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Mechanistic actions of oxygen and methylxanthines on respiratory neural control and for the treatment of neonatal apnea

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Abstract

Apnea remains one of the most concerning and prevalent respiratory disorders spanning all ages from infants (particularly those born preterm) to adults. Although the pathophysiological consequences of apnea are fairly well described, the neural mechanisms underlying the etiology of the different types of apnea (central, obstructive, and mixed) still remain incompletely understood. From a developmental perspective, however, research into the respiratory neural control system of immature animals has shed light on both central and peripheral neural pathways underlying apnea of prematurity (AOP), a highly prevalent respiratory disorder of preterm infants. Animal studies have also been fundamental in furthering our understanding of how clinical interventions (e.g. pharmacological and mechanical) exert their beneficial effects in the clinical treatment of apnea. Although current clinical interventions such as supplemental O_2 and positive pressure respiratory support are critically important for the infant in respiratory distress, they are not fully effective and can also come with unfortunate, unintended (and long-term) side-effects. In this review, we have chosen AOP as one of the most common clinical scenarios involving apnea to highlight the mechanistic basis behind how some of the interventions could be both beneficial and also deleterious to the respiratory neural control system. We have included a section on infants with critical congenital heart diseases (CCHD), in whom apnea can be a clinical concern due to treatment with prostaglandin, and who may benefit from some of the treatments used for AOP.

Keywords

apnea; hyperoxia; caffeine; prostaglandin; control of breathing

1.0. Introduction

The natural process of birth is a remarkable, yet physiologically challenging event. The respiratory system must be adequately developed prior to birth in preparation for the

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transition between the fluid-filled uterine environment to an external air-breathing one. Establishing a rhythmic, stable, and unfailing breathing pattern to ensure effective ventilation and gas exchange, therefore, is of utmost importance for the newborn (Mortola 2001). However, there are frequent (clinical) scenarios in which circumstances are not conducive for the neonate to establish effective ventilation. Perhaps the most notable example is the highly vulnerable preterm infant, who because of an innately immature respiratory system, is generally not adequately equipped to cope unaided in extra-uterine life (Martin et al. 2011). Of primary concern is hypoventilation, respiratory instability, and apnea as a consequence of immature respiratory neural control, which, if severe enough and without appropriate intervention, can be life-threatening. The pathophysiological consequences (specifically associated with intermittent hypoxemia (IH), reviewed in this special issue: Di Fiore and Vento) of recurrent neural apnea can be further exacerbated by insufficient pulmonary development, which constrains gas exchange and compromises blood gas homeostasis. The respiratory and physiological stability of the preterm infant can be confounded by numerous other co-morbidities, which can include infection, congenital abnormalities, malnourishment, and prior *in utero* exposure to drug and alcohol abuse, to name a few (Di Fiore et al. 2013; Gauda et al. 2013). Many preterm infants require some form of respiratory support ranging from pharmacological (which could include supplemental O_2) and if necessary more aggressive interventions including continuous positive pressure support and even tracheal intubation (Di Fiore et al. 2016b, a).

Such advancements in the treatment and prevention of apnea enhance the infant's maturational and survival prospects. Studies in preterm infants have shed light on the pathogenesis of apnea and the efficacy of treatment strategies, but current strategies are not always effective, and in some cases can have adverse unintended consequences. A prime example is supplemental O_2 therapy, which has been proposed to underlie the adverse developmental effects on various organ systems. Animal studies, however, have been crucial to our understanding of the central and peripheral neural pathways that are likely involved in initiating and resolving an apneic event (albeit still far from being fully understood) as well as enhancing our understanding of the possible mechanisms behind the current clinical strategies from both an advantageous and deleterious standpoint. This is not intended to be a comprehensive review of the broad spectrum of respiratory complications associated with early postnatal life, but rather we have chosen to discuss common clinical scenarios in which apnea is prevalent and concerning enough that clinical intervention is required. We will also include discussions on proposed mechanisms of therapeutic benefit, as well as provide speculation about the possible mechanistic basis for some of the unintended consequences they might have specifically on aspects of the respiratory neural control system.

2.0 Apnea and control of breathing

The intricate "design" of the respiratory neural control system is highly complex, but basically comprises a brainstem central pattern generator with both central and peripheral feedback mechanisms (Alheid and McCrimmon 2008; McCrimmon et al. 2008). The preBotzinger Complex (PBC) of the rostral ventral respiratory column (rVRC) contains neurons necessary for respiratory rhythm generation, which are modulated by central inputs from regions including the Retrotrapezoid Nucleus (RTN, central chemoreceptor), the

Parafacial Group, Nucleus of the Solitary Tract (NTS), as well as pontine regions such as the Parabrachial Complex and Kolliker-Fuse Nucleus to name a few (Janczewski and Feldman 2006). The caudal NTS receives sensory input from vagal afferents originating from the lung and the carotid body (CB) chemoreceptor. Abnormalities or dysfunction in any of these regions could in theory contribute to respiratory instability and apnea, but there are still major gaps in our understanding of how these individual respiratory control regions contribute to rhythmic breathing and apnea.

Of primary concern is the life-threatening risk of failure to resolve an apneic event spontaneously, which has been proposed as a contributor to the lethality of conditions such as Sudden Infant Death Syndrome (SIDS), Congenital Central Hypoventilation Syndrome (CCHS) and Sudden Unexpected Death in Epilepsy (SUDEP) (Bolivar et al. 1995; Dimaguila et al. 1997). So far the mechanistic basis underlying a lethal apnea has proven challenging to study, difficult to prevent, and almost impossible to predict. However, significant advances have been made in our explanation of how cyclical or recurrent apnea can develop using the concepts of *loop gain* and *plant gain* (see (Orr et al. 2017; Plataki et al. 2013; Dempsey et al. 2012) for more thorough reviews). Briefly, inappropriate negative feedback from chemoreceptors ultimately resulting in cyclical central apnea separated by periods of hyperpnea is explained in large part by increased loop gain. Specifically, hypersensitivity to increases in arterial CO_2 ($PaCO_2$) provokes hyperpnea which, superimposed with circulatory and feedback delays from chemoreceptor input to central respiratory regions, leads to ventilatory overshoot, hypocapnia (reduced $PaCO_2$) and possible ventilatory undershoot. Loop gain is defined as the ventilatory undershoot/ventilatory overshoot ratio resulting in periodic breathing and, if severe enough, central apnea (Dempsey et al. 2012). Plant gain is defined as the magnitude of the effect that a change in ventilation would have on the $PaCO_2$ (and PaO_2). A high plant gain can result from small dead space, low functional residual capacity, low metabolic rate, or high $PaCO_2$. Much of the research has centered on adults with sleep apnea and the concepts of loop and plant gain have been used to further explain origins of obstructive (particularly during sleep, OSA) and mixed apneas. The same basic neural mechanisms underlying (e.g. central) sleep apnea are in many ways likely very similar across the age spectrum from neonates to adults. However, numerous other factors vary with age including hypothalamic inputs, lung morphology, pulmonary afferent feedback, sleep-state architecture, neurochemical expression, and existing pathophysiology, all of which could influence respiratory control mechanisms underlying apnea (Plataki et al. 2013). Their relative influence on respiratory control, therefore, likely varies across the age spectrum adding to the difficulties in teasing out the origins of respiratory stability/instability and apnea. The pathophysiological consequences of recurrent apnea are fairly well-studied; from a developmental standpoint, perhaps the most widely studied phenomenon is the IH associated with apnea of prematurity (AOP). The immature respiratory neural control system, as well as poor O_2 stores superimposed on various co-morbidities associated with prematurity including infection, sepsis, brain injury, chronic lung disease, and lingering fetal exposures (drug and alcohol abuse) are additional confounding factors that can exacerbate respiratory instability and associated pathophysiological consequences (Di Fiore et al. 2013; Martin et al. 2011). Under these conditions, the etiology of neural apnea in the infant, therefore, would be expected to

