Mechanisms underlying the generation of autonomorespiratory coupling amongst the respiratory central pattern generator, sympathetic oscillators, and cardiovagal premotoneurons

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The respiratory rhythm and pattern and sympathetic and parasympathetic outflows are generated by distinct, though overlapping, propriobulbar arrays of neuronal microcircuit oscillators constituting networks utilizing mutual excitatory and inhibitory neuronal interactions, residing principally within the metencephalon and mesencephalon, and modulated by synaptic influences from the cerebrum, thalamus, hypothalamus, cerebellum, and mesencephalon and ascending influences deriving from peripheral stimuli relayed by cranial nerve afferent axons. Though the respiratory and cardiovascular regulatory effector mechanisms utilize distinct generators, there exists significant overlap and interconnectivity amongst and between these oscillators and pathways, evidenced reciprocally by breathing modulation of sympathetic oscillations and sympathetic modulation of neural breathing. These coupling mechanisms are well-demonstrated coordinately in sympathetic and respiratory-related central neuronal and efferent neuronal recordings and quantified by the findings of cross-correlation, spectra, and coherence analyses, combined with empirical interventions including lesioning and pharmacological agonist and antagonist microinjection studies, baroloading, barounloading, and hypoxic and/or hypercapnic peripheral and/or central chemoreceptor stimulation. Sympathetic and parasympathetic central neuronal and efferent neural discharge recordings evidence classic fast rhythms produced by propriobulbar neuronal networks located within the medullary division of the lateral tegmental field, coherent with cardiac sympathetic nerve discharge. These neural efferent nerve discharges coordinate evidence slow synchronous oscillations, constituted by Traube Hering (i.e., high frequency), Mayer wave (i.e., medium or low frequency), and vasogenic autorhythmicity (i.e., very low frequency) wave spectral bands. These oscillations contribute to coupling neural breathing, sympathetic oscillations, and parasympathetic cardiovagal premotoneuronal activity. The mechanisms underlying the origins of and coupling amongst, these waves remains to be unresolved.

Keywords
Mechanisms; genesis; sympatho respiratory; coupling; modulation; cardiovagal; rostral ventrolateral medulla; sympathetic; hypercapnia; hypoxia
1. Mechanisms underlying generation of the breathing rhythm and pattern, sympathetic oscillations, and cardiovascular premotoneuronal activity

We contextualize a discussion of autonomorespiratory (e.g., sympatho-hyporespiratory, parasympatho-hyporespiratory, sympatho-parasympathetic) coupling (Guyenet et al., 2019; Molkov et al., 2014; Zoccal, 2015) by evaluating the mechanisms generating the individual activities proper (Ghali, 2017a,b,c, 2019a,b,c, 2018) (Figs. 1-14).

Distinct, though overlapping, propriobulbar neuronal microcircuits oscillators disparately distributed throughout and specifically organized within, the brainstem and upper cervical spinal cord emerged: constituting brainstem and myelic subnetworks and networks (Goodchild and Moon, 2009; Guyenet et al., 2018; Molkov et al., 2017) generate neural breathing (Figs. 1-3) (Anderson et al., 2016; Anderson and Ramirez, 2017; Ghali and Marchenko, 2013, 2015, 2016a,b; Marchenko et al., 2016; Richter, 1982; Richter and Spyer, 1990; Richter et al., 1986) and basal and reflexive changes in sympatho-hyporespiratory and cardiovascual tone (Figs. 4 and 5). Multiple distinct (Anderson and Ramirez, 2017) discretely (Molkov et al., 2017) organized metencephalic and myelencephalic nodes constituted by propriobulbar and bulbospinal units exhibiting respiratory-related modulation (Marchenko et al., 2016) RTN (Guyenet et al., 2019); postinspiratory complex (Anderson et al., 2016) coupled by excitatory and inhibitory interneuronal interactions emergently generate triphasic eupnea (defined by Richter (1982); see Richter et al. (1986)) characterizing neural breathing (Ramirez and Baertsch, 2018) and sympatho-hyporespiratory and parasympathetic oscillations modulating arterial and venous tone (Dittmar, 1873; Ghali, 2017a, 2018; Gordon and McCann, 1988; Guyenet, 2006) and myocardial contraction force and frequency (Lindsey et al., 1998; Massari et al., 1998), effectively modulating dynamic arterial and venous pressure, resistance, and flow and sinoatrial rate, atrioventricular conduction, atrial and ventricular contractility, output, and function (Ghali, 2017a, 2018; Guyenet, 2006).

Two bilateral rostrocaudally organized columns of nuclei residing within the ventrolateral and dorsal medulla (Figs. 1-3) (Molkov et al., 2017; Ramirez and Baertsch, 2018; Smith et al., 2009), receiving excitatory and inhibitory tonic and phasic modulatory inputs from chemosensitive neurons residing in the retrotrapezoid nucleus (Figs. 1 and 5) (Guyenet et al., 2019) and propriobulbar modulatory synaptic drive from Kölliker-Fuse and medial parabrachial nuclei in the dorsolateral metencephalic tegmentum (Dutschmann and Herbert, 2006; Mörschel and Dutschmann, 2009) emergently generate breathing. Interactions of neurons within the preBötzinger (pre-BötzC) (Gourévitch and Mellen, 2014; Gray et al., 2010; Morgado Valle et al., 2010) and Bötzinger (BötCZ) (Bongianni et al., 2010; Marchenko et al., 2016) complexes generate a two-phase (i.e., inspiratory and expiratory) neural respiratory rhythm. BötzC decrementing post-inspiratory neurons (EZure and Manabe, 1988) receiving propriobulbar modulatory excitatory synaptic drive from Kölliker-Fuse and medial parabrachial nuclei in the dorsolateral metencephalic tegmentum (Dutschmann and Herbert, 2006; Mörschel and Dutschmann, 2009), reciprocally interacting with BötCZ augmenting late-expiratory neurons via inhibitory neurosynaptic interactions (Smith et al., 2009), segregate expiration into post-inspiratory and late-expiratory phases generating triphasic eupnea. The core rhythm distributes to premotoneurons residing within the rostral and caudal divisions of the ventral respiratory group (see Tian and Duf-
A discrete embryonically homogenous cluster of Phox2b transcription factor-expressing chemosensitive neurons extant near the pontomedullary confluence constitutes the retrotrapezoid nucleus. Hydrogen ion concentration dynamically parallels dynamic retrotrapezoid nucleus glutamatergic neuronal spiking frequency. Hydrogen ions generated by the reaction of arterial CO\(_2\) with H\(_2\)O generate the weak acid H\(_2\)CO\(_3\), which exists in equilibrium with its constituent dissociation products H\(^+\) cation and HCO\(_3^-\) cation. The HCO\(_3^-\) anion dissociates into H\(^+\) and CO\(_2\), with an equilibrium preferentially favoring the formation of HCO\(_3^-\). These equilibria and dynamics are governed by the Henderson-Hasselbach proportionality, pH = pK\(_a\) + log ([H\(^+\)] [A\(^-\)]/[HA]). Retrotrapezoid nucleus glutamatergic units convey prominent tonic excitatory drive and support to propriobulbar and bulbospinal microcircuit oscillators constituting the Bötzinger and pre-Bötzinger complexes, ventral respiratory column nuclei, dorsal respiratory group, and metencephalic elements constituting the brainstem neural respiratory network. Neurons exhibiting differential phase preference extant within the Bötzinger and pre-Bötzinger complexes dynamically interact to generate a core two-phase neural respiratory rhythm and modulate premotoneuronal spiking frequency in the rostral and caudal divisions of the ventral respiratory group. BötzC dec post-I and aug early-E units convey inhibitory modulation to preBötzC pre-I, pre-I/I, and dec early-I units and propriobulbar excitatory drive to cVRG inspiratory premotoneurons. PreBötzC pre-I, pre-I/I, and dec early-I units reciprocally inhibit BötzC dec post-I and aug-E cells. PreBötzC excitatory pre-I and pre-I/I units monosynaptically and paucisynaptically drive rVRG aug-I units. PreBötzC inhibitory dec early-I units putatively shape inspiratory ramp by inhibiting the rVRG aug-I premotoneuronal driver population during the early phase of the inspiratory epoch. Rostral ventral respiratory group premotoneurons drive the phasic activity of phrenic motoneurons through projections conveyed through ipsilateral (i.e., pathways which do not decussate or decussate twice across the midline at medullary then upper C\(_1\)-C\(_2\) cervical spinal cord or phrenic motoneuronal levels) and contralateral (pathways which decussate once at either brainstem, upper cervical spinal cord, or phrenic motor nucleus levels) ventromedial and lateral funiculi of the myellic substance relaying to phrenic motoneuronal neurites crossing the midline into the contralateral hemicord may receive descending axodendritic and axosomatic inputs from rostral ventral respiratory group axonal terminals conveyed through the ventromedial and lateral funiculi of the spinal cord. Phrenic motoneurons with dendrites decussating across the midline constitute a significant fraction of these units during early neonatal age, and evidence rapid age-dependent decreases. Medullophrenic units (chiefly from BötzC or Kölliker-Fuse nucleus bulbospinal cells) may convey phasic inhibitory modulation of PhMNs. Local pre-phrenic interneurons may coordinate phasic inhibition and convey tonic inhibitory modulation of PhMNs. Color traces beneath phrenic neurograms indicate the phase of activity (i.e., inspiratory, expiratory [post-I and E2], or tonically discharging units) of indicated excitatory (+) and inhibitory (-) synapses. RTN, retrotrapezoid nucleus; BötzC, Bötzinger complex; preBötzC, preBötzinger complex; rVRG, rostral ventral respiratory group; cVRG, caudal ventral respiratory group; C\(_1\)-C\(_2\) pre-PhINs, C\(_1\)-C\(_2\) pre-phrenic interneurons; PhNucl, phrenic nucleus; PhL, left phrenic nerve; PhR, right phrenic nerve. Modified with permission from Fig. 10 of Ghali and Marchenko (2016a).
vided initial evidence indicating a diffuse distribution of medullary units exhibiting sympathetic-correlated discharge (Preobrazhenskiî, 1966). A robust set of data validates genesis of sympathetic activity derives from synchronized activity among sympathoexcitatory and sympathoinhibitory propriobulbar interneuronal microcircuit oscillators residing within the medullary lateral segmental field (Fig. 4) (Barman, 2020; Dampney, 1994; Gebber and Barman, 1988; Ghali, 2018; Marchenko and Sapru, 2003), thence conveyed to diffusely distributed presympathetic neurons residing within the rostral ventrolateral and ventromedial medulla (Babic and Cirillo, 2004), caudal raphé, and ventrolateral metencephalic tegmentum projecting to and driving neuronal spiking of, intermedialateral cell column preganglionic sympathetic neurons (Barman, 2020; Ghali, 2017a, 2018; Gilbey et al., 1995; Zhou and Gilbey, 1992). Medullary lateral segmental field neurons oscillate with frequencies of 2 to 6 Hz and 10 Hz, correlated with analogous spectra in cardiac sympathetic nerve discharge precede and drive similar activities in rostral ventrolateral medullary units (Barman, 2020; Ghali, 2018).

Rostral ventromedial medullary presympathetic bulbospinal neurons specifically convey synaptic drive to intermedialateral column preganglionic sympathetic neurons projecting to postganglionic sympathetic neurons modulating cutaneous vasoconstrictor tone and thus contributing prominently to thermoregulation (see Guyenet (2006)) for outstanding review). Rostral ventrolateral medullary presympathetic neurons receive glutamatergic axodendritic, and axosomatic synaptic inputs drive biophysically transduced by N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and kainate-type glutamate receptors. α₂ autoreceptors localizing to the presynaptic axonal membranes of propriobulbar units exhibiting oscillations correlating with cardiac sympathetic nerve discharge negatively modulate the release of excitatory neurotransmitters from axonal terminals, mitigating the release of excitatory amino acid-mediated electrochemical amplification of somatodendritic conductance and contributing to hypotensive effects generated by administration of clonidine and α-methyldopa. Sympathetic-related propriobulbar units receive prominent tonic inhibitory GABAAergic and glycnergic modulation from specific nucleiarily-arranged neuronal clusters and disparately distributed units located in surrounding reticular zones (Gatti et al., 1987). Neurogenesis of sympathetic nerve activity and rhythmic discharge may alternately be generated by a network (Lipski et al., 1996a,b) and/or pacemaker (Sun and Guyenet, 1986; Sun et al., 1988) mechanisms, organized by the medullary lateral segmental field (Barman et al., 2005; Barman, 2020; Dampney, 1994; Ghali, 2017a; Marchenko and Sapru, 2003), rostral ventrolateral medulla (Guyenet, 2006), and distributed regions within the brainstem (Figs. 5) (Ghali, 2018; Goodchild and Moon, 2009), neuroanatomically overlapping and interacting with the neuronal propriobulbar circuitry generating and organizing neural breathing (Figs. 4 and 5) (see Anderson and Ramirez, 2017; Molkov et al., 2017, 2014).

Diffusely distributed nuclearily arranged neuronal clusters residing within functionally distinct subnuclei of the nucleus tractus solitarius (Fig. 5) (Michelini, 1994; Moreira et al., 2007; Takakura et al., 2007) play modulatory roles in, and constitute the chief nodes mediating and contributing to respiratory, sympathetic, and parasympathetic crossmodal modulation and coupling (Guyenet, 2006; Molkov et al., 2014). Nucleus tractus solitarius units monomodally filter and/or multimodally integrate a wide array of propriobulbar interneuronal inputs and axon terminals from peripheral afferent fibers, coordinately conveying monosynaptic and polysynaptic inputs to higher-order neurons (Fig. 5) (Von Euler et al., 1973), coordinately negatively modulating propriobulbar interneuronal sympathetic- and inspiratory-related microcircuit oscillators and positively modulating propriobulbar interneuronal cardiovascular- and expiratory-related microcircuit oscillators (Guyenet, 2006; Moreira et al., 2007; Rogers et al., 2000; Takakura et al., 2007). Dorsal respiratory group bulbospinal premotoneurons convey axodendritic and axosomatic synaptic drive to the brainstem and spinal cord respiratory-related motoneurons (Lipski et al., 1990). Nucleus ambiguus (i.e., N.A.) and dorsal motor nucleus of the vagus (DMV) convey cardiovascular preganglionic neurons en route to cardiac plexus ganglia postganglionic parasympathetic neurons powerfully modulating sinoatrial chronotropy, atrioventricular dromotropy, and atrial inotropy (Dyavanapalli et al., 2013; Eckberg, 2003; Taylor et al., 2009), though a few fibers coordinate supply ventricular myocardiurn (Coote, 2013). Postganglionic sympathetic and parasympathetic cardiovasulal neurons mediate sinoatrial action potential frequency by influencing the slope of spontaneous depolarization mediated by persistent sodium channel current in sinoatrial nodal cells, atrioventricular conductivity by regulating the slope of voltage-gated calcium current rise in atrioventricular nodal cells, and atrial and ventricular contractility by determining magnitude and rate of rising of cytosolic calcium flux deriving from the extracellular space and sarcoplasmic reticulum stores (Ghali, 2017a, 2018). The data collectively substantiates monomodal and multimodal sensory influences effectively converge upon, diverge through, and modulate the discharge of, brainstem sympathetic oscillators and cardiovasual premotoneurons (Ghali, 2017a, 2018; Visceromotor (Duda et al., 1970a,b; Kostiuk and Preobrazhenskiî, 1966; Preobrazhenskiî et al., 1972; Preobrazhenskiî and Tamarova, 1966), somatosympathetic (Ghali, 2019a), and somatorespiratory (Ghali, 2019a) reflexes exhibit sympathosomatic and respirosomatic coupling and extensive interconnectivity amongst propriobulbar interneuronal networks generating and mediating nociceptive responses, sympathetic discharge, and the breathing rhythm.

Prefacing a discussion of autonomorespirophasic modulation (Figs. 5-14), we briefly discuss the neural network and pacemaker mechanisms emergently generating the breathing rhythm and pattern (Molkov et al., 2017), sympathetic oscillations (Barman, 2020; Ghali, 2017a, 2018; Molkov et al., 2014), and cardiovasual premotoneuronal discharge (Bishop, 1974). We discuss respirophasic modulation of brainstem presynaptic neuronal oscillations (Guyenet et al., 1990; Haselson and Guyenet, 1989; Lipski et al., 1996a,b; McAllen, 1987; Miyawaki et al., 1996; Numao et al., 1987), sympathetic preganglionic and postganglionic discharge (Guyenet et al., 1990; Mandel and Schreinhofer, 2006; Zhou and Gilbey, 1992) and cardiovasual premotoneuronal spiking (Gilbey et al., 1984; Lindsey et al., 1998). We reciprocally discuss oscillatory baroreceptor modulation of the breathing pattern (Baekey et al., 2010; Bishop, 1974; Brunner et al., 1982; Dove and Katona, 1985; Lindsey et al., 1998) and respiratory gating of the baroreflex (Baekey et al., 2010).

2. Sympatho-respiratory coupling

Sympatho-respiratory coupling was initially described by Adrian and Bronk in 1932 in the anesthetized rabbit (Adrian et al., 1932),
Fig. 2. Brainstem oscillators generating breathing rhythms. Cells distributed along the ventrolateral column of pontomedullary nuclei generate the neural breathing rhythm and pattern. The retrotrapezoid nucleus/parafacial respiratory group (RTN/pFRG), lies ventral with respect to the facial nucleus (VII). The postinspiratory complex (PiCo) may be found caudal to the facial nucleus, rostral to the preBötzinger complex, and dorsomedial with respect to the rostral pole of the nucleus ambiguous (NA). The Bötzinger (BötC) and preBötzinger complexes (preBötC) may be found ventromedial to the nucleus ambiguous and rostral with respect to the rostral (rVRG) and caudal (cVRG) divisions of the ventral respiratory group. The lateral reticular nucleus (LRt) conceals the preBötC, rVRG, and cVRG from the ventral surface of the medulla. We presume lateral reticular nucleus neuronal somata constitute intermediate relay phrenicomedullary inputs from the phrenic nucleus to the bulbar ventral respiratory column. Analogously, the serpiginous dorsal margin of the inferior olive separates the ventral respiratory group from the ventral surface of the brainstem in humans. Compartmental borders containing the ventral respiratory column nuclei are not markedly distinct. Electrophysiological properties and differential spatiotemporal firing dynamics have characteristically distinguished these regions, though investigators continue to strive to identify specific cell surface proteins and transcription factors distinguishing these zones. PreBötzinger complex neurons frequently express SST1 and/or the transcription factor Dbx1. Modified with permission from (Fig. 1) of Anderson et al. (2016)

demonstrating prominent differential modulation of the sympathetic neural efferent discharge varying according to the respiratory cycle, though perhaps previously intimated by studies conducted in the 1800s. Notably, cervical sympathetic burst amplitude increased markedly and dynamically toward the end of the inspiratory epoch (Adrian et al., 1932). Studies have continued to provide evidence indicating respirophasic modulation of sympathetic neural efferent activity, with variable accentuations and troughs of sympathetic bursting corresponding with precise intervals within the inspiratory and expiratory epochs (Molvik et al., 2014; Moraes et al., 2012a,b,c; Zoccal, 2015; Zoccal and Machado, 2011). Reciprocally, respiratory-related neuronal and neural outputs exhibit baromodulation and strong correlation with dynamic arterial pressure magnitude (Darnall and Guynet, 1990; Gilbey et al., 1986; Lipski et al., 1996a,b; McAllen, 1987; Zhou and Gilbey, 1992). Sympathorespiratory coupling occurs during eucapnic normoxia (Adrian et al., 1932), though it becomes strengthened by hypoxia and hypercapnia (Moraes et al., 2012a,b,c; Zoccal, 2015; Zoccal and Machado, 2011).

