Residual Sleepiness in Patients with Optimally Treated Sleep Apnea: a Case for Hypoxia-Induced Oxidative Brain Injury

Comment on Veasey SC et al. Long-term intermittent hypoxia in mice: protracted hypersomnolence with oxidative injury to sleep-wake brain regions. *SLEEP* 2004;27(2):194-201.

Mary J. Morrell, PhD

Clinical and Academic Unit of Sleep and Breathing, National Heart & Lung Institute, Imperial College, London, UK

THE READERS OF *SLEEP* NEED HARDLY BE REMINDED THAT THE UNDERSTANDING AND AWARENESS OF SLEEP APNEA HAS INCREASED IMMENSELY IN THE 24 YEARS SINCE OREM AND LYDIC[1] REPORTED ON THE POTENTIAL MECHANISMS LEADING TO OBSTRUCTIVE SLEEP APNEA (OSA) IN THE FIRST ISSUE OF THIS JOURNAL. In particular, epidemiologic studies have shown that OSA-hypopnoea syndrome is a prevalent disorder, which causes significant morbidity and is associated with high mortality rates.[2-4] Furthermore, randomized placebo-controlled studies have shown that continuous positive airway pressure (CPAP) is a highly effective form of treatment.[5,6]

CPAP treatment reduces excessive daytime sleepiness (EDS) and improves cognitive function in the majority of patients with OSA.[7] In those with severe disease (apnea-hypopnea index > 30 events per hour), EDS, as measured using the Epworth Sleepiness Scale, improves approximately 4.7 points, and in patients with milder OSA, it improves by 1.1 point. However, sleepiness does not always revert to normal values, and, in a sizeable minority of patients, residual sleepiness persists despite optimal levels of CPAP therapy and high compliance with treatment. It is of note that the prevalence of residual sleepiness in optimally treated patients with OSA is unknown.[8]

Why then is CPAP therapy able to relieve EDS in some patients and not others? Possible explanations include the notion that these patients are, after all, suboptimally treated, which leads to flow limitation and persistent arousals from sleep. Alternatively, treating the OSA could unmask a second sleep disorder (eg, periodic limb movements of sleep) that goes untreated. Thirdly, chronic exposure to the features of OSA, such as repetitive intermittent hypoxia, arousals from sleep, or both, could cause neuronal dysfunction. The increased cell apoptosis, which occurs in the hippocampus and cortex of rats chronically exposed to intermittent hypoxia, supports this latter suggestion.[9] Indeed, in these animals, the neuronal dysfunction has been shown to be in the C1A hippocampal region, an area known to be associated with spatial memory and susceptible to hypoxic damage. Interestingly, in this study, the impaired ability to perform spatial memory tasks was only partially reversed after 14 days of normoxia, suggesting residual damage.

In patients with OSA, focal lesions have been detected in the left hippocampus[10] and in more diffuse areas of the brain[11]; as yet, these changes have not been linked to functional consequences. Further research will doubtless explore these tantalizing links between changes in brain morphology and the neurocognitive functional consequences.

What of the residual EDS that occurs in patients with OSA? In the current issue of *SLEEP,* Veasey et al[12] present convincing data to support the hypothesis that long-term intermittent hypoxia in mice induces oxidative stress, which produces neuronal injury in wake-promoting areas of the brain (basal forebrain and brainstem), and that this injury is associated with residual sleepiness. Attenuation of increased lipid peroxidation and isoprostane concentrations in rats exposed to intermittent hypoxia *and* given an antioxidant also supports the finding that oxidative stress occurs in the cortex.[13] In addition, evidence has begun to accumulate that oxidative stress is an important mechanism in the systemic circulation, underlying the increased incidence of cardiovascular disease and hypertension in patients with OSA (see review[14]). In humans, intermittent hypoxia is correlated with EDS,[15] but, as yet, it has not been linked to neuronal injury in specific sleep-wake–regulating areas.

The findings of Veasey et al[12] immediately open up another question: If intermittent hypoxia causes neuronal injury, is it reversible? In patients with OSA treated with CPAP, the increased superoxide release from neutrophils has been shown to be reduced following CPAP treatment, suggesting that CPAP may reduce oxidative stress in the systemic circulation.[16] In a study by Gozel et al, intermittent hypoxia administered over 14 days was associated with neuronal plasticity in the hippocampus, and the initial apoptosis was followed by increased expression of neuronal progenitors and mature neurones.[17] These changes were linked with a recovery in cognitive function and suggest that some neuronal injury may be reversible. However, the hippocampus is a unique area, being both highly susceptible to hypoxia and possessing the ability to undergo ongoing neurogenesis. The extent to which other wake-promoting areas of the brain are able to recover from the type of injury described by Veasey et al[12] remains to be determined. The residual sleepiness in optimally treated patients with OSA seems to suggest that neurogenesis, plasticity, or a combination thereof does not occur in the basal forebrain and brainstem regions implicated by Veasey et al.[12]

The animal studies discussed here open up exciting new areas of investigation in humans, which may have far-reaching implications—for example, the nature of memory is of interest in many disease processes, such as Alzheimer disease. Could patients with OSA who have intermittent hypoxia provide a lesion-deficit model for memory loss? Of course this raises the question, how much of the memory loss in OSA relates to intermittent hypoxia and how much to sleep disturbance? If the EDS in patients with OSA is due in part to neuronal injury in the sleep-wake systems, this will have implications for the study of memory and cognitive function in these patients.

Veasey et al[12] make it clear in their manuscript that their model of OSA is incomplete. However, one thing that is not clear from their study, and others who have used similar models, is the extent to which the gradual development of OSA in patients influences the amount of neuronal injury. OSA develops over time, sometimes years. Patients do not go from having normal overnight saturation one night to profound intermittent hypoxia the next (equivalent to oxygen saturations of 70% to 80% and approximately 20 events per hour for 12 hours per day[17]). The time-dependent neurogenesis in the hippocampus of adult rats exposed to intermittent hypoxia suggests this may be an important area of further investigation.

In the wider context, the findings of Veasey et al[12] are timely because we are fast approaching the era in which optimally treated patients with OSA who have residual sleepiness may be prescribed modafinil. This

Address correspondence to: Dr. M. J. Morrell, Clinical and Academic Unit of Sleep and Breathing, Royal Brompton Hospital, Sydney Street, London, SW3 6NP UK; Telephone: 0 207 352 8121 ext: 4023; Fax: 0 207 351 8911; E-mail: m.morrell@Imperial.ac.uk

drug has emerged as a "well-tolerated adjunct treatment for residual EDS in patients with OSA who are regular users of CPAP."[8] However, as Saper and Scammel[18] pointed out in a recent editorial in *SLEEP*, modafinil is a drug in search of a mechanism. Understanding the neural consequences that lead to residual EDS in patients with OSA and the mode of action of this drug is urgent if we are to optimize and improve therapy. The use of well-defined animal models, such as those of Veasey and colleagues[12] are likely to be of the utmost importance in this respect.

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