be very different and arguably more complex than the apnea phenotype seen in the adult or in children beyond the NICU setting. It remains unclear how any of the aforementioned features common to preterm infants contribute to the concepts of loop and plant gain. In the following section we will focus on AOP, some of the pathophysiological consequences, therapies, and mechanisms of action, including some unintended side effects these may have on the developing respiratory control system, particularly when such effects could promote respiratory instability and contribute to the perpetuation of apnea (MacFarlane et al. 2013).

3.0 Apnea of prematurity (AOP) and intermittent hypoxia (IH):

A major problem for the preterm infant is an immature respiratory neural control system leading to hypoventilation, inadequate oxygenation, and apnea (i.e. AOP). Apneas are defined as breathing cessation for longer than 20 seconds, or shorter respiratory pauses that are associated with oxygen desaturation or bradycardia (Eichenwald 2016). AOP occurs in inverse proportion to an infant's gestational age and weight (present in almost all infants <30 weeks' gestation or <1000g), and which typically resolves by term gestation (Eichenwald 2016). Apneic events can be characterized as central (associated with cessation of breathing effort), obstructive (pharyngeal airflow obstruction associated with continued inspiratory/ diaphragmatic effort), or mixed events, which are the most common phenotype (Eichenwald 2016). Infants without Respiratory Distress Syndrome (RDS) may present with apnea at birth, while spontaneously breathing premature infants with RDS may present later (Martin 2016). A major pathophysiological consequence of AOP is the accompanying IH which has been associated with oxidative stress and long-term neurodevelopmental impairment (reviewed in more detail in this special issue: Di Fiore and Vento). Similar to the time course of postnatal AOP incidence, IH events are relatively uncommon in the first week of postnatal life, but increase progressively over the first 2 to 4 weeks followed by a steady decline thereafter during the second postnatal month (Di Fiore et al. 2010). Although judicious use of supplemental O_2 is intended to stabilize blood O_2 saturation rather than treat apnea *per se*, standard treatment for AOP includes methylxanthine drugs together with nasal continuous positive airway pressure (nCPAP). High risk infants with more imminent life-threatening respiratory complications can require more aggressive interventions including tracheal intubation and mechanical ventilation. Thus, some therapies are intended to mitigate apnea through "strengthening" or stimulating respiratory neural control pathways (pharmacologically), while others (e.g. supplemental O_2, CPAP) are geared more directly toward stabilizing baseline O_2 saturation and buffering the severity of hypoxemia that ensues with most apneic events. Although there are many modes of noninvasive respiratory support available to the preterm infant with AOP, these do not provide complete relief from respiratory insufficiency and may also have damaging effects on lung parenchyma, albeit to a lesser degree than more invasive modalities.

3.1. Treatment of AOP:

3.1.1 Pharmacological Treatment for AOP: Methylxanthines—Caffeine, theophylline, and aminophylline are methylxanthine compounds that have been in use for the treatment of central apnea of prematurity since the 1970s (Henderson-Smart and Steer 2010). Although the methylxanthines are equally efficacious for apnea treatment, caffeine is

the most widely used because of its lower toxicity, longer half-life, and wider therapeutic window (Henderson-Smart and Steer 2010); as such, caffeine has become the drug of choice for AOP in most NICUs. The exact mechanism of action of methylxanthines still remains speculative, but likely involves multifactorial actions on pathways that include central and peripheral neural pathways controlling breathing.

Methylxanthines as a central respiratory stimulant: Methylxanthines such as caffeine have a stimulatory effect on the respiratory system via actions on chemoreceptor function, neural stimulation, increased metabolic drive, and even enhanced muscle performance (Abu-Shaweesh and Martin 2017). As a respiratory stimulant, caffeine's mechanism of CNS action at the level of the brainstem is thought to involve adenosine receptor (e.g. A1 and A2 receptors) antagonism, which removes an adenosinergic suppression of breathing in medullary respiratory control regions (Mayer et al. 2006). Blocking inhibitory activity of A1 and A2a receptors (Herlenius et al. 2002) prevents GABA release thereby increasing neural excitability and respiratory drive. At relatively high concentrations, caffeine can prevent cyclic AMP breakdown via inhibition of phosphodiesterase, causing release of intracellular Ca^{2+} and antagonism of $GABA_A$ receptors (Atik et al. 2017). This is an unlikely mechanism against AOP as it occurs at non-physiological (i.e. not clinically relevant) doses that would be toxic *in vivo*. Caffeine also increases central sensitivity to CO_2 and increases diaphragmatic excursion, tidal volume, and minute ventilation (Dobson and Hunt 2018; Kraaijenga et al. 2015; Atik et al. 2017). Therefore, the benefits of caffeine as a treatment against apnea could at least involve a direct effect on brainstem respiratory neural pathways; unfortunately, however, caffeine is not fully effective at eliminating apnea (Erenberg et al. 2000), suggesting an ongoing need for more effective interventions.