Crossmodal modulation of neural breathing, sympathetic oscillations, and cardiovagal premotoneuronal spiking couples the activities (Gilbey et al., 1995; McAllen, 1987; Molvik et al., 2014; Zoccal, 2015; Zoccal and Machado, 2011). Propriospinal microcircuit oscillators constituting emergently dynamic networks generate the respiratory rhythm and pattern (Figs. 1-3) (Ghali and Ghali, 2020), sympathetic oscillations (Figs. 4 and 5) (Barman, 2020), and cardiogaval premotoneuronal activity (Figs. 4 and 5) (Frank et al., 2009). The breathing cycle modulates rostral ventrolateral medullary sympathetic propriobulbar and presympathetic units (Gilbey et al., 1995; Lipski et al., 1996a,b; Mandel and Schreinhofer, 2006; McAllen, 1987; Miyawaki et al., 1996; Terui et al., 1986), and spinal cord preganglionic sympathetic neurons (Zhou and Gilbey, 1992) (Fig. 7) sympathetic neural efferent nerve discharge (Fig. 6). Reciprocally, sympathetic and baroreceptor oscillations modulate respiratory-related brainstem and spinal cord neuronal spiking pattern (Baek et al., 2010; Bishop, 1974; Brunner et al., 1982; Dove and Katona, 1985; Eckberg and Orshan, 1977; Grunstein et al., 1975; Lindsey et al., 1998). A large fraction of respiratory-related units recorded in unanesthetized decerebrate vagotomized cats exhibits pulse-synchronous modulation (Lindsey et al., 1998). Accentuations or attenuations of neuronal or neural efferent spiking frequency or burst clustering occurring in response to synaptic inputs conveyed by another group of neurons constitutes modulation (Gilbey et al., 1995; Lindsey et al., 1998; Zhou and Gilbey, 1992). We designate a rostroventrolateral medullary presympathetic neuronal unit exhibiting peak spiking frequency during the inspiratory epoch of breathing to possess inspiratory modulation (Lipski et al., 1996a,b; Mandel and Schreinhofer, 2006; Miyawaki et al., 1996).

During normoxic normocapnia, autonomorespiratory cross-modal modulation chiefly originates from the provision of coordinate inputs deriving from higher-order neural nets (Abdala et al., 2009; Moraes et al., 2012b) and barosensitive, chemosensitive, and pulmonary stretch mechanosensitive monomodal and multimodal nucleus tractus solitarius units (Moreira et al., 2007; Takakura et al., 2007) and direct interaction amongst intermingled propriobulbar interneuronal microcircuits constituting the respiratory central pattern generator, sympathetic oscillators, and dorsal medullary cardiogaval premotoneurons (Moraes et al., 2014a,b, 2012c; Sun et al.,
Fig. 3. Interactions amongst the breathing generator, and sympathetic oscillators in the brainstem. PreBötzinger complex preinspiratory inspiratory phase spanning and decrementing early inspiratory units receive phase inhibitory modulation from Bötzinger complex decrementing post-inspiratory and augmenting expiratory units and tonic excitatory drive from retrotrapezoid nucleus tonic units and parafacial respiratory group pre-inspiratory units, which receive the tonic excitatory drive from CO\textsubscript{2}-driven chemosensitive tonic units extant within the same nucleus. PreBötzinger complex preinspiratory inspiratory phase spanning units drive augmenting inspiratory units in the rostral division of the ventral respiratory group and decrementing early inspiratory units in the preBötzinger complex. Recurrent Excitatory and inhibitory synaptic coupling synchronizes preBötzinger complex spontaneously bursting preinspiratory-inspiratory neuronal spiking. Pre-Bötzinger complex decrementing early inspiratory units convey inhibitory drive to Bötzinger complex augmenting late-expiratory units. Bötzinger complex postsynaptic and augmenting late-expiratory units exhibit reciprocal inhibition and convey inhibitory axodendritic and axosomatic drive to the caudal division of premotoneurons in the caudal ventral respiratory group. Bötzinger complex excitatory postsynaptic units drive metencephalic inspiratory-expiratory phase-spanning units. The firing of metencephalic inspiratory-expiratory phase-spanning units, tonic excitatory glutamatergic retrotrapezoid nucleus units, parafacial respiratory group late-expiratory unit drives and shapes rostral ventrolateral medullary presympathetic bulbo-spinal neuronal spiking. Rostral ventrolateral medullary presympathetic bulbo-spinal neurons receive the inhibitory drive from Bötzinger complex postsynaptic inspiratory units and rostral ventral respiratory group early inspiratory units and convey descending excitatory inputs to intermediolateral cell column preganglionic sympathetic neurons. Propriobulbar units distributed within the vast expanse of the ventral respiratory column nuclei provide the tonic excitatory drive to rostral ventrolateral medullary presympathetic units and caudal ventrolateral medullary GABAergic units. Caudal ventrolateral medullary GABAergic propriobulbar interneurons convey a prominent and physiologically critical inhibitory modulation upon rostral ventrolateral medullary presympathetic units, the pharmacological elimination of which generates rapid and massive rises of dynamic sympathogenic neural efferent activity and arterial pressure magnitude. Rostral ventral respiratory group early inspiratory units convey inhibitory modulation upon co-extant rostral ventral respiratory group augmenting inspiratory premotoneurons, caudal ventral respiratory group expiratory premotoneurons, and rostral ventrolateral medullary presympathetic units. The metencephalon, raphé, retrotrapezoid nucleus, and ventrolateral myelencephalon constitute sources of tonic excitatory drive to respiratory-related and sympathetic units. Metencephalic inspiratory expiratory phase-spanning units receive the tonic excitatory drive from metencephalic propriobulbar units and Bötzinger complex excitatory postsynaptic inspiratory units, dynamic spiking of which confers respirophasic modulation upon the rostral ventrolateral medullary presympathetic units. The phrenic motoneuronal and sympathetic axons constituting the phrenic nerve drive the principal mammalian inspiratory neuroneuror motoneuror displacement. The set of abdominal nerves drive expiratory neuror output. The thoracic sympathetic nerve represents a common, empirically accessible measure of sympathic activity. The model contains two populations of nucleus tractus solitarius units receiving oscillatory baroreceptor inputs. One population of barosensitive nucleus tractus solitarius neurons synaptically excites caudal ventrolateral medullary GABAergic interneurons, and the complement population of barosensitive nucleus tractus solitarius units synaptically excites Bötzinger complex inhibitory decrementing postsynaptic inspiratory units. Barosensitive nucleus tractus solitarius cells, in turn, receive prominent inhibitory modulation from metencephalic inspiratory units and rostral ventral respiratory group early inspiratory neurons. Excitatory (dark red) and inhibitory (purple) populations of units and interactions are indicated. RVLM, rostral ventrolateral medulla; CVLM, caudal ventrolateral medulla; VLM, ventrolateral medulla; RTN, retrotrapezoid nucleus; pFRG, parafacial respiratory group; late-E, late expiration; BöTc, Bötzinger complex; pre-BöTc, preBötzinger complex; rVRG, rostral ventral respiratory group; cVRG, caudal ventral respiratory group; bs-E, bulbo-spinal expiratory; PN, phrenic nerve; AbN, abdominal; tSN, thoracic sympathetic nerve; VRC, ventral respiratory column; I, inspiratory; IE, inspiratory expiratory phase spanning; late-E, expiratory; post-I, postsynaptic; pre-I/I, preinspiratory inspiratory phase spanning; early-l(1), preBötzinger early-inspiratory units; early-l(2), rVRG early-inspiratory units. Modified with permission from Fig. 6 of Molkov et al. (2017).
Fig. 4. Brainstem zones generating and modulating sympathetic oscillations and cardiovagal premotoneuronal spiking. Nissl stained parasagittal sections 1.8 mm lateral with respect to the midline. The chief medullary pre-sympathetic units project to intermediolateral cell column (IML) preganglionic sympathetic neurons reside within the rostral ventrolateral medulla (RVLM), rostral ventromedial medulla (RVMM), caudal raphé, ventrolateral metencephalic tegmentum (A5 catecholaminergic group of neurons), paraventricular nucleus of the hypothalamus, and the medullocervical pressor area (MCPA) spanning the caudal extent of the medulla and rostral extent of the cervical spinal cord. The MCPA extends at least as far caudal as C3/C4. The CVLM may be found caudally positioned with respect to the RVLM, constituted chiefly by GABAergic propriobulbar inhibitory interneurons (I-CVLM), which confer inhibitory modulation upon RVLM presympathetic units. Some I-CVLM units are modulated by the baroreflex arc and are consequently activated by higher-order barosensitive nucleus tractus solitarius (NTS) units, in turn, modulated by barosensitive afferents conveying oscillatory baroreceptor inputs from carotid sinus and aortic arch, relaying via cranial nerves IX and X, respectively. Another group of GABAergic I-CVLM units are baro-independent and tonically inhibit RVLM pre-sympathetic units. Some units in CVLM are glutamatergic (E-CVLM) and convey excitatory drive to RVLM presympathetic units. Chemoreceptor afferents terminate onto second-order neurons in the commissural nucleus of the NTS, which in turn project to and excite RVLM units directly. Chemosensitive commissural NTS units project to, excite, and sensitize RTN glutamatergic chemosensitive units. Prominent rises of arterial pressure were elicited by microinjecting glutamate into the commissural division of the nucleus tractus solitarius (unpublished observations). Cerebellectomy was not required. Careful dissection of the arachnoid bridging the interval between the calamus scriptorius and cerebellum failed to transgress parenchyma and successfully prepared the dorsal medullary surface for micropipette insertion. RTN units convey tonic excitatory drive to RVLM presympathetic units. Water undergoes a carbonic anhydrase-catalyzed chemical reaction to generate carbonic acid, which dissociates into bicarbonate anion and hydrogen cation. Hydrogen ions potently stimulate chemosensitive units within the retrotrapezoid nucleus, raphé, and nucleus tractus solitarius, among other central chemoreceptor sites. The caudal pressor area (CPA) may be found caudally positioned with respect to CVLM and mediates sympathoexcitation through the disinhibition of RVLM presympathetic units by inhibiting CVLM GABAergic inhibitory interneurons, and via facilitation, by activating a population of E-CVLM sympathoexcitatory glutamatergic units. Efferent interneuronal projections from the CPA to the commissural NTS may underlie the commissural NTS-dependence of pressor responses elicited by CPA stimulation. However, further studies are necessary to more fully elucidate the physiological significance of this specific pathway (Takakura et al., 2007). Yet to be determined, sources convey inhibitory modulation upon the CPA, RVLM-independence of sympathoexcitatory pressor responses elicited by chemical microstimulation effectively physiologically distinguishes the medullocervical pressor area from the caudal pressor area (Figs. 4) of Goodchild and Moon (2009).
Peripheral stimuli coordinately driving higher order nucleus tractus solitarius neurons or directly stimulated central chemoreceptors and interactions amongst propriobulbar interneuronal microcircuit oscillators emergently constituting neuronal ensembles generating breathing, sympathetic oscillations, and cardiovagal premotorneuronal spiking emergently generate sympathoexcitatory coupling (Figs. 6-14) (Molkov et al., 2014).

Strengthening of autonomorespiratory coupling (sympathoexcitatory [SRM] and respirophasic [RSM] modulation) by hypoxia and hypercapnia (Figs. 8-11) (Molkov et al., 2014; Moraes et al., 2012a,b,c; Zoccal, 2015; Zoccal and Machado, 2011) indicates peripheral effectors or central genesis mechanisms may alternately or coordinately conceivably mediate evident crossmodal modulation. Autonomorespiratory coupling persists despite decerebrative encephalotomy, vagotomy, and peripheral chemodenervation (Adrian et al., 1932; Marchenko et al., 2016; Zhou et al., 1996) and suggests the direct interaction of the central pattern generators (CPGs) in mediating crossmodal modulation of the respiratory, sympathetic, and parasympathetic activities. We use the term "autonomorespiratory" to efficiently indicate crossmodal modulation and coupling amongst and between the brainstem breathing generator, sympathetic oscillators, and dorsal medullary cardiovagal premotorneurons residing within the nucleus ambiguous and dorsal motor nucleus of the vagus. We thus operantly define autonomorespiratory to constitute the manifestation of, and the mechanisms emergently generating, sympathoexcitatory, parasympathorespiratory, and sympathoparasympathetic crossmodal modulation and coupling across distinct though overlapping propriobulbar interneuronal microcircuit oscillators, nuclei, and reticular zones.

3. Respirophasic modulation of rostral and caudal ventrolateral medullary neurons

Myelencephalic nuclei chiefly constituted by propriobulbar interneurons and presympathetic bulbohypothalamic neurons (Ghali, 2017a, 2018) exhibit respirophasic modulation, in rostral ventrolateral medullary (Fig. 5) (Baek et al., 2010; Lipski et al., 1996a,b; McAllen, 1987; Miyawaki et al., 1995; Terui et al., 1986; Zoccal et al., 2009a,b, 2008), central ventrolateral medullary (Mandel and Schreihofer, 2006), caudal raphé (Gilbey et al., 1995), and ventrolateral medullary A5 catecholaminergic cell group neuronal recordings (McAllen, 1987; Molkov et al., 2017; Zoccal, 2015; Zoccal et al., 2008). Respirophasic modulation of pulmonary mechanosensitive nucleus tractus solitarius units modulate the discharge of presympathetic units modulating sinoatrial bursting frequency (Brodie and Russell, 1900; Daly, 1986). Rostral ventrolateral medullary neurons receive the tonic excitatory and inhibitory synaptic drives from propriobulbar interneuronal microcircuit oscillators (Frank et al., 2009; Gilbey et al., 1984; Guyenet and Koshiya, 1995; Guyenet, 2000; Mandel and Schreihofer, 2006; McAllen, 1986; Mendelowitz, 1999) and phasic oscillatory pulmonary mechanoreceptor, chemoreceptor, and baroreceptor synaptic inputs (Haselton and Guyenet, 1989; Lipski et al., 1996a,b; Rogers et al., 2000). Ventrolateral medullary A5 catecholaminergic cell group presympathetic bulbohypothalamic units exhibit inspiratory, postinspiratory, or expiratory preferential modulation in anesthetized vagotomized rats (Gilbey et al., 1995). Respiratory propriobulbar interneuronal microcircuit oscillators may modulate sympathetic activity through direct synaptic interactions of overlapping propriobulbar interneuronal networks or indirectly by powerfully gating baroreflex influences upon sympathetic oscillators and modifying baroreflex gain, sensitivity, and transfer kinetics (Eckberg and Orshan, 1977; Porta et al., 2015; Wallin and Eckberg, 1982). Respiratory gating of the baroreflex may confer respirophasic modulation upon sympathetic and parasympathetic oscillations by directly regulating dynamic arterial pressure magnitude and/or indirectly influencing sinoatrial action potential frequency (Figs. 13 and 14). Dynamic fluctuations of cardiac interval spectral bands may modulate arterial pressure spectral power (Julien, 2006). Persistence of sympathetic modulation of neural breathing evident in sinoaortic denervated preparations would seem to indicate sympathetic oscillations generated by medullary lateral tegmental field propriobulbar interneurones distributes and propagates to propriobulbar interneuronal microcircuit oscillators constituting the breathing pattern generator (Barman, 2020; Ghali, 2017a, 2018; Molkov et al., 2014). As an aside, acoustic tempo at 80 beats per minutes coordinately elicited increases in myocardial contraction frequency and spectral power of cardiac interval Traube-Hering and Mayer waves in human subjects (Watanabe et al., 2015), with cocontrolled sympathetic coupling putatively organized by the medullary lateral tegmental field (Ghali, 2018).

Catecholaminergic and glutamatergic propriobulbar and spinally projecting bulbar presympathetic neurons constitute the rostral ventrolateral medulla, from which pressor responses may be elicited by electrical activation or glutamate microinjections (Figs. 4 and 5). Rostral ventrolateral medullary neurons exhibit respirophasic modulation of spiking frequency (Haselton and Guyenet, 1989; McAllen, 1987; Miyawaki et al., 1995; Terui et al., 1986), determined by extracellular or intracellular unitary recordings, and membrane voltage trajectories, determined exclusively by intracellular recordings (Lipski et al., 1996a,b). These patterns include early-inspiratory, inspiratory, postinspiratory, and expiratory accentuation and typically phase-correlate with sympathetic neural efferent activity (i.e., cervical, thoracic, splanchnic, lumbar, renal nerves). McAllen (1987) revealed rostral ventrolateral medullary neurons exhibit peak unitary spiking frequency during the inspiratory epoch, with reciprocal postinspiratory attenuation of action potential frequency, in chloralose-anesthetized vagotomized cats. Haselton and Guyenet (1989) demonstrated inspiratory accentuation of rostral ventrolateral medullary neuronal spiking in halothane anesthetized rats. In contrast, Miyawaki et al. (1996) demonstrated inspiratory troughs of rostral ventrolateral medullary neuronal spiking in anesthetized rats. Miyawaki et al. (1995) demonstrated respirophasic modulation of monomodally barosensitive rostral ventrolateral medullary neurons in anesthetized vagotomized rats, and Terui et al. (1986) demonstrated respirophasic modulation of coordinately barosensitive chemosensitive rostral ventrolateral medullary neurons in anesthetized vagotomized rats. Oscillatory baroreceptor inputs inhibit rostral ventrolateral medullary neuronal spiking frequency to a greater extent the inspiratory, compared with the expiratory, epoch, evidencing respiratory gating of baroinhibition of rostral ventrolateral medullary neurons, in vagotomized anesthetized rats (Miyawaki et al., 1995).

Overlapping Bötzinger complex and rostral ventrolateral medullary neuronal microcircuit oscillators constitute a chief node imposing respirophasic modulation upon sympathetic output (Moraes et al., 2012c; Sun et al., 1997), through which proximally-related nuclei (i.e., NTS, RTN) exert common coupling (Ghali, 2017a; Molkov et al., 2014). We conceive the rostral
The nucleus reticularis parvocellularis and nucleus reticularis oralis constitute the medullary division of the lateral tegmental field and span a vast extent of the reticular formation from the caudolateral medulla, becoming more compact with a rostromedial ascent towards the tip of the rostral ventrolateral medulla, giving the architectonic appearance of the cometary tail of the rostral ventrolateral medulla. The medullary lateral tegmental field contains barosensitive units conveying sympatoexcitatory and sympathoinhibitory propriobulbar synaptic inputs to rostral ventrolateral medullary bulbospinal inputs. Most neurophysiologists believe the medullary lateral tegmental field originates the sympathetic activity and conveys this to presympathetic bulbospinal units in nuclei residing within the metencephalon and myelencephalon, including the rostral ventrolateral medulla, rostral ventromedial medulla, caudal raphe, and ventrolateral metencephalic tegmentum. Medullary lateral tegmental field neuronal spiking precedes unitary activity of rostral ventrolateral medullary units and correlates with presympathetic bulbospinal neurons and cardiac sympathetic nerve discharge. Medullary lateral tegmental field propriobulbar interneuronal microcircuit oscillators modulate basal sympatoexcitation and mediate baroreceptor, chemoreceptor, Bezold-Jarisch, somatoautonomic, and visceroauditory reflexes via NMDA and/or non-NMDA dependent glutamatergic fast excitatory synaptic neurotransmission. NRP, nucleus reticularis paragigantocellularis; NRV, nucleus reticularis ventralis; NTS, nucleus tractus solitarius; RVLM, rostral ventrolateral medulla.

Fig. 5. Medullary lateral tegmental field and rostral ventrolateral medulla. The nucleus reticularis parvocellularis and nucleus reticularis oralis constitute the medullary division of the lateral tegmental field and span a vast extent of the reticular formation from the caudolateral medulla, becoming more compact with a rostromedial ascent towards the tip of the rostral ventrolateral medulla, giving the architectonic appearance of the cometary tail of the rostral ventrolateral medulla. The medullary lateral tegmental field contains barosensitive units conveying sympatoexcitatory and sympathoinhibitory propriobulbar synaptic inputs to rostral ventrolateral medullary bulbospinal inputs. Most neurophysiologists believe the medullary lateral tegmental field originates the sympathetic activity and conveys this to presympathetic bulbospinal units in nuclei residing within the metencephalon and myelencephalon, including the rostral ventrolateral medulla, rostral ventromedial medulla, caudal raphe, and ventrolateral metencephalic tegmentum. Medullary lateral tegmental field neuronal spiking precedes unitary activity of rostral ventrolateral medullary units and correlates with presympathetic bulbospinal neurons and cardiac sympathetic nerve discharge. Medullary lateral tegmental field propriobulbar interneuronal microcircuit oscillators modulate basal sympatoexcitation and mediate baroreceptor, chemoreceptor, Bezold-Jarisch, somatoautonomic, and visceroauditory reflexes via NMDA and/or non-NMDA dependent glutamatergic fast excitatory synaptic neurotransmission. NRP, nucleus reticularis paragigantocellularis; NRV, nucleus reticularis ventralis; NTS, nucleus tractus solitarius; RVLM, rostral ventrolateral medulla.

