Pharmacologic Approaches to the Treatment of Obstructive Sleep Apnea

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KEYWORDS

• Sleep • Apnea • Phenotypes • Loop gain • Arousal threshold • Pharmacology

KEY POINTS

- Obstructive sleep apnea is caused by various combinations of 4 phenotypic traits: pharyngeal anatomy, upper airway responsiveness, respiratory arousal threshold, and loop gain.
- There are currently no meaningful methods to influence upper airway muscle responsiveness pharmacologically. However, antagonists to potassium channels may prove to be a novel approach to accomplish this.
- Currently available hypnotics can increase the respiratory arousal threshold modestly; however, these agents have a variable effect on the severity of sleep-disordered breathing.
- Loop gain can be substantially reduced with both oxygen and acetazolamide. Both agents can lead to important decrements in the apnea-hypopnea index if the correct patients (high loop gain) are targeted.
- Although it has not been tested, combining agents to address more than 1 physiologic trait may improve efficacy compared with a single agent.

INTRODUCTION

The mainstays of therapy for obstructive sleep apnea (OSA) have always been devices or surgeries. Although neither is completely satisfactory in terms of efficacy or comfort, there have not been better options available. The concept of a pharmacologic approach to OSA treatment has always held great appeal but no agent to date has had a large enough effect size to drive substantial adoption. However, attempts continue to find the ideal or acceptable drug.

During the last 10 years, a new construct has emerged regarding the pathophysiology of OSA that may drive new thinking regarding pharmacologic therapy (**Fig. 1**). According to the new construct there are 4 primary physiologic traits that dictate who does and does not develop OSA.[1–3] These traits can vary substantially between patients, meaning that sleep apnea may develop for quite different reasons in 1 patient compared with another.[1] These traits are discussed below.

Upper Airway Anatomy or Collapsibility

For pharyngeal collapse to occur during sleep there must be some anatomic predisposition to such collapse. This is generally thought of as an anatomically small or quite collapsible airway. Possible causes of this anatomic abnormality include fat deposition in the tissue surrounding

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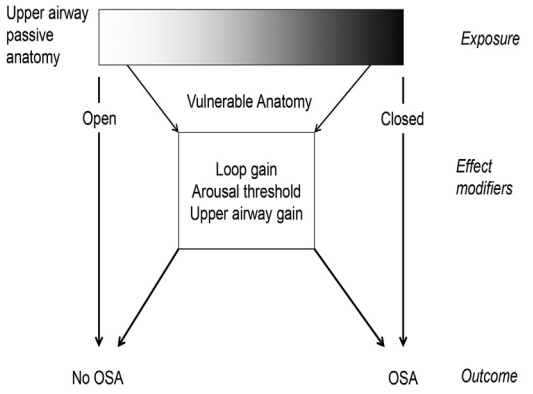

Fig. 1. The relationship between anatomy and OSA is straightforward with very favorable (no OSA) or very poor anatomy (inevitable OSA). However, the relationship of intermediate or vulnerable anatomy and OSA is modified by the other traits to lead to or protect against OSA. These other traits are effect modifiers: they modify the effect of the exposure (anatomy) on the outcome (OSA status). (*From* Owens RL, Edwards BA, Eckert DJ, et al. An integrative model of physiological traits can be used to predict obstructive sleep apnea and response to non positive airway pressure therapy. Sleep 2015;38:967; with permission.)

the airway, a reduced bony skeletal structure, or increased tonsil or adenoid size, among others. This anatomic trait is, in general, the most important single variable in dictating who does and does not develop OSA.

Upper Airway Response

In patients with an anatomically deficient airway, pharyngeal patency during wakefulness is generally maintained by increased upper airway dilator muscle activity. With sleep onset, this muscle activity decreases, yielding reduced airway size or complete collapse. This leads to hypoventilation with rising PCO_2 and increased respiratory drive, manifest as increasing intrapharyngeal negative pressure. Both airway negative pressure and increased PCO_2 can activate pharyngeal dilator muscles. If these muscles are adequately activated and are mechanically effective, they can often restore pharyngeal patency yielding rhythmic respiration and stable sleep. However, this upper airway response is quite variable between patients, with some demonstrating brisk muscle responses and others little at all. Thus, some patients can compensate during sleep for considerable anatomic deficiency, whereas others cannot.

Respiratory Arousal Threshold

In patients who require an upper airway response to restore pharyngeal patency during sleep, stable sleep must be maintained for a long enough period for the upper airway dilator muscles to be adequately recruited. In most patients, this occurs relatively slowly as PCO_2 increases and intrapharyngeal pressure becomes progressively more negative. If arousal from sleep occurs in response to the increased respiratory drive before airway patency can be adequately re-established, stable respiration during sleep cannot be achieved. Thus, a low arousal threshold to respiratory stimuli may not allow an adequate upper airway response to occur even if muscle recruitment is possible.

Loop Gain (Respiratory Control Instability)

Inherent instability in the respiratory control system can lead to a waxing and waning of respiratory drive during sleep. In individuals with an anatomic predisposition to pharyngeal collapse, as described above, airway obstruction may occur at the nadir of the waning respiratory drive yielding an obstructive apnea or hypopnea. Thus, ventilatory control instability can contribute to the development of OSA in patients with a susceptible pharyngeal airway. Loop gain is a measure of ventilatory control instability with a high loop gain indicating greater instability.

Thus, manipulation of these traits using pharmacologic agents would seem a reasonable target in the treatment of OSA.

PHARMACOLOGIC APPROACHES TO THE MANIPULATION OF OBSTRUCTIVE SLEEP APNEA TRAITS

Upper Airway Anatomy or Collapsibility

Upper airway anatomy is, almost by definition, not amenable to pharmacologic manipulation, particularly acute manipulation. The exception to this would be drugs that influence body weight, such as weight loss drugs. Changes in weight can importantly influence sleep apnea severity with substantial weight loss being a meaningful way to treat OSA.[4] Although not fully documented, it seems quite likely that weight loss primarily influences upper airway anatomy yielding a larger, less collapsible airway. It is beyond the scope of this article to address the efficacy and mechanisms of weight loss drugs. However, as appropriate, such drugs could certainly play a role in the treatment of OSA.

Upper Airway Response

The upper airway response is a restoration of a satisfactory level of ventilation primarily through the activation of upper airway dilator muscles during stable sleep. Thus, for some time now, there