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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 intrathoracic 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.

Keywords

Obstructive sleep apnea; autonomic nervous system; peripheral chemoreceptors; carotid body; brainstem; catecholamines; sympathetic; vagus; parasympathetic; pulse transit time; tonometry; sleep fragmentation; hypoxia

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.

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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; Soukhova-O'Hare et al., 2008; Soukhova-O'Hare et al., 2006b), 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 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; Soukhova-O'Hare et al., 2008; Soukhova-O'Hare et al., 2006b).

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;

Sampei et al., 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 CO₂ 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., 2011). 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 synthesize and release CAs. Key organs involved in the crosstalk of CAs include the hypothalamic-pituitary-adrenal (HPA) axis and the autonomic nervous system, consisting of the adrenergic sympathetic nervous system, the vagus-mediated parasympathetic nervous system, and the enteric nervous system (Elenkov et al., 2000).

The synthesis of CAs involves tyrosine as the major substrate, and requires the activity of the key enzymes, tyrosine hydroxylase (TH) and the rate-limiting step in catecholamine synthesis, dopamine β -hydroxylase (DBH), which converts dopamine to norepinephrine (Elenkov et al, 2000). Although both norepinephrine and the methylated derivative epinephrine are stored in synaptic vesicles of neurons, epinephrine is not a neuromediator at the postganglionic sympathetic endings, with norepinephrine operating as the principal neurotransmitter of sympathetic postganglionic endings. Tyrosine is transported into catecholamine-secreting neurons and adrenal medullary cells where catecholamine synthesis occurs. The actions of norepinephrine and epinephrine are exerted via receptor-mediated signal transduction events, with 3 distinct major types of adrenergic receptors, namely α_1 , α_2 , and β receptors that include several sub-classes. Dopamine binds to dopaminergic receptors identified as D-type receptors and there are four subclasses identified as D₁, D₂, D₄, and D₅. Activation of the dopaminergic receptors results in activation of adenylate cyclase (D₁ and D₅) or inhibition of adenylate cyclase (D₂ and D₄). In response to stress stimuli such as hypoxia, hypotension, fear, pain, or extreme temperatures, CAs are released directly into the circulation, activating peripheral adrenergic receptors with subsequent chronotropic and inotropic effects on the heart, redistribution of blood flow to organs and muscles, and release of energy through glycolysis and lipolysis. This systemic effect also includes sensitizing certain receptors to subsequent sympathetic or somatic nerve stimulation, along with concomitant inhibition of pain sensation, thus facilitating the coordinated responses that characterize the “fight or flight” situation (Smith et al, 1998).

4. Autonomic Nervous System Alterations In Children with OSA

For many years, the prevailing assumption was that children were “protected” from any risk of developing cardiovascular morbidities in the context of pediatric OSA. In fact, the only concern for such children was the emergence of pulmonary hypertension and cor pulmonale (Duman et al, 2008; Freed, 1981; Mucklow, 1989; Ramakrishna et al, 2000; Tal et al, 1988). In other words, the assumption was that in the context of major redundancies in cardiovascular mechanisms aimed at preserving homeostasis, the increased vascular capacitance and reserve in children would suffice to prevent the emergence of any measurable alteration in normal cardiovascular functioning. However, such assumptions have been repeatedly refuted, particularly in the last decade. Indeed, Aljadeff and colleagues

showed that the ANS outflow was disrupted by the presence of OSA in children with evidence suggestive of increased sympathetic and reduced parasympathetic tone, such that changes in heart rate variability, serving as non-invasive probes of ANS tone, were apparent and exhibited unique changes that were almost pathognomonic (Aljadeff et al., 1997). One year later, Marcus and colleagues reported on the presence of blood pressure increases in children with relatively severe OSA (Marcus et al., 1998), further dispelling the notion of “cardiovascular immunity” in developing children.

Two possibilities have been raised as playing a role in cardiovascular consequences of pediatric OSA in children: (a) the mechanisms in children are the same mechanisms leading to such morbidity in adults; (b) differential activation of selective pathways may be preferentially occurring in children. As will become apparent, the evidence to support either one of these 2 options is scant at best.

