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Respiratory rhythm generation, hypoxia, and oxidative stress—Implications for development

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Abstract

Encountered in a number of clinical conditions, repeated hypoxia/reoxygenation during the neonatal period can pose both a threat to immediate survival as well as a diminished quality of living later in life. This review focuses on our current understanding of central respiratory rhythm generation and the role that hypoxia and reoxygenation play in influencing rhythmogenesis. Here, we examine the stereotypical response of the inspiratory rhythm from the preBötzinger complex (preBötC), basic neuronal mechanisms that support rhythm generation during the peri-hypoxic interval, and the physiological consequences of inspiratory network responsivity to hypoxia and reoxygenation, acute and chronic intermittent hypoxia, and oxidative stress. These topics are examined in the context of Sudden Infant Death Syndrome, apneas of prematurity, and neonatal abstinence syndrome.

1. Introduction

The challenge of ventilation begins with our first breath. Immediately following birth, the transition from the low oxygen intrauterine environment to the oxygen rich state of room air becomes a significant life-threatening challenge when stable breathing is not yet established (Alvaro and Rigatto, 2016; Hillman et al., 2012). Maternal issues, such as maternal hypertension, preeclampsia (Hubbard and Shingleton, 1985) and gestational diabetes (Gross et al., 1983) can lead to premature birth, which can result in the instability of neonatal breathing. When combined with immediate birthing complications, such as aspiration of meconium-stained amniotic fluids, caesarian-section delivery, and neonatal abstinence syndrome, the risk for respiratory instability increases substantially (“Neonatal drug withdrawal. American Academy of Pediatrics Committee on Drugs,” 1998; Reuter et al., 2014). Unstable breathing during the neonatal period can quickly transition from a couple of skipped breaths to a prolonged hypoxic insult, which can result in life-long problems that extend far beyond breathing, and in the most extreme cases, cause infant death (Bancalari and Claure, 2018). Even after the immediate perinatal period, during the first weeks of life, infants, that otherwise appear healthy, are at risk for Sudden Infant Death Syndrome (SIDS), an outcome where oscillations in blood oxygenation is a factor that can lead to SIDS (Waggener et al., 1990). The gravity of such outcomes due to respiratory instability are clinically well-recognized. Thus, when the potential for unstable neonatal breathing arises,

practitioners place significant effort to monitor neonatal breathing and mitigate the occurrence of hypoxia. However, since our understanding into the basis and development of respiratory control in the neonate remains incomplete, there are few options to treat unstable breathing in the newborn. This review examines current advances made in understanding the development and involvement of brainstem networks in controlling respiration in response to and recovery from hypoxia. We will focus particularly on findings derived from the study of inspiratory rhythm generation from the preBötzinger complex (preBötC) during different forms of hypoxia and exposure to reactive oxygen species.

1.1. The neonatal ventilatory response to hypoxia and the perinatal respiratory networks of the brainstem

Respiratory control can be broadly categorized as sensory input, rhythm generation, and motor output (Barlow and Estep, 2006; Bellingham, 1998; Braman, 1995; Grillner, 2003). Balanced integration across these areas of control is necessary for maintaining stable and dynamically responsive breathing (Estelle B. Gauda and Martin, 2012). Yet in the neonate, many aspects of respiratory control are still developing. In rodents, the adult ventilatory response to hypercapnia appears to plateau following first week of life and into adulthood (Stunden et al., 2001) and similarly, carotid body discharge in response to hypoxia, hypercapnia, or hypoxic hypercapnia is stronger in adult (> 5 weeks of age) when compared to the neonate (P5 to P7 of age) (Pepper et al., 1995). Thus, it is during the neonatal period that susceptibility to experiencing a hypoxic event may be enhanced due to underdeveloped responses to deviations on blood gases.

