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Review

Gestational intermittent hypoxia increases susceptibility to neuroinflammation and alters respiratory motor control in neonatal rats

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ABSTRACT

Sleep disordered breathing (SDB) and obstructive sleep apnea (OSA) during pregnancy are growing health concerns because these conditions are associated with adverse outcomes for newborn infants. SDB/OSA during pregnancy exposes the mother and the fetus to intermittent hypoxia. Direct exposure of adults and neonates to IH causes neuroinflammation and neuronal apoptosis, and exposure to IH during gestation (GIH) causes long-term deficits in offspring respiratory function. However, the role of neuroinflammation in CNS respiratory control centers of GIH offspring has not been investigated. Thus, the goal of this hybrid review/research article is to comprehensively review the available literature both in humans and experimental rodent models of SDB in order to highlight key gaps in knowledge. To begin to address some of these gaps, we also include data demonstrating the consequences of GIH on respiratory rhythm generation and neuroinflammation in CNS respiratory control regions. Pregnant rats were exposed to daily intermittent hypoxia during gestation (G10-G21). Neuroinflammation in brainstem and cervical spinal cord was evaluated in P0-P3 pups that were injected with saline or lipopolysaccharide (LPS; 0.1 mg/kg, 3 h). In CNS respiratory control centers, we found that GIH attenuated the normal CNS immune response to LPS challenge in a gene-, sex-, and CNS region-specific manner. GIH also altered normal respiratory motor responses to LPS in newborn offspring brainstem-spinal cord preparations. These data underscore the need for further study of the long-term consequences of maternal SDB on the relationship between inflammation and the respiratory control system, in both neonatal and adult offspring.

1. Introduction

The neonatal respiratory control system needs to be functional and responsive to chemosensory input while adapting to rapid ongoing developmental changes in respiratory mechanics (Greer, 2012; Greer et al., 2006). Unfortunately, newborn humans are often exposed to pathological challenges, such as gestational intermittent hypoxia (GIH) due to maternal OSA, and postnatal inflammation due to bacterial infection, which compromise respiratory function and ongoing neural development. SDB and OSA during pregnancy are a growing clinical concern (Fung et al., 2012; Louis et al., 2014; Mindell et al., 2015; Pengo et al., 2014) because they are associated with adverse pregnancy and neonatal outcomes (Bourjeily et al., 2013; Ding et al., 2014; Pamidi et al., 2014). Likewise, infection and inflammation in newborn humans leads to life-threatening inhibition of breathing (Black et al., 2010; Chan et al., 2015) and causes neurodevelopmental disabilities (Dammann et al., 2002; Ferreira et al., 2014; Patro et al., 2015; Stoll et al., 2002a; Zanghi and Jevtovic-Todorovic, 2017). Inflammation in newborns can decrease breathing frequency, induce bouts of apneas and hypoxemia, and impair endogenous autoresuscitative responses (Herlenius, 2011). Given that SDB/OSA during pregnancy is increasingly prevalent with the ongoing obesity epidemic (see below), and perinatal infection is common, we propose an interaction between these two phenomena such that infants exposed to GIH are particularly vulnerable to inflammation. Specifically, we suggest that GIH may increase susceptibility of the newborn CNS to inflammatory challenge which will impair the respiratory control system.

Our goal in this review is to briefly summarize the literature regarding SDB and OSA during human pregnancy, and infection-induced inflammation in newborns. Our focus will be on how these conditions adversely affect pregnancy outcomes and the health of newborn infants. The limited literature on relevant experimental animal models will also be reviewed, particularly with respect to respiratory motor control. Our working hypothesis is that these early life experiences (GIH,

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inflammation) alter respiratory motor control in early development through to adulthood, thereby predisposing offspring to suffer from SDB and OSA later in life. Accordingly, we present our preliminary data regarding GIH effects on brainstem and cervical spinal cord inflammatory gene expression *in vivo*, and respiratory rhythm generation *in vitro*.

1.1. Prevalence of SDB and OSA during pregnancy

Sleep-disordered breathing covers a spectrum of disorders characterized by upper airway resistance during sleep, ranging in severity from snoring to OSA, which is characterized by apneas (> 90% reduction in airflow for ≥10 s) and hypopneas (30% or more reduction in airflow for ≥10 s) that cause oxyhemoglobin desaturation and arousals (Amfilochiou et al., 2009; Tsara et al., 2009). The earliest reports of SDB during pregnancy were case studies (Conti et al., 1988; Joel-Cohen and Schoenfeld, 1978; Kowall et al., 1989), and a potential causal link between SDB and adverse perinatal outcomes was proposed (Schoenfeld et al., 1989). During the following 20 years, several studies sought to determine the prevalence of SDB during pregnancy using questionnaires regarding sleep (*e.g.*, sleep duration, snoring, daytime sleepiness) with relatively small sample sizes. But importantly, these results provided the first evidence that SDB during pregnancy is associated with adverse pregnancy outcomes (gestational diabetes mellitus, hypertension, preeclampsia, unplanned Caesarian delivery) and adverse perinatal outcomes (preterm delivery, low birth weight, neonatal intensive care unit admission, and intrauterine growth restriction) (Ding et al., 1997; Pamidi et al., 2014; Venkata and Venkateshiah, 2009). Since the predictive power of questionnaires and overnight portable sleep monitoring devices to detect OSA is limited (Lockhart et al., 2015), there is an ongoing effort to clinically document SDB in pregnant women using polysomnography or at-home ambulatory sleep-monitoring devices while prospectively following their pregnancy, birth outcome, and infant health.