Given the complicated pathophysiological state of the preterm infant, numerous determining factors likely play a role in the relative efficacy of methylxanthines, particularly from a developmental standpoint. Furthermore, there is a regional heterogeneity of adenosine receptor expression in the brain: A1 receptors are widespread, while A2a receptors are concentrated in dopamine-rich areas such as the nucleus accumbens and the striatum (Atik et al. 2017). Receptor expression also likely changes with postnatal development, which together with the increase in apnea and IH incidence over the first postnatal weeks, would suggest the relative efficacy of methylxanthine therapy could be restricted to a time point dependent on receptor expression in relevant areas. Similarly, if methylxanthines modulate GABAergic mechanisms of neurotransmission, then the relative efficacy of these compounds could vary considerably with development, or even have opposite effects when GABA switches from excitatory to inhibitory (Viemari et al. 2011; Liu and Wong-Riley 2012). During early development, a high intracellular Cl^- gradient results in depolarization when GABA opens Cl^- channels, but later, changes in expression of the K^+/Cl^- cotransporter (KCC2) result in decreased Cl^- and neurons become hyper-polarized by GABA activation. In the rat, this switch in neurotransmitter expression occurs toward the end of the second week of postnatal life in various brainstem respiratory control regions (Liu and Wong-Riley 2012), although the functional switch of the excitatory-inhibitory transition of the medullary rhythmogenic regions occurs prior to birth at embryonic day 19 (Rivera et al. 1999). In contrast, however, the developmental timing of the neurochemical and

functional switch varies across brain regions (Rivera et al. 1999). In humans, not a lot is known about the developmental changes in brain KCC2, GABA, or adenosine receptor expression. GABA also plays an important neurotrophic role in early brain development and modulates neuronal proliferation and synapse formation (Owens and Kriegstein 2002). Therefore, inappropriate or unintended inhibition of GABA signaling at key neurodevelopmental stages might not be advantageous to brain development and could have unfortunate consequences to both short and long-term neurodevelopmental outcome. An incident occurred in the 1960's involving accidental omission of vitamin B6 from infant formula which resulted in iatrogenic GABA deficiency and an increased rate of lethal seizures (Frimpter et al. 1969). These data also highlight the importance of appropriate nutritional requirements and demonstrate a critical link between diet and neural development.

Peripheral chemoreceptors: There are several mechanisms by which xanthines could influence peripheral chemoreceptor function and the majority (albeit limited) research has focused on the carotid bodies (CBs). Before discussing the xanthine effects on CB function, a brief overview of the role of these peripheral chemoreceptors in AOP is warranted. CB chemoreceptors are the primary peripheral O_2 and to a lesser extent CO_2 sensors; the maturational changes in sensitivity are not straight forward and at best largely speculative for preterm infants. The primary hypothesis is that hypoxic sensitivity of the carotid bodies resets at birth in response to the relative hyperoxic extrauterine environment compared to the hypoxic *in utero* one. Low chemosensitivity would facilitate a reduction in loop gain and could, therefore, be one explanation for the relatively low incidence of apnea/IH seen in the first postnatal week in preterm infants (Di Fiore et al. 2010). The gradual increase in IH events during postnatal weeks 2–4 in preterm infants, however, could accelerate maturation of CB chemosensitivity (Nock et al. 2004), possibly leading to hyper-sensitivity and increased loop gain, thereby enhancing the propensity for periodic breathing, and thus could be a mechanism that self-perpetuates apnea (MacFarlane et al. 2013).

Unlike the stimulatory effect of xanthines via A1 and A2a receptor antagonism on brainstem respiratory control regions, the opposite appears to be true for the CB chemoreceptor. During hypoxia, adenosine is released from glomus cells and contributes to hypoxic stimulation of the CB suggesting that inhibition of adenosine receptors with xanthines would be inhibitory to hypoxic chemoafferent inputs. In adult rats, caffeine inhibited both basal activity and hypoxic sensitivity of the CB (Sacramento et al. 2015). Whether a depressant effect of xanthines on CB function is of benefit to mitigate apnea is difficult to know. The low CB sensitivity resulting from hyperoxic resetting at birth, could imply there would be little if any beneficial effects of xanthines on peripheral mechanisms underlying apnea. Rather, methylxanthines might be more impactful at a time when peripheral respiratory control is maturing or when IH-induced hyperexcitability of the CBs may contribute more to respiratory instability and apnea. Similarly, postnatal development of adenosinergic receptor expression is also an important determinant in the timing of optimal xanthine therapy efficacy. In rats, A2a receptor expression in the CB is constant throughout the first postnatal week, but declines at 2 weeks of age (Gauda et al. 2000). It is unclear when CB adenosinergic signaling is established in either term or preterm infants or how its expression

might be affected by IH. This is an important consideration in the timing of clinical use of xanthines and whether it is used therapeutically or prophylactically, with an increasing tendency toward the latter in many NICUs (Abu-Shaweesh and Martin 2017).

Finally, there are also conflicting data on the effects of xanthines on CB responsiveness. Caffeine stimulated minute ventilation only in lambs with intact carotid bodies (Blanchard et al. 1986). Further, in piglets, the hypoxic ventilatory depression was reversed also only with intact carotid bodies (Cattarossi et al. 1995). The discrepancies in the excitatory versus inhibitory effects of xanthines on peripheral respiratory control mechanisms across studies are difficult to explain. Species differences and relative receptor expression are simple explanations. Regardless, overall the xanthines are stimulatory to breathing which likely involves a predominantly central nervous system effect, possibly via inhibitory neurotransmission blockade, all of which could be confounded in the preterm infant by prematurity-associated comorbidities (infection, sepsis etc.).

Increased metabolic drive to breathe: An important contributor to the control of breathing, and one that is often ignored and rarely measured, is the influence of metabolic rate on the drive to breathe. Caffeine is a metabolic stimulant and increases oxygen consumption and energy expenditure (Stevenson 2007), so one concern about caffeine treatment was its potential to impact growth. A single bolus (5mg/kg) administration of theophylline increased energy expenditure and carbohydrate metabolism (but not fat oxidation) in preterm infants, which could be detrimental to growth if administered long-term (Carnielli et al. 2000). The Caffeine for Apnea of Prematurity (CAP) trial, however, demonstrated that although caffeine-treated infants gained less weight in the first 3 weeks of treatment relative to untreated controls, there was no difference in weight gain at 4 to 6 weeks (Schmidt et al. 2006). Increased metabolic rate, even a subtle one, increases $PaCO_2$ which in turn enhances the drive to breathe in much the same way as exercise does. Thus, not only is there a direct neural drive to breathe caused by caffeine, but this may also be superimposed on an increased metabolic drive. How these factors play into changes in CO_2 reserve, apneic thresholds, loop and plant gain in a way that influences apnea in the infant are not well understood.