Term and preterm (< 38 week) human infants exhibit a biphasic ventilatory response to drops in oxygen (Martin et al., 1998; Rigatto et al., 1975). It is characterized by an initial rapid, yet transient, increase in minute ventilation. This initial increase is later followed by a decline in ventilation that often falls well-below baseline breathing. This stereotypical ventilatory response to hypoxia is preserved also in neonatal rodents (Garcia et al., 2017), which have served as useful models for studying brainstem networks involved with the control of breathing and the mechanisms that support the responsiveness of neonatal breathing to hypoxia (Garcia et al., 2017; Viemari et al., 2003).

The rodent respiratory network is distributed throughout the brainstem and is composed of at least three groups of network oscillators: the preBötzinger complex (preBötC)(Anderson and Ramirez, 2017; Del Negro et al., 2018); the retrotrapezoid/parafacial respiratory group (RTN/pFRG)(Guyenet and Mulkey, 2010), and the recently discovered post-inspiratory complex (PiCo) (Anderson et al., 2016). While PiCo has been described in neonate (Anderson et al., 2016), it is unknown whether this network is active in the embryo. However, both the preBötC and RTN/pFRG appear to be active well before birth(Guyenet and Mulkey, 2010; Thoby-Brisson et al., 2005). Inspiratory activity from the brainstem can be recorded from the spinal cord respiratory motor pools as early as embryonic day 16 (E16) (Viemari et al., 2003). Respiratory activity from the embryonic brainstem emerges as a result of interactions between the preBötC and the RTN/pFRG (Champagnat et al., 2011; Tupal et al., 2014). While rhythmicity from the preBötC starts between E15 to E18 (Chevalier et al., 2016a,b; Pagliardini et al., 2003; Thoby-Brisson et al., 2005), activity from RTN/pFRG is

present at E14.5 (Thoby-Brisson et al., 2009). During the early postnatal development, RTN/pFRG undergoes a shift in activity from a pre-inspiratory to an inspiratory pattern while preBötC activity remained unchanged (Oku et al., 2007). In juveniles (postnatal day 7 to 13) transection below the RTN/pFRG abolishes active expiration but does not affect inspiration (Janczewski and Feldman, 2006). Thus, while the preBötC is responsible for the inspiratory rhythm, the RTN/pFRG forms the basis of a functionally independent expiratory oscillator (Thoby-Brisson et al., 2009). The RTN/pFRG also contains several cellular constituents such as Phox2b expressing neurons that provide chemosensory drive in response to CO_2 and acidification (Guyenet et al., 2005; Stornetta et al., 2006) and astrocytes that contribute to central chemoreception (Mulkey and Wenker, 2011; Wenker et al., 2010). Inspiratory activity at embryonic ages exhibits sensitivity to neuromodulation (Di Pasquale et al., 1994; Fujii and Arata, 2010; Viemari et al., 2003) and can respond to changes in oxygenation (Chevalier et al., 2016a,b; Viemari et al., 2003) indicating that the respiratory network has the potential to be dynamically responsive well-before birth. However, many cellular and physiological aspects of respiratory control continue to develop and change well-after birth (Prabhakar et al., 2007; Stunden et al., 2001; Wong-Riley and Liu, 2005) which leaves the neonate without the full complement of mechanisms to support the stability of adult breathing and may create vulnerabilities during the neonatal period where the responsiveness of breathing is underdeveloped (Rigatto and Brady, 1972).

1.2. Fundamental elements of inspiratory rhythm generation

The preBötC can be isolated in a single brainstem slice preparation and is where the principles and mechanisms underpinning inspiratory rhythmogenesis have been extensively studied (Butera et al., 1999; Koshiya and Smith, 1999; Smith et al., 1991). In the seminal work localizing the preBötC by Smith et al. (Smith et al., 1991), rhythm generation from the inspiratory network was shown to be attenuated in response to microinjection of the AMPA receptor antagonist, CNQX, suggesting that inspiratory rhythmogenesis from the preBötC is largely dependent on excitatory transmission. Subsequent studies examining the basis of rhythm generation in the preBötC have confirmed this observation (Lieske and Ramirez, 2006; Morgado-Valle and Feldman, 2007; Shao et al., 2003) and the necessity of glutamatergic transmission for rhythm generation is a well-accepted key principle. In isolation of fast synaptic transmission, individual preBötC neurons can be categorized as intrinsic bursting neurons, weak/tonic spiking neurons, or silent neurons (Ramirez et al., 2011). Intrinsic bursting neurons in the inspiratory network can be further divided by the underlying con-ductances that drive bursting into either persistent sodium current (I_{NaP}) bursters or non-specific cation current (I_{CAN}) bursters (Ramirez et al., 2004). Additional intrinsic and synaptic properties contribute to stabilizing and shaping the phenotype of these general preBötC classes of preBötC neurons, and we refer the reader to the following reviews (Ramirez et al., 2012, 2011; Ramirez et al., 2004) for a more extensive understanding of the cellular and network properties that support rhythmogenesis from the preBötC beyond the peri-hypoxic interval.

