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A New Pharmacological Treatment to Treat Obstructive Sleep Apnea?

Commentary on Wirth et al. Sensitization of upper airway mechanoreceptors as a new pharmacologic principle to treat obstructive sleep apnea: investigations with AVE0118 in anesthetized pigs. SLEEP 2013;36:699-708.

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Sleep-related reduction in upper airway muscle activity is a pivotal step in the pathogenesis of obstructive sleep apnea (OSA) in individuals predisposed to this common, problematic disorder.[1] Hence, devising a simple method of augmenting activation of these muscles during sleep is a notion that has occupied the minds of many in the quest for new treatments for OSA. Electrical stimulation of the upper airway muscles or the nerves that supply them has been one approach that has shown promise, although relatively invasive and selective in its effects.[2,3] Pharmacological treatments have been examined that are designed to either augment ventilatory drive generally—these include progesterone, acetazolamide and theophylline—or suppress REM sleep (when loss of muscle tone is most profound)—these include tricyclic antidepressants or clonidine.[4,5]

Other pharmacological approaches that have been tested in animals include drugs with actions intended to mimic the activating effects of wakefulness through stimulation of the hypoglossal nucleus. These compounds have included selective serotonin reuptake inhibitors to stimulate excitatory serotonergic pathways, noradrenalin and noradrenalin reuptake inhibitors to stimulate excitatory noradrenergic pathways, and the possibility of drug therapy to suppress inhibitory muscarinic pathways.[6,7] These efforts have not, to date, proved particularly fruitful due to the challenge of identifying compounds sufficiently specific in their effects to activate the airway muscles without also inducing unacceptable side effects.[6] The complexity of neurochemical pathways involved underscores the difficulty of identifying a satisfactory, sufficiently specific centrally active drug for this purpose.

In this edition of *SLEEP* Wirth and colleagues[8] describe a new treatment principle to achieve this effect that involves augmenting negative pressure reflexes by a local effect on pharyngeal mechanoreceptors, rather than a centrally mediated mechanism. They recognized that pharyngeal mechanoreceptors play an important role in upper airway muscle activation through inspiratory negative pressure induced reflexes, which are obtunded during sleep[9] and by topical anesthesia.[10] They reasoned that sensitization of these receptors could be a method to counteract the reflex inhibition evident during sleep and sedation, thereby augmenting muscle activity and reducing upper airway collapsibility.

Wirth et al.[8] identified a compound—AVE0118—able to increase upper airway reflex activity after topical administration by its potassium channel blocking effects on membrane potentials.[11] Their study demonstrates remarkable augmentation of these reflexes in pigs under chloralose-urethane sedation. The experimental model they used suggests their approach has promise, but it is also premature to conclude it will translate to sleeping humans. While sleep and sedation have their similarities in terms of effects on the upper airway, upper airway muscle activity appears better preserved during chloralose-urethane sedation than with some other sedatives.[8,12,13] How behavior during chloralose-urethane sedation relates to behavior during sleep, particularly the atonia of REM sleep remains unknown, as does the practicality and acceptability of use of topical AVE0118 in humans, including its effects on laryngeal function. Augmentation of the laryngeal adductor reflex could be unhelpful. Nevertheless, the paper describes an important new possibility—that topical sensitization of upper airway reflexes is a principle that could be a used to treat OSA. Expect to see more on this subject.

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