Anti-inflammatory and anti-oxidant properties of caffeine: Caffeine's effects on AOP are widely accepted and there is increasing evidence that its actions also include anti-inflammatory and anti-oxidant properties separate from its antagonistic action on adenosine receptors. A protective effect on lung tissue of A2a agonists has been reported in a mature rat lung injury model, which could suggest that the anti-inflammatory effects ascribed to caffeine may be independent of adenosinergic and GABA signaling (Chen et al. 2009; Li et al. 2011). In fact, adenosine A2a receptors are upregulated in the face of hyperoxia, which may be protective and anti-inflammatory (Dayanim et al. 2014).

The anti-inflammatory effects of caffeine may be dose-dependent and more pronounced if started before the onset of hyperoxic damage. The CAP Trial demonstrated reduced rates of bronchopulmonary dysplasia (BPD) in the caffeine-treated premature infants relative to the control group, which could either indicate a direct anti-inflammatory effect in the lungs or be the result of reduced ventilation-induced lung injury due to fewer days of mechanical

ventilation. A subgroup analysis from this trial showed an enhanced effect when caffeine was started prior to day 3 of life (Davis et al. 2010). A retrospective cohort study demonstrated that premature infants treated with caffeine in the first 3 days of life who were born to mothers with chorioamnionitis had the same rate of BPD as those who did not have chorioamnionitis, suggesting that caffeine had mitigated the effect of chorioamnionitis on BPD, whereas this effect was not seen when caffeine was started later than 3 days after birth (Patel et al. 2013). The only randomized controlled trial concerning early caffeine treatment was stopped prior to full enrollment due to concerns about increased mortality in the early caffeine group, and although ultimately there was no statistically significant difference in mortality rate between the two groups, neither was there a reduction in BPD or days of mechanical ventilation in the early group (Amaro et al. 2018). These data raise the question of whether caffeine has a direct anti-inflammatory/anti-oxidative effect, or whether any benefit is secondary to reductions in IH associated with apnea.

The data on caffeine's impact on inflammation in animal models have conflicted depending on the animal model and dose of caffeine used. Studies in rats and rabbits have demonstrated beneficial effects of caffeine in hyperoxia models including improved cytokine and chemokine profiles, improved lung mechanics, reduced oxidative damage, and less apoptosis, (Teng et al. 2017; Koroglu et al. 2014; Weichelt et al. 2013) whereas in several mouse studies caffeine failed to show benefit and even caused harm (Dayanim et al. 2014; Rath et al. 2017). The dosing of caffeine among these studies was not standardized, not all studies measured serum caffeine levels, and the length of time the animals were followed varied as well. Elevated caffeine levels (>20 μg/ml) have been reported to be associated with a pro-inflammatory cytokine profile (increased TNF-α and decreased IL-10) in a small group of preterm infants (Chavez Valdez et al. 2011), so the pro- versus anti-inflammatory effects of caffeine likely exist in a dose-response relationship.

Regardless of how caffeine or other methylxanthines mitigate apnea or IH events, overall the evidence points to both immediate and long-term beneficial effect in human infants. Caffeine is associated with additional benefits including reduced risk of BPD, reduced need for patent ductus arteriosus treatment, reduced incidence of severe retinopathy of prematurity (Schmidt et al. 2006), a reduced risk of motor impairment at age 11(Schmidt et al. 2017), and lower risk of developmental coordination disorder (Doyle et al. 2014). There remain important unresolved questions concerning the optimal use of caffeine in premature infants: how early to start it, when should it be stopped, and in what dose should it be given. Although it is an effective treatment for AOP, its mechanism of action is not completely understood and since apnea can still persist in preterm infants receiving caffeine (Mohr et al. 2015) suggests there remains an important need for more effective treatment strategies.

3.2. Supplemental Oxygen

The lungs of extremely preterm infants (<28 wks gestation) are in the canalicular or saccular stage of development (depending on the severity of prematurity) and are not adequately developed to achieve effective gas exchange because they lack true alveoli. During apnea, ineffective gas exchange and low O_2 stores can contribute to the rapid onset and severity of hypoxemia associated with IH (Martin 2016). Supplemental O_2 is one of the most widely

used, convenient, non-invasive lifesaving modes of respiratory support (even for late preterm infants) and it is intended to serve two primary functions: 1) stabilize basal arterial O_2 saturation (SaO_2); and 2) prevent or mitigate the severity and duration of O_2 desaturation (ie. IH) associated with apnea. There are clear benefits to maintaining an adequate O_2 saturation, although the challenging dilemma is the wide range of unintended adverse effects oxygen therapy can have on various organ systems. Further, not only are there practical challenges in the delivery of supplemental O_2 in a way that achieves accurate and stable SaO_2 levels, the appropriate target range of SaO_2 has and continues to be an ongoing matter of debate, which is centered around the fine line between the benefits and consequences of both high and low SaO_2. This appears to be associated with physiological changes in oxygen/hypoxia tolerance that accompany the premature transition from a hypoxic *in utero* environment to an external air breathing and relatively hyperoxic one.

3.2.1. Consequences of a premature fetal-neonatal transition - the unusual dilemma of hypoxia/hyperoxia "intolerance": At birth, the preterm infant transitions from the relatively hypoxic *in utero* environment (PaO_2 ~25mmHg), from within which the hypoxia itself provides a critical stimulus for normal fetal development. In the setting of preterm birth, however, there is evidence showing that the transition into an air-breathing environment results in a rapid loss of tolerance to hypoxia. In a prior clinical trial involving two cohorts of preterm infants (24–28 wks gestation), one cohort was maintained at a baseline SaO_2 target range of 91–95%, while the other cohort was maintained at a relatively hypoxic level of 85–90% SaO_2 (Carlo et al. 2010). However, there was a high rate of later infant mortality in the latter cohort; the cause of the mortality was unknown, although it was surprising since despite being relatively hypoxic compared to the high SaO_2 target group, the infants were relatively hyperoxic compared to what they would have experienced had they remained in utero and delivered at term (~40wks gestation). The loss of hypoxia tolerance following the fetal-neonatal transition has also been shown in animal studies. In rats, continuous hypoxia exposure starting from postnatal day 1 (P1) resulted in a rapid onset of unexpected mortality toward the end of the second postnatal week (~P13–14), whereas little if any significant mortality was seen when hypoxia was started on P5 (Mortola 2001). These data suggest that the mortality which occurs following postnatal continuation of the *in utero* hypoxic environment following the fetal-neonatal transition results in a rapid expression of a postpartum intolerance to hypoxia followed by a gradual improvement over subsequent postnatal days. Similarly, studies from our lab have shown that rats born into a hypoxic environment (11% inspired O_2) do not survive more than a few hours (unpublished data). The reason for the intolerance is unclear but it could suggest a "resetting" of O_2 sensitive physiological processes. There is, however, some evidence of a later brief reappearance of vulnerability/intolerance to hypoxia. Exposure confined to the second postnatal week of life in the rat (P11–15 days) also resulted in a significant degree of mortality which was associated with impairment of ventilatory responses to acute hypoxia (HVR) and reduced brainstem serotonergic expression (MacFarlane et al. 2016). The brief postnatal reappearance of hypoxia vulnerability was unique to the P11–15 time frame because the same exposure in either older (starting P21) or younger (P1) rats had no significance effect on either mortality or the HVR (Mayer et al. 2014). It is perhaps not surprising that the P11–15 window of vulnerability to hypoxia encompasses a critical period