In a series of studies spanning 2 decades in both animal and human models, it has become apparent that the combination of intermittent hypoxia, sleep fragmentation, episodic hypercapnia and increased intrathoracic pressure swings, can separately and together activate or amplify the onset and propagation of endothelial dysfunction, atherogenesis, increased systemic inflammation, oxidative stress, and activation of adhesion molecules and coagulation (Gozal and Kheirandish-Gozal, 2008; Gozal et al., 2007; Kim et al., 2011; Parish and Somers, 2004; Somers et al., 1995; Somers et al., 1989a). Two major and potentially interactive pathways have been proposed as underlying the increases in SNA (Figure 1): (1) peripheral chemoreceptor- and baro-receptor-dependent pathway (Iturriaga et al., 2009; Prabhakar and Kumar, 2010); and (2) interactions between peripheral and central CNS-located pathways (Fletcher, 2001; Sica et al., 2000).

4.1. What is the evidence that some or all of the cardiovascular phenotypic alterations that may occur in children with OSA derive from peripheral chemoreceptor-dependent pathway activation?

Before we address this specific question, it would be appropriate to briefly review the existing body of work on this issue that has been carried out in both adult animals and adult humans. Since the initial ground-breaking work by Fletcher and collaborators (Lesske et al., 1997; Fletcher, 2001), it has become quite apparent that intact carotid bodies are a pre-requisite for the increases in SNA and the development of systemic blood pressure elevations that occur in the context of chronic intermittent hypoxia (Prabhakar et al., 2005, 2007; Iturriaga et al., 2009; Marcus et al., 2010). Furthermore, it appears that such events are accompanied by significant changes in the CNS, particularly in regions that are traditionally associated with processing of afferent signals from the carotid bodies. Indeed, in an elegant study de Paula and colleagues (2007) showed that neurons within the nucleus of the solitary tract that receive direct inputs from the carotid body display changes in the functional release and activation of glutamatergic receptors that are compatible with enhanced chemoreflex and ventilatory responses, and that such changes promote increased tonic and responsive sympathetic outflow. Subsequent studies have thus far confirmed that the functional changes in chemoreceptors and baroreceptors induced by intermittent hypoxia do not remain confined to the carotid body, but in fact are associated with forms of neural plasticity that modify the integration and processing of such signals, leading to increased SNA (Kline, 2010; Gonzalez-Martín et al., 2011; Costa-Silva et al., 2012). A less well explored of this important facet underlying the network modifications pertaining to chronic intermittent hypoxia involves changes in parasympathetic activity. In a series of studies, Cheng and collaborators showed that exposures to chronic intermittent hypoxia during sleep were accompanied by structural remodeling of nucleus ambiguus projections to cardiac principal neurons, and by functional changes in tonic parasympathetic inputs and responses to vagal stimulation (Lin et al., 2007, 2008; Gu et al., 2007; Yan et al., 2008, 2009; Ai et al.,

2009). Thus, the cumulative evidence in rodents supports the concept that in the context of intermittent hypoxia, the carotid bodies play a critical initial role in a process that ultimately leads to structural and functional remodeling of the afferent and efferent pathways underlying both sympathetic and parasympathetic systems. In other words, augmentation of peripheral chemoreflex sensitivity, and either direct or indirect (via afferent inputs) effects on sites of central sympathetic and parasympathetic regulation will ultimately lead to heightened sympathetic outflow and consequent changes in cardiovascular homeostasis. Although the ability to explore these pathways in humans is obviously limited, the contribution of carotid bodies to ANS dysfunction in the context of sleep apnea has been consistently reported (Narkiewicz et al. 1998; 1999; Loreda et al., 2001; Smith et al., 2003; Weiss et al, 2007). Thus, it would be reasonable to postulate that similar processes are indeed operational in children.

