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Review

Chemoreceptors, baroreceptors, and autonomic deregulation in children with obstructive sleep apnea☆

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ABSTRACT

Obstructive sleep apnea (OSA) is highly prevalent sleep disorder of breathing in both adults and children that is fraught with substantial cardiovascular morbidities, the latter being attributable to a complex interplay between intermittent hypoxia (IH), episodic hypercapnia, recurrent large intra-thoracic pressure swings, and sleep disruption. Alterations in autonomic nervous system function could underlie the perturbations in cardiovascular, neurocognitive, immune, endocrine and metabolic functions that affect many of the patients suffering from OSA. Although these issues have received substantial attention in adults, the same has thus far failed to occur in children, creating a *quasi* misperception that children are protected. Here, we provide a critical overview of the evidence supporting the presence of autonomic nervous system (ANS) perturbations in children with OSA, draw some parallel assessments to known mechanisms in rodents and adult humans, particularly, peripheral and central chemoreceptor and baroreceptor pathways, and suggest future research directions.

1. Introduction

Obstructive sleep apnea (OSA) is the most prevalent form of sleep disordered breathing in children. It has been estimated that 1–3% of all children suffer from clinically relevant OSA, but a larger percentage of children (10–15%) present the cardinal symptom of increased upper airway resistance, i.e., snoring (Lumeng and Chervin, 2008). Furthermore, with the concurrent pandemic in obesity that clearly encompasses children of all ages, it can only be anticipated that the true incidence of OSA in the pediatric age range will continue to rise (Tauman and Gozal, 2006). There is no doubt that the repetitive closure or near closure of the upper airway during sleep markedly increases the risk for the occurrence of substantial adverse effects on multiple organ systems in both adults and children, such that there is a clear need to advance our understanding on the underlying pathophysiological mechanisms underlying the morbid consequences of OSA.

There is substantial evidence supporting a major role for the repetitive hypoxia in altering autonomic nervous system (ANS) control. However, the individual and integrated roles and contributions of hypercapnia, sleep fragmentation, and increased respiratory effort remain unclear (Kim et al., 2011; Hakim et al., 2012). For example, increased negative inspiratory intrathoracic pressures generated against the occluded airway will increase left ventricular transmural pressures and afterload. Furthermore, venous return will increase and promote right ventricular pre-load. Hypoxia in turn will yield vasoconstriction in the pulmonary circulation, and therefore increase the right ventricle afterload. With the occurrence of an arousal, sympathetic activity, blood pressure, cardiac output, and heart rate will rapidly increase, and result in further augmentation of cardiac oxygen demand at a time when oxyhemoglobin saturation is at its lowest (Eckert et al., 2009), potentially compromising myocardial contractility. Over time, the cumulative effects of such stresses are unclear, but could clearly promote cardiac remodeling as well as alter structural and functional aspects of the arterial vasculature, and even be irreversible if occurring during specific windows of developmental regulation (Soukhova-O'Hare et al., 2006a,b, 2008), possibly via epigenetic changes (Kim et al., 2012; Nanduri et al., 2012; Nanduri and Prabhakar, 2012). Indeed, in very exciting albeit preliminary work, Prabhakar and colleagues showed that the presence of sustained increases in peripheral chemoreceptor sensitivity following neonatal exposures

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to intermittent hypoxia was associated with decreased expression of anti-oxidant genes and reciprocal increases in the gene expression of pro-oxidant enzymes in the carotid body. More interestingly, Sod2 gene expression was reduced and increased methylation of a single CpG site in the vicinity of the transcription start site was detected. Prevention of such epigenetic modification abrogated all the functional changes in chemoreflexes associated with early life exposures to intermittent hypoxia (Nanduri et al., 2012). Thus, the lifelong changes in autonomic nervous system function and blood pressure regulation reported by Soukhova-O'Hare and collaborators in the context of perinatal intermittent hypoxia may reflect more expansive epigenetic changes to include genes encoding for important regulators of autonomic and vascular functions (Soukhova-O'Hare et al., 2006a,b, 2008).