Ventral lateral medulla represents a compact specialized extension of the medullary lateral tegmental field supplying presympathetic bulbospinal drive to intermediolateral cell column preganglionic sympathetic neurons (Marchenko and Sapru, 2003; personal communication, V. Marchenko; see Ghali (2018). RVLM units receive the pre-presympathetic drive from the medullary division of the LTF. The coordinate drive of multiple sets of preganglionic sympathetic neurons residing in the intermediolateral cell column by RVLM and extra-RVLM supraspinal presympathetic units constitutes a mechanism emergently generating common coupling across heterologous and homologous sympathetic neural discharges. Most commonly, sympathetic activity exhibits postinspiratory or a phase-spanning late-inspiratory post-inspiratory accentuation of burst amplitude during normoxic or hyperoxic eucapnia. Mild, moderate, and severe degrees of hypercapnia, acute hypoxia, and chronic intermittent hypoxia incipiently shift this modulation to the late-expiratory phase and synchronously elicit late-expiratory abdominal nerve bursting (Figs. 8-11) (Molkov et al., 2017; Zoccal, 2015; Zoccal and Machado, 2011; Zoccal et al., 2008). Oscillatory synchrony amplifies the sympathetic activity. Interrogating the mechanistic underpinnings of this behavior informs emergent synchrony across disparate neural networks and fundamental strategies of neuro-computational processing.

Mandel and Schreihofer (2006) demonstrated varying patterns of respirophasic modulation imposed upon caudal ventrolateral medullary neurons in chloralose-anesthetized vagotomized
rats (Mandel and Schreihofer, 2006). These included inspiratory augmentation, inspiratory inhibition, inspiratory augmentation with postinspiratory inhibition, and postinspiratory augmentation of respirophasic bursting (Mandel and Schreihofer, 2006). Baro-modulated caudal ventrolateral medullary neurons (Mandel and Schreihofer, 2006) may constitute a chief mechanism conveying inhibitory modulation upon rostral ventrolateral medullary excitatory presynaptic neurons via GABAergic interneuronal projections respirophasic modulation (see Fig. 5). GABAergic caudal ventrolateral medullary units exhibiting postinspiratory preferential modulation may generate rostral ventrolateral medullary neuronal spiking troughs during the postinspiratory epoch. respirophasic modulation Electrical stimulation of aortic depressor nerve generates greater inhibitory effects upon rostral ventrolateral medullary neuronal spiking during the inspiratory, compared with the expiratory, epochs. Baro- and respiratory- modulated caudal ventrolateral medullary neurons exhibiting inspiratory preferential spiking analogously exhibit robust postinspiratory inhibition (Mandel and Schreihofer, 2006). Postinspiratory accoutenations and troughs of rostral ventrolateral medullary neuronal spiking frequency may result from the influences of excitatory and inhibitory populations of Bötzinger complex decrementing postinspiratory cells (Sun et al., 1997) or caudal ventrolateral medullary postinspiratory modulated neurons (Mandel and Schreihofer, 2006), respectively. Occasional differential phase-specific respirophasic modulation of rostral ventrolateral medullary and caudal ventrolateral medullary neuronal spiking frequency suggests dynamic network reconfiguration of common propriobulbar interneuronal microcircuit oscillators coupling these zones (Mandel and Schreihofer, 2006).

4. Respirophasic modulation of caudal raphé units

Caudal raphé presynaptic neurons convey axodendritic and axosomatic drive to preganglionic sympathetic units residing in thoracolumbar intermediolateral cell column propriospinal interneuronal microcircuit oscillators driving preganglionic sympathetic neurons (Morrison and Gebber, 1982) and are modulated by respiratory-related propriobulbar interneuronal microcircuit oscillators residing within a few discrete zones. Respirophasic modulation of brainstem presynaptic units thence propagates throughout the sympathetic and parasympathetic neural networks (Gilbey et al., 1992; Lindsey et al., 1992). Gilbey et al. (1995) interrogated respirophasic modulation of caudal raphé presynaptic neurons in anesthetized vagotomized rats by conducting extracellular recordings of the cellular somata of raphé neurons. Antidromic activation conducted at upper thoracic spinal cord segments T1 to T3 electrophysiologically identified presynaptic units (Gilbey et al., 1995) in raphé pallidus, obscurus, and magnus (Gilbey et al., 1995), with a significant fraction of units exhibiting respirophasic modulation evidenced in a significant fraction of units (19 of 27 neurons). Neuronal modulatory patterns included inspiratory, expiratory, post-inspiratory, and biphasic early-inspiratory and post-inspiratory preferential discharge (Gilbey et al., 1995), recapitulating patterns of respirophasic modulation observed in rostral ventrolateral medullary presynaptic and caudal ventrolateral medullary GABAergic interneurons (Gilbey et al., 1995).

5. Respirophasic modulation of preganglionic sympathetic neurons

Preganglionic and postganglionic sympathetic neuronal spiking variably manifests inspiratory, expiratory, and/or postinspiratory patterns of modulation (Johnson and Gilbey, 1994; Zhou and Gilbey, 1992). In pentobarbital-anesthetized vagotomized rats, upper thoracic preganglionic sympathetic neurons exhibit a higher fraction of cells exhibiting respirophasic modulation compared with lower thoracic and lumbar preganglionic sympathetic neurons. These units exhibit predominantly postinspiratory patterns of modulation (Gilbey et al., 1986; Zhou and Gilbey, 1992). A rostrocaudal gradient in the magnitude of inspiratory and expiratory related respirophasic modulation of sympathetic activity exists along the length of the spinal cord, with differential convergence of inputs to the intermediolateral cell column preganglionic sympathetic neurons varying according to spinal segmental level. Respirophasic modulation of intermediolateral cell column preganglionic sympathetic neurons exhibits homology with unitary discharge patterns exhibited by the intercostal motoneurons supplying thoracic wall respiratory musculature (Gilbey et al., 1986). Cervical sympathetic preganglionic neurons exhibiting spontaneous spiking or activity elicitable by iontophoretically applied glutamate variably exhibit inspiratory or expiratory accentuation of burst amplitude, though some units remain non-modulated (Gilbey et al., 1986).

Spinal sympathoexcitatory neurons receiving convergent inputs from a specific zone within the rostral ventrolateral medulla characteristically span only a few spinal segments, consistent with the somatotopic organization of presynaptic neurons located within this region. Respirophasic modulation conferred upon intermediolateral cell column preganglionic sympathetic neurons likely derives from the composite influences of axodendritic and axosomatic synaptic inputs conveyed by presynaptic neurons residing within the rostral ventrolateral medulla (Baekey et al., 2010; Guyenet et al., 1990; Haselton and Guyenet, 1989; Lipski et al., 1996a,b; McAllen, 1987; Miyawaki et al., 1995; Terui et al., 1986; Zoccal et al., 2009a,b, 2008), caudal raphé (Gilbey et al., 1995), and ventrolateral metencephalic A5 catecholaminergic cell group, propriobulbar interneuronal networks, and somatic thoracic afferent fibers relaying proprioceptive information regarding chest wall muscle contraction. Thoracic wall non-respiratory-related afferents may confer inhibitory or excitatory modulatory synaptic drive upon intermediolateral cell column preganglionic sympathetic units.

Zhou and Gilbey (1992) conducted an elegant study investigating the respirophasic modulation of thoracolumbar myelic preganglionic sympathetic neurons in pentobarbital-anesthetized rats. Investigated perikarya were distributed throughout segments T13-L2 of the ipsilateral intermediolateral cell chain (Zhou and Gilbey, 1992). Antidromic stimulation of the lumbar chain interposed between the 4th and 5th lumbar paravertebral ganglia electrophysiologically identified preganglionic sympathetic neurons (Zhou and Gilbey, 1992). Patterns of discharge of thoracolumbar preganglionic sympathetic neurons included inspiratory, early expiratory, and non-segmented expiratory preferential modulation, though a significant fraction of units lacked specific respirophasic modulation (Zhou and Gilbey, 1992). Glutamate iontophoresis elicited the resurgence of a quiescent population of neurons into readily evident neuronal spiking, with a similar proportion and distribution of active units exhibiting specific respirophasic modulation (Zhou and Gilbey, 1992). Preganglionic sympathetic neurons exhibiting...
respirophasic spiking coordinately demonstrated modulation varying with respect to the cardiac cycle (Zhou and Gilbey, 1992). Pre-ganglionic sympathetic units are located at the T2 spinal level innervated neurons constituting the cervical sympathetic nerve (Zhou and Gilbey, 1992).

**6. Respirophasic modulation of sympathetic neural efferent activity**

Sympathetic neural efferent activity exhibits respirophasic modulation of lumbar sympathetic neural efferent activity, including inspiratory modulation, inspiratory inhibition, and early inspiratory inhibition, followed by postinspiratory modulation, in halothane anesthetized rats. Microinjections of the GABA<sub>A</sub> receptor antagonist bicuculline into the rostral tip of the ventrolateral medulla, but not median raphe, coordinately enhanced phrenic nerve burst amplitude and frequency, lumbar sympathetic nerve burst amplitude and extent modulation by phrenic nerve activity, and dynamic mean arterial pressure magnitude and blunted the baroreflex in halothane-anesthetized vagotomized rats. However, microinjections of the glycine receptor antagonist strychnine and the GABA<sub>B</sub> receptor antagonist phaclofen were without effect (Guyenet et al., 1990). Empirically demonstrated patterns of respirophasic modulation of sympathetic bursting have included exclusively postinspiratory accentuation of cervical and lumbar sympathetic nerve activity and preferentially inspiratory accentuation of cardiac, splanchnic, renal, adrenal, and muscle sympathetic nerve activity in vagotomized sinoaortic-denervated halothane anesthetized rats (Numao et al., 1987; Seals et al., 1993; St. Croix et al., 1999), inspiratory accentuation of splanchnic sympathetic nerve discharge of vagotomized chloralose-anesthetized rats (Mandel and Schreihofer, 2006), and inspiratory postinspiratory modulation of inferior cardiac sympathetic nerve in chloralose-anesthetized vagotomized rats, and inspiratory and postinspiratory accentuation of splanchnic sympathetic nerve discharge in sinoaortic-denervated vagotomized urethane-anesthetized rats (Koshiya and Guyenet, 1995). These findings collectively indicate significant interstudy heterogeneity of patterns of respirophasic modulation of sympathetic oscillators.

Experimental interventions powerfully modifying respirophasic modulation of the sympathetic nerve discharge inform a thoughtful understanding of mechanisms emergently generating sympatho-respiratory coupling (Miyawaki et al., 1996). Microinjections of specific N-methyl-D-aspartate (NMDA) (DL-2-amino-5-phosphonovaleric acid), a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) (6-cyano-7-nitroquinoxaline-2,3-dione), and kynurenic acid-type glutamate receptor antagonists into the rostral ventrolateral medulla abolish postinspiratory modulation of splanchnic sympathetic neural efferent activity in pentobarbital anesthetized rats, without modifying inspiratory modulation of efferent discharge persisted (Miyawaki et al., 1996). Postinspiratory modulation of lumbar sympathetic neural efferent activity may...
be augmented by Hypercapnia, and pharmacological antagonism of GABA, but not GABA\textsubscript{A} or glycine, receptor modulated signaling in the rostral ventrolateral medulla abolished postinspiratory modula-
tion of lumbar sympathetic neural efferent activity (Miyawaki et al., 1996). Postinspiratory modulation of lumbar sympathetic neu-
ral efferent activity decreased in parallel with dynamic increases of arterial pressure magnitude, indicating baroinhibition of respirophasia-
mic modulation of sympathetic neural efferent activity, and in re-
sponse to microinjections of the nonselective glutamate receptor antagonist kynurenic acid, in halothane-anesthetized vagotomized rats. These findings corroborate fast excitatory glutamate receptor modulated signaling that contribute to sympatho- 
refs though medulla (RVLM) (Haselton and Guyenet, 1989; Lipski et al., 1996a,b; McAllen, 1987; Miyawaki et al., 1996, 1995; Moraes et al., 2014a,b), caudal ventrolateral medulla (CVLM) (Mandel and Schreinhofer, 2006), retrotetropezoid nucleus (RTN) and parafacial respiratory group (pFRG) (Fig. 5) (Abdala et al., 2009; Molkov et al., 2017, 2014; Moraes et al., 2012a) dorsolateral (Baekey et al., 2010; Hayward et al., 2004) and ventrolateral metencephalic tegmentum (Dawid Milner et al., 2003), mesencephalic colliculi (Ghali, 2020; ligaya et al., 2012; Martin and Booker, 1878; Subra-
manian and Holstege, 2014) and periaqueductal gray matter (PAG) (ligaya et al., 2010; Martin and Booker, 1878; Subramanian and Holstege, 2014), and dorsomedial hypothalamus (DMH) (Horiiuchi et al., 2009) and paraventricular nucleus (Koba et al., 2018). The mesencephalic colliculi (ligaya et al., 2012; Martin and Booker, 1878) and dorsomedial and dorsolateral divisions of the periaque-
ductal gray matter (Ghali (2020) mesencephalon reference; Subra-
manian and Holstege (2014)) coordinately modulate breathing rate and depth, sympathetic neural efferent activity, eliciting promi-

4 nent increases of dynamic arterial pressure magnitude and myocardial contraction frequency, hyperpnea, and behavioral defense re-

4 sponses.

4 Direct interaction amongst the propriobulbar interneuronal mi-
crocircuitry underlying neurogenesis of breathing, sympathetic oscilla-
tions, and parasympathetic cardiovascular premotor neural spiking may modulate the described network mechanisms (Fig. 5) (Molkov et al., 2017). Bötz\texttextsubscript{C} propriobulbar expiratory interneur-
ons overlap with rostral ventrolateral medullary presynaptic units (Guyenet et al., 1990; Moraes et al., 2012c; Sun et al., 1997), likely representing a critical myelencephalic node subjectable to coordinate modulation of breathing rhythm and amplitude and respirophasic modulation of sympathetic bursts. Excitatory synap-
tic drive deriving from chemosensitive retrotetropezoid nucleus units or chemoreceptors relaying through nucleus tractus solitarius units shifts the bulk of sympathetic burst spectral power towards the expiratory epoch (Molkov et al., 2011; Sun et al., 1997), perhaps offsetting expiratory-related reductions of preload by gener-
ating venoconstriction and enhancing microcirculatory tissue perfusion during troughs of oscillatory oxygen tension, a set of conjec-
tures subjectable to empirical validation. Experimental excitatory chemical microstimulation of hypothalamic, Kölliker-Fuse, and med-
dial parabrachial (Dutschmann and Herbert, 2006; Mörschel and Dutschmann, 2009), ventrolateral metencephalic (Dawid Milner et al., 2003), vestibular, and reticulospinal zones coordinately modu-
late breathing, sympathetic oscillations, and cardiovascualar premo-
toneuronal spiking. Complexly organized brainstem neuronar al ar-
rows of bulboisal and propriobulbar reticular units (Anastasievich et al., 1974; Kostiuk and Preobrazhenskii, 1966; Kostiuk and Pre-
obrazechenskii, 1967) monosynaptically or polysynaptically receiv-
ing afferent inputs may prominently modulate coupling amongst 
and within somatovisceral, respiratory, and sympathetic neural networks (Diachenko and Preobrazhenskii, 1991). Vocal cord stimulation potently enhances gigantocellular tegmental field de-
sending medullospinal neuronal spiking frequency in Nembutal-
anesthetized cats (Diachenko and Preobrazhenski, 1991). The 
described pathways constitute critical mechanisms by which neu-
ral networks emergently generate soi-disant vaso-cardio-respiratory 
coupling.
Brainstem propriobulbar and myelic propriospinal interneuronal microcircuit oscillators generating sympathetic oscillations (Barmen, 2020; Ghali, 2018; Guyenet, 2006) receive prominent modulatory influences deriving from oscillatory vagal baroreceptors (Rogers et al., 2000), chemoreceptors (Guyenet et al., 2019), and pulmonary stretch receptors (Breuer, 1868; Hering, 1868; Luck, 1969; Moore, 1927) conveyed through nucleus tractus solitarius units (Fig. 5) and respiratory-related neurons (Guyenet, 2006; Molkov et al., 2017, 2014; Moraes et al., 2014a; Rogers et al., 2000).

Neural respiratory propriobulbar and bulbospinal premotoneuronal, sympathetic propriobulbar, presympathetic bulbospinal, and preganglionic sympathetic, and cardiovagal preganglionic neurons receive mutually convergent inputs conveyed monosynaptically and polysynaptically from coordinate higher-order neuronal ensembles and peripheral afferent inputs, providing common coupling mechanisms organizing the direct interaction of the central pattern generators (Fig. 5) (Baekey et al., 2010; Ghali, 2017a, 2018; Molkov et al., 2017). We provide a few examples of sympatheo...
modulation and coupling in the brainstem and spinal cord neurons and sympathetic efferent neural discharge (Figs. 5 and 14) (Zoccal, 2015).

7.2 Kölliker-fuse and medial parabrachial nuclei

Neurons residing within the Kölliker-Fuse and medial parabrachial nuclei constituting a significant bulk of the dorsolateral metencephalic tegmentum (Dutschmann and Herbert, 2006; Mörschel and Dutschmann, 2009) generate inspiratory off switching via the provision of a tonic excitatory glutamatergic drive to glycinergic Bötzinger complex decrementing post-inspiratory neurons (Fig. 5) (Dutschmann and Herbert, 2006; Mörschel and Dutschmann, 2009; Smith et al., 2009). These cells powerfully modulate the discharge of rostral ventrolateral medullary presympathetic units and cardiovagal premotoneurons residing within the dorsal motor nucleus of the vagus and nucleus ambiguus (Baekey et al., 2010; Molkov et al., 2014). Eliminating respirophasic modulation of sympathetic oscillations by transectively interrupting pontomedullary continuity (Molkov et al., 2014) supports a requisite contribution of Kölliker-Fuse and medial parabrachial nuclei glutamatergic neurons in crossmodally modifying and rhythmically entraining sympathetic output (Baekey et al., 2010). Metencephalogenic sympathorespiratory modulation may be conveyed via direct monosynaptic phasic inputs deriving from Kölliker-Fuse and medial parabrachial neurons to rostral ventrolateral medullary cells (Fig. 5) (Dutschmann and Herbert, 2006; Mörschel and Dutschmann, 2009), or through polysynaptic propriobulbar interactions relaying through neuronal ensembles extant within the medullary ventral respiratory column nuclei (Molkov et al., 2014). The metencephalon imposes modulatory influences upon rostral ventrolateral medullary presympathetic neurons via the provision of a tonic excitatory glutamatergic drive to Bötzinger complex decrementing postinspiratory neurons and through the provision of tonic excitatory glutamatergic drive conveyed by inspiratory-expiratory phase-spanning neurons (Fig. 5) (Baekey et al., 2010; Farmer et al., 2016). Metencephalic units, directly and indirectly, provide coordinate phasic and/or tonic excitatory drive to rostral ventrolateral medullary presympathetic units and Bötzinger complex expiratory cells, emergently generating the evident crossmodal modulation typifying sympathorespiratory coupling (Fig. 5) (Baekey et al., 2010; Molkov et al., 2014).