The ages at which OSA prevalence peaks are also a period of development during which peripheral chemoreceptor function is increased when compared to adults. Indeed, Springer *et al* showed that the degree of hyperoxic ventilatory reduction was greater in pre-pubertal children than in adults (Springer et al., 1988). Furthermore, we have shown that ventilatory transients to hypoxia, hyperoxia, and hypercapnia, serving as surrogate reporters of peripheral chemoreceptor function, were enhanced in pre-pubertal children (Gozal et al., 1994), thereby confirming that peripheral chemoreceptors are more sensitive to stimulation in childhood. However, the implications and adaptations of such intrinsic differences in the functional properties of the peripheral chemoreceptor responses (PCR) to the gas exchange alterations that occur during OSA have not been examined. As such, it is unclear whether the intermittent hypoxia and recurrent arousals that occur in the context of pediatric OSA lead to maladaptive increases in PCR responsiveness, and contribute to the increased SNA in such children. This issue will have to be critically examined in future studies. Of note, a recent study in juvenile rats seems to support the plausibility of the assumption that children may in fact be more susceptible to intermittent hypoxia by virtue of increased carotid body sensitivity and consequent amplification of the reflexive arcs described above, and initiated by the onset of OSA (Braga et al., 2006).

4.2. Sympathetic Alterations in Pediatric OSA

We and others have provided initial evidence that alterations in autonomic nervous system function occur in children with OSA, and may be reflected by the presence of either increased sympathetic nervous system tone, increased sympathetic responsiveness, or the emergence of sympathetic-parasympathetic imbalance (Bhattacharjee et al., 2009; Baumann et al., 2011; Liao et al., 2010a; O'Driscoll et al., 2011; Brockmann et al., 2011; Bhattacharjee and Gozal, 2011). Studies exploring alterations in autonomic function in children with sleep-disordered breathing are relatively sparse, particularly because of the difficulties associated with invasive assessments such as nerve recordings (Narkiewicz and Somers, 2003). Therefore, all studies have utilized non-invasive probing ANS assessment techniques. As mentioned earlier, Aljadeff and colleagues (Aljadeff et al., 1997) used heart rate variability analyses including both linear and non-linear dynamic analyses and Poincaré scatter plots, and showed the presence of substantial increases in sympathetic tone along with evidence of reduced parasympathetic activity in children with OSA. These findings were subsequently confirmed using power spectral analysis of heart rate (Baharav et al., 1999), which uncovered the presence of sympathetic predominance during REM sleep being present in pediatric OSA patients. The presence of sleep state specific alterations in ANS has been subsequently confirmed (Liao et al., 2010b). O'Brien and Gozal (O'Brien and Gozal, 2005) measured sympathetic vasoconstrictor responses during wakefulness in 28 children with OSA and 29 healthy controls using Peripheral Arterial Tonometry (PAT), and showed enhanced sympathetic responses following vital capacity breaths as well as during ice-cold

hand pressor tests in OSA children. The potential advantage on the use of dynamic challenge tests aimed to perturb the ANS and elicit sympathetic or parasympathetic stimulation, it that the responses can be then modeled, and elucidate specific imbalances that may not be readily apparent during static conditions (Chaicharn et al., 2006). For example, assessment of sympathetic responses to exercise or acute hypoxia may reveal increased sympathetic responses and blood pressure changes that may not be detected during rest or normoxia. Other studies using heart rate dynamics suggest that sleep states and OSA are important co-determinants of SNA outflow, and that such assessments provide not only insights into SNA alterations but can also serve as diagnostic algorithms (Deng et al., 2006; Shouldice et al., 2004).

Reductions in the increased HR variability and increases in R-R intervals during sleep after treatment was initially reported with adenotonsillectomy in OSA children (Constantin et al., 2008; Kaditis et al., 2011), and subsequently confirmed (Muzumdar et al., 2011). In a study involving 25 children (mean age 10.2 ± 2.3 years) undergoing a diagnostic assessment for OSA, and 25 age-matched healthy control subjects, children were subjected to tests aiming to assess autonomic function (head-up tilt test, Valsalva maneuver, and deep breathing tests). Increased basal sympathetic activity during wakefulness and also impaired severity-dependent responses to the autonomic challenges were apparent in children with OSA (Montesano et al., 2010). Of note, periodic arousals even when induced by non-respiratory events can also trigger alterations in autonomic function in children (Walter et al., 2009), and differences in cardiac responses to arousal can be detected in children afflicted with OSA (O'Driscoll et al., 2010).