when natural neurodevelopmental changes in brainstem constitutive neurochemistry take place, particularly in key cardiorespiratory control regions (reviewed in further detail in this Special Issue: Wong-Riley et al.,). The vulnerability was also associated with increased microglia (MacFarlane et al. 2016) and various components of the extracellular matrix (Stryker et al. 2018), and likely involves undesirable and even lethal disturbances in various other critically important neurodevelopmental events. Overall, the mechanisms behind the vulnerability associated with loss of hypoxia tolerance either at birth or during other windows of later postnatal development are an important unmet research need that may provide insight into the lethal vulnerability of preterm infants to inadequate SaO_2 during the early postnatal period.

Given the rapid manifestation of neonatal hypoxia intolerance, it isn't surprising that supplemental O_2 is a necessary life-saving mode of respiratory support for preterm infants (Di Fiore et al. 2016b, a). However, there are also unfortunate adverse side-effects associated with excessive O_2 exposure ranging from retinopathy of prematurity, BPD (lung disease), oxidative stress, and disturbances in brain development (Abu-Shaweesh and Martin 2017). Increased mortality has been seen in asphyxiated infants resuscitated with high compared to low O_2 concentrations (Saugstad et al. 2014). Given the preterm infants vulnerability to both hypoxia and hyperoxia, the strategies of implementing the optimal level of O_2 support are made complicated by the risk of morbidity and mortality, which can be determined by the level, duration, and timing of exposure. Several recent reviews have addressed the adverse consequences of O_2 therapy in the preterm infant (Perrone et al. 2018) and, therefore will not be covered here. However, relatively little is known about the neurodevelopmental effects of hyperoxia in the context of central and peripheral mechanisms of respiratory neural control.

3.2.2. Hyperoxic effects on respiratory control: An important consideration for the use of hyperoxia or supplemental O_2 as a mode of respiratory support for preterm infants are the secondary deleterious effects it can have on the respiratory neural control system. Animal models of hyperoxia exposure range from mice, rats, rabbits, lambs, piglets, primates and even quail to name a few (reviewed in more detail in this special issue: Dylag and Raffay). Much of the focus has been on the effects of O_2 on lung development, but there are still significant gaps in our understanding of the effects it has on the pathways associated with central and peripheral neural control of breathing. *In vivo* whole-animal hypoxic and hypercapnic ventilatory responses are commonly used to assess the functional capabilities of the respiratory control system following an insult expected to interfere with their respective neural pathways. Generally, neonatal (days-to-weeks) hyperoxia exposure attenuates the hypoxic ventilatory response through mechanisms related to impairments in both peripheral (e.g. the CB) and central (brainstem) pathways. Interpreting the significance of the effects of hyperoxia on these pathways can be complicated by the severity (level of O_2), duration (days-to-weeks) and timing (postnatal age) of exposure as well as developmental status across species. The latter is an important consideration since altricial (born relatively developmentally immature) species such as mice and rats represent models of immaturity rather than prematurity and are very challenging to model prematurity because of low survivability following preterm delivery. More precocial (born relatively developmentally

mature) species, however, while less convenient and requiring more extensive resources as an investigative model, survive preterm birth and provide an optimal model of respiratory control in the context of prematurity.

Regardless of the species, however, the effects of hyperoxia on the HVR are generally similar and lead to its permanent attenuation ((Ling et al. 1997). Dissection of the different time domains of the HVR are critical for teasing out how and when the different anatomical and neurochemical pathways become engaged in the defense response to hypoxia. The different components of the HVR comprise an “early phase” (within minutes) increase in ventilation followed by a decline by ~3rd minute of hypoxia exposure, termed the biphasic HVR (Pamenter and Powell, 2016). The biphasic HVR is fairly well characterized and is a common feature of young/immature animals and gradually dissipates with advancing postnatal age. That is, the magnitude of the ventilatory decline comprising the “late phase” of the HVR is reduced with maturation as it transitions into a sustained elevation of ventilation. The effects of hyperoxia on the different components of the HVR vary depending on the timing of exposure. For a given level of inspired hyperoxia exposure (in this example, 60% FIO_2), both the early and late phase of the HVR are diminished after 4 days of exposure, whereas with <4 days the late phase remains elevated and the HVR resembles that of a more mature animal (Bavis et al. 2014). There are, however, numerous variations in the pattern of hyperoxia exposure, which could be expected to have varying effects on the HVR. These will not be discussed in detail here, but variations in experimental application of hyperoxia exposure include different severities of O_2, patterns (ie. intermittent exposure, as well as with or without combined hypercapnia exposure (Bavis et al. 2019). The variations in O_2 paradigms are important because they address the considerable variability in the clinical use of O_2 in the NICU.

Hyperoxic effects on brainstem development: The biphasic ventilatory response commonly seen in neonatal animals is abolished by hyperoxia exposure by augmenting the late phase of the HVR. In other words, hyperoxic exposed rats exhibit a sustained elevation in ventilation during acute hypoxia exposure. This is in large part due to several changes in brainstem neurochemistry and neuronal function. One week of neonatal hyperoxia decreased BDNF and increased p75 neurotrophic factor in the nTS which could indicate an imbalance of neurotrophic support in favor of apopotosis (Chavez-Valdez et al. 2012). Neonatal hyperoxia increased excitatory synaptic input to caudal nTS neurons (Bavis et al. 2017). In the same region, acute hyperoxia followed increased neuronal excitability, which was associated with increased superoxide and nitric oxide production (Matott et al. 2014). Collectively, these data would be consistent with the sustained late phase of the HVR. The latter was inhibited by the NMDA receptor antagonist MK-801 indicating that the sustained late phase HVR involves NMDA receptors (Bavis et al. 2014) similar to adults (Gozal et. al., 2000). Thus short term (days) exposure to hyperoxia appears to accelerate development of an excitatory brainstem neurochemistry. Hyperoxia has also been shown to modify neurochemistry (cytochrome oxidase, BDNF, TrkB receptor, 5-HT1A and 2A receptors, SERT, and tryptophan hydroxylase) in various key cardio-respiratory control regions including the pre-Botzinger complex, serotonergic raphe, nTS, and XII nucleus (Mu et al. 2018). Specifically, there are unique, in some cases transient, and abrupt changes in the

