

Editorial

The scent of love is in the air(way): a potential drug target for sleep apnea?

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Fundamentally, obstructive sleep apnea (OSA) is characterized by the interaction between impaired pharyngeal anatomy and inadequate dilator muscle function during sleep [1]. Accordingly, strategies to reactivate upper airway dilator muscle activity during sleep are a key target for emerging pharmacotherapy for OSA [1–7]. Indeed, several preclinical, e.g. [8–12] and translational clinical proof of concept findings e.g. [2, 5, 6, 13–18] show considerable promise for the development of OSA pharmacotherapy.

Pharyngeal dilator muscle activity changes throughout the breathing cycle with increased activation during inspiration to stiffen and dilate the upper airway to maintain airway patency in response to negative airway pressure [19, 20]. People with OSA have greater levels of dilator muscle activity during wakefulness which may be, at least in part, to compensate for impaired pharyngeal anatomy [21]. In addition, certain people with pharyngeal anatomical compromise due to obesity are protected from OSA via enhanced upper airway dilator muscle responsiveness during sleep [22]. The transition from wakefulness to sleep is associated with reduced pharyngeal muscle activity [23]. This places the airway prone to collapse in those with an anatomically narrow airway. Thus, interventions to reactivate pharyngeal dilator muscle activity during sleep, including hypoglossal nerve stimulation [24, 25] or targeted pharmacotherapy [2, 5, 13–15] represent key therapeutic targets for OSA. This is especially true for the ~30% of people with OSA who have severely impaired pharyngeal dilator muscle responsiveness during sleep [1]. As OSA is a heterogeneous disorder, in addition to impaired pharyngeal anatomy and dilator muscle function, there are also other pathophysiological contributors to OSA including unstable ventilatory control and waking too easily to minor airway narrowing events (a low respiratory arousal threshold) [1]. As highlighted in Figure 1, these traits also represent targets for pharmacological e.g. [26–28] and non-pharmacological e.g. [29] treatment for OSA either solely for certain patients or when combined with other therapies.

Oxytocin is a neuropeptide produced in the hypothalamus that, amongst other behavioral and physiological functions, plays important roles in social bonding and sexual responses. For this reason, it has been called the “love hormone.” Why then would OSA researchers be interested in the effects of oxytocin on the tongue? While love is in the eye rather than the airway of the beholder, oxytocin receptors are localized within the human brainstem that mediate upper airway motor control including hypoglossal and solitary nuclei [30]. Animal studies also indicate that oxytocin can activate the brain stem respiratory network neurons to increase the respiratory drive to the genioglossus muscle and diaphragm [31]. Hence, their potential mediating role in OSA. The therapeutic potential for intranasal oxytocin has been investigated across a range of conditions including psychiatric disorders [32–35], autism spectrum disorder [36], pain [37], cardiovascular diseases [38] and more recently, sleep disorders [39–41].

In this issue of *Sleep*, Dergacheva *et al.* [42] conducted a comprehensive, elegant series of in vitro electrophysiological experiments in mice to show that 12µg nasal administration of oxytocin increased the amplitude of inspiratory-related electromyographic bursts in tongue muscles versus saline control. These findings were complemented by in vivo and fluorescent imaging studies in transgenic mice. Collectively, the findings are consistent with a central mediated role whereby oxytocin preferentially stimulates tongue protruder hypoglossal motoneurons over retractor muscles to promote airway opening. While the precise underlying mechanisms remain incomplete, this work represents a major advance in knowledge of the underlying mechanisms by which intranasal oxytocin may improve pharyngeal patency.

Although the current mechanistic findings provide further insight into upper airway motor control and highlight a potentially important novel therapeutic target for OSA, to date, positive preclinical findings have not translated to major therapeutic benefits for OSA [39, 40]. In an initial non-randomized proof of