Another frequently used noninvasive tool allowing for assessment of changes in ANS tone consists in the measurement of the pulse transit time (PTT). Indeed, PTT changes can gauge moment-to-moment changes in sympathetic burst activity by measuring the delay from the initial left ventricular electrical depolarization in the electrocardiogram to the appearance of the corresponding plethysmographic signal of the oximetry waveform at the wrist. (Foo and Lim, 2006). In initial studies conducted in control children in whom recordings of PAT and PTT were concomitantly performed, spontaneous arousals were associated with predictable changes in both PAT and PTT signals, indicating that the magnitude of sympathetic responses can be reliably quantified using noninvasive measures in children (O'Brien and Gozal, 2007; Tauman et al., 2004; Katz et al., 2003; Pillar et al., 2002). These findings have further enabled PTT to be used as a potentially valuable diagnostic screening tool for OSA (Brietzke et al., 2007; Foo et al., 2006; Paruthi and Chervin, 2010; Pepin et al., 2005).

4.3. Baroreceptor and Baroreflex Alterations in Pediatric OSA

In the only study in children published to date, McConnell and colleagues assessed 169 children (with no OSA or with OSA of different severity) using polysomnography and continuous blood pressure measurements (McConnell et al., 2009). The baroreflex gain was then calculated in both the time and frequency domains using well established and validated approaches (Dietrich et al., 2006). Nighttime baroreflex gain in children with OSA was significantly reduced when compared to healthy children. These findings further indicated that the reductions in baroreflex gain in OSA reflected diminished heart rate responses to BP variability. Smaller responses of heart rate to blood pressure changes in children with OSA are very similar to observations in adults with OSA (Narkiewicz et al., 1998).

4.4. Blood Pressure Alterations in Pediatric OSA

Alterations in blood pressure are one of the important cardiovascular morbidities that have been closely linked to perturbations in autonomic and sympathetic function in OSA. As mentioned above, Marcus and collaborators first reported changes in systemic blood

pressure in children with OSA (Marcus et al., 1998). Subsequently, several groups of investigators have confirmed the presence of systemic blood pressure abnormalities in pediatric OSA, with such changes being more pronounced during NREM sleep and also more likely to occur in the context of repeated arousals (O'Driscoll et al., 2009a; O'Driscoll et al., 2009b; Kohyama et al., 2003; Leung et al., 2006; Bixler et al., 2008; Amin et al., 2004). Furthermore, severity-dependent reductions in left ventricular function with decreased diastolic relaxation and systolic contractility have also been clearly identified in pediatric OSA (Amin et al., 2008; Kaditis et al., 2010; Ugur et al., 2008). Again, the contributions of specific autonomic alterations to these vascular changes remains unexplored in children.

4.5. Metabolic Abnormalities and Autonomic Nervous System Function in Children with OSA

In the past decades, the prevalence of obesity and diabetes has greatly increased in both developed and developing countries, and both sleep duration and OSA are becoming recognized as contributing factors, alongside increased caloric intake and decreased physical activity. The autonomic nervous system is an important regulator of metabolic function in major organs including the liver, adipose tissue, muscle and pancreas, whereby alterations in autonomic function contribute to metabolic dysfunction and obesity (Straznicki et al., 2011; Lambert et al., 2011; Enriori et al., 2011). Since OSA is strongly connected to autonomic dysfunction, the potential contribution of autonomic alterations to metabolic morbidities in the context of OSA can not be ignored (Trombetta et al., 2010; Spiegel et al., 2004). The extent of such connection in children has however not been as thoroughly explored as it should (Oliveira et al., 2010). Indeed, a substantial number of studies has suggested the presence of significant associations between the spectrum of sleep disordered breathing in children and insulin resistance and alterations in lipid homeostasis (Alexopoulos et al., 2011; Canapari et al., 2011; Deboer et al., 2012; Hannon et al., 2011; Nakra et al., 2008; Tauman et al., 2005; Tsaoussoglou et al., 2010; Verhulst et al., 2009; Waters et al., 2007). However, only a very restricted number of studies has examined potential relationships between ANS alterations and such metabolic consequences, although the mediation of metabolic dysfunction being specifically correlated to catecholamine increases was not specifically sought (Kelly et al., 2010). To further elucidate the potential contributions of OSA to metabolic abnormalities, we previously studied 62 consecutive pre-pubertal children (40% of whom were non-obese), and examined metabolic parameters before and after undergoing adenotonsillectomy for OSA (Gozal et al., 2008). In non-obese children, treatment resulted in significant improvements in cholesterol levels, but did not seem to affect fasting insulin levels. In contradistinction, improvements emerged in both serum cholesterol levels and in fasting insulin and insulin/glucose ratios following treatment in obese children. Taken together, these findings strongly support that disrupted sleep and episodic hypoxia in the context of OSA do impose substantial changes in lipid regulatory mechanisms in all children, and may lead to altered glucose homeostasis when underlying obesity is present, but the contribution of autonomic dysregulation to these processes remains to be elucidated.

