Will Intranasal Leptin Mitigate Opioid-induced Sleep-disordered Breathing?

Leptin, a peptide produced by adipocytes, is a satiety hormone with significant direct effects on ventilation and regulation of upper airway function. Animal studies show that in the central nervous system (CNS), leptin effects an increase in minute ventilation via simulation of multiple areas relevant to ventilatory control, including phrenic and hypoglossal nerve nuclei, effectively increasing diaphragmatic and genioglossus activity (1). This translates into preserved ventilation and upper airway patency during sleep. Leptin also increases the CNS chemoreceptor activity in response to hypercapnia and increases carotid body chemoreceptor activity in response to hypoxia, two salient noxious stimuli in obstructive sleep apnea (OSA) (1). Obesity and intermittent hypoxia, both features of OSA, are catalysts for leptin release, leading to hyperleptinemia. The hyperleptinemia in OSA is associated with a state of leptin resistance because of a saturation of the leptin transport system across the blood–brain barrier and a reduction in leptin receptor expression or intracellular leptin signaling (1). The propensity for hypoventilation and obstructive apneas during sleep in OSA is attributed to selective leptin resistance in the CNS, as the peripheral effects of hyperleptinemia, such as sympathetic activation and hypertension, appear to be preserved in obesity (2).

In this issue of the *Journal*, the study by Freire and colleagues (pp. 502–509) capitalizes on the pleiotropic CNS effects of leptin on ventilation and upper airway patency to target opiate-induced sleep-disordered breathing (SDB) (3). Opiates can induce complex SDB characterized by bradypnea, central apneas, ataxic/Biot's breathing, hypoventilation, and increased upper airway resistance or frank obstructive apneas (4). One or more of these abnormal respiratory patterns may be present in an individual patient depending on the dose and duration of opiate use, age, obesity, craniofacial anatomy, and comorbidity (5). The current serious opioid epidemic is associated with a high mortality, wherein approximately 128 people in the United States die every day after overdosing on opioids (6). Given that SDB and hypoventilation might play a role in this unexplained excess mortality in patients treated with opioids (7), innovative strategies to eliminate opiate-induced SDB are critically essential. Positive airway pressure therapy for opiate-induced SDB has limited benefit (7). Nonopioid respiratory stimulants, theoretically, could be used to prevent opioid-induced respiratory depression (8). Thus, the strategy of increasing CNS leptin levels to ameliorate opiate-induced complex SDB by harnessing leptin's multipronged respiratory effects, without compromising analgesia, is quite novel.

In a series of elegant, controlled experiments, the authors tested both leptin's efficacy as a stimulant of ventilation and upper airway neuromuscular activity and the lack of interference with analgesia in obese C57BL/6J mice. Notably, intranasal leptin had sustained stimulatory effects on ventilation during periods of low and high upper airway resistance and eliminated one-fifth of inspiratory flow–limited breaths. These findings were supported by *ex vivo* experiments demonstrating that leptin restored hypoglossal nerve postsynaptic activity after opiate receptor agonist application. Moreover, the application of intranasal leptin significantly increased sleep efficiency and consolidated non–rapid eye movement (NREM) sleep while maintaining morphine analgesia. An important translational implication of this study is that intranasal leptin may help alleviate hypoventilation and increased upper airway resistance, two significant aspects of opiate-induced SDB, particularly in patients with obesity.

The authors acknowledge several limitations of the study. In addition to leptin effects on breathing not being characterized during wakefulness, the effects during rapid eye movement (REM) sleep were not described. Morphine can suppress REM sleep modestly, but this effect is variable. REM sleep is a particularly vulnerable period for respiratory depression and severe hypoxia. Hence, evaluating any potential therapy for SDB during REM sleep is critical. A related issue is the short duration of action of intranasally administered leptin. Two hours is just over one NREM-REM cycle or less than one-third of human nocturnal sleep. REM sleep occurs more in the second half of the night, when intranasal leptin no longer has bioavailability. The terminal half-life of morphine is 1.5–4.5 hours in humans. In this context, intranasal leptin could counteract respiratory depression in the postoperative setting, in which the opiate dosing is needed, but would not be effective in chronic pain conditions treated with longer-acting opiates. Moreover, there was an incomplete effect of the drug on upper airway resistance, with persistence of inspiratory flow–limited breaths. Whether the positive effects of intranasal leptin on SDB can be sustained across several nights cannot be determined from this study.