1.3. Oxygenation and the preBötC

The isolated preBötC is capable of generating different neural rhythms reminiscent of eupnea, gasping, and sighing (Lieske et al., 2000) and can be revealed by changing the state

of oxygenation surrounding the network (Garcia et al., 2017, 2013b; Hill et al., 2011; Lieske et al., 2000). When the inspiratory network becomes initially hypoxic, normal rhythmogenesis (Fig. 1A) increases in frequency and begins to generate augmented bursts (Fig. 1B) while later in hypoxia, augmented bursting ceases and rhythmogenesis slows (Fig. 1C). This initial augmentation followed by depression is remarkably similar to the neonatal ventilatory response to hypoxia (Garcia et al., 2016; Pena et al., 2008). Upon reoxygenation, a paradoxical depression in in vitro rhythmogenesis occurs (Fig. 1D) which is also strikingly similar to post hypoxic ventilatory depression (Coles et al., 1998; Garcia et al., 2013b). The similarities between the stereotypical in vitro response of the rhythm generating network to hypoxia and the stereotypical hypoxic response of neonatal breathing supports the notion that the preBötC is a significant contributor to all phases of breathing during the peri-hypoxic interval.

Although it is tempting to conclude that the preBötC is responsible for driving changes in the breathing rhythm during transitions in oxygenation, rhythmogenesis from the preBötC appears to stereotypically respond to relative changes in oxygenation as opposed to sensing absolute changes in the oxygen environment (Hill et al., 2011). This observation suggests that the contribution of the preBötC is only responsive to changes in oxygenation and sensory input from outside inspiratory network is still required for normal adult physiology. Indeed, targeted microinjections of colchicine to block axonal transport in the adult preBötC reduces, but does not eliminate, both hypercapnic and hypoxic ventilatory responses (Wu et al., 2005). During the neonatal period when central CO_2/H^+ chemoreception (Cerpa et al., 2017; Stunden et al., 2001), peripheral O_2 (Pawar et al., 2008) and peripheral CO_2/H^+ (Pepper et al., 1995) chemoreception are still developing, the intrinsic responsiveness of the preBötC to changes in oxygenation may have a greater role in influencing neonatal breathing responses to deviations in blood gases.

1.4. Neuromodulation of rhythmogenesis during hypoxia

Intrinsic properties of individual preBötC neurons play an important role in maintaining hypoxic rhythmogenesis. In particular, I_{NaP}-dependent activity appears to be critical for driving the preBötC rhythm under low O_2 tensions as riluzole and R56865, I_{NaP} blockers, prevent hypoxic rhythmogenesis, but has little effect on rhythmogenesis under well-oxygenated control conditions (Paton et al., 2006; Pena et al., 2004). Intracellular recordings from synaptically isolated preBötC neurons also demonstrate that I_{NaP} dependent bursters are intrinsically active during hypoxia while I_{CAN} and weak/tonic spiking neurons are silenced by hypoxia (Pena et al., 2004).

