COMMENTARY

DOI: 10.5665/SLEEP.1144

Activation of the Upper Airway Dilator Muscle Genioglossus during Sleep Is Largely Dependent on an Interaction between Chemical Drive and Mechanoreceptor Feedback

Commentary on Loewen et al. Response of genioglossus muscle to increasing chemical drive in sleeping obstructive apnea patients. SLEEP 2011;34:1061-1073.

John Trinder, PhD; Amy S. Jordan, PhD

Department of Psychological Science, The University of Melbourne, Parkville, Victoria, Australia

Current hypotheses as to the etiology of obstructions in obstructive sleep apnea (OSA) and symptoms in patients with obstructive sleep apnea syndrome (OSAS) have been gravitating towards the view that the disorder is due to a number of physiological traits, but that these traits are differentially important in different individuals.[1] The traits considered important include a narrow and/or compliant airway, poor upper airway muscle responsiveness, high ventilatory responsiveness, and a low arousal threshold. Further, these traits are thought to interact in an idiosyncratic manner over individuals. Thus, for some individuals one may be predominant, for example a narrow airway, while in others two or more traits may interact, for example high airway compliance in association with a low arousal threshold. The study reported by Loewen and colleagues in this issue of *SLEEP*[2] was conducted within this framework and focused on the responsiveness of the upper airway dilator muscle genioglossus (GG) to respiratory stimuli during sleep, with a view to determining the conditions under which upper airway muscle activity can increase sufficiently to open the airway without the benefit of an arousal from sleep. This is a central consideration as an arousal from sleep augments the ventilatory response to apnea termination, potentially resulting in respiratory instability, and because many of the adverse aspects of OSAS are thought to derive from repetitive arousals associated with obstructive apnea termination.[3]

Loewen et al. note that two reflex mechanisms are thought to activate upper airway dilator muscles, chemical stimuli (hypercapnia and hypoxia) and mechanoreceptor feedback (primarily negative pharyngeal pressure).[2] Further, during a complete obstruction an increase in negative pharyngeal pressure is due to an increase in respiratory effort against the occluded airway, which in turn is due to chemical stimulation. During hypopneas the relationship is slightly more complicated, as the degree of airway obstruction itself will alter the strength of mechanoreceptor feedback in addition to the effect of chemical drive. However, this difference does not invalidate the experimental approach. The initial aim of Loewen et al. was to determine the responsiveness of the upper airway muscle GG in sleeping OSA patients to two conditions: elevated chemical stimulation with the airway kept open through application of CPAP; and elevated negative pressure created by dialing down CPAP in the presence of various levels of chemical stimulation. Their second aim was to determine whether there was an inflection in the relationship between GG activity and respiratory drive, indicating a sudden increase in the sensitivity of the muscle to stimulation, a phenomena referred to as the GG recruitment threshold.

The study by Loewen and colleagues was conducted in 20 patients with OSA. Their experimental strategy was to progressively increase CO_2 levels under fully effective CPAP (with and without steady state hypoxia) and then to produce partial or complete airway obstruction by a CPAP dial down in the presence of various levels of hypercapnia. Levels of respiratory drive reflecting chemical drive were inferred from the increase in ventilation from baseline to the last breath before CPAP dial down. With CPAP dial down the negative pressure generated was assumed to be proportional to the level of ventilation on the last CPAP breath. The raw GG EMG signal was integrated and reported as tonic, peak, and phasic values. The change in ventilation and GG EMG activity during the increase in CO_2 while on full CPAP assessed the responsiveness of GG to chemical drive during sleep, while the GG response to the first breath of an obstruction in the presence of a range of CO_2 levels assessed the response to the combined effects of chemical drive and mechanoreceptor feedback.

The results of Loewen et al. indicated that GG had a weak response to increases in chemical drive during sleep. Further, there was little response to obstructions at eucapnic levels of chemical drive. Critically, at higher levels of chemical stimulation the addition of negative pressure (resulting from elevated chemical drive increasing respiratory effort against the obstructed airway) produced a vigorous response in most patients. This finding directly corresponds with data obtained in healthy individuals during NREM sleep, where chemical or mechanical stimulation alone induced small (nonsignificant) increases in genioglossal activity, but that combined mechano-chemoreceptor stimulation significantly increased the muscle's activity.[4] Importantly, in the Loewen et al.[2] study, the responsiveness of GG to chemical drive on breath one of the dial down was shown to vary widely between patients. Finally, with respect to the concept of a GG recruitment threshold, it was argued that in a subset of six patients a threshold value could be observed as an inflection point in the relationship between ventilation and GG activity. In the remaining 11 patients on whom data were avail-

Submitted for publication June, 2011
Accepted for publication June, 2011
Address correspondence to: John Trinder, PhD, University of Melbourne, Department of Psychological Sciences, Parkville, Victoria 3010 Australia; Tel: 011 613 8344 6365; E-mail: johnat@unimelb.edu.au

able, the inflection point was not apparent, either because the patients had high levels of responsiveness throughout the range of chemical drive, or they failed to respond at any level of drive.

The collection of data in studies of this nature is highly intrusive in patients, and methodological compromises are required in order that data be collected at all. In this study,[2] chemical drive and negative pharyngeal pressure were both inferred from ventilation. Given that analyses were restricted to within patient comparisons, this is unlikely to be a major problem, although as noted by the authors, direct measures of airway pressure would be desirable in subsequent studies. In a similar vein, the use of a hypnotic to assist sleep is unlikely to compromise the data, as illustrated by the analyses reported.

One aspect of the data from Loewen et al. that is perhaps less compelling is the identification of an inflection point in the function relating ventilation and phasic GG activity for six of the patients. The method used appeared to be visual inspection of the function. Such a method is inevitably subjective, and indeed inspection of Figure 3, Panel D in their paper does not, to our eyes, clearly indicate an inflection point in six of the patients. The identification of inflection points, and thus of recruitment thresholds, would be more convincing if a statistical approach was employed.

Loewen and colleagues[2] provide us with a particularly valuable study because it indicates that reflex stimulation from both pharyngeal mechanoreceptors and chemical drive are required to activate GG sufficiently to open the occluded airway without a cortical arousal from sleep, and that the strength of the GG activation response varies over patients. Whether the individual differences are best described as variations in a recruitment threshold or variations in GG responsiveness requires more extensive investigation. An important corollary of the study's findings, which is presented in the discussion, is that the opening of the airway before cortical arousal would be facilitated if the patient had a high arousal threshold. As arousal threshold can be manipulated by the use of hypnotics; hypnotics that do not have muscle relaxant properties are a potential therapeutic avenue for patients with OSAS.

DISCLOSURE STATEMENT

The authors have indicated no financial conflicts of interest.

REFERENCES

1. Wellman A, Eckert DJ, Jordan AS, et al. A method for measuring and modeling the physiological traits causing obstructive sleep apnea. J Appl Physiol 2011;110:1627-37.
2. Loewen AH, Ostrowski M, Laprairie J, Maturino F, Hanly PJ, Younes M. Response of genioglossus muscle to increasing chemical drive in sleeping obstructive apnea patients. Sleep 2011;34:1061-73.
3. Younes M. Role of arousal in the pathogenesis of obstructive sleep apnea. Am J Resp Crit Care Med 2004;169:623-33.
4. Stanchina ML, Malhotra A, Fogel RB, et al. Genioglossus responsiveness to chemical and mechanical stimuli during non-rapid eye movement sleep. Am J Resp Crit Care Med 2002;165:945-9.