Chapter 5

INTERMITTENT HYPOXIA AND COGNITIVE FUNCTION: IMPLICATIONS FROM CHRONIC ANIMAL MODELS

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Abstract: Obstructive sleep apnea syndrome (OSAS) is a frequent sleep disorder in which the upper airway collapses repeatedly during sleep, resulting in intermittent hypoxia (IH) and asphyxia, and leading also to sleep fragmentation due to the recurrent nocturnal arousals necessary to relieve the upper airway obstruction. In addition to cardiovascular and metabolic morbidities, OSAS also causes serious neurocognitive daytime dysfunction and is associated with regional alterations in brain morphology in humans. These findings suggest that the anatomical brain lesions may underlie the behavioral deficits associated with the disease. In rodents, chronic exposure to intermittent hypoxia (IH) during sleep, which model the hypoxia/re-oxygenation patterns observed in moderate to severe OSAS patients, replicates many of the neurocognitive features of OSAS in humans, such as learning and memory deficits and impaired vigilance. Exposure to experimentally-induced IH in the rodent is also associated with age- and time-related neurodegenerative changes in addition to alterations in brain regions and neurotransmitter systems involved in learning and memory, attention, and locomotor activity. Multiple pathophysiological processes appear to be involved in the mechanistic aspects of the behavioral and neuronal susceptibility to IH during sleep, and include pathways leading to increased oxidative stress and inflammation, altered gene regulation, and decreases in the cellular and molecular substrates of synaptic plasticity. In addition, both environmental and genetic factors modulate the end-organ susceptibility to IH-induced cognitive dysfunction in rodents. Collectively, the available data indicate that exposure to IH during sleep is associated with adverse behavioral and neuronal consequences in the rodent. Improved understanding of the determinants of IH-related susceptibility may help explain the phenotypic variance in OSAS-associated morbidities, and enable improved therapeutic approaches in the future.

Key Words: sleep apnea, oxidative stress, inflammation, learning
OBSTRUCTIVE SLEEP APNEA SYNDROME (OSAS)

Obstructive sleep apnea syndrome (OSAS) is a frequent sleep disorder in which the upper airway collapses repeatedly during sleep, resulting in intermittent hypoxia (IH), asphyxia, and associated sleep fragmentation due to the recurrent nocturnal arousals necessary to relieve the upper airway obstruction. The hypoxic pattern most often observed in patients with OSAS consists of apneic episodes of relatively short duration interspersed between normoxic periods that last several minutes, and typically recur throughout the sleep cycle. The constellation of neuronal, cardiovascular, and metabolic pathologies now known to be associated with OSAS has intensified interest in the long-term consequences of exposure to such episodic hypoxic profiles, particularly as they relate to neuropathology (16, 80, 102). Impaired cognition, excessive daytime sleepiness, and mood disturbances are typically observed in adult patients with sleep apnea (16, 44, 82). In addition, increased neurodegenerative changes and enhanced susceptibility to oxidative injury has been postulated as a likely consequence of the intermittent hypoxia associated with OSAS (66), a prediction that has been borne out by a number of neuroimaging studies reporting that adult patients who suffer from OSAS develop regional gray and white matter losses and display alterations in markers of neuronal integrity, as well as show changes in prefrontal lobe perfusion (2, 6, 25, 45, 46, 57, 94). Although not all studies have replicated these findings (72), the majority of such imaging studies support the existence of neurodegenerative processes in patients with OSAS (67). The loss of gray matter that occurs in the hippocampal and parahippocampal brain regions of OSAS patients (63) lends further credence to the hypothesis that disruption of neuroanatomical integrity in brain regions involved in learning and memory is a consequence and underlying factor in OSAS-associated neurocognitive morbidity. Although such studies do not allow separation of the hypoxemia associated with OSAS from additional features of the disease, such as hypercapnia and sleep fragmentation, it is clear that knowledge of the effects of chronic cyclical hypoxia alone is important for evaluating the impact of specific components of the disease in the overall clinical picture of patients with sleep apnea.

INTERMITTENT HYPOXIA

Intermittent hypoxia (IH) is traditionally defined as the episodic occurrence of hypoxia, interspersed between normoxic periods with subsequent reoxygenation. This definition obviously encompasses a wide variety of hypoxic exposures, which can exert both adaptive and maladaptive effects, depending on both the manner of presentation of the hypoxic stimulus as well as the target tissue examined (15, 32, 66, 90). The degree of chronicity of the IH presentation has been postulated to trigger the shift towards pathological consequences (66). Given that even within an experimental paradigm, factors such as the frequency and duration of the hypoxia-reoxygenation cycles, variations in severity, as well as the overall time course of exposure can have a dramatic impact on the response to IH (60, 80), this mini-review will focus primarily on recent