

Introduction

Sleep-Disordered Breathing across the Life Span: Exploring a Human Disorder Using Animal Models

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Abstract

Sleep-disordered breathing (SDB) is a constellation of breathing disorders that occur during sleep. Obstructive sleep apnea (OSA), the most common form, is characterized by complete or partial airway obstruction, hypoventilation, and central apneas, all of which lead to recurrent episodes of hypoxia, hypercapnia, sleep fragmentation, and elevated sympathetic tone. OSA occurs throughout the life span and is associated with significant cognitive, metabolic, and cardiovascular consequences that impair the quality of life. Building on observations that the upper airway collapses during sleep, obesity increases the risk of upper airway obstruction, and this obstruction leads to periods of hypoxia and reoxygenation that cause oxidative stress, researchers used large and small animal models to study the genetic pre-determinants of OSA, the neuromechanical control of the upper airway during development and aging, and the metabolic consequences of oxidative stress. From the early canine models of experimentally induced upper airway obstruction to the current rodent models of intermittent hypoxia, the information now available has significantly improved scientists' understanding of the pathogenesis of OSA and its consequences, leading to better care for individuals with sleep-disordered breathing.

Sleep-disordered breathing (SDB¹) is a constellation of breathing disorders that occur during sleep. Obstructive sleep apnea (OSA¹) is the most common form, and is characterized by complete or partial upper airway obstruction (snoring is a common symptom of such obstruction), hypoventilation, and central apneas, all of which lead to recurrent

episodes of hypoxia, hypercapnia, sleep fragmentation, and elevated sympathetic tone. Seminal research findings over the last 100 years have led to the identification, characterization, and effective treatment of sleep-related breathing disorders. The review articles in this issue illustrate the animal model studies that have built on earlier findings to improve understanding of the anatomical, molecular, and cellular events that are not only associative but also causative in OSA and its comorbidities.

Background

The occasional description of obese individuals who snored and exhibited hypersomnolence appeared in earlier medical literature, but it was not until 1918 that Sir William Osler coined the term *Pickwickian syndrome* (based on the overweight and hypersomnolent boy in Charles Dickens' *Pickwick Papers*). In 1956 Henri Gastaut and colleagues observed that patients with Pickwickian syndrome had repetitive apnea events while asleep, and in 1969 W. Kuhlo established that tracheostomy markedly improved the hypersomnolence, respiratory difficulty, and cardiac failure in these patients (Kuhlo et al. 1969). In the next decade Christian Guilleminault and colleagues (1976) first described pediatric OSA and John Remmers and colleagues (1978) showed that adults with OSA had increased collapsibility of the upper airway.

There are few naturally occurring models of OSA in animals; the English bulldog is the closest (Hendricks et al. 1987), but researchers have also developed experimental models of upper airway obstruction in dogs (Kimoff et al. 1994; Pack 1994), lambs (Fewell et al. 1990), and piglets (Waters and Tinworth 2005). Among rodent models, the Zucker obese rat (Strohl and Thomas 2001) and the ob/ob (leptin-deficient obese) mouse (O'Donnell et al. 2000) have been used to better characterize metabolic and cardiovascular consequences of obesity and its relationship to OSA. The serendipitous observation in the Jackson Laboratories that the New Zealand obese (NZO) mouse slept upright led to the supposition that this may be an effective rodent model of upper airway obstruction. Using volumetric MRI, Michael Brennick and colleagues (2009) characterized the fat deposition of the upper airway of the NZO mouse and found it to be similar to that of obese humans with OSA. Moreover, these

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¹ Abbreviations used in this Introduction: IH, intermittent hypoxia; OSA, obstructive sleep apnea; SDB, sleep-disordered breathing; SIDS, sudden infant death syndrome

mice have dilation of the pharynx during inspiration in contrast to airway narrowing in wild-type mice. These findings further suggest that the NZO mouse may be a robust rodent model of OSA. Research to better characterize its sleep patterns and to determine whether there is evidence of dynamic upper airway obstruction leading to altered ventilation and hypoxemia would be of considerable interest.

Prevalence and Risk Factors

SDB, especially OSA, occurs in humans from infancy to old age, with the greatest incidence in obese middle-aged and older adults. The prevalence of OSA is 0.5-3% in children (Lumeng and Chervin 2008) and 0.4-8.5% in adults (Al Lawati et al. 2009), and is highest among elderly males, ranging from 28% to 67% (Al Lawati et al. 2009).