expression of various neurochemical components in multiple brain regions that take place ~P12–13 days (reviewed in this special issue: Wong-Riley et al.). These neurochemical changes represent normal maturational events necessary for establishing the adult architectural neurocircuitry (Mu et al. 2018). However, this also represents a period of development during which there is a heightened vulnerability to exogenous challenges including inflammation (Rourke et al. 2016), hypoxia (Mayer et al. 2014), and hyperoxia (Bisgard et al. 2003; Mu et al. 2018). The profound and in some cases lethal effects of otherwise seemingly benign challenges during such a brief period of development raises important concerns about the possible presence of similar periods of vulnerability in preterm infants.

Hyperoxic effects on the carotid body: A logical explanation for the blunted early phase of the HVR following developmental hyperoxia is the impairment in CB growth (Erickson et al. 1998; Wang and Bisgard 2005). Trophic factors are important for CB growth. Neonatal hyperoxia decreased CB BDNF expression and the number of retrogradely labeled afferents in the petrosal ganglion (Chavez-Valdez et al. 2012). Chronic hyperoxia decreased CB BDNF protein expression and mRNA for the GDNF receptor Ret and neuropeptide Vgf were also downregulated (Dmitrieff et al. 2011). As little as 3–5 days of hyperoxia (60% O_2) attenuated ex vivo CB single unit responses to acute hypoxia and glomus cell calcium responses (Donnelly et al., 2009). In contrast, and counter-intuitively, however, 1 day of hyperoxia increased CB sensitivity and calcium responses, which could have been the result of excitation due to transient production of ROS. A surge in oxidative stress/injury was observed in asphyxiated infants resuscitated with high % O_2 at birth, coincidentally there is a higher rate of mortality when preterm infants are resuscitated with high (60–100%) O_2 (vs low O_2, 21–30%) (Vento and Saugstad 2010; Saugstad et al. 2014). O_2 silences CB tonic activity and reduces afferent inputs to the nTS (Chavez-Valdez et al. 2012). Inputs to the CNS from the CB may be critical for neural development and loss of afferent inputs increases mortality. As little as 5 days of neonatal hyperoxia exposure decreased respiratory frequency responses to anoxia and the time to last gasp in studies using the brainstem spinal cord preparation (Bierman et al. 2014). Further, surgical denervation of the CB resulted in increased mortality especially in immature rats (Serra et al. 2001). The possibility that the hyperoxia-induced silencing of the CB's and subsequent reduction in afferent signals into brainstem cardiorespiratory control regions is a contributing factor to mortality is plausible.

Developmental hyperoxia also affects CB neurochemistry. It is important to consider that the summation of the CB (more specifically the glomus cells) output in response to a depolarizing stimulus comprises both inhibitory and excitatory neurochemical release (Gauda et al. 2009). TASK1, 3, and 5 background K^+ channel mRNA expression was reduced following neonatal hyperoxia suggesting a decrease in excitatory neurotransmission (Kim et al. 2006). Several other neurochemical contributors of CB activity could also be expected to be affected by prolonged exposure to hyperoxia. Dopamine is an inhibitory neurotransmitter acting primarily on D2-autoreceptors and post-synaptic receptors (Dinger et al. 1981), but whether they are affected by hyperoxia has not been investigated. There is an increase in dopamine signaling during hypoxic stimulation of the CB's associated with maturation, which paradoxically parallels a strengthening of hypoxic chemosensitivity

(Kholwadwala and Donnelly 1992). This could suggest there is a greater maturation of excitatory neurotransmitters that outweighs any increase in inhibitory neurotransmitter expression. Acetylcholine (Nurse and Zhang 1999), serotonin (Jacono et al. 2005), purinergic (P2X receptors/ATP, (Conde et al. 2017; Buttigieg and Nurse 2004)), adenosine (A2a and A2b receptors (Conde et al., 2006)), and nicotine are other modulators of CB sensitivity. Several animal studies have assessed the postnatal expression of various neurotransmitters in the CB (Bairam et al. 2006, 2007; Bairam et al. 2013), but virtually nothing is known about their postnatal developmental expression or whether they are affected by neonatal hyperoxia exposure especially in infants. There is also increasing evidence that CBs exhibit immune- (Del Rio et al. 2012; Porzionato et al. 2013) and glucose-sensing capabilities suggesting disturbances in CB development are far more diverse than hypoxic (or hypercapnic) sensitivity (Conde et al. 2018). There are still major gaps in our understanding of CB development and how it might be affected by various insults commonly encountered by preterm infants.

Since the CB is also sensitive to CO_2, a recent study showed neonatal hyperoxia exposure attenuated CB single unit responses to bath-applied CO_2 in ex vivo CB's (Bavis et al. 2017). However, there was no effect of hyperoxia on the hypercapnic ventilatory response, suggestive of CNS compensatory plasticity. Unlike the effects of hyperoxia on the oxygen sensitivity of the CB, which are permanent, the effects on CB CO_2 sensitivity are not (Bavis et al. 2017). The role of the CB in CO_2 sensitivity is important in the context of prematurity because of the fluctuations in circulating CO_2 levels, which can oscillate due to hypoventilation, period breathing and apnea.