In addition to ventilation and upper airway function, the cardiometabolic effects of leptin must be considered in OSA, in which obesity and leptin resistance are common (see Figure 1). Metabolic studies in humans have shown that exogenous leptin fails to overcome leptin resistance peripherally (9) and affects weight loss only in leptin-deficient states. In contrast, obesity-induced hyperleptinemia is a recognized mechanism for sustained sympathetic activation and hypertension (10). These pathophysiological consequences are a prevalent cause of morbidity in OSA. A recent review concluded that the effects of exogenous leptin on sympathetic activity and blood pressure vary by dosing (acute or chronic) and species (11). Preclinical studies evaluating the role of leptin in obese OSA animal models should consider

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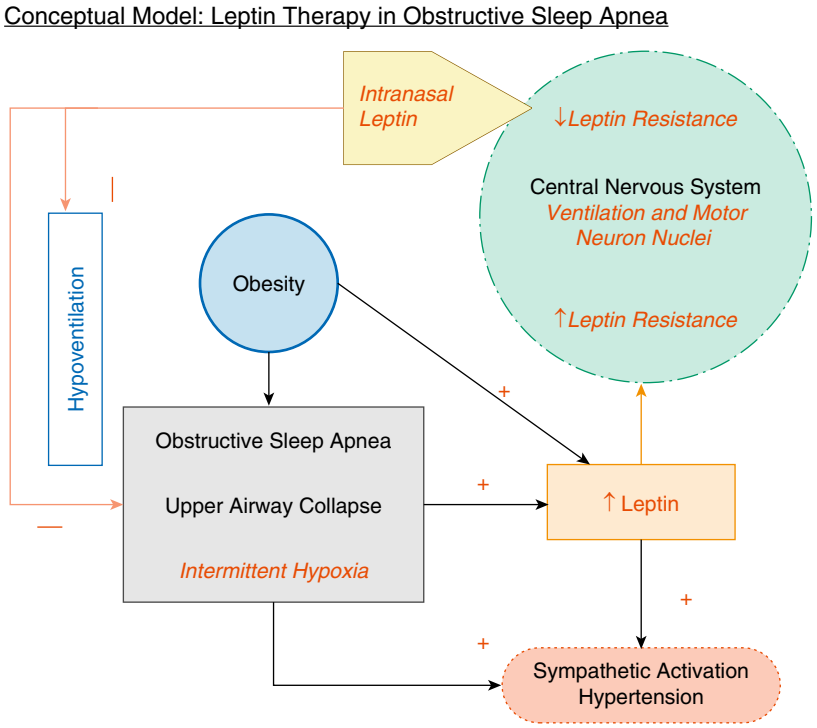

Figure 1. The simplified schematic indicates the links between obstructive sleep apnea, obesity, systemic leptin levels, and leptin resistance within the central nervous system, which is the site of action for intranasal leptin. For clarity, unidirectional effects are denoted by arrows, plus and minus signs outside the blood–brain barrier, and up and down arrows within the central nervous system. The plus and minus signs and up and down arrows indicate the inhibition and potentiation of effect at each site, respectively. These effects explain the physiological basis for the potential therapeutic effects of leptin in sleep-disordered breathing.

including cardiometabolic assessments for the evaluation of potential adverse effects.

Given that SDB may be the missing link to explain excess mortality with chronic opioid use, pathophysiology-guided therapies for opioid-induced SDB are the strategic need of the hour. Of note, intranasal leptin may be less effective in humans because of differences in the anatomy of the cribriform plate. Thus, future studies should carefully examine the impact of variable dosing and long-acting formulations of leptin applied intranasally across multiple nights during REM and NREM sleep in both sexes of human and animal experimental models of SDB. The effects of leptin on cardiometabolic, sleep, and pain outcomes need to be incorporated into these studies.

In conclusion, the study by Freire and colleagues (3) is a first step toward creating a novel pharmacologic therapeutic strategy to target the manifold heterogenous phenotypes of SDB. If effective intranasal-to-brain delivery can be achieved in humans, intranasal leptin has the exciting potential for translation to application in individuals with obesity and SDB, irrespective of chronic opioid use. Whether IN leptin could be an alternative to positive airway pressure therapy in specific phenotypes of SDB remains to be further explored in a stepwise fashion in preclinical and clinical models of SDB. ■

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