The causes of OSA differ across the life span: in newborns maladaptive central or peripheral respiratory control mechanisms predominate (and likely contribute to sudden infant death syndrome, SIDS¹; Ramanathan et al. 2001), in preschool and school-age children the most common cause is anatomical narrowing from hypertrophy of tonsils and adenoids,² and in adolescents and adults obesity is most often the culprit (although not all individuals who are obese have OSA). Whatever the causes of OSA, its physiological consequences are sleep fragmentation associated with cortical and subcortical arousals and swings in blood oxygen tension between periods of hypoxemia and reoxygenation. The following review articles illustrate that these events contribute to remodeling of heart muscle and of systemic and pulmonary vasculature, adverse metabolic consequences, and short- and long-term impairments in cognitive function.

For infants in their first year of life, SIDS is the leading cause of death, with an incidence of 0.5 per 1000 in those born at term and a three- to fourfold increase in premature babies (Malloy and Freeman 2000, 2004). The etiology of SIDS has not been completely elucidated, but the “triple risk” model of James Filiano and Hannah Kinney (1994) provided a framework for discussion and investigation. They proposed that infants who die of SIDS were exposed to a prenatal event that led to alterations in brainstem mechanisms that control respiratory and circulatory homeostasis; as a result, during a critical period of early postnatal development (1-3 months) the infant is unable to compensate for a stressor such as hyperthermia, face-down position, or a viral infection, and a combination of these three risks leads to a fatal event. Human anatomical and epidemiological studies have given credence to this “multihit” hypothesis, showing (1) abnormalities in brainstem neuroanatomy and

neurochemistry in infants that have succumbed to SIDS (Kinney 2005, 2009), (2) overwhelming evidence that prenatal exposure to nicotine is highly correlated with an increase in the risk of SIDS (Chong et al. 2004; Mitchell and Milerad 2006), and (3) correlation with an infant’s face-down position in soft bedding (Kemp et al. 1994). Carefully designed studies using newborn animals have been instrumental in efforts to tease apart the influences of genetic, anatomical, or physiological conditions combined with environmental exposures that contribute to SDB during early postnatal development.

Several recent reviews describe studies of the effect of prenatal nicotine exposure on cardiorespiratory control mechanisms during sleep in newborn infants and animal models (Hafström et al. 2005), the ontogeny of effective autoteresuscitation mechanisms (Thach 2008), the role of early prenatal exposure to extremes of oxygen tension (sustained hyperoxia and hypoxia) in respiratory responses to subsequent hypoxic events (Gauda et al. 2007), and the role of early postnatal laryngeal chemoreflexes in SIDS (Gauda et al. 2007). Among animal models, in addition to targeted gene disruptions in rodents, technical advances that allow investigators to measure respiration in unanesthetized neonatal rodents without inducing pain, stress, or distress and that enable longitudinal studies have contributed substantially to the field. Claude Gaultier and colleagues (2006) described these novel techniques in the newborn mouse with targeted disruption in the *PHOXB* gene, which leads to congenital central hypoventilation syndrome (CCHS). Studies in newborn mice have led to better understanding of the pathogenesis of this and other genetically determined respiratory-control abnormalities (e.g., Rett syndrome, Prader-Willi syndrome) in human infants (Gaultier and Gallego 2008).

In this issue David Baekey and colleagues (2009) discuss the experimental effects of both genetics and the environment, and explain that stress is known to modify cardiac and respiratory responses in animals in general and in newborn animals in particular. For example, maternal separation is a well-known stressor that can significantly modify a multitude of physiological responses in the newborn animal and these changes can persist throughout the animal’s life (Genest et al. 2007; Kinkead et al. 2005). The authors present strategies to help eliminate these confounders. They also describe invasive and noninvasive methods to measure changes in respiratory parameters in animal models; for example, the use of indwelling electrodes facilitates the measurement of sleep in unanesthetized young and old animals, and this and other techniques enable longitudinal study of the same animal from as early as 15 postnatal days. These are robust experimental models that can support efforts to identify individual and overlapping mechanisms that contribute to disorders of respiratory control during early development, specifically the effects of genetics and/or pre- and postnatal environmental exposures that result in changes to the peripheral and central nervous systems that control arousal and ventilation.