3.3. Continuous positive airway pressure:

Nasal CPAP is another noninvasive respiratory modality that is often used in combination with supplemental O_2 to support baseline oxygenation and enhance O_2 delivery. Pressure is delivered into the nasopharynx via nasal prongs or mask. The severity and frequency of AOP and IH is reduced via stenting of both the upper (Miller et al. 1985) and lower airways where it helps maintain a stable functional residual capacity which may reduce the severity of O_2 desaturation during apneic events (Eichenwald 2016). Lower lung volumes lead to lower pulmonary O_2 stores and this reduced reserve results in quicker onset of desaturation and bradycardia after a central apnea (Martin 2016). Preterm infants on CPAP can still exhibit apnea and IH, which indicates even non-invasive forms of mechanical interventions lack full efficacy. Of interest is that IH events still exist even during mechanical ventilation and have been shown to be preceded by active exhalation, decreased end-expiratory lung volume, and hypoventilation associated with changes in inspiratory mechanics (Bolivar et al. 1995; Dimaguila et al. 1997). A relatively under-explored area of research is the effects that positive pressure support could have on the neural control of breathing. Animal models of CPAP have shown there is significant remodeling of the airways (Mayer et al. 2015; Reyburn et al. 2016), which could have implications for the neural innervation of the lungs including the slowly adapting stretch receptors. The stretch receptors mediate the Hering-Breuer inspiratory inhibition reflex. The lung remodeling that takes place with positive pressure support could alter vagal afferent control of breathing via the Hering-Breuer reflex. The reflex in preterm infants decreases with postnatal age (Stocks et al. 1996) and they

exhibit fewer myelinated vagus nerve fibers than term infants (Sachis et al. 1982). In some preterm infants, the Hering-Breuer reflex was reduced while on CPAP compared to while off CPAP (Martin et al. 1977). Interestingly, aminophylline increased the strength of Hering-Breuer reflex suggesting increased inhibitory inputs (Gerhardt et al. 1983). A detailed review of how CPAP or other modes of positive pressure support could impact the control of breathing is beyond the scope of this review, but given the extent of lung remodeling that takes place (also as a result of O_2), the possible long-term adverse (or even beneficial) effects they might have on peripheral (e.g. lung-vagal) and central (nTS integrative regions) mechanisms of respiratory control should not be underestimated.

3.4. Implications for apnea and intermittent hypoxia events:

Therefore, while continuous hyperoxia exposure has practical convenience utilizing pre-mixed gases comprising any level of O_2, the reality is that preterm infants receiving supplemental O_2 therapy experience a premature elevation in SaO_2 (vs *in utero*), superimposed on O_2 desaturation events (ie. IH) commonly associated with apnea (Di Fiore et al. 2010; Di Fiore et al. 2013). Thus while significant advances have been made in our understanding of the effects of continuous hyperoxia on neural development (and other pathophysiological effects), more refined paradigms of oxygen exposure that utilize intermittent hyperoxia (Logan et al. 2016) or intermittent hyperoxia superimposed on intermittent hypoxia (Dylag et al. 2017) to more closely mimic the clinical setting may reveal more complex effects than just continuous hyperoxia alone. For example, oxygen sensitivity of the CB of preterm infants is low at birth due in part to the resetting that accompanies the rapid rise in PaO_2 following the fetal-neonatal transition (Blanco et al., 1988). Subsequent prolonged exposure to relative hyperoxia (even as a result of breathing room air) or as a result of supplemental O_2 therapy would initiate a trajectory of impairing CB maturation. However, a recent study which assessed CB size using computed tomography angiography in former preterm infants who had received prior supplemental O_2 failed to detect a significant effect of O_2 (Bates et al. 2018), even though former preterm infants exhibit an attenuated HVR (Bates et al. 2014; Calder et al. 1994). These data are not consistent with the permanent reduction in CB size into adulthood in rats following neonatal hyperoxia. However, the gradual increase in the incidence of IH events over the first weeks of life implies increased CB sensitivity (Nock et al. 2004), which is consistent with the effects of chronic intermittent hypoxia (CIH) in rodent studies (Pawar et al. 2008). Neonatal CIH did not increase CB size, although it did increase the number of glomus cells and also CB sensitivity; the latter persisted into adulthood, although the effects of CIH on morphology were not investigated (Pawar et al. 2008). Overall, given the complexity of oxygen exposure of the preterm infant, it is difficult to anticipate how the interaction between prematurity, excess O_2 exposure (supplementation), and the timeframe of changes in IH incidence would determine the short- (weeks-months) and long-term consequences on respiratory control.

4.0. Prostaglandins: critical congenital heart disease:

In utero, the ductus arteriosus (DA) is a necessary shunt that allows fetal blood flow to bypass the lungs. After birth, however, increased O_2 tension and reduced endogenous

prostaglandin (PGE, a potent relaxer of DA smooth muscle) stimulates constriction of the DA with complete functional closure typically occurring within 4 days after birth (Benitz et al. 2015). In infants with some types of critical congenital heart disease, such as left and right-sided obstructive lesions and transposition of the great arteries, the patent DA performs a crucial role in permitting blood flow to the lungs for oxygenation. In this scenario, therefore, closure of the DA results in cyanosis, prostaglandin (e.g. PGE1, alprostadil) is used to promote DA patency and provide pulmonary blood flow until surgical repair or palliation of the congenital anomalies is possible. In contrast, an undesirable delay in DA closure in premature infants can result in pulmonary over-circulation with left-to-right shunting, and if severe enough can lead to a host of problems including respiratory distress, heart failure, and acute kidney injury (Benitz et al. 2015; Majed et al. 2019). In symptomatic infants the PDA can be closed using non-steroidal anti-inflammatory drugs (NSAIDS) or acetaminophen. Not only does the DA have clinical consequences to the respiratory control system (e.g. via blood gas chemistry), but the compounds used to modulate DA patency (which exhibit opposing mechanisms: dilation vs constriction) have direct effects on respiratory neural control and can cause apnea which may require intubation and mechanical ventilation.

4.1 Prostaglandin E1:

The DA is uniquely sensitive to the vasodilatory effects of PGE which maintains DA patency by acting on PGE receptors (EP2, 3, and 4). In utero, both the placenta and DA synthesize and release PGE, which also has direct effects on the respiratory control system. The presence of PGE inhibits fetal breathing movements (Wallen et al. 1986; Kitterman et al. 1979); shortly after birth, abrupt separation from the placental supply of PGE and its metabolism by the lungs contributes to a cascade of events that results in establishment of continuous breathing in the newborn. Given PGE's effects on the fetus, it is not surprising that PGE1 infusion (structurally very similar to PGE2) can cause hypoventilation and apnea in the neonate (Hallidie-Smith 1984; Huang et al. 2013; Lewis et al. 1981). This effect on breathing is likely to be primarily centrally mediated, although CB glomus cells produced PGE2 (and other cytokines) (Porzionato et al. 2013). A study in fetal sheep showed bilateral section of the carotid bodies and vagus nerve had the same degree of breathing movement suppression in response to PGE2 infusion as the sham-operated group (Murai et al. 1987). PGE2 receptors have been demonstrated in fetal brainstem respiratory control regions near the nTS, nucleus ambiguus, and parabrachial nucleus (Tai et al. 1994). Prostaglandin is a lipid-soluble molecule that crosses the blood-brain barrier and vascular endothelial cells around the brain produce PGE in response to IL-1β (Cao et al. 1996; Knoll et al. 2017). Furthermore, PGE's impact on breathing control has been implicated in the observation that infants with sepsis often present with increased apneic events. Human infants with increased C reactive protein (a marker of infection) were found to have increased cerebrospinal fluid PGE2 levels, and this was associated with increased apneic events (Hofstetter et al. 2007). Direct application of PGE1 to brainstem-spinal cord preparations abolished inspiratory nerve activity and was reversible with the addition of agents that increased cyclic AMP levels (Ballanyi et al. 1997), suggesting that methylxanthines such as caffeine and theophylline, adenosine antagonists that act to prevent cAMP breakdown, could be therapeutic for PGE1-mediated respiratory depression. One small study showed benefit of