Under well-oxygenated conditions, the majority of preBötC neurons normally exist as weak/tonic spiking neurons while silent and intrinsic bursting neurons only constitute a minority (Carroll and Ramirez, 2013; Carroll et al., 2013; Nieto-Posadas et al., 2014). This composition provides sufficient stability in well-oxygenated states, yet in the presence of enhanced serotonergic (Tryba et al., 2006), substance P-ergic (Pena and Ramirez, 2004), or adrenergic (Viemari and Ramirez, 2006) neuromodulation, weak/tonic spiking neurons can assume a burster phenotype. These observations show that firing phenotype is not a fixed property among all preBötC neurons. Increasing intrinsically bursting neurons throughout

the respiratory network may enhance the robustness of rhythm generation when the inspiratory network is burdened. Recent multielectrode studies examining network interaction during hypoxic rhythmogenesis indicate that during the hypoxia, functional connectivity appears to wane when compared to rhythmogenesis under normal conditions (Nieto-Posadas et al., 2014). However, when serotoninergic 2A (Pena and Ramirez, 2002) or alpha-2 adrenergic receptors (Viemari et al., 2011) are blocked during a transition to hypoxia, the loss of neuromodulatory signaling increases the likelihood for failed rhythmogenesis.

in vivo exposure to intermittent hypoxia leads to an increase in catecholaminergic neurons of the ventral lateral medulla and in gene expression of serotonin transporter (Slc6a4) 5-HTT and tryptophan hydroxylase 2, two critical components important to maintenance of serotoninergic neuromodulation (Givan and Cummings, 2016). Furthermore, loss of central serotonergic neuromodulation increases the chance of failed autoresuscitation (Chen et al., 2013), impairs hypoxia-triggered arousal (Young et al., 2017), and increases apneas (Hodges et al., 2009; Young et al., 2017). Combined with the observations made in the inspiratory network, these findings suggest that enhancing neuromodulation is a natural response to the recurrence of hypoxia and may serve as a potential mechanism that defends against unstable breathing by supporting reliable rhythmogenesis in response to changing blood gases.

1.5. SIDS, hypoxia, and post-hypoxic recovery

Sudden infant death syndrome (SIDS) is a diagnosis provided when the death of an infant less than one year of age cannot be explained by other means(Byard, 2018; Ferguson, 2015). The triple-risk model of SIDS first proposed by Filliano and Kinney (Filiano and Kinney, 1994) states that the SIDS emerges as the result of intersection among three factors: a vulnerable infant, a critical developmental period, and an exogenous stressor (i.e., environmental challenge). Biological sex and age are thought to be significant factors that contribute to the first two factors in the triple-risk model of SIDS. Males are more likely to succumb to SIDS (Mage and Donner, 2004, 2014) while the peak occurrence of SIDS is between three and six months (Mage and Donner, 2009). Furthermore, postmortem analysis suggests that deficits in serotonergic neuromodulation may further increase vulnerability to SIDS (Kinney et al., 2001). Thus, if a vulnerable infant encounters even the briefest hypoxic challenge, the threshold for SIDS may be much lower (Ramirez et al., 2018; Thach, 2008). In the sleeping infant, the prone position increases likelihood for unescapable hypoxic exposure and the susceptibility for suffocation due to the potential inability of the infant in repositioning his or her head to prevent rebreathing into the cushion, pillow, or bedding (Erck Lambert et al., 2019). Rebreathing into cushion, pillow, or bedding, will initially lead to hypercapnia and subsequently, if left unchecked hypoxia. Impaired central and peripheral chemoreception have been is largely recognized as significant contributing factors to SIDS occurrence (For review see: (E. B. Gauda et al., 2007; Porzionato et al., 2018)). For example, hyposensitivity of peripheral chemoreception may contribute not only to the blunted ventilatory response to hypoxic hypercapnia, but also may lead to a failure in arousal. Thus, deficits in the arousal response during these hypoxic challenges are thought to contribute to these outcomes (Garcia et al., 2013a). Together hypoxia and the failure to arouse to such challenge may be considered two significant factors contributing to SIDS.