7.3 Retrotrapezoid nucleus

Homogenously phox2b transcription factor-expressing glutamatergic propriobulbar interneurons exhibiting exquisite chemosensitivity to arterial and neural interstitial carbon dioxide tension and hydrogen ion concentration constitute the retrotrapezoid nucleus (Guyenet et al., 2019). Glutamatergic retrotrapezoid nucleus units convey tonic excitatory glutamatergic drive to ventrolateral medullary respiratory nuclei and sympathetic oscillators (Figs. 1 and 5) (Guyenet et al., 2019; Molkov et al., 2014). These cells overlap with a cluster of parafacial respiratory group pre-inspiratory modulated units, which may convey synaptic drive to the preBötzinger complex pre-inspiratory driver population. The overlapping parafacial respiratory group oscillator contains rhythmically and spontaneously bursting neurons (Onimaru et al., 2018) exhibiting prespiratory discharge (Onimaru et al., 2006). These pFRG pre-I units project to, and may putatively drive, the activity of preBötzinger complex preinspiratory neurons and Bötzinger complex expiratory abdominal premotoneurons in Bötzinger complex (Molkov et al., 2017), as well as rostral ventrolateral medullary cells. The zone represents an auxiliary expiratory rhythm generator according to studies conducted by Janczewski and Feldman (2006) in the brainstem-spinal cord preparation of the juvenile rat in situ. It constitutes an opioid-insensitive inspiratory rhythm generator operant within the incipient minutes of post-womb life. Vaginal-birth-mediated generation of opiates inhibits preBötzinger complex premotor neuronal spiking, though parafacial respiratory group units remain refractory (Feldman and Del Negro, 2006). The retrotrapezoid nucleus and parafacial respiratory group complex likely constitute a region mediating and organizing common crossmodal coupling of breathing, sympathetic oscillations, and cardiovagal premotoneuronal spiking through the coordinate provision of excitatory drive to rostral ventrolateral medullary and Bötzinger complex cells (Abdala et al., 2009; Moraes et al., 2014a, 2012a), effectively generating coupled and synchronous late-expiratory bursting in abdominal and thoracic sympathetic neural efferent activities (Abdala et al., 2009; Molkov et al., 2017; Moraes et al., 2012a; Zoccal, 2015). Sympathetic neuroplasticity of retrotrapezoid nucleus and parafacial respiratory group units may be critically implicated in strengthening sympathorespiratory crossmodal modulation in rats subjected to hypercapnia and acute and chronic intermittent hypoxia (Molkov et al., 2017; Zoccal, 2015), the pathogenesis of neurogenic arterial hypertension, and sustained coordinate synchronous late-expiratory bursting in sympathetic and thoracic sympathetic nerve activity persisting at rest in response to hypercapnia and chronic intermittent hypoxic conditioning (Molkov et al., 2014, 2011; Moraes et al., 2013; Zoccal et al., 2008).

7.4 Bötzinger complex

Chiefly glycinergic, decrementing post-inspiratory (Ezure and Manabe, 1988) and, principally GABAergic, augmenting late expiratory (Jiang and Lipski, 1990) propriobulbar interneurons (Fig. 5), exhibiting mutual and reciprocal inhibition (see models by Molkov et al. (2017) and Smith et al. (2007, 2009)) constitute the Bötzinger complex, Bötzinger complex decrementing post-inspiratory and augmenting late-expiratory neurons convey inhibitory synaptic drive upon preBötzinger complex preinspiratory (pre-I), preinspiratory-inspiratory (pre-l-I) phase-spanning, and decrementing early-inspiratory (dec-lI) neuronal somatodendritic membranes (Molkov et al., 2017) and excitatory drive to caudal ventral respiratory group (cVRG) expiratory premotoneurons (Smith et al., 2009). A population of GABAergic Bötzinger complex bulbophrineic units conveys supraspinal descending inhibitory modulation upon inspiratory-related phrenic motoneuronal somatodendritic membranes (Figs. 1 and 2). Bötzinger complex augmenting late expiratory neuronal spiking (Fig. 7) generates correlated late expiratory bursting in abdominal and thoracic sympathetic nerve discharge in response to eucapnic hypoxia and hypercapnia (Figs. 8-11) (Moraes et al., 2014a). Chronic intermittent hypoxia could increase the activity of Bötzinger complex augmenting late expiratory neuronal spiking (Fortuna et al., 2008; Janczewski and Feldman, 2006) via increased excitability of these units or by reciprocal reductions of Bötzinger decrementing postsynaptic neurons (Ezure and Manabe, 1988; Molkov et al., 2017; Smith et al., 2009), amplifying generating late-expiratory activity via disinhibition, conjectures supported by interactions amongst coupled distinct propriobulbar interneuronal microcircuit oscillators generating the breathing
rhythm and pattern (Molkov et al., 2017).

Bötzinger complex decrementing postinspiratory units receive excitatory glutamatergic synaptic inputs from neurons residing within the Kölliker-Fuse and medial parabrachial nuclei (Fig. 5) (Dutschmann and Herbert, 2006; Mörschel and Dutschmann, 2009), barosensitive nucleus tractus solitarius neurons (Miyazaki et al., 1999), and nucleus tractus solitarius pump cells conveying spatiotemporally dynamic alveolar wall and septal stretch (Marchenko and Sapru, 2000) PreBötzinger complex augmenting pre-inspiratory, augmenting early-inspiratory inspiratory phase-spanning, and decrementing early-inspiratory neurons and rostral ventral respiratory group decrementing early inspiratory neurons (Molkov et al., 2017; Smith et al., 2007) dynamically impose inhibitory modulation upon Bötzinger complex decrementing postinspiratory units. The sequential activity of ventrolateral medullary late-inspiratory neurons and Bötzinger complex decrementing postinspiratory units terminate the inspiratory epoch (Cohen et al., 1993; Okazaki et al., 2001) and the post-inspiratory component of the cervical vagus and recurrent laryngeal nerve discharge (see Bruce (1988) and Marchenko et al. (2016)). Bötzinger complex decrementing postinspiratory units modulate spatiotemporally dynamic sympathetic propriobulbar (see Moraes et al. (2012c) and Sun et al. (1997)) and cardiovagal premotoneuronal (see Gilbey et al. (1984)) neuronal spiking.

Overlap of rostral ventrolateral medullary presympathetic neurons with inspiratory and Bötzinger complex expiratory propriobulbar interneurons and inspiratory propriobulbar interneurons within ventral respiratory column nuclei (see Moraes et al. (2012c) and Sun et al. (1997)) may generate tightly-coupled sympathoautonomic modulation (Mandel and Schreihofer, 2006; McAllen, 1987; Molkov et al., 2014; Moraes et al., 2012a,b,c; Zoccal, 2015; Zoccal and Machado, 2011; Zoccal et al., 2008). Bötzinger complex propriobulbar and rostral ventrolateral medullary propriobulbar and presympathetic bulbospinal neurons are intermingled and make direct synaptic contacts (see Moraes et al. (2012c) and Sun et al. (1997)). Increased activity among either of these neuronal ensembles, though functionally distinct, could effectively amplify and augment the activity of the other group (Molkov et al., 2014). Specifically, rostral ventrolateral medullary neurons receive inhibitory modulation by Bötzinger complex decrementing post-inspiratory units during early expiration (Baekey et al., 2010). Postsynaptic and inspiratory neurons may thus effectively modulate rostral ventrolateral medullary unitary activity via direct monosynaptic projections or indirectly via relays through caudal ventrolateral medullary GABAergic propriobulbar interneurons (Zoccal et al., 2008). Rostral ventrolateral medullary neurons exhibit peak spiking frequency during the inspiratory epoch and trough spiking frequency during the postinspiratory epoch during rest (Haselton and Guyenet, 1989), a pattern of modulation putatively generated by inhibitory axodendritic and/or axosomatic drive deriving from Bötzinger complex decrementing postinspiratory units (see Molkov et al. (2014) and Sun et al. (1997)). Differential modulation patterns of rostral ventrolateral medullary propriobulbar and presympathetic units vary across the animal model, preparation type, and experimental conditions (Lipski et al., 1996a,b; Mcallen, 1987; Miyawaki et al., 1996) may result from corresponding state-dependent reconfiguration of propriobulbar interneuronal microcircuit oscillators constituting the neural breathing and myelencephalic sympathetic (Zoccal, 2015). Synaptic neuroplasticity may coordinateantly amplify the discharge of these nuclei in response to hypercapnia and acute and chronic intermittent hypoxia (Molkov et al., 2014). Excitatory glutamate microstimulatory activation of Bötzinger complex neurons in the ventrolateral medulla powerfully reduces the amplitude of phrenic nerve discharge. It augments dynamic arterial pressure magnitude in isoflurane-anesthetized adult and unanesthetized decerebrated juvenile rats (Marchenko et al., 2016). Conversely, muscimol inhibition of Bötzinger complex, preBötzinger complex, and/or rostral ventral respiratory group units abolishes sympathoautonomic coupling, experimental findings indicating entrainment amongst expiratory and sympathetic oscillators (Koshiya and Guyenet, 1996).

Accordingly, emergent generation of coordinate late-expiratory bursting in abdominal and thoracic sympathetic neural effenter activity in response to hypoxia and hypercapnia (Figs. 8-11) (Molkov et al., 2014; Zoccal and Machado, 2011; Zoccal et al., 2008) may be mediated and organized by direct interaction amongst and between Bötzinger complex and rostral ventrolateral medullary propriobulbar interneuronal oscillators (Fig. 5) (Molkov et al., 2014; Moraes et al., 2012a,b,c; Zoccal and Machado, 2011; Zoccal et al., 2008).

7.5 Rostral ventrolateral medulla

Direct interaction of the respiratory, central pattern generator and sympathetic oscillators constitutes an elegant mechanism mediating sympathoautonomic coupling (Molkov et al., 2014; Moraes et al., 2012c; Sun et al., 1997). Interactions amongst propriobulbar and bulbospinal neuronal ensembles residing withing the overlapping rostral ventrolateral medulla and Bötzinger complex (Fig. 3) (see Paxinos et al. (1985) and Sun et al. (1997)) may couple presympathetic and expiratory units and emergently generate inspiratory, postsympathetic, and late-expiratory patterns of modulation conveyed to sympathetic oscillations (Figs. 6-9 and Figs. 12-14) (Moraes et al., 2014a, 2012a, 2014b, 2012b,c; Zoccal et al., 2008). Overlap of caudal ventrolateral medullary GABAergic interneurons with preBötzinger complex augmenting pre-I, augmenting pre-I, and decrementing early-I units and rostrally extant rostral ventral respiratory group augmenting inspiratory neurons (Fig. 3) (see Goodchild and Moon (2009)), as well as caudal ventrolateral medullary GABAergic propriobulbar interneuronal synaptic drive conveyed to rostral ventrolateral medullary presympathetic units, may impose respirophasic modulation upon sympathoautonomic oscillations (Mandel and Schreihofer, 2006) and autonomic modulation upon a respiratory-related activity (see Baekey et al. (2010)). Coordinate excitatory synaptic drive conveyed by the glutamatergic retrotroapezoid nucleus and parafacial respiratory group neurons to Bötzinger complex expiratory neurons and rostral ventrolateral medullary presympathetic cells (Guyenet et al., 2019), as well as direct interaction of overlapping propriobulbar excitatory and inhibitory neuronal ensembles of the Bötzinger complex and rostral ventrolateral medulla (Moraes et al., 2012c; Sun et al., 1997), may constitute robust mechanisms contributing prominently and mediating, sympathoautonomic modulation at rest and hypoxia and hypercapnia-mediated generation and strengthening of sympathoautonomic coupling (Fig. 5) (Molkov et al., 2014). Excitatory glutamate stimulatory activation of ventral respiratory column nuclei occasionally elicits coordinate enhancement or attenuation of dynamic arterial pressure magnitude (Marchenko et al., 2016), reflecting intimate intermingling of the propriobulbar interneuronal microcircuit oscillators generating the breathing rhythm.
Fig. 8. Respiratory-related modulation of abdominal and thoracic sympathetic neural efferent discharge in rats. A: Integrated (∫) and raw abdominal nerve discharge (AbN), thoracic sympathetic nerve activity (tSNA), and phrenic nerve discharge (PND) during normocapnia. Abdominal nerve rhythmic bursting exhibits postinspiratory modulation of its rhythmic bursting activity contrasted with late-expiratory activity elicited by subjecting to chronic intermittent hypoxia. Thoracic sympathetic nerve bursting manifests late-inspiratory postinspiratory modulated amplification. The phrenic neurogram exhibits regular rhythmic augmenting-inspiratory bursting, with only a few diminutive sparse spikes during the postinspiratory epoch (second and third bursts). B: Integrated (∫) and raw abdominal nerve discharge, thoracic sympathetic nerve activity, and phrenic nerve discharge in rats conditioned with chronic intermittent hypoxia. Subjecting rats to chronic intermittent hypoxia confers late expiratory modulation upon abdominal nerve discharge and coordinately enhances postinspiratory modulation, and elicits phase-spanning late-expiratory-early-inspiratory modulation of thoracic sympathetic nerve discharge. The phrenic neurogram exhibits regular rhythmic augmenting inspiratory bursting, with only a few sparse spikes constituting a diminutive postinspiratory epoch, challenging to discern, but present, in all three bursts. Hypercapnia augments phrenic burst amplitude, contracts duration of the inspiratory epoch, and fails to modulate bursting frequency. C: Expanded views of integrated (∫) and raw abdominal, thoracic sympathetic, and phrenic nerve bursts during normal conditions. Abdominal nerve bursts evidence post-inspiratory modulation, and thoracic sympathetic nerve bursts evidence phase-spanning late-expiratory post-inspiratory modulation. D: Integrated (∫) abdominal and thoracic sympathetic and raw phrenic nerve activity in rats conditioned by chronic intermittent hypoxia. Abdominal and thoracic sympathetic nerve activity acquire synchronous late-expiratory modulation. E: Differential fractional distribution of integrated thoracic sympathetic nerve activity across inspiratory, postinspiratory, and late expiratory epochs in normotensive (solid boxes) versus spontaneously hypertensive (open boxes) rats. Thoracic sympathetic nerve discharge exhibits significantly greater amplitude during the late expiratory epoch during chronic intermittent hypoxia compared with normoxic normocapnic conditions. AbdN, abdominal nerve; tSN, thoracic sympathetic nerve; PN, phrenic nerve; SH, spontaneously hypertensive. Modified with permission from Fig. 5 of Moraes et al. (2014a).
Fuse and medial parabrachial nuclei neurons to Bötzinger complex decrementing postinspiratory neurons (dec post-I) (Dutschmann and Herbert, 2006; Mörschel and Dutschmann, 2009) and from pontine inspiratory expiratory (IE) phase spanning units to rostral ventrolateral medullary presympathetic cells in organizing and mediating sympatho-respiratory modulation (Baekey et al., 2010). Accordingly, postinspiratory modulation of rostral ventrolateral medullary presympathetic units may coordinate derive from excitatory synaptic drive conveyed by the correlated spiking of a population Bötzinger complex glutamatergic decrementing postinspiratory neurons (Sun et al., 1997), heterosynaptic inhibition of inhibitory synaptic drive conveyed to rostral ventrolateral medullary units during the post-inspiratory sub-epoch by Bötzinger complex glycinergic decrementing post-inspiratory units (Sun et al., 1997), and inspiratory-related inhibition of rostral ventrolateral medullary presympathetic units by caudal ventrolateral medullary GABAergic interneurons (Mandel and Schreihofer, 2006) receiving excitatory inputs from higher-order neurons within ventrolateral and interstitial divisions of the nucleus tractus solitarius subnuclei.

7.6 Caudal ventrolateral medulla

GABAergic propriobulbar interneurons, interspersed amongst a few glutamatergic propriobulbar interneurons, constitute the caudal ventrolateral medulla, providing the chief and principal inhibitory projection modulating discharge of rostral ventrolateral medullary presympathetic units (Fig. 3) (Ghali, 2017a, 2018; Guyenet, 2006; Mandel and Schreihofer, 2006). Caudal ventrolateral medullary GABAergic interneurons units receive NMDA and non-NMDA glutamatergic excitatory synaptic drive from barosensitive nucleus tractus solitarius units (Mandel and Schreihofer, 2006) and inhibitory synaptic drive from GABAergic propriobulbar interneurons residing within the caudal pressor area (CPA) (Guertzenstein and Silver, 1974). A population of excitatory glutamatergic units within the caudal ventrolateral medulla may convey a glutamatergic drive to rostral ventrolateral medullary presympathetic units (Ghali, 2017a). Caudal ventrolateral medullary GABAergic propriobulbar interneurons exhibiting differential patterns of respiratory-related modifications of unitary activity (Mandel and Schreihofer, 2006) may impose respirophasic modulation upon rostral ventrolateral medullary presympathetic neurons, distributing to the entire sympathetic output (Haselton and Guyenet, 1989; Miyawaki et al., 1995; Molkov et al., 2014). These conjectures are advanced by empirical findings obtained by Baekey et al. (2010) in the in situ myenteric cord preparation of the juvenile rat, the works of Miyawaki et al. (1996) demonstrating abolition of inspiratory-related inhibition of rostral ventrolateral medullary presympathetic neurons by chemical inhibition of the caudal ventrolateral medulla in anesthetized rats (Miyawaki et al., 1996), and computational models generated by Molkov et al. (2014). Botzinger complex glycinergic synaptic inputs may coordinate impose tonic inhibitory modulation upon rostral ventrolateral medullary presympathetic neurons (see Moraes et al. (2012c) and Sun et al. (1997)), putatively crossmodally augmenting caudal ventrolateral medullary GABAergic inhibition of unit threshold excitability. This hypothesis may be validated by conducting intracellular recordings of RVL M cells and exposing somatodendritic membranes to individual or coordinate microiontophoresis of GABA and/or glycine.

Caudal ventrolateral medullary propriobulbar inhibitory synaptic influences may attenuate the dynamic magnitude of respirophasic modulation conferred upon rostral ventrolateral medullary presympathetic units and distributing to sympathetic neural effenter activity (Guyenet et al., 1990; Mandel and Schreihofer, 2006; Miyawaki et al., 1996; Numao et al., 1987). Augmentation of postinspiratory modulation of rostral ventrolateral medullary presympathetic neuronal activity in response to microinjections of pharmacological antagonists of GABA receptors in the rostral ventrolateral medulla and muscimol chemical inhibition of caudal ventrolateral medullary GABAergic interneurons (Mandel and Schreihofer, 2006; Miyawaki et al., 1996; Numao et al., 1987) substantiates the preceding conjecture. Postinspiratory modulation of rostral ventrolateral medullary neurons may be buffered by fast inhibitory synaptic inputs deriving from caudal ventrolateral medullary cells exhibiting analogous postinspiratory modulation of spatiotemporally-variant neuronal spiking dynamics (Mandel and Schreihofer, 2006). Caudal ventrolateral medullary neurons exhibiting postinspiratory modulation may receive the excitatory glutamatergic drive from an excitatory population of Botzinger complex decrementing postinspiratory neurons. They may indirectly impose postinspiratory inhibition upon rostral ventrolateral medullary presympathetic neurons (Mandel and Schreihofer, 2006).

The existence of inspiratory- and postinspiratory-related neurons exhibiting neurochemical repertoires alternately consistent with excitatory or inhibitory phenotypes support the presented conjectures (Smith et al., 2007). Further studies are necessary to elucidate an understanding of patterns of neuronal projectivity and crossmodal electrophysiological modulation amongst Botzinger complex excitatory glutamatergic and inhibitory glycinergic decrementing postinspiratory neurons and rostral ventrolateral medullary propriobulbar and presympathetic bulbospinal neurons and caudal ventrolateral medullary GABAergic interneurons.