aminophylline infusion in infants receiving PGE infusions, who had fewer apneas and were less likely to require intubation compared to non-aminophylline treated infants (Lim et al. 2003). It has also been observed that the effect of PGE on control of breathing changes at different ages and is less likely to cause apnea and hypoventilation in older and larger infants. In adults, a PGE infusion is a breathing stimulant (Carlson et al. 1969). This may be explained by differences in location of PGE receptor expression across the lifespan (Tai et al. 1994). The DA itself also becomes less receptive to PGE with age as it progresses toward complete anatomic closure and may not respond or may require larger doses to re-open. A recent study showed activation of brain EP2 receptors by LPS or directly via an EP2 agonist causes microglial death (Fu et al. 2015), which may not be advantageous given the role microglia play in the modulation of breathing (Funk et al. 2015).

4.2 Closing the Duct: NSAIDs and Acetaminophen

Acetaminophen and the NSAIDs ibuprofen and indomethacin have all been used to close the DA in premature infants. NSAIDs work via inhibition of cyclooxygenase, the rate-limiting enzyme in the production of prostacyclin and PGEs. The effect of indomethacin on the DA is primarily due to blockade of PGE2 production (as discussed above). Interestingly, as postnatal age advances in premature infants, DA patency becomes less dependent on PGE2 and more on other vasodilators produced in the DA, so NSAID therapy becomes less effective (Waleh et al. 2005). Similarly, indomethacin's effect on neural control of breathing is likely referable to blockade of PGE2 production. Indomethacin infusion has been shown to increase fetal breathing movements (Kitterman et al. 1979), an effect which continues beyond infancy. One small study in premature infants receiving indomethacin for PDA closure demonstrated increased tidal volume and minute ventilation after the therapy (Yeh and Wilks 1989). In adults, indomethacin alters responsiveness to carbon dioxide via reduction in cerebral blood flow, leading to increased hypercapnic ventilatory response due to increased hydrogen ion detectable by central chemoreceptors (Xie et al. 2006).

Ibuprofen has been shown to be equally efficacious (Ohlsson et al. 2018) and is assumed to function in the same manner as indomethacin for DA closure. However, ibuprofen does not cause cerebral blood flow alterations as has been described for indomethacin (Pellicer et al. 1999). In humans, ibuprofen blunted features of the ventilatory acclimatization to hypoxia, which included attenuation of both the progressive increase in ventilation and also the augmented HVR (Basaran et al. 2016). Ventilatory acclimatization to hypoxia involves induction of mechanism of plasticity in both central and peripheral neural control regions. In rats, chronic hypoxia increased acid-sensitive ion channels in the petrosal ganglion, which was associated with increased carotid sinus nerve activity (Liu et al. 2011). Ibuprofen, an inhibitor of acid-sensitive ion channels, attenuated both the increased acid-sensitive ion channel expression and the CB sensitivity (Liu et al. 2011). Both intermittent and chronic hypoxia also increase CB PGE2 and cytokines including IL1β, IL6, and TNFα, which are attenuated by Ibuprofen (and dexamethasone) (Porzionato et al. 2013). The mechanism of action of acetaminophen is less well-understood. It is believed to be a weak inhibitor of PGE synthesis through inhibition of the peroxidase function of COX-1 and COX-2 enzymes, and perhaps more selective for COX-2; while it does appear to modulate mild inflammation, it cannot suppress severe inflammation in the manner of NSAIDs (Graham et al. 2013).

Overall, there are significant effects of prostaglandins on the neural control of breathing in both fetal and postnatal life. The inhibitory effects of prostaglandin appear to be predominantly central, although further work is necessary to determine their effects on peripheral mechanisms as well. There is significant concern for hypoventilation, apnea, and the requirement for intubation and mechanical ventilation in infants treated with PGE for critical congenital heart disease; however, caffeine or other methylxanthines could be a safe and convenient treatment to prevent respiratory instability and reduce the risk of requiring intubation.

5.0. Concluding remarks

Although important progress has been made toward our understanding of the effects of clinical therapies used in the treatment and prevention of (e.g.) AOP there are still major gaps in our understanding of their mechanisms of action and possible unintended consequences they might have on the respiratory neural control system. Examining the short term effects (both beneficial and detrimental) continue to be an area of important research, but studies on the long-term effects, particularly in the human population (e.g. former preterm infants), are lacking. Many of the probing questions that remain to be answered relate to the way fetal and postnatal experiences shape the developmental trajectory of the respiratory neural control system. Specifically, are there fetal-neonatal origins of later health and disease? Experimentally, methodology that more closely mimics the clinical setting will be a major step toward bridging the gap between animal models and humans. For example, in the context of supplemental O_2, the experimental paradigms used in recent studies have become more refined to more closely mimic the clinical setting with milder treatments and varying the pattern of exposures (e.g., sustained vs. intermittent exposures). There are also other clinical scenarios not discussed here where apnea or respiratory instability is a primary concern including: congenital central hypoventilation syndrome, which involves PHOX2B mutations; SIDS, which involves brainstem and CB neurochemical abnormalities (e.g. serotonin and dopamine, respectively); fetal alcohol and drug exposure (e.g. neonatal abstinence syndrome) among others. There are also other considerations to the development of the respiratory control system including the impact of nutrition (MacFarlane and Di Fiore 2018) and the interactions between the wide range of scenarios experienced by both term and preterm infants. However, an important and often overlooked viewpoint is the need for a fundamental understanding of even the basic mechanisms of how the respiratory neural control system functions in the “normal”, healthy setting. Research into the latter area will be crucial to our progress in teasing out how the developing respiratory system is affected and functions in the “diseased” state, which will lead the way toward developing more effective and safe treatment strategies and a healthier, longer lifespan.

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Highlights

- Oxygen and caffeine are standard therapies for apnea of prematurity
- Both oxygen and caffeine have beneficial actions on both central and peripheral mechanisms of respiratory control
- The early use of these interventions on later development of the respiratory neural control system still remain unknown