Further supporting the perspective that hypoxic challenge is a significant factor that can lead to infant death, increased rates of both SIDS (Barkin et al., 1981) and unexplained neonatal hospital death (Yangzom et al., 2008) have been documented in high altitude populations. Hypoxia may alter neonatal cardiac maturation, leading to the impaired cardiac conduction, and decreasing the threshold for cardiac arrhythmias and the occurrence of sudden death (Neary et al., 2013). In cases of prematurity, hypoxia may result from underdevelopment of respiratory centers that cause hypoventilation and diaphragmatic malfunction. Other studies have also demonstrated that intrauterine growth restriction via prenatal hypoxia not only leads to a modification in inspiratory rhythm but also alterations in catecholaminergic modulation (Tree et al., 2016). However, recent findings suggest the period of post-hypoxic recovery of breathing and rhythmogenesis from the preBötC may also be a factor contributing to SIDS.

Following hypoxia, rhythmogenesis is initially suppressed but later frequency rebounds (Garcia et al., 2013b; Hill et al., 2011). This biphasic response of preBötC rhythm may contribute to the paradoxical occurrence of post-hypoxic ventilatory depression—a transition period that can increase the chance for unstable breathing and contribute to the risk of SIDS. Both postnatal age and sex appear to be factors that can influence inspiratory rhythmogenesis during reoxygenation (Garcia et al., 2013b). The latency of post-hypoxic recovery in rhythmogenesis from the preBötC increases with postnatal age (Garcia et al., 2013b). During the second week of life, NMDA receptor expression (Liu and Wong-Riley, 2005), $GABA_A$ receptor subunit expression (Liu and Wong-Riley, 2006) and chloride homeostasis (Liu and Wong-Riley, 2012) change and may contribute to the prolongation of post-hypoxic recovery. In addition to the prolongation of post-hypoxic recovery, a sex-based difference emerges in the post-hypoxic recovery of preBötC rhythms during the second week of life (Garcia et al., 2013b) whereby post hypoxic depression is prolonged in the preBötC rhythms from males when compared to females. This sex-based difference in post-hypoxic recovery was eliminated by either activating or blocking the ATP-sensitive potassium channel (K_{ATP}), suggesting that the dynamic activity of the K_{ATP} largely contributes to the post-hypoxic recovery of the rhythmogenesis form the preBötC as opposed to other potential differences such as expression of the channel. Thus, as the activity of K_{ATP} is regulated by the availability of ATP, sex-based differences in metabolic activity within the respiratory network may impact the breathing rhythm during peri-hypoxic intervals.

1.6. Reactive oxygen species

As discussed in the previous section, the transition from hypoxia to a well-oxygenated state (i.e., reoxygenation) may be a period of vulnerability for breathing, as respiratory rhythmogenesis has a delayed recovery upon reoxygenation. Many biological systems exhibit an oxidative burst during reoxygenation(Granger and Kvietys, 2015; Spranger et al., 1998) that can cause cellular injury(Granger and Kvietys, 2015) and, in the context of the preBötC, affect stable rhythmogenesis. The oxidative burst results from one or more types of reactive oxygen species (ROS) being produced (Granger and Kvietys, 2015; Halliwell, 1991; Li and Jackson, 2002). During reoxygenation, one type of ROS, superoxide anion, may be produced from the mitochondria (Bao et al., 2009; Gruber et al., 2013) or other cellular

processes (Bedard and Krause, 2007; Berry and Hare, 2004). Superoxide anion is rapidly converted, via superoxide dismutase, into hydrogen peroxide (H_2O_2)(Granger and Kvietys, 2015). H_2O_2 is another type of ROS and can be further metabolized by catalase or other peroxidases(Granger and Kvietys, 2015). Both superoxide anion and H_2O_2 have been implicated in cell signaling, but when they accumulate, can also be sources for oxidative stress (Granger and Kvietys, 2015). For example, in presence of a transition metal, like Fe^{2+}, H_2O_2 is rapidly converted into the short-lived ROS, hydroxyl radical(Granger and Kvietys, 2015). Unlike superoxide anion and H_2O_2, hydroxyl radical does not act as a signaling molecule but rather, serves as a source of oxidative stress (Halliwell, 1991).