7.7 Nucleus tractus solitarius

Two bilateral groups of rostrocaudally and mediolaterally organized subnuclei located within the dorsal medulla presenting to the floor of the fourth ventricle constitute the nucleus tractus solitarii (Fig. 2) (Jean, 1992) and prominently contribute to autonomorespiratory modulation (Zoccal, 2015) in their chief function as a common initial relay for afferent inputs deriving from the periphery (Michelini, 1994; Moreira et al., 2007; Rogers et al., 2000; Takakura et al., 2007). Commissural (Zhang et al., 2011), medial and interstitial (Rogers et al., 2000) and ventrolateral (Von Euler et al., 1973) subdivisions segregate the paired nucleus tractus solitarii into functionally distinct heterotopic zones (Marchenko and Sapru, 2000). Neurons extant within the nucleus tractus solitarii generate autonomorespiratory coupling (Zoccal, 2015) by monomodally or multimodally integrating (Li et al., 1999a,b) oscillatory baroreceptor (Michelini, 1994; Moreira et al., 2007; Rogers et al., 2000; Takakura et al., 2007), chemoreceptor (Zhang et al., 2011), and slow and fast adapting pulmonary stretch receptor (Marchenko and Sapru, 2000) inputs from glossopharyngeal and/or vagal afferents to higher-order neurons in brainstem zones generating the neural breathing pattern, sympathetic oscillations, and cardiovagal premoneuronal spiking (Molkov et al., 2014). Nucleus tractus solitarii units and efferent neuronal targets thus constitute pathways mediating vasorespiratory and cardiorespiratory crossmodal modulation (Fig. 5) (Molkov et al., 2014; Von Euler et al., 1973). For example, slow (Fenik, 1992; Preobrazhenskii and Fenik, 1989) and fast adapting stretch receptors relay spatiotemporally dynamic alve-
otor stretch to pump cells (Moreira et al., 2007; Takakura et al., 2007) via vagal afferents encoded in spike cell trains. Nucleus, tractus solitary pump cells, project to caudal ventrolateral medullary GABAergic interneurons (Mandel and Schreihofer, 2006), which make synaptic contacts with, and convey an inhibitory modulation upon, rostral ventrolateral medullary presympathetic neurons. Conglomerate caudal ventrolateral medullary GABAergic interneuronal spiking, driven by excitatory glutamatergic synaptic drive conveyed from barosensitive nucleus tractus solitary neurons in response to rises of dynamic arterial pressure magnitude, generate prominent reductions of sympathetic outflow, mediating the sympathetic component of the Hering Breuer reflex (Ghali, 2017a; Guyenet, 2006). Comparatively attenuated respirophasic variation of caudal ventrolateral medullary GABAergic interneuronal basal activity generates congruous respirophasic variations in rostral ventrolateral medullary presympathetic neuronal discharge. Wasserman et al. (2002) demonstrated ventrolateral nucleus tractus solitary GABAergic interneurons modulate diaphragmatic pump motor output in urethane- and α-chloralose-anesthetized vagotomized spontaneously breathing adult rats. Pulmonary stretch receptor spiking frequency increases in parallel with sympathoinhibitory-mediated reductions of dynamic arterial pressure magnitude and myocardial contraction force and frequency during the inspiratory epoch, synergistically conveying inhibitory modulation upon inspiratory-related propriobulbar interneurons and brainstem and spinal motoneurons, generating inspiratory disfacilitation and expiratory augmentation (Breuer, 1868; Daly, 1986; Hering, 1868). Thus, afferents relaying dynamic pulmonary stretch information powerfully modulate breathing, sympathetic oscillations, and cardiovagal premotoneuronal spiking and emergently generate crossmodal coupling amongst the generators.

8. Respirophasic modulation of cardio sympathetic and cardioparasympathetic output: respiratory sinoatrial dysrhythmia

8.1 Overview

Neural and hemodynamic variability spectra exhibit high, low, and very-low-frequency oscillations (Guyton et al., 1951; Julien, 2006; Porta et al., 2018; Schweitzer, 1945; Ursino et al., 1992), constituting a mathematically interrogable set of phenomena (Seydnejad and Kitney, 2001) informing mechanisms generating sympatho respiratory modulation amongst and between disparate central oscillators (Ghali and Ghali, 2020). Stephan Hales initially reported oscillatory variability in the crural arterial pressure of a bound mare in 1733 (Hales, 1887). In the 19th century, Traube (1865) and Hering (1869) curiously observed oscillations of dynamic arterial blood pressure magnitude covarying with breathing, having acquired the designation Traube-Hering waves a few years before Hering and Breuer describing and characterizing pulmonary stretch receptor modulation of expiratory and inspiratory phase durations and activities (Breuer, 1868; Hering, 1868). Several years after that, Mayer (1876) observed lower frequency 0.3 Hz oscillations of dynamic arterial pressure magnitude of anesthetized rabbits, later manifesting in spectra of cardiac interval, arterial resistance, blood flow, and neuronal and neural efferent sympathetic and parasympathetic activity (Julien, 2006). Very low-frequency oscillations previously described to coordinately occur in dynamic arterial blood pressure magnitude and splenic volume (Barcroft and Nisimaru, 1932) were later identified in arteriolar tone (Ursino et al., 1992). Investigating these oscillations has thus proven especially fruitful in uncovering the mechanistic underpinnings of sympathorespiratory, parasympathorespiratory, and sympathoparasypathetic crossmodal modulation (Julien, 2006).

Traube Hering waves constituting the high-frequency band of respiratory-related oscillatory spectral variability evident in neural and hemodynamic variables were seminally described by Traube (1865) and Hering (1869) in the 19th century. Traube-Hering waves expressed in cardiac interval oscillations constitute soi-disant respiratory sinoatrial dysrhythmia (Julien, 2006). We operantly define inspirophasic sinoatrial acceleration to constitute respiratory sinoatrial dysrhythmia. These oscillations may alternately or coordinately be generated by central and/or peripheral mechanisms, several of which are presented with their relative merits and evidence base evaluated (Anrep et al., 1936; Brodie and Russell, 1900; Daly, 1986; Eckberg, 2009; Mendelowitz, 1999). Cardiovagal pre motoneuronal disfacilitation likely generates respiratory sinoatrial dysrhythmia (Daly, 1986). Gradual reductions of intrathoracic pressure and increasing negativity of intrapleural pressure occurring dynamically in parallel with the inspiratory epoch generate a gradient augmenting venous return, thus enhancing preload delivered to the atria and stroke volume generated by ventricular contractions (Lansdorp et al., 2014). Increased preload delivered to the ventricles may reflexively reduce myocardial contraction frequency by volume mechanisms or enhance myocardial contraction frequency by activating the Bainbridge reflex (Schroeder and Brehm, 1952; Vatter and Zimpfer, 1981). [N.B.: An increase in afterload presented to the ventricular myocardium induces a reflexive increase in the cardiac contractility, constituting the soi-disant Anrep effect (Anrep and Segall, 1926)]. Importantly, inspirophasic changes in heart rate must be distinguished from changes in heart rate variability occurring during, and paralleling, variations of the respiratory cycle. However, similar and overlapping mechanisms likely coordinate both processes (Julien, 2006). The relative balance of sympathetic and parasympathetic inputs to the heart conveyed via cardiac plexus ganglia constitutes the chief neural effector mechanisms determining the rate of the spontaneous depolarization of the soi-disant sinoatrial nodal cell funny current determining discharge frequency and thus heart rate and heart rate variability (Guyenet et al., 2019).

8.2 Modulation patterns of cardiac vagal preganglionic neurons

Inspiratory-synchronous disfacilitation of cardiovagal premotoneuronal spiking in the dorsal motor nucleus of the vagus and nucleus ambiguous constitutes the chief mechanism underlying the neurogenesis of respiratory sinoatrial dysrhythmia (Figs. 2 and 3) (Daly, 1986). Accordingly, cardiovagal premotoneurons exhibit nadir spiking frequency during inspiration and a reciprocal peak of spiking frequency during expiration, consistent with the phase preference of sinoatrial accelerations and decelerations typifying the most common pattern of respiratory sinoatrial dysrhythmia (Daly, 1986). Critically, several studies have paradoxically revealed sinoatrial acceleration occurring during the expiratory epoch in urethan eanesthetized preparations. Though modulatory patterns of cardiovagal premotoneurons residing in the nucleus ambiguus are typically consistent across studies (Neff et al., 2003), exhibiting prominent inspirophasic inhibition and expirophasic facilitation (Gilsey et al., 1984; Mendelowitz, 1999), these units may be preferentially excited
During inspiratory or expiratory phases.

Inspirophasic peak spiking frequency and post-inspirophasic nadir spiking frequency of cardio vagal premotoneurons (Lindsey et al., 1998) corroborate studies demonstrating inspirophasic sinoatrial deceleration and expirophasic sinoatrial accelerations, though controversies the more commonly observed inspirophasic sinoatrial acceleration (Daly, 1986). Cardiovagal premotoneurons predominantly exhibit expiratory modulation in adult rabbits and cats (Gilbey et al., 1984), inspiratory modulation in urethane-anesthetized adult rats, and inspiratory inhibition in the in vitro preparation of rat medullary brainstem slices (Neff et al., 2003). GABAergic inhibitory modulation of cardio vagal preganglionic neurons may require tonic excitation by $\alpha_1\beta_2$ nicotinic acetylcholinergic inputs (Neff et al., 2003). Differential patterns of respirophasic modulation of cardio vagal premotoneuronal spiking may result from physiological differences across species, preparation types, and experimental conditions (Gilbey et al., 1984; Jordan et al., 1982; Neff et al., 2003).

8.3 Mechanisms contributing to modulation of cardiac vagal preganglionic neuronal spiking

Cardiovagal preganglionic neurons convey acetylcholinergic drive to dendrites and somata of cardiac plexus cardio vagal postganglionic neurons investing the aortic arch and supplying sinoatrial and atrioventricular nodal cells and atrial and ventricular cardiomyocytes (Eckberg, 2003). Fast excitatory glutamatergic and fast inhibitory GABAergic and glycinergic inputs coordinate dynamically modulate dynamic membrane voltage trajectories and discharge properties of cardio vagal preganglionic units. Neuroanatomic and neurophysiologic evidence variably indicates the putative provision of excitatory drive to cardio vagal premotoneurons deriving from Kölliker-Fuse and medial parabrachial nuclei, Bötzinger complex (Dergacheva et al., 2010), preBötzinger complex (Ellenberger, 1999), and nucleus tractus solitarius units via monosynaptic and/or polysynaptic axonal projections. Several zones may provide inhibitory modulation of cardio vagal premotoneurons (Dergacheva et al., 2010); Frank et al. (2009). In a study conducted by (Frank et al., 2009), the photostimulation of transverse brainstem slices containing cardio vagal premotoneurons in nucleus ambiguus identified several zones containing GABAergic interneurons from which inhibitory postsynaptic currents (IPSCs) could be elicited. Regions from which IPSCs could be elicited were located 200 $\mu$m medial, 400 $\mu$m lateral, 1200 $\mu$m ventral, and 1200 $\mu$m dorsal and 1000 $\mu$m medial with respect to patch-clamped ambiguous units (Frank et al., 2009). Retrograde labeling studies may be exploited to determine the neurochemical identity of these zones. Accordingly, pseudorabies virus microinjections in the phrenic nucleus identified units located in the lateral recticular nucleus medial with respect to the nucleus ambiguus cardio vagal premotoneurons (Lois et al., 2009) and nucleus ambiguus fluoroagold and rhodamine microinjections labeled magnocellular recticular and lateral paragangiocellular nucleus units (Lois et al., 2009), regions exhibiting overlap with areas from which IPSCs could be elicited and containing units with a predominantly GABAergic neurochemical character (Frank et al., 2009).

Cardiovagal premotoneurons constituting the nucleus ambiguus Figs. 2 and 3 receive a wide convergence of glutamatergic fast excitatory and GABAergic fast inhibitory inputs deriving from distributed zones located throughout the brainstem (Dergacheva et al., 2010; Frank et al., 2009). Barosensitive and chemosensitive nucleus tractus solitarius units and pump cells, exhibiting glutamatergic or GABAergic, and/or glycinergic phenotypes project to, and alternate convey excitatory or inhibitory synaptic drive upon, higher-order units and cardio vagal premotoneurons (Moreira et al., 2007; Takakura et al., 2007). Pharmacological GABAergic antagonism of ambigual cardio vagal premotoneurons abolishes sinoatrial acceleration elicited by rostral ventrolateral medullary stimulation, indicating RVL may enhance sinoatrial frequency by conveying GABAergic inhibitory modulation upon nucleus ambiguus cardio vagal premotoneurons monosynaptically or through glutamatergic excitation of a pre-ambiguous population of GABAergic units. RVL-mediated blunting of cardio vagal premotoneuronal spiking, coordinate with the provision of presympathetic descending excitatory inputs to upper thoracic, cardio preganglionic neurons deriving from the rostral ventrolateral medulla, may constitute a critical mechanism augmenting heart rate. Rostral ventrolateral medullary GABAergic propriobulbar interneurons providing coordinate inputs to Bötzinger complex units (Babic and Ciriello, 2004) and nucleus ambiguus cardio vagal premotoneurons (Babic and Ciriello, 2004) may contribute to crossmodal modulation between and synchrony amongst fast synchronous oscillations generated by these zones. GABAergic propriobulbar interneurons, in turn, may be subjected to excitatory modulation by glutamatergic, cholinergic, and adenosinergic inputs and inhibitory modulation by GABAergic and glycinergic inputs (Neff et al., 2003).

Glycinergic Bötzinger complex decrementing postinspiratory units mediate cardiorespiratory (i.e., parasympathoerespiratory) coupling by coordinate conveying inhibitory axodendritic and axosomatic modulation upon cardio vagal premotoneurons (Dergacheva et al., 2010; Frank et al., 2009) and preBötzinger complex preinspiratory, pre-inspiratory-inspiratory phase-spanning, and decrementing early-inspiratory neurons, rostral ventral respiratory group inspiratory neurons, and Bötzinger complex augmenting late expiratory neurons (Molkov et al., 2017; Rybak et al., 2014; Smith et al., 2007). GABAergic Bötzinger complex and augmenting late-expiratory neurons receive the tonic excitatory drive from gluta matergic retrotrapezoid nucleus units (see Molkov et al. (2017, 2014) and Smith et al. (2009)). Glycinergic Bötzinger complex decrementing post-inspiratory neurons receive the tonic excitatory drive from Kölliker-Fuse and medial parabrachial propriobulbar units residing within the dorsolateral metencephalic tegmentum (Dutschmann and Herbert, 2006; Mörschel and Dutschmann, 2009; Rybak et al., 2014; Smith et al., 2007). Though decrementing Bötzinger complex decrementing post-inspiratory neurons most commonly exhibit a glycnergic neurochemical phenotype, decrementing postinspiratory units may commensurately exhibit an excitatory neurochemical repertoire (Smith et al., 2009). Neurochemical heterogeneity of Bötzinger complex expiratory units indicates a more complex regulation of nucleus ambiguus cardio vagal premotoneurons by respiratory-related units within the core respiratory rhythm generating circuitry (Dergacheva et al., 2010; Frank et al., 2009).
9. Strengthening of sympathorespiratory coupling by hypoxia and hypercapnia

9.1 Overview

Normal breathing during normoxic normocapnia involves active inspiratory chest wall excursions with passive expiratory relaxation of the thoracic cavity (Janczewski et al., 2013). Hypercapnia (Marchenko et al., 2016; Molkov et al., 2011; Zoccola et al., 2009) and acute and chronic hypoxia (Moraes et al., 2014a, 2012a, 2014b, 2016) and/or postinspiratory accentuation with late postinspiratory or late expiratory collapse of the thoracic cavity (Figs. 8-11), empirically evident in abdominal neurogram and electromyogram recordings (Janczewski and Feldman, 2006; Zoccola et al., 2008). The strategy enhances ventilatory carbon dioxide exchange and, in parallel, improves tissue oxygenation (Ghali and Marchenko, 2016b). Experimentally conditioning animals with chronic intermittent hypoxia renders expiratory excursions active during baseline normocapnic normoxia (Moraes et al., 2014a, 2012b; Zoccola et al., 2007, 2009a, 2008). During rest, rostral ventrolateral medullary neurons exhibit varying patterns of respirophasic modulation of neuronal spiking (i.e., inspiratory, postinspiratory, or nonsegmented expiratory), with sympathetic neural efferent activity typically evidencing inspiratory and/or postinspiratory accentuation with late expiratory attenuation (Koshiya and Guyenet, 1995; Lipski et al., 1996a,b; Miyawaki et al., 1996; Zoccola et al., 2008). Hypercapnia (Molkov et al., 2014) and acute and chronic hypoxia (Moraes et al., 2014b, 2012b; Zoccola et al., 2007, 2009a, 2008) powerfully enhances the strength of respirophasic modulation and sympathetic neural burst amplitude and elicit synchronous late-expiratory sym-
pathetic and abdominal nerve bursting. Distinct mechanisms are mediating evident respiratory neuroplasticity in \textit{in vivo} and \textit{in situ} preparations of the anesthetized, unanesthetized decerebrate, and conscious (Moraes et al., 2013) adult and juvenile (Zoccal et al., 2007, 2009a, 2008) rats. In general, rats subjected to either hypercapnic (Molkov et al., 2014) or acute or chronic normocapnic hypoxia develop sustained amplifications of dynamic arterial pressure magnitude, correlated with parallel increases in sympathetic neural efferent activity and plasma levels of catecholamines (Zoccal et al., 2007, 2009a, 2008), with the genesis of contemporaneous and synchronous late-expiratory bursting manifest in sympathetic and expiratory abdominal nerve bursting (Molkov et al., 2014). We dissect mechanisms mediating, and contributing to, hypercapnia- and hypoxia-induced amplification of the strength of respirophasic variation of discharge properties of the brainstem and spinal cord sympathetic-related units and modulation of sympathetic neural efferent activity (Molkov et al., 2017; Zoccal, 2015).

9.2 Hypercapnia

Hypercapnia elicits late-expiratory burst-clustered spiking in abdominal nerve correlated, coherent, and synchronous with late-expiratory modulation of sympathetic neural efferent activity (Figs. 8-11) (Molkov et al., 2014), consistently demonstrated across \textit{in vivo} and \textit{in situ} preparations. The behavior increases quantally, parallelly increasing levels of hypercapnia, eventually becoming coupled 1: 1 with phrenic nerve discharge (Abdala et al., 2009; Molkov et al., 2010). In the \textit{in situ} brainstem spinal cord preparation of the unanesthetized decerebrate juvenile rat, hypercapnia elicits quantal amplification of synchronous late-expiratory bursting, quantitatively manifest in sympathetic and abdominal neural efferent activity (Molkov et al., 2014). Amplification of late-expiratory quantally synchronized across abdominal nerve and thoracic sympathetic bursting paralleled increasing levels of arterial blood carbon dioxide. At 5% hypercapnia, abdominal-sympathetic-synchronized late-expiratory bursting exhibited 1: 2 at 5% hypercapnia and 1: 1 coupling with phrenic nerve discharge at 7% and 10% hypercapnia see Molkov et al. (2011).

Pharmacological inactivation of the retrotrapezoid nucleus and parafacial respiratory group zone abolishes hypercapnia-induced late expiratory abdominal nerve bursting (Abdala et al., 2009); inhibition of Phox2b transcription factor expressing neurons elicits a similar effect (Marina et al., 2010). Retrotrapezoid nucleus Phox2b transcription factor-expressing glutamatergic chemosensitive units (Guyenet et al., 2019) convey excitatory axodendritic and axosomatic synaptic drive upon bulbospinal expiratory cells residing within the caudal ventral respiratory group, driving late expiratory bursting in abdominal nerve discharge (Abdala et al., 2009; Molkov et al., 2010). These findings indicate late-expiratory bursting coherent amongst abdominal and sympathetic neural efferent discharge induced by hypercapnia (Molkov et al., 2014) originates from a common source, putatively from chemosensitive retrotrapezoid nucleus units and spontaneously bursting parafacial respiratory group preinspiratory units (Abdala et al., 2009; Molkov et al., 2010), with cells in these zones exhibiting isoelectric neural silence at 5% CO2 (considered normocapnia in hypothermic \textit{in situ} preparations) and acquiring remarkable bursting only when exposed to higher levels of carbon dioxide tension (Abdala et al., 2009; Molkov et al., 2010). Interactions amongst overlapping Botzinger complex and rostral ventrolateral medullary propriobulbar interneuronal mi-crocircuits oscillators (Moraes et al., 2012c; Sun et al., 1997) may also generate hypercapnia and/or hypoxia-mediated accentuation of sympathoexcitatory coupling. Experimental collectively indicates chemosensitive retrotrapezoid nucleus cells (Guyenet et al., 2019; Molkov et al., 2017) and parafacial respiratory group pre-inspiratory microcircuit oscillators (Onimaru et al., 2018) strengthen hypercapnia and/or acute and chronic hypoxia-mediated sympathoexcitatory coupling (Abdala et al., 2009; Molkov et al., 2010), by providing coordinate inputs to caudal ventral respiratory group expiratory premotoneuronal bulbospinal units and rostral ventrolateral medullary presynaptic units (Molkov et al., 2014). Molkov et al. (2011) describe a model detailing mechanism putatively underlying sympathoexcitatory crossmodal modulation building upon the work dos Baeyck et al. (2010) and the group's previously developed models see Molkov et al. (2010). Molkov's models incorporate a population of RTN and pFRG conveying common tonic excitatory drive to respiratory and sympathetic generators (Molkov et al., 2017). Accordingly, Botzinger complex respiratory neurones impose various patterns of respirophasic modulation upon rostral ventrolateral medullary unitary spiking frequency according to the state of the network (i.e., whether exposed to normocapnic normoxia, hypercapnia, or hypoxia) and predecessor exposures to chronic intermittent hypoxic conditioning, a mechanism which powerfully and emergently generates sympathoexcitatory crossmodal coupling (Moraes et al., 2012a,b,c; Zoccal et al., 2008). Botzinger complex and rostral ventrolateral medullary neurones are intermingled, exhibit significant overlap, and make extensive heterologous neurosynaptic contacts (see Moraes et al. (2012c) and Sun et al. (1997)). Botzinger complex decrementing post-inspiratory or augmenting late-expiratory neurones making synaptic contacts with rostral ventrolateral medullary presynaptic membranes could influence intermedullary cell column preganglionic sympathetic neuronal spiking frequency.

