RESIDUAL SLEEPINESS IN OSA: POSSIBLE FACTORS

By Regina Patrick, RPSGT, RST

In obstructive sleep apnea (OSA), the upper airway tissues intermittently collapse into the airway during sleep and block airflow. The blood oxygen level falls and ultimately triggers a brief arousal during which a person takes a few deep quick breaths to restore the oxygen level. The arousals disrupt sleep, which results in excessive daytime sleepiness. The most effective treatment for OSA is continuous positive airway pressure (CPAP) therapy in which pressurized air is blown through the upper airway to prevent its collapse. By preventing apnea-related arousals, CPAP treatment should ideally resolve daytime sleepiness in all patients. However, approximately 10–13 percent of treated OSA patients continue to experience residual sleepiness,[1-3] although noncompliance with CPAP therapy, insufficient CPAP pressure, improper sleep hygiene, and undiagnosed sleep disorder have been ruled out as causes of the residual sleepiness. To increase daytime wakefulness, OSA patients with residual sleepiness are often prescribed wake-promoting drugs such as modafinil. Even with wake-promoting medications, daytime sleepiness persists in some CPAP-treated OSA patients, which suggests that other factors could be contributing to the sleepiness.

Many brain neuroimaging studies[4-6] have compared differences in the brains of people with and without OSA. In such studies, changes in the function of the frontal lobe and gray matter loss in the frontal and parietal cortex, right hippocampus, and deep cerebellar nuclei were noted in people with OSA. However, these studies did not investigate differences in the brains of OSA patients with and without residual sleepiness. In 2007, Antczak et al.[7] were the first investigators to use a brain imaging technology—positron emission tomography (PET)—to investigate whether residual sleepiness in OSA patients is associated with brain injury and whether this injury is limited to certain areas in the brain. Antczak compared OSA patients with and without residual sleepiness. All patients had been on CPAP therapy for at least one year. In the patients with sleepiness, other causes of residual sleepiness had been ruled out before the study.

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In PET, glucose molecules containing the isotope fluorine-18 (i.e., fluorodeoxyglucose) are used to detect metabolically active areas of the brain—the more active a brain tissue, the greater the uptake of fluorodeoxyglucose. Based on this phenomenon, Antczak noted that the PET scans revealed a greater degree of decreased activity (as reflected by reduced fluorodeoxyglucose uptake) in the frontal area in OSA patients with residual sleepiness, compared to OSA patients without residual sleepiness. Antczak proposed that the more substantial decreased activity in the frontal regions may explain residual sleepiness in treated OSA patients.

Since the Antczak study, some factors that have been investigated in the wake-activating pathways in the brain of OSA patients with and without sleepiness are neuronal degeneration, metabolic alterations, and intermittent hypoxia/reoxygenation-induced neuronal damage. The findings of various studies suggest the existence of OSA subtypes, which would explain the different responses to CPAP treatment, and suggest possible new therapeutic targets for treating residual sleepiness.

For example, in a mouse model of OSA-induced sleep disruption, researchers Yan Zhu et al.[8] demonstrated a significantly reduced number of locus ceruleus neurons and orexinergic neurons (both of which promote wakefulness) in mice that had been exposed to chronic sleep disruption for 14 weeks, compared to the number in mice that had not undergone this treatment. They believed that this degeneration may be related to metabolic stress occurring in the mitochondria (i.e., intracellular structures that are involved in cellular respiration and energy utilization), as reflected by the decreased level of antioxidant enzymes and increased level of tumor necrosis factor-alpha in the neurons.

Ying Xiong and colleagues[9] used diffusion tensor imaging (DTI) to compare differences in the white matter of the brains of CPAP treatment-compliant OSA patients with and without residual sleepiness. Diffusion tensor imaging creates images by detecting water molecule movement. Water molecules travel in a straight line along a nerve fiber. Therefore, a disruption in this flow (i.e., diffusivity) indicates neuronal damage. The DTI scans revealed that the sleepy patients had a greater number of disrupted nerve fiber tracts (as indicated by a larger mean diffusivity value) in the white matter, compared to the non-sleepy patients. Fiber tracts involved in wakefulness were altered in basal structures of the brain (e.g., internal and external capsule, corona radiata, corpus callosum, and sagittal stratum). Xiong concluded that differences in the degree of disruption in white matter may explain why

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CPAP treatment-compliant OSA patients can have different treatment responses with regard to sleepiness.