Acute H_2O_2 suppresses synaptic transmission in both the adult and neonatal hippocampus (Avshalumov and Rice, 2002; Garcia et al., 2011) yet H_2O_2 differentially affects rhythm generation from the preBötC (Garcia et al., 2011). Application of H_2O_2 to the in vitro slice triggers a biphasic change in the frequency of rhythmogenesis that is characterized by an initial depression followed by an augmentation phase. This response was remarkably similar to the stereotypical response of the isolated preBötC to reoxygenation from hypoxia and could be traced to induvial neuronal responses to H_2O_2. The initial depression of rhythmogenesis by H_2O_2 appears to be the result of oxidative stress, as hydroxyl radical, produced by co-application of Fe^{2+} and H_2O_2 (to produce hydroxyl radical) leading to monotonic depression in rhythmic frequency. By contrast, in the presence of the iron chelator, deferox-amine, H_2O_2 only causes augmentation of rhythmic frequency from the preBötC. The chelation of free iron minimized the conversion of H_2O_2 to hydroxyl radical, presumably unmasking the action that H_2O_2 has independent of hydroxyl radical. Indeed, optogenetic stimulation of microglia and hypoxia causes increases in extracellular H_2O_2 in ventrolateral medullary slices (Pardo-Pena et al., 2018). Thus, rhythmogenesis from the preBötC may be influenced by ROS in a species dependent fashion and such effects may have particular relevance to reoxygenation.

1.7. Intermittent hypoxia

While it may only take a single bout of hypoxia to destabilize breathing, intermittent oscillations in arterial O_2 are common to several conditions during neonatal life. To determine how such oscillationsin-fluence neonatal respiratory control, exposure to intermittent hypoxia has been used to experimentally model unstable breathing (Garcia et al., 2017, 2016; Peng et al., 2004; Prabhakar et al., 2007; Zanella et al., 2014). Studies in the preBötC have used both acute intermittent hypoxia and chronic intermittent hypoxia to understand the consequences of intermittent hypoxia versus hypoxia on inspiratory rhythmogenesis relevant to conditions where neonatal apneas are evident(Garcia et al., 2016; Zanella et al., 2014).

1.8. Acute intermittent hypoxia

Neonatal abstinence syndrome (NAS) is a condition where the neonatal infant experiences drug withdrawal due to maternal narcotic use or abuse during pregnancy (Kocherlakota, 2014; “Neonatal drug withdrawal. American Academy of Pediatrics Committee on Drugs, 1998). As many drugs readily pass from the maternal blood stream through the placenta to the fetus(Ross et al., 2015), illicit drug abuse during pregnancy can cause the fetus to

become addicted to the substance(s) used by the mother (Behnke et al., 2013). As a result, the sudden discontinuation of fetal exposure to substances that were used or abused by the mother during pregnancy commonly lead to withdrawal symptoms in the newborn and is associated with increased adrenergic tone (Oji-Mmuo et al., 2019) and disrupted serotonergic tone (Lunden and Kirby, 2013). Such departures from the normal neuromodulatory state could increase the risk of unstable breathing and oscillations in blood gases. Indeed, in premature infants suffering from NAS, intermittent hypoxemic episodes can worsen (Abu Jawdeh et al., 2017).

At the level of the preBötC, acute intermittent hypoxia (IH) produces the stereotypical responses of rhythmogenesis during each cycle of hypoxia and reoxygenation (Blitz and Ramirez, 2002; Zanella et al., 2014) and leads to long-lasting augmentation in the frequency of rhythmogenesis during the post-hypoxic period (Blitz and Ramirez, 2002; Camacho-Hernandez et al., 2018). Acute IH also has little impact on the transmission of the premotor rhythm originating from the preBötC and generated by the hypoglossal motor pool demonstrating the robustness of the network to repeated changes in oxygenation (Zanella et al., 2014). However, when combined with enhanced adrenergic tone, acute IH can cause long-lasting instabilities in inspiratory rhythmogenesis.

