Re: Effects of leptin and obesity on the upper airway function by Polotsky et al.

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Obesity and central adiposity are well established risk factors for obstructive sleep apnea-hypopnea (1). One implied mechanism for their effects is by increasing the mass of tissues, including the lateral pharyngeal fat pads surrounding the airway, thus decreasing the size of the channel for air; another is by a reduction in functional residual capacity in recumbency and by tracheal linkage reducing the size and increased resistance of the extrathoracic channel (10). The other anatomic features (retrognathia, tonsillar and adenoidal hypertrophy, macroGLOSSia, enlargement of peritonsillar folds, and size increases in the soft palate) are found in patients and inferred to alter the mechanical properties of the upper airway, thus leading to snoring and obstructive events (1). But as Polotsky et al. (7) in this issue of the Journal of Applied Physiology, “the mechanisms linking obstructive sleep apnea with obesity are not well understood.” How can this be?

In a pro/con editorial exchange in 2003, Dr. Richard Schwab and I exchanged words on the issue of whether sleep apnea is or is not an anatomic disorder. To summarize this exchange Dr. Schwab identified and stuck with the position that the risk factors of obesity and abnormal upper airway function drive the anatomy and airway size to produce the disorder (9), whereas I emphasized the importance of state-related reductions in neuromuscular drive as the fundamental cause of all obstructive events (14), not just those in patients who present to clinic. Since 2003, I have not changed my stance. Indeed, I continue to emphasize that this is sleep apnea rather than wake apnea and that the anatomic predisposition is present in all potential states and not just sleep. Moreover, I now take a position that the cause or “moment of truth” at the start of an obstructive sleep apnea-hypopnea syndrome has to be not only a reduction in drive that leads to mechanical naso- or oropharynx closure, but a mechanism to propagate events (apneas or hypopneas) over time. The studies by Wellman et al. (2, 16) and the historical record on models of apnea support the concept of “loop gain” as one unifying mechanism for both recurrent obstructive and central (or nonobstructive) apnea (19, 20). Our group also thinks that the stability of breathing around eupnea during wakefulness may also be something that predicts the types of sleep apnea (17, 18). Thus the intermediate pathophysiological factors for sleep apnea are those of respiratory control and that of critical closing pressure (Perit), which historically is derived from the work of the Johns Hopkins group (11–13). These physiological indexes are measureable, intermediate risk factors I would use to plan therapy for any individual patient with sleep apnea of any type.

In looking at the current work by Polotsky et al. (7), my initial bias would be that it would be unlikely that one could discover mechanisms for obstructive apnea by the study of a mouse, especially if it was caused by a single mutation of a gene, leptin (5). The a priori problems are the anesthetized state rather than sleep state, the potential differences in upper airway structure (and function) of man/women and mouse, the direction of flow, and positional effects. The genetic model is also not really like the human, where the problem is usually leptin resistance rather than the absence of leptin. These weaknesses notwithstanding, the model for this study addresses a need for our field for inventive ways to examine intermediate factors for sleep apnea.

This group has established the mouse in which one can reliably measure Perit and identify the site of obstruction at the level of the palate (4). This animal model has shown that age and obesity interact (6) and measures for inspiratory flow limitation (IFL) and critical closing pressure, called PN threshold, and a measure of maximal flow (V_{max}) to define the capacity of the airway to conduct flow. Of these, IFL is probably relevant to baseline mechanical state. In addition, there are global measures of submental (“genioglossus”) electromyographic (EMG) activity and maneuvers to alter neuromuscular drive and thus give an idea about the “actively” driven airway and the “passively” derived mechanical properties of the flow limiting segment. There is also an understanding of the value of the leptin-deficient model (the ob\textsuperscript{-}/ob\textsuperscript{-} mouse, a spontaneous mutation out of the C57BL/6J strain) in regard to the ability of reversing the neural control abnormality (low hypercapnic drive) with exogenous leptin (8, 15). These strengths led to the present study in which the upper airway mechanical problems are measured in the presence and absence of leptin.

Results are that both obesity and leptin deficiency were associated with more IFL and a higher critical pressure and lower V_{max} (7). Yet very obese ob\textsuperscript{-}/ob\textsuperscript{-} mice treated with leptin compared with nontreated mice showed less IFL frequency and an improved PN threshold and increased maximal flow when there is maximal drive. When the group controlled for EMG activity, the “passive” closing pressure in leptin-treated mice did not differ from that seen in nontreated ob\textsuperscript{-}/ob\textsuperscript{-} mice. This means that in this model it is a defect in upper airway control and that leptin acts in this instance to increase active neuromuscular responses without a change in mechanical load. So it is not the obesity per se that is the link to how the upper airway transmits flow. It is worth noting that all these variables are measureable in humans, so that this model translates well to clinical studies (3).

To answer the question posed earlier, the mechanisms by which obesity produce an unstable upper airway are not so...
straightforward, and there may be an opening to use these results to address future therapy. To this end, this study focuses attention (again) on how alterations in neuromuscular control affect the neuromuscular factors on upper airway mechanics and how this pathway might give insight into novel treatments of obstructive sleep apnea. I know that in this model one does not know how leptin replacement increased drive in the anesthetized animal, but I suspect as do the authors that this is not just an effect on the hypoglossal drive or the genioglossus muscle but an overall increase in drive. In the broader picture of this disease, the reasons for understanding the mechanisms are directed at the tough task of finding pharmacologic solutions. In this context, given that humans are leptin resistant and how this pathway might give insight into novel treatments of this disease, the reasons for understanding the mechanisms are poised for application to other selective and nonselective agents.

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author.

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REFERENCES