A recent prospective polysomnography study (n = 1509 subjects) estimated OSA prevalence to be 4.9%, and identified obesity and hypertensive disorders as risk factors for SDB (Antony et al., 2014). With respect to obesity, an early case-controlled study showed that obese pregnant women had increased SDB parameters that further increased over pregnancy (Maasilta et al., 2001). In a larger, more recent prospective study to screen for OSA among obese pregnant women (n = 175), OSA prevalence was estimated at 15.4% and was associated with preeclampsia, Caesarian delivery, and neonatal intensive care unit admissions (Louis et al., 2012). The increased rate of OSA during pregnancy from 1998 to 2009 represents an annual increase of 24%, and exactly parallels the increased number of obese pregnant women (Louis et al., 2014). The increased incidence of OSA during pregnancy is suggested to be due to the increased prevalence of obesity in pregnant women (Louis et al., 2012; Pien et al., 2014). A 5–15% prevalence in otherwise healthy, pregnant women nonetheless represents a large patient population given that there are ~4 million births/year in the United States. Furthermore, the rise in obesity among fertile women suggests that the prevalence will continue to increase, increasing the number of patients who will be at risk for hypertensive disorders that further exacerbate their condition. Also, pregnant women with hypertensive disorders (chronic hypertension, gestational hypertension, preeclampsia) are particularly at risk for OSA, as 41% of these women had OSA compared to only 16% of normotensive pregnant women (O'Brien et al., 2014). In agreement with this study, sleep monitoring testing revealed that OSA-positive pregnant patients tended to have had greater BMI's and higher rates of hypertension (chronic and gestational), pre-gestational diabetes mellitus, asthma, and preeclampsia (Lockhart et al., 2015). Thus, OSA prevalence is estimated to be ~20% in a prospective observational study in pregnant women with other risk factors (Facco et al., 2014), much higher than in the population of healthy pregnant women.

1.2. Causes of SDB/OSA during pregnancy

Pregnancy causes widespread changes in respiratory function, sex hormone levels, and upper airway patency that paradoxically promotes and protects against SDB/OSA. The increasing size of the fetus elevates the diaphragm and significantly reduces maternal functional reserve capacity, expiratory reserve volume, and residual volume (Edwards et al., 2002), which decrease oxygen reserves in the lungs and compromise the ability to withstand apneas. The decrease in expiratory reserve volume may cause early airway closure during tidal ventilation (Holdcroft et al., 1977) and reduce oxygenation of the blood (Awe et al., 1979). Maternal nasal passage patency is also reduced during pregnancy due to chronic hyperemic congestion and rhinitis (Bende and Gredmark, 1999). Indeed, there is an associated increase in the Mallampati score (visual measure of ease of intubation) with pregnancy (Pilkington et al., 1995), coinciding with smaller upper airways in pregnant women at the oropharyngeal junction (Izci et al., 2006). During pregnancy, high progesterone levels increase ventilatory drive, which is thought to be protective (Lyons and Antonio, 1959). However, high progesterone also induces a respiratory alkalosis (pH = 7.44) that may promote instability in respiratory control, especially during sleep. For example, in non-pregnant subjects, hypocapnia and respiratory alkalosis induce central apneas during non-REM sleep, especially when transitioning from wakefulness to sleep (Skatrud and Dempsey, 1983). These wide-ranging physiological changes in respiratory function due to pregnancy may predispose the mother to experience nocturnal bouts of intermittent hypoxia.

1.3. Perinatal consequences and outcomes of maternal SBD/OSA

Although we are now becoming aware of the detrimental effects of SDB/OSA during pregnancy on the mother, the consequences of maternal SDB/OSA on the developing fetus are only beginning to be identified. Several studies link SDB/OSA during pregnancy with adverse perinatal outcomes (Chen et al., 2012a; Ding et al., 2014; Louis et al., 2012; Louis et al., 2014), but there is variability in the findings. A recent meta-analysis of the literature showed that moderate-to-severe SDB during pregnancy is associated with poor fetal outcomes, such as preterm delivery, low birth weight, neonatal intensive care unit admission, intrauterine growth restriction, and a low Apgar score (Ding et al., 2014). Likewise, women with documented sleep apnea prior to becoming pregnant are more likely to have preterm deliveries, Caesarian section, small-for-gestational age infants, preterm deliveries, low Apgar scores at delivery, and babies that are admitted more frequently to neonatal intensive care/special care units (Bin et al., 2016; Chen et al., 2012a). Similarly, mothers diagnosed with SDB during pregnancy (via in-home polysomnography) had increased odds of delivering an infant small for gestational age (Pamidi et al., 2014). In contrast, a prospective study that recruited a high-risk cohort of pregnant women (n = 128, BMI > 30 kg/m^2, history of chronic hypertension, pre-gestational diabetes, prior preeclampsia, or twin gestation) with documented sleep apnea showed no correlation with preterm delivery or extremely low birthweights (Facco et al., 2014). However, it is important to note that although there were no acute adverse effects on the newborns, some adverse effects may not be revealed until later in development. For example, in a study of 74 pregnant women with SDB, social development was impaired in their infants at one year of age (Tauman et al., 2015). Thus, infants and children of mothers with SDB/OSA should be carefully observed and tested to reveal potential long-lasting pathophysiological conditions.

It is hypothesized that cyclical episodes of maternal hypoxemia/reoxygenation due to SDB reduces placental oxygen delivery to fetus, thereby restricting fetal growth. Pregnant women with SDB had a mean apnea-hypopnea index of 63 ± 15 events/h, which exposes the fetus to a significant number of hypoxia/reoxygenation events (Edwards et al., 2005). This idea is also consistent with the findings that maternal