To further resolve relative contributions of Phox2b-expressing chemosensitive glutamatergic retrotrapezoid nucleus cells and parafacial respiratory group pre-inspiratory neurones to synaptic neuroplasticity of sympathetic, inspiratory, and inspiratory oscillators, Zoccal et al. (2018) determined the effects of 10% hypercapnia upon thoracic sympathetic, abdominal. Phrenic nerve bursting before and following selective ablation of neurokinin 1-expressing retrotrapezoid neurones utilizing substance P-saporin conjugate and pharmacological antagonism of parafacial respiratory group neuronal glutamate receptors utilizing kynurenic acid. Lesioning neurokinin 1-expressing glutamatergic retrotrapezoid nucleus units by microinjecting substance P saporin-conjugate significantly attenuated the magnitude of late-expiratory bursting synchronized across thoracic sympathetic and abdominal neurograms and amplification of phrenic inspiratory bursting elicited by 10% hypercapnia in the \textit{in situ} arterially perfused preparation of the unanesthetized decerebrate juvenile rat (Zoccal et al., 2018). In contrast, pharmacological antagonism of parafacial respiratory group glutamate receptor modulated signaling to utilize microinjections of the nonsensitive glutamate receptor antagonist kynurenate (100 mM) completely abolished late-expiratory bursting synchronized across thoracic sympathetic and abdominal nerve discharge, though failed to modify phrenic nerve responses to hypercapnia in this preparation (Zoccal et al., 2018). The results indicate an absolute requirement of parafacial respiratory group units constituting the expiratory oscillator and the critical importance of chemosensitive glutamatergic retrotrape-
zoid nucleus neurons in generating synchronous late-expiratory bursting in thoracic sympathetic and abdominal nerve in response to chemoreceptor stimulation (Zoccal et al., 2018). Accordingly, the results appear to be most consistent with a model whereby hypoxia and hypercapnia-induced amplification of phrenic inspiratory amplitude and frequency critically require drive-by chemosensitive retrotrapezoid nucleus units, though remains essentially independent of parafacial respiratory group unitary activity.

9.3 Hypoxia

Acute and chronic intermittent hypoxia potently elicit late-expiratory bursting synchronized across abdominal and thoracic sympathetic neural efferent discharge (Figs. 8-11) (Moraes et al., 2014a,b; 2012b; Zoccal et al., 2007, 2009a, 2008). Acute hypoxia specifically augments thoracic splanchnic sympathetic nerve activity during the early or late segments of the expiratory epoch (see Moraes et al. (2014a)). Chronic intermittent hypoxic conditioning elicits a pattern of long term facilitation in propriobulbar interneuron microcircuit oscillators generating the breathing pattern and sympathetic activity typified by late-expiratory bursting synchronized across abdominal and thoracic sympathetic neurograms (Moraes et al., 2014b). Late-expiratory sympathetic bursting may amplify the sympathetic vasoconstrictor tone conveyed to the vessels during active expiratory efforts (Gilbey, 2007). Chronic intermittent hypoxic conditioning elicits long-term facilitation in phrenic motor output by amplifying the resting amplitude of population phrenic motoneuronal discharge (Fuller et al., 2003), chiefly utilizing serotonergic neuromodulation. An intimate understanding of these mechanisms may prove useful in the rational therapeutic design of novel strategies effectively ameliorating respiratory dysfunction in the setting of injury to the bulb and spinal cord (Fuller et al., 2003; Ghali, 2017c). Chronic intermittent hypoxia experimentally imposed or pathologically experienced by individuals suffering from central and/or obstructive sleep apnea elicits arterial hypertension, likely resulting from originating long-term potentiation of the glutamatergic retrotrapezoid nucleus and commissural nucleus tractus solitarius units conveyed to the medullary lateral tegmental field and rostral ventralateral medullary propriospinal interneuronal microcircuit oscillators. Individuals developing arterial hypertension in the setting of chronic intermittent hypoxia may exhibit increased dynamic gain and sensitivity of the peripheral chemoreflex and baroreflex and augmented basal and reflexogenic sympathoexcitation and neurogenic arterial hypertension (Molkov et al., 2011; Zoccal and Machado, 2011).

Afferent denervation of the chemosensitive carotid bodies eliminates neither the development of late-expiratory bursting activity synchronized across abdominal and sympathetic efferent discharge nor sympathetic potentiation in in situ arterially-perfused unanesthetized decerebrate juvenile rat previously conditioned with chronic intermittent hypoxia (Zoccal et al., 2008). Reducing chemosensory drive coordinately and significantly reduces late-expiratory synchronous bursting in abdominal and thoracic sympathetic neural discharge, effects evaluated in the in situ preparation of the arterially-perfused unanesthetized decerebrate juvenile rat, inspiring the wise construct of computational models by Molkov et al. (2014, 2011) capturing this behavior accordingly (Molkov et al., 2011). The supraspinal genesis of late-expiratory synchronous bursting in abdominal and sympathetic neural efferent discharge elicited by hypoxia represents coupled events (Molkov et al., 2014). Mechanisms strengthening sympathorespiratory coupling in response to oxygen deprivation may include altered sensitivity of peripheral chemoreceptor glomus cells, membrane voltage trajectories of which become depolarized by moderate and severe levels of hypoxia (Lahiri et al., 2006). Hypoxia generates an electrophysiological spike train in glossopharyngeal and vagal afferents relayed centrally, filtered, and integrated by, nucleus tractus solitarius neurons (Machado, 2001). Computational processing of these dynamic oscillatory inputs modulates the neural breathing rhythm, sympathetic oscillations, and ambigual cardiovagal premotoneural spiking (Moraes et al., 2014b, 2012b; Zoccal et al., 2007, 2009a, 2008). Hypoxia could strengthen sympatho-respiratory coupling (Moraes et al., 2014b, 2012b; Zoccal et al., 2007, 2009a, 2008) by directly activating or sensitizing central and/or peripheral chemoreceptors (Blain et al., 2010). Hypoxia generates hydrogen ion oxidizing equivalents in the microenvironmental milieu of chemosensitive glutamatergic retrotrapezoid nucleus units by preferentially favoring steps of the glycolytic pathway preceding prefacings diis-diss antioxidant phosphorylation. Compensatory amplification of lactate dehydrogenase mediated conversion of pyruvate to lactate to regenerate NAD+ oxidizing equivalent to sustain adenosine triphosphate generation, which may enhance glutamatergic RTN unit discharge frequency, coordinate enhancing Bötzinger complex and rostral ventrolateral medullary neuronal spiking (Molkov et al., 2014). A similar set of studies conducted in the unanesthetized decerebrate preparation of the rat will elucidate the mechanisms underlying hypercapnia, acute hypoxia, and chronic intermittent hypoxia-mediated strengthening of sympatho-respiratory coupling (see Ghali and Marchenko (2016b) and Marchenko et al. (2016) for precedence).

In the presence of pharmacological inhibition of the retrotrapezoid nucleus and parafacial respiratory group, pharmacological activation of peripheral chemoreceptors fails to elicit late-expiratory bursting synchronized across abdominal and sympathetic neural efferent discharge in the in situ brainstem spinal cord preparation of the unanesthetized decerebrate juvenile rat (Moraes et al., 2012a). These results imply chronic intermittent hypoxia-mediated genesis of late-expiratory synchronous bursting in abdominal and sympathetic neurograms could be mediated by coordinate synaptic inputs conveyed by chemosensitive glutamatergic retrotrapezoid nucleus units and parafacial respiratory group pre-inspiratory oscillators or neurosynaptic coupling of Bötzinger complex decrementing post-inspiratory and augmenting late-expiratory neurons and rostral ventrolateral medullary propriobulbar interneuronal microcircuit oscillators and presynaptic bulbospinal units (Molkov et al., 2014; Zoccal et al., 2008). Enhanced Bötzinger complex and rostral ventrolateral medullary neuronal spiking may express the composite influences of enhanced synaptic drive conveyed from the retrotrapezoid nucleus and parafacial respiratory group, sensitization of metencephalic and myelencephalic chemoreceptors by peripheral chemoreceptor inputs (Guynet et al., 2019), or blunted inhibitory drive from Bötzinger complex postinspiratory neurons (Molkov et al., 2010), compromised by hypoxic step reduction of the subpopulation of functionally active GABA and glycine receptor modulated neurosynaptic interactions (see Ghali and Ghali (2020)). These neuroplasticity mechanisms may utilize serotonergic (Mulkey et al., 2007) or purinergic (Mulkey et al., 2006) neuron transduction or be generated by oxidative stress. Accordingly, Barnett et al. (2017) provide a conceptual and computational model expressing interac-
9.4 Chemoreceptor vagal modulation

Dynamic spiking of vagal axons transducing alveolar stretch tempers hypercapnia mediated augmentation of phrenic burst amplitude in unanesthetized decerebrate (Ghali and Marchenko, 2016b) and urethane-anesthetized (Lemes and Zoccal, 2014; Takakura et al., 2007) rats and peripheral chemosensory facilitation of sympathetic neural bursting (vis-à-vis Ghali and Marchenko, 2016b). Dynamic vagal axonal spiking may similarly powerfully modulate the strength of sympathorespiratory coupling elicited by hypercapnia and hypoxia (Ghali and Marchenko, 2016b). [N.B.: The strategy of soi-disant "permissible hypercapnia" in mechanically-ventilated patients in the intensive care unit was managed according to ARDS protocol constitutes a natural pressor synergistically enhancing intravenously administered phenylephrine, norepinephrine, dopamine, and/or vasopressin, though paradoxically hindering the inotropic effects of these agents by generating a mild systemic acidosis (inotropic agents elicit cardiac contractility with less potency in the presence of tissue acidosis), coordinately supporting blood pressure and rendering attempts at weaning from mechanical ventilation more likely to be successful]. Crossmodal modulation amongst central and peripheral chemoreceptor and nucleus tractus solitarius pump cells, evident across a variety of animal models, preparation types, and experimental conditions (Ghali and Marchenko, 2016b; Lemes and Zoccal, 2014; Takakura et al., 2007), may contribute to emergently generating sympathorespiratory coupling (see excellent and concise review by Zoccal (2015)).

In urethane-anesthetized rats, vagotomy powerfully enhances the amplitude of expiratory abdominal nerve bursting elicited by the administration of hypercapnic and hypoxic gas mixtures (Lemes and Zoccal, 2014). Dynamic and tonic vagal influences powerfully differentially modulate hypercapnia-induced augmentation of hypoglossal pre-inspiratory and hypoglossal and phrenic inspiratory bursting amplitude in unanesthetized decerebrate adult rats (Ghali and Marchenko, 2016b), effects powerfully attenuated by vagotomy (Ghali and Marchenko, 2016b). GABAergic nucleus tractus solitarius pump cells inhibitory axodendritic and axosomatic modulation of chemosensitive glutamatergic retrotrapezoid nucleus units may contribute to pulmonary stretch-mediated attenuation of supraspinal chemoreceptor neuronal spiking elicited by hypercapnia and/or hypoxia in the presence of vagal continuity (Takakura et al., 2007). Constitutively spiking vagal afferents may restrict the preinspiratory, and attenuate the inspiratory, component of hypoglossal inspiratory bursting (Ghali, 2015; Ghali and Marchenko, 2016b).

10. Respiratory gating of baromodulation of sympathetic oscillations

Sympathetic oscillators receive the powerful modulatory synaptic drive from barosensitive nucleus tractus solitarius units (Fig. 5) (Mendelowitz, 1999). This constitutes a negative feedback mechanism regulating dynamic arterial pressure magnitude, dumping of spurts of blood into the microcirculation, and tissue perfusion dynamics (Alexander and Cuir, 1963). Dynamic arterial pressure rises
Fig. 11. Network changes contributing to modifications of sympatho-respiratory coupling following chronic intermittent hypoxic (CIH) conditioning. Traces within the boxes in the upper aspect of the left and right panels represent inspiratory-related, expiratory-related, and rostral ventrolateral medullary neuronal extracellular recordings. Integrated (∫) recordings of abdominal (AbN), sympathetic (Symp), and phrenic (Phr) nerve discharge are depicted by the lower traces. Sympathetic neural efferent activity exhibits phasic increases during the inspiratory phase (insp), with peak spiking frequency occurring during the late inspiratory and early post-inspiratory epochs (post-I), followed by dynamic reductions of bursting amplitude during the late post-inspiratory and late-expiratory epochs (E2) in the presence of normoxic normocapnia (left panels). Inputs deriving from inspiratory-(insp) and expiratory-(exp) related neurons constituting the soi-disant central respiratory pattern generator (CRPG) to rostral ventrolateral medullary (RVLM; (Moraes et al., 2012b) presympathetic neurons (symp) form and contribute to the emergent generation of the respiratory pattern. Inspiratory chest excursions constitute a dynamic, active process during normoxic normocapnia, with expiratory relaxation of the thoracic cavity occurring passively. In rats subjected to chronic intermittent hypoxia, propriobulbar interneuronal microcircuit oscillators generating active expiration become constitutive during resting normoxic normocapnia (Molkov et al., 2011; Zocca et al., 2008). Consequently, expiratory neurons, which natively exhibit isoelectric neural silence during rest, become active and supply excitatory neuronal inputs to bulbospinal expiratory units and rostral ventrolateral medullary presympathetic neurons, leading to the emergence and development of coupled and synchronous late-expiratory bursting activity in the discharge of abdominal and sympathetic nerve outputs (indicated by the arrows). Modified with permission from Fig. 1 of Zocca (2015).
tractus solitarius units via the aortic depressor nerve, carotid sinus nerve, and distributed afferent fibers join cranial nerves en route to myelencephalic oscillators may coordinate receive inputs from Hering's nerve and vagal afferents relaying fast oscillatory chemoreceptor inputs and vagal afferents relaying slow oscillatory alveolar stretch. Multimodal barosensitive, chemosensitive, and/or pulmonary stretch mechanosensitive units residing within the nucleus tractus solitarius may constitute a mechanism of respiratory gating and multiplicatively synergistic chemoreceptor augmentation of oscillatory baroreceptor inputs to higher-order neural networks. Nucleus tractus solitarius propriobulbar internuneuron microcircuit oscillatory convey synaptic drive to caudal ventrolateral medullary GABAergic units mediating state-dependent respirophasic and "baro-phasic" inhibition of rostral ventrolateral medullary presynaptic and parallel amplification of ambiguous cardiovagal premotoneuronal spiking (Ghali, 2017a, 2018; Guyenet, 2006). The magnitude of sinoatrial deceleration in response to a given incremental augmentation of dynamic arterial pressure magnitude constitutes the chief metric characterizing baroreflex gain (Rogers et al., 2000), powerfully crossmodally modulated by neural respiratory rhythmicity and dynamic changes in pulmonary stretch (Baekey et al., 2010), along with spectral peaks nestled within dynamic arterial pressure magnitude and cardiac interval. The magnitude of sinoatrial deceleration elicited by a fixed rise of dynamic arterial pressure varies with respect to respiratory cycle phase (Baekey et al., 2010), implying phase-dependent differential stimulability or inhibitoryity of sympathetic and cardio vagal preganglionic premotoneuronal spiking, with peak unitary discharge frequency occurring during the period which they are most excitable (Rogers et al., 2000). Sinoatrial decelerations elicited by the baroreflex are preferentially more prominent during the early expiratory epoch when afferents are most activated (Gilbey et al., 1984).

Respiratory-related neurons exhibiting arterial pulse modulation indicates baromodulation of the expiratory epoch and supports barostimulation facilitates expiratory-related neural activity. Lindsey et al. (1998) demonstrated the inspiratory phase, in response to chronically elevated dynamic arterial pressure magnitude. Metencephalic zones gate baroreceptor influences upon the propriobulbar internuncial microcircuit oscillators generating breathing. Accordingly, barosensitive nucleus tractus solitarius units receive modulatory synaptic drive preferentially exhibiting higher spiking frequency during the inspiratory epoch from neurons constituting dorsolateral metencephalic nuclei (Molkov et al., 2014). Electrical stimulation of propriobulbar internuncial microcircuit oscillators constituting the Kölliker-Fuse nucleus reduces the barosensitivity of monodurally or multimodally sensitive nucleus tractus solitarius cells in response to carotid sinus oscillatory inputs. Enhanced metencephalic neuronal spiking frequency specifically reduces baroreceptor gain during the inspiratory epoch (Brunner et al., 1982; Dove and Katona, 1985; Li et al., 1999b;a; Lindsey et al., 1998). These findings illustrate propriobulbar internuncial microcircuit oscillator inputs to sympathetic oscillators, and ambiguous cardiovagal premotoneurons constitute critical mechanisms mediating sympathorrespiratory modulation (Molkov et al., 2017).

11. Baromodulation of neural breathing

Respiratory-related unitary spiking subjected to baromodulation constitutes a mechanism emergently generating sympathorespiratory coupling (see Lindsey et al. (1998)). Extracellular recordings of brainstem respiratory-related units exhibit pulse-synchronous modulation in vagotomized unanesthetized decerebrate cats (Lindsey et al., 1998). Higher unitary discharge frequency during the expiratory epoch parallels augmentations of dynamic arterial pressure magnitude (Lindsey et al., 1998). Oscillatory baroreceptor inputs modulate respiratory-related neuronal spiking occurring in response to dynamic changes of arterial pressure magnitude, coordinate with evidence provided validating supraspinal mechanisms generate the described coupling (Morrison et al., 1984). Accordingly, in the unanesthetized decerebrate juvenile cat, vagotomy significantly reduces the pulse-synchronous modulation of pontine respiratory-related neurons by the arterial pressure waveform, contemporaneously amplifying the augmenting inspiratory pattern of respirophasic modulation of the units (Dick et al., 2009). Barostimulation elicits barosensitive medial and interstitial glutamatergic nucleus tractus solitarius neuronal spiking, which reduces sympathetic activity by activating a population of GABAergic interneurons residing within the caudal ventrolateral medulla conveying inhibitory axodendritic and axosomatic drive to rostral ventrolateral medullary propriobulbar internuncial microcircuit oscillators and interneuronally-coupled presynaptic bulbo spinal cells (Dampney, 1994; Ghali, 2017a, 2018; Goodchild and Moon, 2009; Guyenet et al., 1990). As a parallel pathway, barosensitive glutamatergic nucleus tractus solitarius units convey excitatory synaptically to Bötzinger complex glycinegic decrementing postsynaptic neurons, mediating coordinate enhancement of rostral ventrolateral medullary presynaptic and Bötzinger complex expiratory neuronal spiking, imposing baromodulation upon the respiratory rhythm and mediating sympatho-expiratory coupling (Baekey et al., 2010; Molkov et al., 2014).