² Other causes of such anatomical narrowing—for example, craniofacial disorders (Hoeve et al. 1999) and macroglossia (associated with Down syndrome)—also predispose some infants and children to OSA (Mitchell et al. 2003).

Comorbidities and Consequences

In addition to the fragmented sleep that contributes to daytime sleepiness in adults and children with OSA, cardiovascular and neurocognitive effects are significant, reducing quality of life and increasing mortality. Inspiratory efforts against an obstructed upper airway are associated with acute changes in pulmonary artery pressure and blood flow and, eventually, compromised cardiac function.

Maurice Dematteis and colleagues (2009) categorize cardiovascular OSA models that are (1) homologous (sharing the cause or pathophysiology of the human disease), (2) predictive (responding to treatment in ways similar to the human disease), or (3) isomorphic (sharing symptoms similar to the human disease although the cause and pathophysiology may differ). Most SDB models are partially isomorphic, focusing on one aspect of the human disorder, but they have yielded most of the available knowledge. Dematteis and his coauthors catalogue the different models and describe their strengths and weaknesses in helping to elucidate the cardiovascular consequences of OSA.

Although the cycling of oxygen tension was known to occur in OSA, it is only in the past 2 decades that experimental paradigms of intermittent hypoxia (IH¹) have become widely used as a model of OSA. Since Eugene Fletcher and colleagues (1992a,b) reported that repetitive episodic hypoxia in rats, patterned after the hypoxia seen in sleep apnea patients, induced diurnal elevation of blood pressure, there have been approximately 300 published manuscripts using this experimental paradigm. Most of these studies have used rodents (young and old) to characterize the molecular and cellular effects of intermittent hypoxia on multiple organ systems. One important limitation of the IH experimental paradigm is that in response to hypoxia, an animal hyperventilates and becomes hypocapnic, whereas humans experience transient hypercapnia or eucapnia (no change in partial pressure of carbon dioxide, pCO₂). But the experimental paradigm of IH in rodents has led to a significant increase in research that is unraveling key mechanisms that are likely causative in many of the consequences of OSA.

In her article on vascular and endothelial consequences, Nancy Kanagy (2009) focuses on the specific role of IH and thus oxidative stress on endothelial pathobiology. The swings in oxygen desaturation and reoxygenation that occur as a consequence of airway obstruction promote oxidative stress through the formation of reactive oxygen species (ROS) and are hypothesized to play a causative role in cardiovascular and endothelial dysfunction. OSA in humans augments sympathetic activity and decreases the sensitivity of the baroreflex, and these two changes contribute to the development of systemic hypertension; the rodent model of IH demonstrates similar findings of autonomic dysfunction. Kanagy describes IH experimental protocols in rodents that result in hypercapnic, hypocapnic, or eucapnic hypoxia and the associated differences in vascular parameters. She concludes that the level of pCO₂ matters: eucapnic IH induces a faster and greater increase in arterial blood pressure than hypocapnic hypoxia.

Furthermore, elevated pCO₂ may protect the animal from developing pulmonary hypertension and polycythemia, which often occur in animal models using hypocapnic IH (the latter experimental paradigm is easier to perform, thus the preponderance of published data on IH are from this model).

Among OSA comorbidities, obesity is the number one risk factor in adults. It is also associated with metabolic syndrome (MetS), a constellation of signs and symptoms that, in addition to abdominal obesity, includes dyslipidemia, hypertension, and elevated plasma glucose, which leads to diabetes mellitus, atherosclerosis, and nonalcoholic steatohepatitis. Jonathan Jun and Seva Polotsky (2009) consider whether the oxidative stress and increased markers of inflammation in patients with OSA contribute to the development of metabolic syndrome. The national Sleep Heart Health Study showed that nondiabetic patients with OSA who had more oxygen desaturation and a higher apnea-hypopnea index were more likely to have impaired glucose tolerance, suggesting that oxidative stress may contribute to altered glucose metabolism (Punjabi et al. 2004). Studies using the rodent model of IH have revealed that IH alters circadian glucose homeostasis, impairs muscle carbohydrate uptake, and induces hyperlipidemia. And several clinical studies support the observation that glucose tolerance significantly improves after treatment with continuous positive airway pressure (CPAP) in obese individuals with diabetes mellitus and OSA. The data thus strongly suggest that OSA substantially contributes to the development of diabetes mellitus and that the increase in sympathetic activity and sleep fragmentation that occurs in OSA is contributory.

