MAYO CLINIC

EDITORIAL

December 2014
Volume 89
Number 12

MAYO CLINIC
PROCEEDINGS

Sleep Medication Failure and Newly Diagnosed Obstructive Sleep Apnea: The Role of Brain Function Modulation by Muscle Afferent Activity

In this issue of *Mayo Clinic Proceedings*, Krakow et al[1] report the results of a retrospective evaluation of 1210 patients with insomnia disorder. All 899 patients who were taking over-the-counter or prescription sleep aids had pharmacotherapeutic failure. Of the 942 patients objectively tested (77.9% of the total cohort), 860 (91.3%) met standard criteria, on average, for a moderate to severe sleep-related breathing disorder.

Although insomnia as a presenting symptom of a sleep-related breathing disorder is well recognized in patients evaluated at sleep centers, the association is likely less appreciated during primary care evaluations. Underdiagnosis may be related in part to the failure of simple screening techniques to accurately identify those patients at highest risk for a sleep-related breathing disorder. For example, in the study by Krakow et al,[1] a screening technique commonly used in primary care yielded a false-negative result for breathing disorder more than 30% of the time. On the basis of an inadequate or erroneous diagnosis, primary care physicians may initiate behavioral or pharmacological therapy for insomnia rather than refer the patient for sleep-related breathing disorder studies.

The findings of the study by Krakow et al[1] are particularly important because in patients who experience the constellation of a sleep disorder, sleep medication failure, and obstructive sleep apnea (OSA), increasing the dose or intensity of sleep-augmenting drugs can potentially worsen the problem (as we will later discuss). In reporting these observations, Krakow et al highlight the need for a more effective approach to accurately diagnosing sleep disorders associated with OSA, a relatively common combination of pathologies encountered in primary care clinics.

The report by Krakow et al[1] stopped short of identifying the mechanisms underlying the fascinating association between insomnia and sleep-related breathing disorders. We will attempt to illuminate the underlying physiology, using clinical observations and data from both clinical and laboratory research. In our synthesis, OSA is assigned several components relevant to sleep interruption, which we will group under 2 categories: (1) the afferentation theory of cerebral arousal, in which afferent nerve impulses into the brain, originating from muscle stretch receptors, activate brain activity and (2) changes in blood gases and circulating stress hormones triggered by airway obstruction. We will discuss how these mechanisms relate to the observations of Krakow et al and how they have broader implications for assessing multiple other forms of brain function alterations in humans.

See also page 1608

Afferentation Theory

Intermittent airway obstruction during OSA is associated with pulsatile and crescendo-decrescendo activity within the usual complement of respiratory muscles and oftentimes the recruitment of supplemental muscles to increase the respiratory effort or to reposition the patient. The muscles commonly involved include those of the diaphragm and—superior to the diaphragm—muscles of the thorax, neck, and head. During repositioning, muscles of the arms, legs, abdominal wall, and elsewhere may also become involved. Each contraction of these skeletal muscles results in a mechanically coupled activation of muscle afferent receptors. Further, the transmission within nerves of this muscle afferent

activity (MAA) to the brain has the potential to profoundly arouse the brain and hinder normal sleep.

Ironically, this link between muscle activity and sleep interruption is not a new discovery. It was first reported by Nathaniel Kleitman, as documented in his classic textbook *Sleep and Wakefulness* published in 1963.[2] Kleitman is widely credited as the father of modern sleep research, and his discoveries contributed to the development of sleep medicine as a distinct clinical discipline. As retold by Lanier et al,[3] Kleitman began a particular set of studies in which volunteers were deprived of sleep for prolonged periods of time while being observed in the confines of his laboratory. He discovered that sleep-deprived volunteers who were encouraged to increase their motor activity were able to maintain wakefulness for days and for much longer than volunteers who remained quiescent or recumbent. In the decades that have ensued since these sentinel studies, the mechanism underlying this effect has been determined, and it relates to the afferentation theory of cerebral arousal.

Afferentation theory predicts that agents or maneuvers that produce muscle stretch or contraction of extrafusal striated muscles or that directly stimulate muscle stretch receptors (primarily the intrafusal muscle spindles) will stimulate the brain.[3,4] In contrast, agents or maneuvers that lessen muscle stretch or contraction tend to stabilize brain function or encourage its quiescence.[5] Perhaps some of the most dramatic and nonconfounded observations of this type of brain stimulation are observed in highly controlled experiments in animal models. In these models, increases in MAA result from mechanical coupling between muscle stretch receptors (primarily the intrafusal muscle spindles) and the extrafusal striated muscle fibers whose contraction allows us to perform mechanical work.[3,4,6] Muscle spindles can also be activated chemically by the depolarizing muscle relaxant succinylcholine (SCh), which produces activation primarily by interacting with gamma efferent receptors on the spindles.[4] Succinylcholine has particular utility as a study drug for afferentation theory because SCh does not cross the blood-brain barrier and has no effect on cerebral function when injected into the carotid arteries.[4] However, SCh has a profound effect on cerebral function when injected intravenously, a response that is attributed to its effect on activating muscle spindles.[4,6]

In accordance with afferentation theory, any MAA increase to the brain will result in cerebral stimulation, regardless of the origin of the MAA (eg, muscle contraction, muscle stretch, or drug-induced effect).[3] The same cerebral phenomenon occurs after electrical stimulation of MAA-carrying peripheral nerves.[7]

Once activated, afferent traffic from the muscle spindles is carried to the brain by several different sensory pathways that converge on the cerebellum, the motor cortex (area 4), and the somatosensory cortex (area 3a) (see Lanier et al[3] for review). As such, increases in MAA have the potential to influence the functional activity within large areas of the brain. Stimulation of the brain by MAA results in a near-instantaneous activation of the electroencephalogram (EEG) and increases in cerebral blood flow (far greater than required to meet basal metabolic demands of the brain). Lanier et al[3] have theorized that this mechanism developed teleologically to arouse the brain instantaneously and provide luxury perfusion to brain tissues during periods of "fight and flight," using a mechanism that is independent of circulating chemical transmission.

When these concepts are brought back to the clinical arena, there is growing evidence that increases in MAA can not only contribute to sleep resistance (as reported by Kleitman[2]) but also modulate the extent of focus during periods of wakefulness. These same MAA/cerebral stimulation phenomena may be apparent in everyday scenarios in which practitioners, engaged in activities that have long periods of low stimulation interrupted by requirements for intense focus to deal with intermittent stimuli, consciously or subconsciously rely on techniques to enhance their level of arousal. For example, Fidler et al[8] reported that radiologists who walked on a treadmill at 1 mph while interpreting medical images on an electronic workstation identified radiographic findings of clinical importance 10% to 18% more frequently ($P<.001$) when compared with interpreting medical images while sedentary. In another example, professional baseball players, a group that has historically relied on smokeless tobacco products to raise their level of brain stimulation, have considerably diminished their tobacco use and the rate of associated oral pathology,[9] presumably out of fear of acquiring

Mayo Clin Proc. ■ December 2014;89(12):1591-1595 ■ http://dx.doi.org/10.1016/j.mayocp.2014.10.009
www.mayoclinicproceedings.org