Barostimuli elicits differential effects upon neural breathing pattern, whether applied during the inspiratory versus expiratory epochs, effects prominently demonstrated in the in situ arterially-perfused preparation of the unanesthetized decerebrate juvenile rat (Figs. 13 and 14) (Baekey et al., 2010). The behavior elucidates an understanding of interactions amongst oscillatory baroreceptor inputs with propriobulbar internuncial microcircuit oscillators generating breathing and indicate the latter gate the former. Barostimuli delivered during neural inspiration often fail to modify phrenic burst pattern, though successfully eliminate respirophasic modulation of sympathetic neural activity (Baekey et al., 2008). In contrast, barostimuli delivered during neural postinspiration and late expiration augment expiratory neural activity and eliminate respirophasic modulation of sympathetic neural efferent discharge (Baekey et al., 2008), supporting a model predicated upon prominent inhibition conveyed to Bötzinger complex decrementing postsynaptic neurons by decrementing early inspiratory neurons residing within the and rostral ventral respiratory group during neural inspiration (Molkov et al., 2017; Smith et al., 2007), preventing barostimuli delivered during inspiration from eliciting modifications of phrenic nerve bursting.

Baekey et al. (2010) present a characterizing model mechanism underlying the baromodulation of propriobulbar internuncial microcircuit oscillators generating neural breathing. According to this model, predicated upon reciprocal interaction of decrementing postsynaptic neurons with augmenting expiratory neurons, two classes of barosensitive nucleus tractus solitarius neurons included one group conveying synaptic drive to caudal ventrolat-
Mechanical transection between the metencephalon and myelencephalon abolishes respirophasic modulation of thoracic sympathetic (thSNA) nerve bursting in the in situ arterially-perfused preparation of the unanesthetized decerebrate juvenile rat. Upper panels: Thoracic sympathetic nerve bursting evidence late-inspiratory and postinspiratory accentuation during normoxic normocapnia in the presence of pontomedullary continuity. Prior to pontomedullary transection (intact pons; upper panels), integrated (∫) and raw thoracic sympathetic nerve activity exhibit a clear respirophasic modulation. Lower panels: Encephalotomy between the metencephalon and myelencephalon abolishes or significantly attenuates respirophasic modulation of raw and integrated (∫) thoracic sympathetic nerve activity. Top to bottom: integrated (∫) and raw thoracic sympathetic nerve activity (thSNA); integrated (∫) and raw phrenic nerve activity (PNA). Modified with permission from Fig. 1 of Molkov et al. (2014).

Fig. 12. Effects of pontomedullary transection on respirophasic modulation of thoracic sympathetic nerve activity. Mechanical transection between the metencephalon and myelencephalon abolishes respirophasic modulation of thoracic sympathetic (thSNA) nerve bursting in the in situ arterially-perfused preparation of the unanesthetized decerebrate juvenile rat. Upper panels: Thoracic sympathetic nerve bursting evidence late-inspiratory and postinspiratory accentuation during normoxic normocapnia in the presence of pontomedullary continuity. Prior to pontomedullary transection (intact pons; upper panels), integrated (∫) and raw thoracic sympathetic nerve activity exhibit a clear respirophasic modulation. Lower panels: Encephalotomy between the metencephalon and myelencephalon abolishes or significantly attenuates respirophasic modulation of raw and integrated (∫) thoracic sympathetic nerve activity. Top to bottom: integrated (∫) and raw thoracic sympathetic nerve activity (thSNA); integrated (∫) and raw phrenic nerve activity (PNA). Modified with permission from Fig. 1 of Molkov et al. (2014).

eral medullary GABAergic interneurons and another group conveying synaptic drive to metencephalic-dependent post-inspiratory units. Dynamically incrementing postinspiratory neuronal spiking frequency parallels correlated reductions of augmenting late-expiratory neuronal spiking frequency. Barostimuli delivered during the expiratory epoch coordinately elicit resurgence of postinspiratory neuronal spiking frequency commensurate with dynamic reductions of discharge precluding waning activity and attenuating augmenting late-expiratory neuronal spiking, in essence resetting the expiratory epoch. An excitatory population of Bötzinger complex expiratory-related neurons, putatively glutamatergic, may convey direct axodendritic and axosomatic synaptic drive to rostral ventrolateral medullary neurons (Molkov et al., 2014). Bötzinger complex decrementing postinspiratory neurons are released from inhibitory modulation by preBötzinger complex decrementing early inspiratory neurons and rostral ventral respiratory group inspiratory neurons during early neural expiration (Smith et al., 2007), in effect coordinately amplifying neural expiratory activity and attenuating respirophasic modulation of sympathetic discharge (Baekey et al., 2010). Bötzinger complex decrementing postinspiratory neurons (see Ezure and Manabe (1988)) convey excitatory and/or inhibitory modulation to Bötzinger complex augmenting late expiratory neurons (Smith et al., 2009), preBötzinger complex pre-inspiratory, pre-inspiratory-inspiratory phase-spanning, and decrementing early-inspiratory units (Molkov et al., 2010), and rostral ventrolateral medullary presympathetic cells (Molkov et al., 2014;
In contrast, Bötzinger complex augmenting late-expiratory neurons making direct synaptic contacts with adjacent rostral ventrolateral medullary cells (Moraes et al., 2012c; Sun et al., 1997) augment presympathetic bulbospinal neuronal spiking during late expiration, constituting a chief mechanism mediating sympathovagal coupling and strengthening the same in response to hypercapnia (Molkov et al., 2014) and acute and chronic intermittent hypoxia (Moraes et al., 2014b, 2012b; Zoccal et al., 2007, 2009a, 2008).

12. Signal analysis

12.1 Overview

The signal analysis seeks to generate static or dynamic time-frequency representations of unitary, multi-unitary, or population firing behavior and inter-ensemble synchrony in the frequency and/or time domains (Ghali and Marchenko, 2013; Marchenko et al., 2012; Preobrazhenskii and Jarovitskii, 1963). Oscillations generated by the breathing generator, sympathetic oscillators, and cardiovagal premotoneurons interact nonlinearly and dynamically (Christakos et al., 1991; Dittler and Garden, 1912; Julien, 2006; Wyss, 2003). Nonlinear interactions occur amongst preganglionic sympathetic neurons supplying the heart with oscillatory waves conferred by mechanical ventilatory fluctuations in vagotomized unanesthetized decerebrate cats (Montano et al., 1992) and slow and fast components of postganglionic sympathetic discharges in pentobarbital-anesthetized sinoaortic denervated vagotomized cats (Zhong et al., 1998). Linear techniques, including cross-spectral density and coherence analyses, adequately characterize nature and stringency of synchronization amongst waves, thus inferring the probability of coordinate genesis by a common oscillatory mechanism or local coupling mechanisms at the level of the individual oscillators (Marchenko et al., 2012). However, these techniques suffer from providing inadequate descriptions of the precise nature and causality of oscillatory interactions. Thus, the development and use of nonlinear techniques may inform and improve an understanding of dynamics and interactions of these oscillations according to a precise and elegant mathematical formalism (Hesse et al., 2003; Smirnov et al., 2008; Sysoev et al., 2016; Sysoeva et al., 2014).

The signal analysis permits the faithful conduct of coherence analysis between individual neuronal activity with en masse continuous neural efferent discharge (Marchenko et al., 2012). While most studies have correlated neuronal waveforms to determine coupling amongst the sympathetic and respiratory activities utilizing classic techniques (Christakos et al., 1991), a plethora of exploitable techniques abound in the literature. They may prove to be of significant potential in describing the behavior and character of these interactions. We point to the classic techniques of Fourier transformation, cross-correlation, autocorrelation, spectral power determination, cross-spectral density coherence, and dynamic time-frequency representations of coherence (Gavrovskaya et al., 2014; Ghali and Marchenko, 2013; Marchenko et al., 2012). We concurrently detail more intricate techniques which may prove useful in precisely determining wave coupling, including nonlinear correlation (Pijn et al., 1992), partial directed coherence (Baccalá and Sameshima, 2001), structure determination (Baccalá and Sameshima, 2001), linear (Hesse et al., 2003) and nonlinear Granger causality (Sysoeva et al., 2014), transfer entropy (Schreiber, 2000), and phase modeling (Smirnov et al., 2008), among other nuanced and specific techniques and approaches (Sysoev et al., 2016).

12.2 Coherence between motoneuron and neurogram recordings

To perform correlation or coherence analysis between two signals, the signals must remain continuous (Marchenko et al., 2012). This requirement precludes performing coherence analysis between unitary neural spiking with neural efferent output. Accordingly, we previously presented a study seeking to determine the presence of high-frequency oscillations in the spectra of individual phrenic motoneuronal recordings correlated with similar spectra observed in the Fast Fourier transforms of monopolar phrenic nerve recordings and provided evidence indicating high-frequency phrenic motoneurons oscillating at this frequency directly contribute to this spectral band of rhythmic activity in the phrenic neurogram (Marchenko et al., 2012). To achieve these goals, we needed to identify phrenic motoneurons (PMNs) spiking at these rates and correlate this discharge with population activity in efferent phrenic nerve (PhN) recordings (Marchenko et al., 2012). Phrenic motoneuron action potentials were derived at peak electroporative membrane voltage using Spike2CED software, and this unitary activity transformed into a continuous semicosine wave utilizing custom-designed scripts (Marchenko et al., 2012). We subsequently normalized the inspiratory epoch from 0 to 1 and averaged phrenic motoneuronal and neurogram activities gated by phrenic inspiratory burst onset and offset (Marchenko et al., 2012).

A magnified view of the phrenic burst reveals a difficult to appreciate, though discernible distinction, during the transition between inspiratory and postinspiratory epochs, with an apparent, though subtle segmentation of the burst components by a narrow inter-burst segment containing a paucity of oscillations (Ghali, 2015). Less magnified views of the phrenic burst effectively identify the border separating inspiratory and postinspiratory phases by a transition from augmenting to decrementing spatiotemporal dynamics of activity (Ghali, 2015). This strategy permitted us to determine coherence between the two waves with respect to discrete times within the inspiratory epoch and frequencies of observed phrenic motoneuronal and nerve discharge by performing smoothed pseudo-Wigner Ville distribution (SPWVD) time-frequency representation (TFR) coherence analysis between the phrenic motoneuron semi cosine wave and efferent phrenic nerve discharge using custom-designed MATLAB scripts (Gavrovskaya et al., 2014; Ghali and Marchenko, 2013; Marchenko et al., 2012; Pereira de Souza Neto et al., 2001; Tağlık et al., 2005). To perform smoothing in the time and frequency domains, we applied the previously described moving kernel function (Marchenko et al., 2012).

13. Perspectives and significance

Several mechanisms conspire to emergently generate sympatho-respiratory, parasympatho-respiratory, and sympatho-parasympathetic coupling at rest and during hypercapnic and hypoxic conditions (Molkov et al., 2017; Moraes et al., 2014a, 2012a, 2014b, 2012b; Zoccal, 2015; Zoccal et al., 2007, 2009a; Zoccal and Machado, 2011; Zoccal et al., 2009b, 2008). Common inputs may generate Autonomorrespiratory coupling conveyed to propriobular interneuronal microcircuit oscillators constituting the breathing pattern generator, sympathetic oscillators, and ambient cardio-vagal premotoneurons, i.e., RTN/pFRG, see Abdala et al. (2009), coordinate and heterologous regulation by common ascending inputs relaying peripheral oscillatory baroreceptor, chemoreceptor, and pulmonary stretch receptor inputs (Takakura et al., 2007), and
direct neurosynaptic interactions amongst overlapping propriobulbar interneuronal microcircuit oscillators of the constituent generators (i.e., Bötzinger complex and rostral ventrolateral medulla, see Moraes et al. (2012c) and Sun et al. (1997)). The presented set of conjectures and hypotheses carry equivalent empirical validity and naturally evolve the construction of an elegant model recapitulating and elucidating the mechanistic behavior of experimentally-evident autonomosympathoeryngeal coupling (Molkov et al., 2014).

Bötzinger complex decrementing post-inspiratory (Ezure and Manabe, 1988) and augmenting late-expiratory (Jean, 1992) neurons overlap with rostral ventrolateral medullary catecholaminergic, and glutamatergic presynaptic bulbospinal units (Ghali, 2017a, 2018; Guyenet et al., 2018; Guyenet, 2006) and pre-Bötzinger complex preinspiratory, preinspiratory-inspiratory phase spanning, and decrementing early inspiratory units (Molkov et al., 2017; Morgado-Valle and Beltran-Parrazal, 2015) overlap with causal ventrolateral medullary GABAergic interneurons (Goodchild and Moon, 2009; Mandel and Schreinhofer, 2006; Paxinos et al., 1985). Excitatory and inhibitory neurosynaptic interactions coupling these cells emergently generates and strengthens sympatho-respiratory coupling (Marchenko et al., 2016; Molkov et al., 2014). Thus, the relative balance of excitatory and inhibitory drive conveyed by, and synaptic contacts with, intermingled Bötzinger complex gluta
matergic decrementing postinspiratory, glutamatergic decrementing postinspiratory, and GABAergic augmenting late augments propriobulbar neuronal spiking across abdominal and thoracic sympathetic neurons (see Guyenet et al., 2017a, 2018; Guyenet et al., 2006) and pre-Bötzinger complex preinspiratory, preinspiratory-inspiratory phase spanning, and decrementing early inspiratory units (Molkov et al., 2017; Morgado-Valle and Beltran-Parrazal, 2017) overlap with causal ventrolateral medullary GABAergic interneurons (Goodchild and Moon, 2009; Mandel and Schreinhofer, 2006; Paxinos et al., 1985). Excitatory and inhibitory neurosynaptic interactions coupling these cells emergently generates and strengthens sympatho-respiratory coupling (Marchenko et al., 2016; Molkov et al., 2014). Thus, the relative balance of excitatory and inhibitory drive conveyed by, and synaptic contacts with, intermingled Bötzinger complex glycinergic decrementing postinspiratory, glutamatergic decrementing postinspiratory, and GABAergic augmenting late augments propriobulbar neuronal spiking across abdominal and thoracic sympathetic neurons (see Guyenet et al., 2017a, 2018; Guyenet et al., 2006) and pre-Bötzinger complex preinspiratory, preinspiratory-inspiratory phase spanning, and decrementing early inspiratory units (Molkov et al., 2017; Morgado-Valle and Beltran-Parrazal, 2015) overlap with causal ventrolateral medullary GABAergic interneurons (Goodchild and Moon, 2009; Mandel and Schreinhofer, 2006; Paxinos et al., 1985). Excitatory and inhibitory neurosynaptic interactions coupling these cells emergently generates and strengthens sympatho-respiratory coupling (Marchenko et al., 2016; Molkov et al., 2014). Thus, the relative balance of excitatory and inhibitory drive conveyed by, and synaptic contacts with, intermingled Bötzinger complex glycinergic decrementing postinspiratory, glutamatergic decrementing postinspiratory, and GABAergic augmenting late augments propriobulbar neuronal spiking across abdominal and thoracic sympathetic neurons (see Guyenet et al., 2017a, 2018; Guyenet et al., 2006) and pre-Bötzinger complex preinspiratory, preinspiratory-inspiratory phase spanning, and decrementing early inspiratory units (Molkov et al., 2017; Morgado-Valle and Beltran-Parrazal, 2015) overlap with causal ventrolateral medullary GABAergic interneurons (Goodchild and Moon, 2009; Mandel and Schreinhofer, 2006; Paxinos et al., 1985). Excitatory and inhibitory neurosynaptic interactions coupling these cells emergently generates and strengthens sympatho-respiratory coupling (Marchenko et al., 2016; Molkov et al., 2014). Thus, the relative balance of excitatory and inhibitory drive conveyed by, and synaptic contacts with, intermingled Bötzinger complex glycinergic decrementing postinspiratory, glutamatergic decrementing postinspiratory, and GABAergic augmenting late augments propriobulbar neuronal spiking across abdominal and thoracic sympathetic neurons (see Guyenet et al., 2017a, 2018; Guyenet et al., 2006) and pre-Bötzinger complex preinspiratory, preinspiratory-inspiratory phase spanning, and decrementing early inspiratory units (Molkov et al., 2017; Morgado-Valle and Beltran-Parrazal, 2015) overlap with causal ventrolateral medullary GABAergic interneurons (Goodchild and Moon, 2009; Mandel and Schreinhofer, 2006; Paxinos et al., 1985). Excitatory and inhibitory neurosynaptic interactions coupling these cells emergently generates and strengthens sympatho-respiratory coupling (Marchenko et al., 2016; Molkov et al., 2014). Thus, the relative balance of excitatory and inhibitory drive conveyed by, and synaptic contacts with, intermingled Bötzinger complex glycinergic decrementing postinspiratory, glutamatergic decrementing postinspiratory, and GABAergic augmenting late augments propriobulbar neuronal spiking across abdominal and thoracic sympathetic neurons (see Guyenet et al., 2017a, 2018; Guyenet et al., 2006) and pre-Bötzinger complex preinspiratory, preinspiratory-inspiratory phase spanning, and decrementing early inspiratory units (Molkov et al., 2017; Morgado-Valle and Beltran-Parrazal, 2015) overlap with causal ventrolateral medullary GABAergic interneurons (Goodchild and Moon, 2009; Mandel and Schreinhofer, 2006; Paxinos et al., 1985).
thororespiratory coupling. Oscillatory baroreceptor inputs transduced by pressure-sensitive receptors exhibiting highest density within the carotid sinus and aortic arch, though diffusely distributed throughout the internal carotid (Toorop et al., 2013), vertebral (Agadzhanyan and Kupriianov, 2008; Kupriyanov, 2009), and subclavian arteries (Chevalier-Cholat and Friggi, 1977, 1976; Kidd et al., 1974) relays centrally to neurons residing within the medial and interstitial divisions of the nucleus tractus solitarius covarying dynamically with changes of arterial pressure magnitude (Rogers et al., 2000). Spatiotemporal bursting dynamics of integrated baroreceptor discharge frequency assumes the form of a sine wave. Oscillatory baroreceptors inputs emergently generate sympathorespiratory coupling by modulating overlapping Botzinger complex and rostral ventrolateral medullary propriobulbar interneuronal microcircuit oscillators (Moraes et al., 2012c; Sun et al., 1997) through GABAergic caudal ventrolateral medullary interneurons (Guyenet et al., 2019; Guyenet, 2006; Mandel and Schreihofer, 2006).