Zhu et al.[10] investigated the impact of repeated hypoxia/reoxygenation episodes on wake-activating neurons in a mouse model of sleep apnea. Zhu exposed mice to eight weeks of hypoxia/reoxygenation episodes. An examination of their brain tissues revealed injury to adrenergic locus ceruleus neurons and dopaminergic ventral periaqueductal gray neurons (which are involved in the control of respiration). However, nearby cholinergic, histaminergic, orexinergic, and serotonergic neurons involved in wakefulness remained undamaged. In another investigation in the same study, Zhu focused on the role of the enzyme nicotinamide adenine dinucleotide phosphate (NADPH) oxidase in the wake-promoting regions of the brain. This enzyme is involved in the generation of reactive oxygen species, molecules that have a role in the oxidative injury of tissues. On examining brain tissues, Zhu found subunits of the NADPH oxidase molecule in wake-promoting catecholaminergic neurons (i.e., neurons producing or activated by catecholamines such as adrenaline, noradrenaline, and dopamine), which may explain nerve injury. In another investigation in the study, Zhu treated a group of mice with the NADPH oxidase inhibitor apocynin throughout the hypoxia/reoxygenation exposure and found that this treatment protected catecholaminergic neurons. Based on these findings, Zhu suggested that certain wake neurons, particularly catecholaminergic neurons, may become persistently and then permanently damaged after long-term exposure to hypoxia/reoxygenation. Zhu further proposed that severe OSA in humans may destroy catecholaminergic wake neurons, and thereby result in residual sleepiness.

In a different study, Zang et al.[11] hypothesized that mitochondrial metabolic responses fail with extended wakefulness, and neuronal injury consequently occurs. In this study, mice lacking the SIRT3 gene (i.e., SIRT3 knockout mice) and wild-type mice (i.e., mice that had the SIRT3 gene) were subjected to extended wakefulness. On examining their brains, Zhang found a greater loss of locus ceruleus neurons in the knockout mice. Based on these findings, Zhu concluded that wake-induced mitochondrial stress within the locus ceruleus neurons reduces *SIRT3* activity, which ultimately leads to the degeneration of the locus ceruleus neurons.

Deepti Nair et al.[12] demonstrated that excessive NADPH oxidase activity may be involved in central nervous system dysfunction induced by intermittent hypoxia. They exposed wild-type mice and NADPH knockout mice to intermittent hypoxia in a model of OSA. The animals' respective control groups were exposed to room air. After intermittent hypoxia exposure, the wild-type mice had significantly higher levels of NADPH oxidase expression and activity in tissues derived from the cortex and hippocampus, compared to the knockout mice. When the mice were subjected to learning tasks, the intermittent hypoxia-exposed mice performed worse than their control counterparts, whereas learning was unaffected in knockout mice, compared to their counterparts. Nair et al.[12] concluded that oxidative stress responses induced by intermittent hypoxia during sleep are mediated by excessive NADPH oxidase activity.

Modafinil and armodafinil are the only wake-promoting drugs approved to treat residual sleepiness in people with OSA. Their mechanism of action is unknown, but they may exert their effects by modulating wake-promoting substances such as glutamate, gamma-aminobutyric acid, histamine, hypocretin, and the monoamines. Some adverse effects of modafinil and armodafinil are headache, dizziness, upper respiratory tract infection, nausea, diarrhea, nervousness, anxiety, agitation, dry mouth, insomnia, chest pain, and fast/pounding/irregular heartbeat. Modafinil and armodafinil also have the potential for dependence, although they are less addictive than other stimulants such as amphetamines.

Treatment approaches that can avoid these drawbacks while improving sleep are needed. Pharmacological agents targeting specific systems involved in wake such as NADPH oxidase production may provide new therapeutic strategies to treat residual sleepiness in OSA patients.[12] For example, NADPH oxidase inhibitor drugs could provide neuroprotection of wake-activating neurons. Continued investigations may soon clarify the factors that contribute to residual sleepiness in treated OSA patients and provide more treatment options for these patients.

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