2. What happens to the ANS during normal sleep?

During normal sleep there are changes in sympathetic nerve activity (SNA) that are tightly regulated by sleep state. Indeed, SNA (measured using non-invasive approaches such as heart rate variability (HRV), blood pressure and heart rate are lower in normal subjects while they are in non-REM sleep than when awake, and during REM sleep SNA increases above the levels recorded during wakefulness, even though blood pressure and heart rate return to the same levels recorded during wakefulness (Hornyak et al., 1991; Somers et al., 1993). These characteristic patterns undergo substantial changes during postnatal development, whereby SNA is higher in infants and very young children, and progressively declines till age 5–7 years, after which it remains stable till the beginning of puberty, the latter being associated with increases in SNA (Dalmaz and Peyrin, 1982; Finley et al., 1987; Finley and Nugent, 1995; Yeragani et al., 2005; De Rogalski Landrot et al., 2007; Weise et al., 2002; Yiallourou et al., 2012). Secondly, in addition to complex regulatory processes inherent to normal maturation, the confounding effect of body weight on ANS tonic and reactive response characteristics cannot be ignored (Aldo Ferrara et al., 1989; Rodriguez-Colon et al., 2011). Thirdly, the sleep state dependency of the normal ANS changes throughout the sleep cycle may be altered by intrinsic factors such as the frequency of spontaneous arousals. Indeed, in children with paucity of spontaneous arousals during sleep, sleep duration was shorter, and the parasympathetic activity was significantly lower when compared to children with more frequent awakenings. Furthermore, heart rate was significantly increased in the children without spontaneous awakenings (Sampei et al., 2006, 2007). Since changes in ANS activity are modulated by sleep states themselves, attention to these issues needs to be implemented during testing (Villa et al., 2000). Thus, in addition to the substantial precautions and awareness to limitations being required when using any of the methodologies in the context of performing assessments of the ANS (Mancia and Grassi, 1991; Guild et al., 2010; Kamath and Fallen, 1993; Skrapari et al., 2006; Dietrich et al., 2010; Bosch et al., 2011; Fitzgibbon et al., 2012), there is an urgent need to establish normative data and standard operating procedures in children. The current availability of several non-invasive techniques and physiological paradigms to elicit specific responses should permit more extensive characterization of the ANS in children throughout the age and sleep state continuum, such as to enable the use of such measures in improving our understanding in pathological states such as OSA.

From studies in adult OSA patients, it has become apparent that the repetitive respiratory events leading to intermittent hypoxia and CO_2 retention may augment SNA via stimulation of both central and peripheral chemoreceptors (Somers et al., 1989a). Of course, carotid sinus baroreceptors may also increase SNA outflow coincident with unloading, i.e., during the reductions in blood pressure and stroke volume that occur during obstructive apneic events. The presence of apnea also enhances SNA by curtailing the reflex inhibition of SNA that originates from pulmonary stretch receptors (Somers et al., 1989b). Sleep fragmentation and arousals from sleep at apnea termination will also enhance SNA and reduce parasympathetic outflow to the heart, even though spontaneous arousals can precipitate similar alterations in autonomic processes (Horner et al., 1995; Walter et al., 2009)

Direct measurements of autonomic activity, particularly during sleep, are not an easy task, and have traditionally required invasive approaches thereby precluding their use in children. Among the surrogate indirect non-invasive markers of ANS activity, linear and non linear dynamic analyses of heart rate variability, peripheral arterial tonometry, continuous beat-to-beat blood pressure monitoring, assessment of baroreflex sensitivity, non-invasive radionuclide imaging, or quantitation of serum and urine catecholamines and their metabolic products have been used in the last 20 years or so in pediatric subjects, and have provided initial useful insights into changes in ANS function and responsiveness, thereby permitting more extensive probing of the autonomic system in health and disease (Baharav et al., 1995; Massin et al., 2000; O'Brien and Gozal, 2007; Smith et al., 1998; Tauman et al., 2004). For example, assessment of the baroreflex sensitivity is an interesting window into ANS regulation. Indeed, the baroreflex provides a negative feedback loop in which elevated blood pressure inhibits sympathetic outflow, decreases heart rate, and, thus, lowers blood pressure. In a similar fashion, decreased blood pressure activates baroreflex mechanisms, causing heart rate increases and blood pressure to rise (Golbidi et al., 2012). Consequently, attenuated baroreceptor sensitivity is proposed to increase sympathetic activation, and conversely, increases in SNA will attenuate the baroreflex sensitivity.

As indicated above, sleep is involved in the regulation of peripheral organ function, such as endocrine and cardiovascular function, and specific changes in peripheral organ systems occur during both rapid eye movement (REM) and non-REM (NREM) components of sleep in healthy children. One well established sleep-associated cardiovascular change is the decrease in blood pressure and heart rate that occurs during sleep onset, also called "blood pressure dipping" (Antic et al., 2001; Bald, 2002; Perciaccante et al., 2007; Gilardini et al., 2008). The sleep-related decrease in blood pressure occurs in addition to the blood pressure changes induced by the circadian clock and changes in body posture that typically accompany sleeping behaviors (Eissa et al., 2001). Blood pressure dipping is contingent upon a reduction in global SNA (reflecting increased parasympathetic tone along with sympathetic withdrawal) since non-dippers manifest an increase in sympathetic tone at sleep onset (Ziegler, 2003), but dynamic changes during sleep state transitions can be very revealing (Schwimmer et al., 2010). Many of these phenomena can be altered with the presence of OSA in children, and potentially promote the risk for hypertension and endothelial dysfunction.

3. Catecholamine production and sympathetic activation

Catecholamines (CAs) (e.g., norepinephrine and epinephrine) are critically important hormones underlying the "fight or flight" response, and measurements of these compounds may provide useful information of changes in ANS balance in children. CAs exert a multitude of physiologic effects such as enhancing the contractility and conduction velocity of cardiomyocytes, increasing cardiac output and rising blood pressure, all the while promoting bronchodilation and recruiting bioenergetic reserves via enhanced lipolysis and glycogenolysis. We are now cognizant of the fact that in addition to the adrenal medulla and the postganglionic fibers in the sympathetic nervous system, phagocytic cells, lymphocytes (Flierl et al., 2008) and adipocytes (Vargovic et al., 2011) can also