Enhanced adrenergic tone co-incidental with acute IH leads to the emergence of post-hypoxic subnetwork bursting in the preBötC (Zanella et al., 2014). This subnetwork bursting in the premotor network fails to produce the motor bursts in the hypoglossal motor nucleus and subsequently, enhances irregularities both in the preBötC rhythm and inspiratory motor rhythm. This appears to be the result of functional remodeling that involves changes in glycinergic inhibition and activation ofalpha 2 adrenergic receptors (Zanella et al., 2014). Thus, increased adrenergic tone and acute IH may serve to perpetuate perinatal respiratory instability causing the preBötC to enter into an unstable state where synaptic inhibition disrupts transmission from the premotor network to respiratory motor pools.

1.9. Chronic intermittent hypoxia

The occurrence of intermittent hypoxia during perinatal life is often experienced over the course of days and even weeks. For the majority of infants (< 30 weeks of gestation) suffering from apneas of prematurity, chronic intermittent hypoxemia associated with the condition does not diminish until after the 40th week of gestation (Eichenwald and Committee on, F., and Newborn, A. A. o. P., 2016). Perinatal exposure to chronic intermittent hypoxia (IH) enhances the neonatal ventilatory response to acute hypoxia (Garcia et al., 2016; Peng et al., 2004). The effects of chronic IH on neonatal ventilation involve both enhanced peripheral O_2 chemosensitivity of the carotid bodies (Peng et al., 2004; Prabhakar et al., 2007) and changed inspiratory rhythmogenesis from the preBötC (Garcia et al., 2017, 2016). Chronic IH impacts inspiratory rhythmogenesis in a state dependent manner. Following exposure to chronic IH, excitability during a network burst is reduced among individual inspiratory neurons and is co-incidental with a loss of fidelity of individual neurons with the network rhythm (Garcia et al., 2016). These cellular effects on preBötC neurons result in increased short-term variability of both amplitude and period of the network rhythm and consequently increases transmission failure of the preBötC rhythm

to the hypoglossal motor pool in local respiratory circuit. Biochemically, chronic IH increases oxidative stress in the preBötC and irregular rhythmogenesis and transmission failure can be mitigated by administration of the antioxidant, manganese(III) tetrakis(1-methyl-4-pyridyl) porphyrin (MnTMPyP), during neonatal chronic IH exposure.

Neonatal CIH causes ROS-dependent endothelin signaling to augment the hypoxic response of the carotid bodies (Pawar et al., 2009). Similarly, in the adrenal medulla, neonatal chronic IH leads to a ROS-mediated suppression of multiple nicotinic receptor subunits which thereby impairs nicotinic receptor mediated activation of the adrenal medulla (Souvannakitti et al., 2010) and can last into adulthood (Souvannakitti et al., 2009). Thus, the role of chronic IH-dependent ROS in remodeling cellular and physiological activity does not appear to be a unique feature at the level of the preBötC but rather, is evident throughout the neonatal nervous system.

In adults, chronic IH causes oxidative stress that also potentiates the activity from the carotid bodies (Del Rio et al., 2010; Peng et al., 2006) and may be an upstream contributor to the pro-inflammatory state caused by chronic IH that promotes the potentiation of the carotid body (Del Rio et al., 2012) and the hypoxic central chemoreflex pathway (Oyarce & Iturriaga, 2018). Increased hypoxia inducible factor 1a signaling (HIF1a) in the nervous system is upstream of oxidative stress produced by chronic IH (Peng et al., 2006). Although it is unknown whether chronic IH causes increased HIF1a signaling in the preBötC, recent transcriptional analysis of neonatal preBötC neuronshas revealed that HIF1a is expressed approximately three times higher in glutamatergic Dbx1 preBötC neurons than in non-Dbx1 neurons (Hayes et al., 2017). These observations suggest that chronic IH may indeed increase HIF1a signaling in the preBötC but this remains to be demonstrated. Should chronic IH increase HIF1a signaling in the preBötC, the role of such signaling remains to be determined. On one hand, HIF1a signaling may serve to be protective promoting survival during hypoxia, while on the other, increased HIF1a signaling due to oxidative stress may serve to promote a pro-oxidant state (Semenza and Prabhakar, 2007) to destabilize function in inspiratory brain circuit. However, the protective role and the pro-oxidant role for IH-dependent HIF1a signaling may not be mutually exclusive given the potential for reactive oxygen species to modulate rhythmogenesis (Garcia et al., 2011).