Mechanosensitive pulmonary stretch receptors residing within the alveolar interstitium may be electrophysiologically segregated into slow (Fenik, 1992; Preobrazhenskii and Fenik, 1989) and fast (Zhdanov, 1984) adapting types of stretch receptors, with discharge frequency nonlinearly covarying according to an absolute, or static or dynamic rate of change of, pulmonary stretch (Preobrazhenskii and Fenik, 1989). Slow adapting pulmonary stretch receptors chiefly sensitive to the absolute magnitude of stretch generate com-

Fig. 13. Dynamic changes of arterial pressure magnitude elicit coordinate modification of phrenic and sympathetic neural bursting. A: Barostimuli applied during the inspiratory, postinspiratory, or late expiratory epochs in the in situ arterially-perfused unanesthetized decerebrate juvenile rat elicit differential effects upon neural breathing pattern. Barostimuli delivered during the inspiratory epoch failed to modify breathing rhythm or burst parameters. However, barostimuli applied during the postinspiratory, and late-expiratory epochs elicited robust amplification of expiratory epoch duration. Following mechanical transection separating the metencephalon from the myelencephalon, a barostimulus applied during late expiration contracted apneustic inspiratory bursts in the phrenic nerve discharge. Barostimuli most powerfully elicits reductions of sympathetic neural efferent activity when applied during inspiration, putatively consequent to preferentially inspiratory accentuation of sympathetic neural bursting during resting eucapnic hyperoxia and reduced excitatory synaptic drive from the glutamatergic excitatory population of Botzinger complex decrementing postinspiratory neurons. ∫ SNA, integrated sympathetic nerve activity (mV, millivolts); ∫ PNA, integrated phrenic nerve activity (V, Volts); PP, perfusion pressure (mmHg); Timescale bar is shown in the lower right-hand corner (5 seconds). B: Computational model simulation of baroreceptor stimulus applied during inspiratory and expiratory epochs in preparations with theoretically preserved pontomedullary continuity intact model and during the inspiratory epoch following removal of the metencephalic compartment. The effects recapitulate empirically-observed respirophasic-variant influences of oscillatory baroreceptor inputs upon the breathing pattern. A simulated barostimulus presented during the inspiratory epoch with preserved pontomedullary continuity negligibly modifies breathing rhythm parameters, though effectively reduces sympathetic neural bursting. A simulated barostimulus applied during the late expiratory epoch elicits modest enhancement of expiratory epoch duration with reflex augmentation of amplitude and duration of ensuing inspiratory bursts coordinately with attenuation of sympathetic neural activity. Reflex augmentation of inspiratory bursting succeeds expiratory facilitation elicited by a barostimulus applied during late expiration, putatively resulting from recovery and resetting of phrenic motoneuronal membrane voltage trajectories and replenishing of neuronal metabolic adenosine triphosphate stores, permitting successively conveyed bulbospinal axodendritic and axosomatic synaptic drive conveyed from rostral ventral respiratory group augmenting inspiratory neurons to elicits early-inspiratory high-frequency oscillations exhibiting more robust coherence and synchrony amongst the population of phrenic motoneurons. Removal of the metencephalic compartment abolishes respirophasic modulation of sympathetic neural activity in the model, with barostimuli delivered during inspiration contracting aapneustic inspiratory epochs and reducing sympathetic neural activity. Barostimuli applied during inspiration, and late expiration elicits similar reductions in sympathetic neural activity in preparations with preserved pontomedullary continuity. SNA; sympathetic nerve activity (amplitude normalized from 0 to 1); PNA, phrenic nerve activity (amplitude normalized from 0 to 1). Modified with permission from Fig. 3 of Molkov et al. (2014).
plex spike trains during the phrenic burst (Chen et al., 2011, 2010, 2008; Marchenko and Rogers, 2007b), compared with fast adapting pulmonary stretch receptors, which possess rapid desensitization kinetics and are thus specifically tuned to detecting the onset and offset of the inspiratory epoch (Zhdanov, 1984). Spike trains of these receptors relay centrally via pulmonary stretch mechanosensitive vagal afferents to pump cells chiefly residing in the ventrolateral division of the nucleus tractus solitarius (Moreira et al., 2007; Takakura et al., 2007). Higher-order nucleus tractus solitarius units may alternately receive the monomodal or multimodal convergent somatodendritic synaptic drive from afferents relaying oscillatory inputs from baroreceptors (Rogers et al., 2000), chemoreceptors (Takakura et al., 2007), or pulmonary stretch mechanoreceptors (Li et al., 1999b, c; Moreira et al., 2007; Takakura et al., 2007). Rises of dynamic arterial pressure magnitude occurring during the inspiratory epoch elicit multiplicative amplification of neuronal spiking frequency of multimodal nucleus tractus solitarius units, contrasted with rises of dynamic arterial pressure magnitude during expiration which elicit comparatively more attenuated augmentations of NTS neuronal spiking frequency (Rogers et al., 2000).

These findings collectively mechanistically indicate oscillatory mechanosensory pulmonary stretch spike cell trains heterosynthetically gates oscillatory baroreceptor inputs to NTS units. Reciprocally, oscillatory baroreceptor spike cell trains heterosynthetically gates oscillatory pulmonary stretch inputs to NTS units (Baekey et al., 2010). More simply stated, neural inspiratory activity gates baroreceptor oscillations and dynamic arterial pressure magnitude gates pulmonary stretch receptor spike trains conveyed to nucleus tractus solitarius units (Baekey et al., 2010). Glutamatergic barosensitive nucleus tractus solitarius units convey excitatory axodendritic and axosomatic synaptic drive to caudal ventrolateral medullary GABAergic propriobulbar interneurons and may heterosynthetically blunt the discharge of glutamatergic chemosensitive retrotrapezoid nucleus units (Guyenet, 2006), conferring oscillatory baroinhibition of rostral ventrolateral medullary presympathetic unitary spiking (Mandel and Schreihofer, 2006). By this mechanism, baroreceptor oscillations modulate the sympathetic neural efferent output (Diedrich et al., 2009; Ghali, 2017a, 2018; Guyenet et al., 2019). Critically, barosensitive nucleus tractus solitarius unitary spiking coordinately influences cardiovagal premotoneuronal spiking within the dorsal motor nucleus of the vagus and nucleus ambiguous innervating dendrites and somata of postganglionic parasympathetic cholinergic neurons in the cardiac plexus (Eckberg, 2003), accordingly modulating sinoatrial action potential frequency, atrioventricular conductility, and myocardial contractility. Oscillatory fluctuations of arterial pressure, thus confer an oscillatory fluctuation upon the cardiac interval (Rogers et al., 2000), influencing spectral variability of dynamic arterial pressure magnitude.

A host of mechanisms reflecting the overall state and condition of the breathing generator, sympathetic oscillators, and ambigual cardiovagal premotoneurons impose respirophasic modulation upon cardiovagal premotoneuronal spiking (Dergacheva et al., 2010; Farmer et al., 2016). The Bötzinger complex contains decrementing postinspiratory neurons exhibiting a predominantly glycnergic neurochemical repertoire (Ezure and Manabe, 1988), though a few of these units also exhibit a glutamatergic phenotype (Molkov et al., 2017; Smith et al., 2007). Bötzinger complex glycnergic and glutamatergic decrementing postinspiratory modulate cardiovagal premotoneuronal membrane voltage trajectories during the early expiratory epoch. The relative balance and weighing of synaptic inputs conveyed by these cells determine whether afferent influences generate predominantly expiratory facilitation or inhibition of efferent cardiovagal premotoneurons residing within the nucleus ambiguus and dorsal motor vagal nucleus (Dergacheva et al., 2010; Farmer et al., 2016). Direct synaptic drive conveyed by Bötzinger complex GABAergic cells to ambigual cardiovagal premotoneurons (Dergacheva et al., 2010; Farmer et al., 2016) may represent a parallel mechanism generating attenuation of cardiovagal premotoneuronal tone and reciprocal sinoatrial accelerations.

Bötzinger complex decrementing postsipiratory neurons coordinate receive excitatory axodendritic and axosomatic drive from Kölliker-Fuse and medial parabrachial nucleus propriobulbar units (Dutschmann and Herbert, 2006; Mörschel and Dutschmann, 2009) and monosynaptic direct and polysynaptic indirect modulation conferred by monomodal or multimodal nucleus tractus solitarius units (Molkov et al., 2017; Smith et al., 2007) (Fig. 5). Bötzinger complex decrementing postsipiratory neurons modulate normal triphasic eupnea by segmenting the expiratory epoch through reciprocal inhibitory neurosynaptic interactions with Bötzinger complex augmenting late-expiratory neurons and via the provision of prominent inhibitory modulatory influences upon preBötzinger complex preinspiratory, preinspiratory inspiratory phase spanning and decrementing early inspiratory neurons (Molkov et al., 2017; Rybak et al., 2014; Smith et al., 2007). The direct overlap of the Bötzinger complex with rostral ventrolateral medullary propriobulbar and bulbo-spinal circuitry provides a neuroatomic substrate generating common sympatho-respiratory coupling and crossmodal modulation amongst these oscillatory zones (Moraes et al., 2014a, b).

According to the described neuroatomic organization and patterns of electrophysiological interactions, any peripheral stimulus or set of influences modulating nucleus tractus solitarius unitary spiking frequency (Chen et al., 2011; Moreira et al., 2007; Rogers et al., 2000; Takakura et al., 2007) may coordinately modulate cardiovagal premotoneuronal (Bishop, 1974; Lindsey et al., 1998) and rostral ventrolateral medullary presympathetic unitary spiking (Moraes et al., 2012c; Sun et al., 1997) through axodendritic and axosomatic synaptic drive conveyed to Bötzinger complex neurons (Molkov et al., 2014). However, the specific type of stimulus modulating nucleus tractus solitarius neuronal spiking differential influences pattern of modulation conveyed upon propriobulbar interneuronal microcircuit oscillators generating breathing, sympathetic activity, and cardiovagal premotoneuronal discharge (Baekey et al., 2010; Lindsey et al., 1998). The magnitude and dynamic rates of changes of alveolar stretch detected by slow and fast adapting pulmonary stretch receptors (Chen et al., 2011) conveyed centrally through vagal afferents to the ventrolateral and interstitial divisions of the nucleus tractus solitarius (Marchenko and Sapru, 2000) commensurately modulate Bötzinger complex decrementing postsipiratory and augmenting late expiratory neuronal spiking to disfacilitates inspiratory and enhance expiration (Molkov et al., 2017) and rostral ventrolateral medullary presympathetic units to generate sympathoinhibitory effects via the soi-disant sympathetic arm of the Hering Breuer reflex (Guyenet, 2006) and sinoatrial acceleration through disfacilitation of cardiovagal premotoneurons, consequent to inhibitory axodendritic and axosomatic modulation by Bötzinger complex GABAergic propriobulbar interneuronal microcircuit os-
...post-inspiratory neuronal spiking frequency and reduce Bötzinger complex augmenting late-expiratory activity, recapitulating model predictions. Modified...

Fig. 14. Mechanism mediating resetting of expiration elicited by transient barostimuli. A: Computational modeling prediction of Bötzinger complex postinspiratory neuronal and phrenic nerve discharge to a barostimulus applied during the late expiratory epoch. Bötzinger complex post-inspiratory and augmenting late-expiratory neuron membrane voltage trajectories (first and third traces) and action potential spiking among both neuronal populations (second and fourth traces) are depicted. Shaded intervals within segregable respiratory epochs highlight inspiratory, early expiratory (E1), and late expiratory (E2) epochs. Barostimulation resets expiration by activating populations of Bötzinger complex postinspiratory units neurosynaptically inhibiting Bötzinger complex augmenting late-expiratory cells. Delivery of a barostimulus amid late expiration restores augmenting expiratory neuronal spiking and elicits a second complete expiratory effort. B: Extracellular recordings (first among each pair of upper and middle traces) and unitary spiking histograms (second among each pair of upper and middle traces) of Bötzinger complex decrementing post-inspiratory (upper pair of traces) and augmenting late expiratory (middle pair of traces) neurons. Integrated phrenic nerve activity (F PNA) and perfusion pressure (PP) are successively depicted in the lower pair of traces. Barostimulus delivered during late expiration generates expiratory resetting in the in situ arterio-venous preparation of the unanesthetized decerebrate juvenile rat. Barostimuli delivered during the late-expiratory epoch in the in situ preparation of the unanesthetized decerebrate juvenile rat enhances Bötzinger complex post-inspiratory neuronal spiking frequency and reduces Bötzinger complex augmenting late-expiratory activity, recapitulating model predictions. Modified with permission from Fig. 4 of Molkov et al. (2014).

cillators (Fenik, 1992; Preobrazhenskiï and Fenik, 1989; Zhdanov, 1984; Zhdanov et al., 1989).

Chemosensory stimulation of commissural nucleus tractus solitarius units coordinate enhances Bötzinger complex expiratory neuronal discharge and rostral ventrolateral medullary presympathetic unitary activity (Michelini, 1994; Moreira et al., 2007; Rogers et al., 2000; Schwaber et al., 1993; Takakura et al., 2007). Accordingly, hypercapnia or acute or chronic intermittent hypoxia enhances glutamatergic excitatory and GABAergic inhibitory modulation conveyed to dorsal medullary cardiovagal premotoneurons (Dergacheva et al., 2010; Farmer et al., 2016) permitting sinoatrial acceleration elicited by sympatheoexcitation (see Gueney et al. (2018, 2019)) to support chemoreceptor-driven amplifications of myocardial output and dynamic arterial pressure magnitude. Factors influencing baroreflex gain and sensitivity (see Rogers et al. (2000)) may modify patterns of modulation of Bötzinger complex decrementing post-inspiratory and augmenting late-expiratory neurons by chemosensitive commissural nucleus tractus solitarius neuronal synaptic inputs. Chemosensitive glutamatergic retrotrapezoid nucleus units convey diffuse tonic excitatory drive to the Bötzinger complex, chiefly augmenting late-expiratory neurons, and receive prominent GABAergic modulatory synaptic drive deriving from nucleus tractus solitarius pump cells (Guyenet et al., 2019). These pathways constitute a network mechanism permitting pulmonary stretch receptor-mediated blunting of chemosensory amplification of neural respiratory output, relaying to glutamatergic retrotrapezoid nucleus units via nucleus tractus solitarius pump cells (Takakura et al., 2007) and conjecturally powerfully restricting the preinspiratory component of hypoglossal bursting in the presence of preserved vagal continuity (Ghali, 2015, 2019c; Ghali and Marchenko, 2016b).

Peripheral chemoreceptors constituted glomus cells exquisitely sensitive to hypercapnia, and moderate and severe levels of hypoxemia chiefly utilize purinergic signaling (Baby et al., 2006) and convey stimulus mediated modifications of neuronal spiking frequency centrally to chemosensitive glutamatergic commissural nucleus tractus solitarius neurons (Zhang et al., 2011). Glutamatergic chemoreceptor neurons distributed throughout the retrotrapezoid nucleus and parafacial respiratory group complex (Guyenet et al., 2019; Onimaru et al., 2018), nucleus tractus solitarius (Nichols et al., 2008), raphé group of nuclei (Sobrinho et al., 2014), pre-Bötzinger complex, and fastigial nucleus (Hernandez et al., 2004) are chiefly sensitive to elevations of carbon dioxide tension or hydrogen ion concentration, with a few zones coordinate exhibiting hypoxic sensitivity (e.g., preBötzinger complex, fastigial nucleus). Hypercapnia and hypoxia elicit and amplify discharge of peripheral chemoreceptor glomus cells (Zoccal, 2015) and chemosensitive bulbar units (Guyenet et al., 2019) conveying coordinate synaptic...
drive to breathing generators (Marchenko et al., 2016; Molkov et al., 2014; Zoccal and Machado, 2011; Zoccal et al., 2008), sympathetic oscillators (Gilbey et al., 1995), and cardiovagal premotoneurons (Bishop, 1974; Lindsey et al., 1998), crossmodally sensitizing each other's discharge (Blain et al., 2010) and conveying augmented coherent neuronal spiking through propriobulbar interneuronal pauce-synaptic interactions (Molkov et al., 2014).

Intravenous sodium chloride administration coordinately enhanced phrenic nerve bursting frequency and thoracic sympathetic neural burst amplitude in decorticate Holtzman rats, both effects of which were abolished by precollicular transection, supporting paraventricular and supraoptic nuclei mediate the effects (da Silva et al., 2019). Carotid body removal prevented the enhancement of thoracic sympathetic nerve activity elicited by intravenous administration of sodium chloride, though failed to prevent tachypnea, supporting carotid body glomus cells may represent effective osmoreceptors (da Silva et al., 2019). Peripheral and central chemoreceptor driven augmentation of the respiratory, central pattern generator and sympathetic oscillators becomes synchronized and commonly coupled through coordinate and independent bulbobulbar, spinoreticular, and peripheral afferent inputs couple and synchronize central and peripheral chemoreceptor mediated augmentation of neuronal ensembles constituting the constituent generators, strengthened by direct interactions between overlapping propriobulbar interneuronal arrays constituting the respiratory rhythm and pattern generator, sympathetic oscillators, and cardiovagal premotoneurons (Molkov et al., 2017; Zoccal, 2015). These pathways constitute mechanisms generating autonomorespiratory coupling and crossmodal modulation amongst disparate oscillators and nuclei at rest during normoxic normocapnia, which becomes amplified by hypercapnia and acute and chronic hypoxia (Figs. 1-5) (Molkov et al., 2017; Zoccal, 2015).

Sympathorespiratory, parasympathorespiratory, and symp-thopathyparasympathetic coupling may further be subject to modulation by cardiovascular and respiratory muscle training, putatively mediated by amplifying the cardiovagal sinoatrial decelerator tone, evidenced in powerful modifications of the cardiovascular spectral variabilities (de Abreu et al., 2019).

14. Conclusions

The respiratory rhythm (Anderson et al., 2016; Anderson and Ramirez, 2017; Ghali, 2019c; Morgado-Valle and Beltran-Parrazal, 2017; Ramirez and Baertsch, 2018) and pattern (Ghali, 2018; Marchenko et al., 2016; Ramirez and Baertsch, 2018; Smith et al., 2009), sympathetic oscillations (Ghali, 2017a, 2019b, 2018), and cardiovagal premotoneuronal activity (Baekey et al., 2010; Bishop, 1974) are generated by distinct, though overlapping, networks residing chiefly within the metencephalon and myelencephalon (Ghali, 2017a,b,c, 2019a,b; Marchenko et al., 2016; Molkov et al., 2017) and powerfully modulated by descending synaptic inputs from the cerebrum (Antal, 1985), hippocampus (Ruit and Neafsey, 1988), amygdala (Lacuey et al., 2019), thalamus (Ogundele et al., 2017), hypothalamus (Fukushi et al., 2019), midbrain (Ghali and Ghali, 2020), and cerebellum (Horn and Waldrop, 1997; Schmid et al., 1988; Subramanian and Holstege, 2014). The widespread presence of autonomorespiratory coupling, manifest as baroreceptor and sympathetic modulation of neural respiratory activity (Baekey et al., 2010; Bishop, 1974; Lindsey et al., 1998), respirophasic modulation of sympathetic discharge (Haselton and Guyenet, 1989; Mandel and Schreihof, 2006; McAllen, 1987; Molkov et al., 2017), and ambiguous cardiovagal premotoneurons (Dergacheva et al., 2010), and crossmodal modulation between sympathetic and parasympathetic outflows evidence coordinate inputs to, and direct interaction amongst and between, propriobulbar interneuronal microcircuit oscillators constituting the pattern generators mediating the neurogenesis of these activities and heterologous peripheral modulation of breathing, sympathetic oscillations, and cardiovagal premotoneurons by vagal afferents conveying oscillatory baroreceptor, chemoreceptor, and pulmonary stretch receptor inputs (Molkov et al., 2017; Zoccal, 2015). Sympathorespiratory and cardiorespiratory coupling thus critically requires integrity and functionality of the core metencephalonmyelencephalic generator circuitry and elements diffusely distributed within the ventrolateral and dorsolateral metencephalic tegmentum, brainstem reticular formation, vagal inputs, and postinspiratory neurons (Fig. 5) (Molkov et al., 2017), elucidating mechanisms contributing to emergent genesis of autonorespiratory coupling through studies utilizing contemporary respiratory and sympathetic neural (Terui et al., 1986) and peripheral sympathetic neural efferent recordings (St. Croix et al., 1999), directed lesioning (Dick et al., 2009; Molkov et al., 2011), stereotaxic localized pressure microinjections of pharmacological agonists and antagonists of excitatory and inhibitory neurotransmission and neuromodulation (Abdala et al., 2009; Moraes et al., 2012b), and cross-correlation, spectral, and coherence analyses of the recorded electrophysiological activities. While the alternating rhythmic discharge of inspiratory and expiratory activities of breathing neurally segmented into inspiratory, postinspiratory, and late expiratory epochs effectively serves a clear and identifiable functional purpose (Marchenko et al., 2016), the significance of rhythmic discharge in, and crossmodal modulation of, sympathetic oscillations, sympathetic neural efferent discharge, and ambiguous cardiovagal premotoneurons is not immediately obvious (Zoccal, 2015). Some have posited respirophasic modulation of the sympathetic neural output may contribute to and mediate coordinate changes in ventilation and vascular tone to contemporaneously optimize tissue oxygenation and perfusion during resting conditions and amplify vasoconstrictor arteriolar tone and amplitude of the microcirculatory vasomotion (Zoccal et al., 2009b). Accordingly, modeling studies have indicated interactions among the respiratory, central pattern generator, sympathetic oscillators, and parasympathetic nuclei may serve to robustly improve myocardial function (Ben-Tal et al., 2012). Further studies are thus necessary to more thoroughly elucidate functional utility and mechanisms underlying the genesis and functional utility of autonomorespiratory coupling (Molkov et al., 2017).

Author contributions

M.G.Z.G.: conception and design, acquisition of data, analysis and interpretation of data, drafting the article, and revising critically for intellectual content; approval of the final version of the manuscript.

Ethics approval and consent to participate

Compliance with ethical standards.

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Conflict of Interest

We have no conflicts of interest to disclose.

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