Jun and Polotsky also consider the effect of intermittent hypoxia on lipid metabolism. They note that chronic IH in the C57BL/6J-Lep^{ob} mouse adversely affects lipid metabolism even before the onset of obesity, and that dyslipidemia significantly contributes to the development of atherosclerosis. Their article includes helpful tables listing a variety of studies on OSA and dyslipidemia and other MetS-related comorbidities.

OSA also has cognitive consequences in humans. The repetitive arousals and associated sleep fragmentation and sleep deprivation result in daytime hypersomnolence and learning and memory impairments, and the accompanying hypoxia and reoxygenation may also contribute to these effects. Snoring, daytime sleepiness, and impaired learning and memory are common symptoms of OSA across all age groups, and recent data also show a strong association between symptoms of attention deficit hyperactivity disorder (ADHD) and OSA in children (Goraya et al. 2009).³

Sigrid Veasey (2009) outlines the clinical data that collectively indicate a strong correlation between the severity of nocturnal hypoxemia in sleep apnea and the severity of impairment in memory and executive function. Functional MRI studies in adults suggest that there is either brain loss or hypometabolism

³ Snoring in children is never considered normal and thus children who snore should be evaluated for OSA (Carroll et al. 1995).

in regions of the brain involved in learning, memory, and executive function, and these deficits improve in patients treated with CPAP. Animal models show that IH in rodents alters learning and is associated with apoptosis in neurons in the hippocampus and frontal cortex. Veasey includes discussion of her findings that IH also causes injury and cell loss in select wake-active regions, such as the locus coeruleus. The pattern of IH-induced brain injury in rodents appears to preferentially damage catecholamine-containing neurons, which are particularly vulnerable to oxidative stress, as suggested by numerous studies of oxidative injury and Parkinsonism (reviewed in Sayre et al. 2008). What is particularly exciting about the studies described by Veasey is that targeting mediators of oxidative stress by blocking NADPH oxidase activity significantly reduces the injury to wake-active neurons. Whether these mediators can be targets for therapeutic intervention in humans is yet to be determined.

Excessive daytime sleepiness and behavioral and neurocognitive dysfunction are common symptoms in children with OSA. Up to one-third of children with frequent loud snoring or another form of SDB display hyperactivity and inattention, which improve after adenotonsillectomy. Catecholaminergic neurons, an important part of the neurocircuitry involved in ADHD (O'Brien and Gozal 2002), appear to be particularly vulnerable to oxidative injury, as indicated in the adult models of OSA described by Veasey. Newborn rodent models of sleep disruption and IH confirm that the newborn is also vulnerable to neuronal loss in the hippocampus and prefrontal cortex (O'Brien and Gozal 2002). Thus, the animal data support the hypothesis that the behavioral and neurocognitive consequences of OSA seen in humans may be related to oxidative injury of developing neurons. Functional MRI studies could be quite important for the translation of the neuroanatomical consequences of IH in the developing rodent to the developing brain in children.

Summary

Early experimental efforts focused on characterizing the neuromechanical properties of the upper airway using large animal models. Researchers learned much from these large animal models but were unable to fully characterize the multiple organ system dysfunction that occurred in humans with OSA. In the 1980s there was a great surge of research describing the pathobiology of oxygen following the discovery of two key transcription factors—hypoxia-inducible factor (HIF-1 α ; master gene regulator in response to tissue hypoxia) and nuclear factor-kappa B (master regulator of oxidative injury and inflammation)—concurrent with the observation that individuals with OSA have repetitive episodes of hypoxia and reoxygenation. These findings led to development of the rodent model of intermittent hypoxia, which has enabled enormous gains in understanding of the cellular and molecular events that mediate tissue injury and remodeling in the myocardium, vasculature, brain, pancreas, and liver, all of which decrease the quality of life and increase mortality from OSA.

With the current epidemic of obesity in children and adults, OSA and its comorbidities are having a major impact on individual health in particular and on health care systems in general. The use of animal models is essential as investigators continue to learn about OSA and advance the transition from identifying mechanisms of injury to developing therapeutic interventions.

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