2. Conclusion

Neonatal breathing possesses the capability to respond to hypoxia but is often still vulnerable to disturbances that cause repeated oscillations in blood oxygen. Such destabilization can arise from a host of conditions, yet hypoxic challenge and unstable breathing must be overcome by the neonate in order to survive. While several parts of the nervous system contribute the control over breathing, inspiratory rhythm generation from the preBötC appears to emerge well-before full gestational age. The cellular and network properties of the inspiratory network normally permit a robust response to hypoxic challenge yet the transitions from well-oxygenated states to hypoxia and back reveal vulnerabilities in rhythm generation relevant to understanding conditions such as SIDS. Moreover, the response to recurrent hypoxia and reoxygenation, whether acute orchronic, reveals a hysteresis in rhythmogenesis from preBötC which may serve to perpetuate unstable

breathing when respiratory control is underdeveloped. Even if hypoxic insult during neonatal life does not result in sudden death, exposure to hypoxia early in life may have consequences that are not yet fully understood. This underscores the importance for continued the study of respiratory control and the premotor circuits that drive breathing. Pinpointing critical vulnerabilities in the control of breathing, whether to under-development or to pathophysiology may facilitate novel therapies to better mitigate or even prevent neonatal hypoxic insult and its negative consequences.

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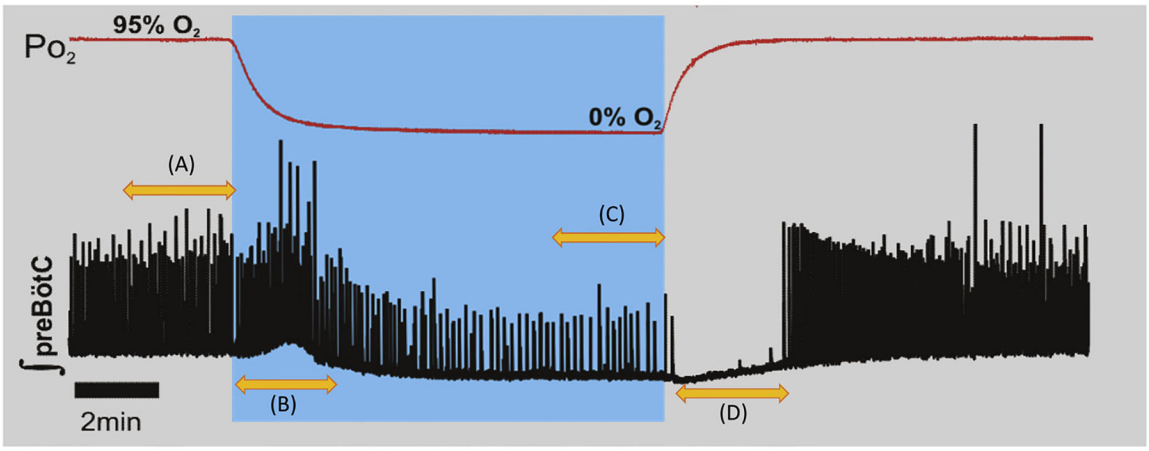

Fig. 1.

The stereotypical response of the isolated preBötC to hypoxia and reoxygenation. (A) The in vitro preBötC generates a spontaneous rhythm in well-oxygenated conditions (95% O_2 5% CO_2). (B) Switching from to 95% N_2 5% CO_2 produces hypoxic conditions as oxygen can still be measured in the circulating media (see Hill et al., 2011). During the initial period of hypoxic exposure, the in vitro rhythm increases in frequency and begins to generate augmented bursts. (C) Later during hypoxia augmented bursting ceases and rhythmogenesis slows. (D) Upon reoxygenation, the preBötC rhythm is initially suppressed delaying post-hypoxic recovery.