inspiratory activity, expiratory segmentation, eupnoeic ramp and high-frequency oscillations in inspiratory-related motoneurons, causing emergent genesis of monophasic decrementing inspiratory bursting (Marchenko et al., 2012; Ghali et al., 2014). Restorative dynamic incorporation of GABAergic units into the neural respiratory network progressively increases successive epoch segmentations. Understanding peripheral modulation and central generation of pre-I activity contextualizes findings regarding the phrenic motor system subserving eupnoea (e.g. Marchenko et al., 2012) within the more general problem of generating successful inspiratory efforts through the coordination of upper airway resistance and transpulmonary pressure gradients. The mechanisms underlying the apparently paradoxical effects of different levels and types of vagal stretch loading on XII pre-I await further investigations. Exclusion of unmyelinated C fibres exhibiting continuous discharge or rapidly desensitizing stretch receptors exhibiting background firing during expiration after mechanical interruption of vagal continuity might underlie successive augmentation of the amplitude and/or duration of the pre-inspiratory component of XII pre-inspiratory activity. Mechanisms underlying the resurrection of hypoglossal pre-inspiratory activity from an amplitude of zero to visually appreciable after elevation of end-expiratory pressure from 0 to 3 cmH2O remain to be elucidated more precisely (Lee et al., 2007a).

Differential patterns of augmentation of the amplitude and/or duration of the inspiratory and inspiratory component of phrenic neural efferent discharge and pre-inspiratory and inspiratory components of hypoglossal neural efferent discharge by hypoxia (Lee & Fuller, 2010a,b) and hypercapnia (Ghani & Marchenko, 2016a) indirectly validate a model whereby distinct oscillators subject to differential control emergently generate heterologously disparate activities. Concurrent intracellular recordings of neurons residing within the hypoglossal motor nucleus and candidate premotoneuronal sources with the faithful conduct of collision tests, spike-triggered averaging and dynamic coherence analyses will prove requisite in order to develop a more precise understanding of the mechanisms underlying genesis of pre-inspiratory and inspiratory components of hypoglossal neural discharge. Several renditions of experiments requiring the placement of micropipettes in close proximity will enhance the natively rare probability of serendipitously co-recording synchronously coupled hypoglossal motoneurons and premotoneuronal interneuronal drivers (see Morris et al., 2010; Ott et al., 2011).

COMPETING INTERESTS

None declared.

RESEARCH INVOLVING HUMAN PARTICIPANTS

AND/OR ANIMALS

All procedures performed involving human subjects were in accordance with the institutional ethical standards committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Express written consent was obtained from all patients in this study, although I present no identifying personal data.

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