Existing and emerging targeted therapies for OSA

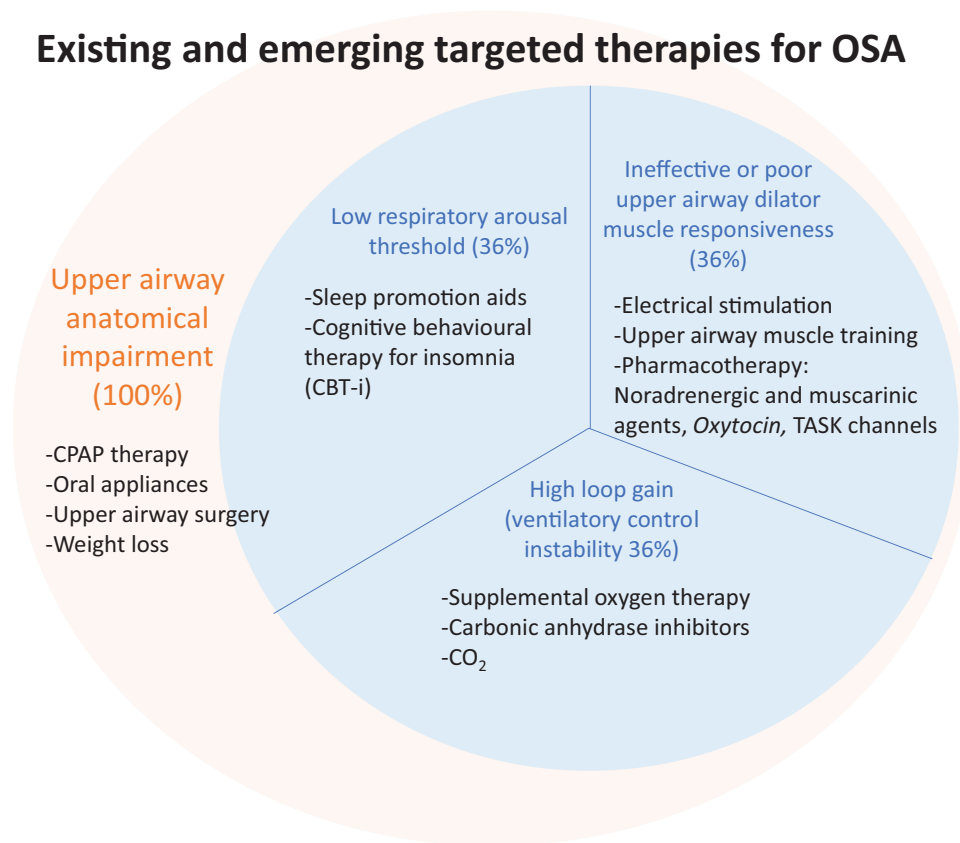


Figure 1. Schematic highlighting the 4 key obstructive sleep apnea (OSA) endotypes and corresponding examples of existing and emerging potential targeted therapy options. Numbers in parentheses indicate the estimated proportion of people with OSA who have impairment in this endotype (from ref #1, Eckert DJ et al, *Defining phenotypic causes of OSA. Identification of novel therapeutic targets. Am J Respir Crit Care Med.* 2013; 188 (8): 996-1004.). Larger circle indicates anatomical targets and smaller circle indicates non-anatomical targets.

concept study in eight people with moderately severe OSA [40], 40 IU of intranasal oxytocin just prior to sleep reduced the hypopnea index by ~10% and modestly reduced respiratory event duration. Consistent with a possible sleep promotion/sleep stability effect (i.e. increase in arousal threshold) which has been noted in pre-clinical studies but less so in clinical studies with oxytocin [41], total sleep time increased by ~10% with intranasal oxytocin in the Dergacheva et al. study [42]. There was also an accompanying reduction in the proportion of respiratory events that ended with cortical arousal and self-assessed sleep quality also improved. However, there was no change in the overall AHI and first night/order effects remain a possible confounder [40]. In a follow-up, double-blind, randomized, cross-over designed trial, sleep data were collected in 19 people with OSA during 40 IU of intranasal oxytocin just prior to sleep versus placebo [39]. Respiratory rate increased by ~1 breath per minute in the first 2 hr following administration in line with peak concentration. Obstructive event duration decreased by ~2 sec and nadir oxygen saturation increased by ~2% with intranasal oxytocin [39]. Both studies also highlighted potential cardiovascular benefits with intranasal oxytocin as reflected by increased parasympathetic but no change in sympathetic tone [40] and reduced rates of respiratory event-related bradycardia [39]. There were also no major adverse events reported in these acute single-night studies. Thus, while these initial studies showed some potential benefit for OSA and a favorable safety profile at this dose, therapeutic effect sizes were modest at best. Thus, there is scope to conduct dose-finding studies with intranasal oxytocin including higher dose formulations.

Nasal delivery of oxytocin is believed to yield a rapid increase in central oxytocin levels [42]. If demonstrated to be efficacious, a simple intranasal spray has the potential to be more tolerable than current device-based therapeutic approaches for OSA. However, at higher doses, the potential for off-target systemic effects of repeated doses of intranasal oxytocin would need to be carefully considered. Oxytocin has powerful effects on uterine muscle, so is commonly used as an intravenous infusion to induce labor or to manage postpartum bleeding. It is also an important hormone in lactation. These would be important side effects to assess for in human oxytocin studies, especially in women already breastfeeding and in people taking medications that can increase breast milk production, including antipsychotics, metoclopramide, and domperidone.

To date, considerable research efforts over several decades have failed to deliver a broadly efficacious pharmacotherapy alternative to continuous positive airway pressure. Initially, several excitatory receptor subtypes in the hypoglossal nucleus were identified [3]. However, in general, investigation of agents to target these receptors in humans were no match for the hyperpolarization of hypoglossal motoneurons that occurred during sleep [43]. As highlighted, more recent drug repurposing investigations with agents such as noradrenergic reuptake inhibitors, including when combined with muscarinic agents, have shown promise [2, 5, 13–18]. However, their effectiveness may be limited to people with specific OSA endotypes [13, 16, 17]. Longer-term efficacy [44] and safety profiles also require further investigation.

These two points are relevant for intranasal oxytocin; genioglossus activity is mediated by a complex combination of excitatory inputs mediated by multiple neurotransmitters [3, 43], amongst which oxytocin likely plays a partial role, and the magnitude of the effect of oxytocin on OSA severity may vary between individuals with different OSA endotypes. Thus, oxytocin may have a part to play in future endotype-directed drug therapy that combines more than one neurotransmitter target. Rather than act on its own, oxytocin may find its place by partnering up and sharing the love.

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