4.6. Catecholamine Alterations in Pediatric OSA

In an effort to obtain more accurate correlates of changes in SNA, measurements of the concentrations of catecholamines in plasma or urine samples have also been undertaken in pediatric OSA patients. Kaditis and collaborators measured urinary catecholamines in 44 habitually snoring children with different levels of OSA severity and of nocturnal hypoxemia, and also included 10 healthy children without OSA. Norepinephrine and epinephrine urine levels correlated significantly with the obstructive apnea-hypopnea index. Since concentrations of catecholamines were measured in morning urine specimens collected after arousal from sleep, the significant associations between urinary

catecholamines and polysomnographic indices most likely indicate preceding increases in the nocturnal activity of sympathetic neurons, although the contribution of adrenal medulla can not be inferred (Kaditis et al., 2009). In a larger cohort, Snow and collaborators assessed 159 habitually snoring children who underwent overnight polysomnography in whom first morning voided urine samples were collected to measure the levels of norepinephrine, epinephrine and dopamine (Snow et al., 2010). In a subset of children, blood samples were also drawn for gene expression of catecholamine-related pathway genes. Similar to Kaditis et al (2009), those children with OSA in the Snow et al study had significantly higher urinary norepinephrine and epinephrine levels, but not dopamine, compared to habitual snorers without OSA (for example: norepinephrine: 40.1 ± 24.7 ng/mg creatinine vs. 31.6 ± 16.2 ng/mg creatinine, $P < 0.01$). Based on these findings, altered sympathetic activity appears to occur in pediatric OSA, and is accompanied by increased expression of genes mediating the synthesis and transport of catecholamines including selective up-regulation of their receptors. Taken together, increased bioavailability of catecholamines is a consequence of OSA in children (Snow et al., 2010). Other groups have subsequently confirmed that the apnea-hypopnea index is a significant and independent predictor of catecholamine levels (Kelly et al., 2010; O'Driscoll et al., 2011; Oliveira et al., 2010). Of note, catecholamine levels decrease after treatment further confirming the effect of OSA on sympathetic outflow (Nakra et al., 2008).

5. Summary

There is no doubt that based on the evidence presented heretofore, sleep disturbances in children can lead to alterations in autonomic nervous system function, primarily manifesting as increased SNA and potentially some degree of parasympathetic withdrawal. These alterations could in turn facilitate the occurrence of metabolic and cardiovascular morbidities. In children, there is solid evidence indicating that OSA alters heart rate responses and elevates systemic blood pressure, and that treatment of OSA will either reverse or ameliorate such abnormalities. Studies in developing rodents also indicate that there may be long-term implications to the autonomic nerve system alterations induced by sleep-disordered breathing, particularly if they occur during specific developmental windows in infancy and childhood or if underlying genetic susceptibility factors that govern cardiovascular and metabolic function are present. However, the mechanisms underlying the ANS changes in pediatric OSA have not been extensively explored, such that the contributions of peripheral chemoreceptors and baroreceptors, other sympathetic organs such as the adrenal glands, and the role of specific regions of the CNS (e.g., nucleus of the solitary tract, nucleus ambiguus, paraventricular nucleus, etc...), and even those of circulating lymphocytes as sources of local catecholamines are completely unclear. Furthermore, considering the developmental trajectory of the maturation of ANS structures, whether children behave as “small adults” or not in the context of their chemoreceptor, baroreceptor and ANS adaptations to OSA is also unknown, and clearly merits further study.

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Figure 1. Schematic diagram underlying the putative pathways associated with autonomic nervous system alterations in pediatric OSA, and their potential reversibility based on a neonatal window of vulnerability (see text for more details)