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Sleep Apnea: A Redox Edge with Aging?

Commentary on Dalmases et al. Brain tissue hypoxia and oxidative stress induced by obstructive apneas is different in young and aged rats. SLEEP 2014;37:1249-1256.

Sigrid Veasey, MD

Center for Sleep and Circadian Neurobiology, Department of Medicine, Perelman School of Medicine, University of Pennsylvania Philadelphia, PA

Almost as inevitable as death and taxes, sleep deteriorates with aging, and common sleep disorders increase in prevalence. So the results of a study by Dalmases and colleagues[1] in this issue of *SLEEP* come as a welcome surprise that there may be some advantage to aging in the brain's physiological responses to obstructive apneas. Specifically, the researchers found that older, relative to young adult, rats showed a greater increase in anti-oxidant enzymes and evidenced less oxidative stress in the brain in response to acute obstructive apneas.[1] An additional finding was that brain tissue oxygenation changed across repeated apneas differentially for the two age groups. These intriguing findings support the concepts that physiological responses to obstructive sleep apnea can vary with age and suggest that a given severity of obstructive sleep apnea may not be as damaging in older as in younger subjects. To more accurately interpret the findings and relate the work to clinical obstructive sleep apnea, however, requires several considerations, including whether the oxidative stress response is actually detrimental; determining the significance of varied brain oxygenation patterns across time; and whether similar responses are anticipated in humans with sleep apnea.

Over the past two decades, a great deal of insight into the mechanisms underlying sleep apnea neural injury has been gained through study of animal models. With limited availability of animals with spontaneous obstructive sleep apnea, compartmentalized models of physiological disturbances observed in obstructive sleep apnea have been used to advance mechanisms of injury. One of the models most extensively used is intermittent hypoxia in mice and rats. Exposure to severe (> 30 events/h), long-term (> 2 weeks) intermittent hypoxia induces oxidative stress injury in the brain, neurobehavioral impairments, and with longer exposure, loss of neurons.[2-7] Oxidative stress is essential for the intermittent hypoxia-induced loss of neurons and cognitive impairments, while transgenic models and pharmacological agents that minimize the availability of reactive oxygen and nitrogen species prevent neuronal injury.[6,8,9] Of note, models implementing mild intermittent hypoxia for brief exposures have shown beneficial effects on neuronal responses and on neural repair following injury.[10,11] Thus, oxidative stress is not always harmful. In fact, in the models of mild intermittent hypoxia, reactive oxygen species are essential for both neuronal plasticity and repair.[11-14] In the study reported by Dalmases et al.,[1] young rats exposed to 3 hours of obstructive apneas demonstrated a small increase in oxidized glutathione and lipid peroxidation in frontal cortical brain tissue samples. Both of these redox modifications are reversible and can be involved in healthy signaling.[15,16] Thus, further studies are needed to examine neuronal injury in this new model in young and older animals and to examine the reversibility and roles of oxidative stress in the model. Longitudinal or chronic studies would be helpful to delineate adaptive versus injurious or detrimental responses. If the oxidative stress in young rats represents neuronal injury, then repeated exposures should result in additive or synergistic injury. If this is an adaptive response, less injury will be evident across time. As obstructive sleep apnea is typically detected and managed as a chronic condition, the long-term observations in this model and the role of oxidative stress will be important to determine.

Arguably, the most striking age-dependent finding in the report of Dalmases et al. is that the effect of time into apnea induction on oxygen tension in the brain varies with age, despite no age differential for arterial oxygenation.[1] The authors propose that the increase in brain tissue oxygenation in young rats across time may contribute to the higher oxidative stress in young animals. But without modulating the brain oxygen partial pressure, their hypothesis cannot be confirmed. Similarly, mechanisms for the steady rise in brain oxygen tension have not yet been delineated. This particular apnea model induces complete apneas resulting not only in intermittent hypoxia, but also in hypercapnia and hemodynamic swings. The research team previously showed that acute intermittent hypoxia alone does not progressively increase brain oxygen tension in young adult rats.[21] Increased brain oxygen tensions, relative to arterial oxygenation, can occur as a consequence of increased blood flow within the cortex from hypercapnia, greater hemodynamic changes, or reduced neural oxygen utilization. The authors correctly point out that the vasodilatory response to hypercapnia can diminish with aging, and this is true not only in similarly aged rats, but also in humans.[17,18]

The steady increase in brain oxygen tension with time would suggest a linear increase in hypercapnia across time. This can be easily examined in the model. Alternatively, age-related changes in astrocyte responses to apneas could be at play. Astrocytes regulate numerous homeostatic responses to neuronal activity, and may also increase blood flow accordingly.[19] Through adenosine signaling in response to hypercapnia, astrocytes can also modulate local blood flow.[20] The change in brain oxygen tension in this model has only been

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Address correspondence to: Sigrid C. Veasey, MD, University of Pennsylvania, Translational Research Bldg., 125 S. 31st St., Philadelphia, PA; Tel: (217) 746-4801; Fax: (215) 746-4814; E-mail: veasey@mail.med.upenn.edu

observed for one hour as the effect of anesthesia may then wear off. The group previously developed a similar chronic obstructive sleep apnea model[21]; this model will be important to better understand chronic oxygenation responses to obstructive sleep apnea and the importance of the age-dependence in response.

Overall, it remains uncertain whether older age confers resistance to apnea oxidative stress, or whether clinical studies will find less vulnerability to neural damage from untreated sleep apnea in older adults. These speculations seem unlikely since sympathetic activity increases in response to oxidative stress in sleep apnea,[22] yet the AHI predicts sympathetic activity similarly in young and older adults.[23] Most importantly, older individuals can derive improved health outcomes for cardiovascular disease and mortality and for cognitive function when treated with continuous positive airway pressure for sleep apnea,[24-27] suggesting that treating sleep apnea is important in older individuals. There is an old Swedish proverb, "The afternoon knows what the morning never suspected." Wisdom, it seems, may be the truest and perhaps the only advantage of aging.

CITATION

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DISCLOSURE STATEMENT

Dr. Veasey has indicated no financial conflicts of interest.

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