A new therapy for sleep apnea?

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Editorial Comment

Sleep apnea (SA) still stands as an overlooked chronic condition, which impacts upon cardiovascular disease in the general population and various patients’ populations including patients with stroke, heart failure, atherosclerotic cardiovascular disease [1], and chronic kidney disease [2]. The most common clinical phenotype of SA is the obstructive type (OSA) that depends on upper airway obstruction secondary to a variety of factors, including obesity, larger neck circumference, old age, and male. Central sleep apnea (CSA), that is, disturbed control of breathing by the central nervous system, is much less frequent than OSA and is particularly frequent among patients with congestive heart failure. These two clinical phenotypes, OSA and CSA, may also coexist (mixed SA) in some patients.

Obesity is the main risk factor responsible for OSA at the population level. In obese individuals, fat accumulation in the retropalatal and retroglottal region narrows the upper airway. Smooth muscle activity decreases in this area, which becomes more collapsible further compounding the narrowing by fat accumulation. Rostral fluid redistribution during supine sleep underlies airway obstruction in conditions characterized by fluid retention like heart failure and chronic kidney disease [3].

Upper airway occlusion in OSA triggers cyclical hypoxemia and hypercapnia, which activate sympathetic activity [4], blood pressure (BP) surges and eventually hypertension persistent beyond nocturnal sleep. Because of hyper-responsiveness of the carotid body to hypoxia, patients with OSA show augmented ventilatory responses and this hyper-responsiveness is the key for triggering sympathetic overactivity and BP surges [5]. Carotid body hyper-responsiveness in part depends on hypoxia-induced inflammatory changes and oxidative stress in this chemoreceptor organ [6].

Therapy of SA includes changes in lifestyle aimed at reducing body fat excess in obese patients and quitting smoking. Correction of volume excess mitigates the severity of OSA in conditions characterized by fluid overload like heart failure and chronic kidney disease (CKD) [2,3]. However, these interventions are only partially effective and difficult to implement on a long-term basis. The majority of patients with severe OSA eventually is treated with continuous airway positive pressure (CPAP) during the night, but this treatment is poorly tolerated by most patients and has a high drop-out rate [7].

In this issue of the Journal, Andrade et al. [8] present data showing that a synthetic analog of erythropoietin (EPO), carbamylated erythropoietin (CEPO) in an animal model of SA, namely chronic intermittent hypoxia in the rat. Current treatments of OSA are still largely unsatisfactory (see above). Therefore, experimental and clinical research in this area is a public health priority. Findings by Andrade et al. may have potential implications for the treatment of SA in humans. Herein, we will discuss the validity of the experimental model adopted by Andrade et al. and the characteristics of the drug tested by the same authors. Finally, we will mention the perspective of testing CEPO in the clinical trial scenario.

ANIMAL MODELS OF SLEEP APNEA

OSA can be induced mechanically in the cynomolgus monkey by infiltration of collagen in the upper airway [9]. OSA naturally occurs in several animal species (reviewed by Kim et al. [10]). The bulldog has a large soft palate coupled with a narrow upper airway and shows breathing alterations almost identical to human OSA even in the absence of obesity. Obese rats develop signs typical of OSA including upper airway narrowing and dysfunction. New Zealand obese mice show fat accumulation in the upper airway and display a larger number of spontaneous apneas and hypopneas than lean New Zealand black mice. The leptin-deficient ob/ob mice is another model of OSA. These mice are hyperphagic and severely obese and show hypercapnia and reduced CO\textsubscript{2} sensitivity. Leptin per se improves upper airway patency and the ventilatory drive indicating that the deficiency of this fat hormone has a direct role in OSA in the ob/ob mice [11]. However, the respiratory disturbance in these rodents is mild without complete obstructive apneas [12]. Until now, obese rodent models have never been used for the development of new drugs aimed at treating OSA.

By definition, OSA is confined to sleep, that is, during the period when ventilation control is almost entirely governed by chemoreflexes. During wakefulness, conscious stimul...
generated in suprapontine centers may override of the chemoreflex control [13]. This type of control of ventilation is fundamental to coordinate breathing with emotion and movement and breath holding in special situations like swimming. During sleep, the conscious control of ventilation is lost and ventilation is governed by chemoreflexes. If the arterial CO₂ pressure (PaCO₂) drops just a few mmHg below eupneic levels, the central chemoreceptor drive to ventilation stops (central apnea) and ventilation restarts only when PaCO₂ rises to levels sufficient to re-establish the central ventilatory drive. The ventilatory drive extends to thoracic muscles and the upper airway dilator muscles as well. Even though typical of central apneas, altered ventilatory chemoreflex control may contribute to OSA because the upper airway may collapse when PaCO₂ is low [13].

Exposure to intermittent hypoxia in rodent models can induce a sustained increase in a ventilatory drive that persists beyond exposure to hypoxia. This phenomenon may lower CO₂ below normal, eupneic levels and may generate an OSA phenotype characterized by a mild increase in the number of apneas during sleep [14]. In general, hypoxemia in these models is more severe than that observed in OSA patients and the same models do not reproduce some characteristic features of OSA including respiratory efforts and hypercapnia during upper airway obstruction [15]. In the study by Andrade et al. in this issue of the Journal [8], Sprague-Dawley rats were sequentially exposed to room air (oxygen 20%) for 7 days and then to intermittent hypoxia for 21 days (5% O₂ for 20 s, followed by room air for 280 s, repeated 12 times per hour for 8 h per day). Predictably, chronic intermittent hypoxia increased ventilatory responses and the number of apneas during sleep and produced hypertension. The role of the carotid body for the induction of the respiratory disturbance and hypertension in this model is supported by the crucial observation that the ablation of this body abolishes these alterations [16]. Even though the chronic intermittent hypoxia model reproduces some features of OSA, we should keep in mind that it represents an imperfect model of human OSA, a disturbance initiated by mechanical alterations of the upper airway like in the most common disease-causing OSA, that is, obesity (e.g., fat accumulation in the upper airway). Obesity models of OSA in rodents induce just a very mild form of OSA and are difficult to exploit in pharmacological research targeting OSA. Because intermittent hypoxia may contribute to OSA (see above), this model may be useful to explore compounds impinging upon inflammatory-oxidative stress mechanisms implicated into the augmented reflex ventilatory response of the carotid body. However, like in the obesity models, the number of apneas during sleep induced by chronic intermittent hypoxia is just mild. Nevertheless, treatment with antioxidant compounds like Tempol (a superoxide dismutase mimetic) or Apocynin (a NADPH oxidase inhibitor) normalizes the number of apneas during sleep in this model [14].

This is an important property because cytoprotection by EPO demands high doses, whereas the accompanying excessive stimulation of erythropoiesis poses relevant risks. The risk of death and cardiovascular disease by EPO is the reason why the hemoglobin threshold for starting the treatment of anemia in patients with end-stage kidney disease is set between 9.0 and 10 g/dl [17]. The erythropoietic and the cytoprotective effects of EPO are mediated by different receptors and cEPO targets a cell receptor different from the classical EPO receptor, that is, the β common receptor (βcR), a heterodimer consisting of one EPO receptor monomer and CD131, the cytokine β common subunit. This cEPO receptor is shared by granulocyte-macrophage colony-stimulating factor, interleukin (IL)-3, and IL-5 [18].

The neuroprotective effects of cEPO are mainly attributed to the attenuation of inflammation and oxidative stress at the neural level [19]. Interestingly, EPO decreases the ventilatory response to low oxygen (10% O₂ for 15 min) in men but potentiates the same response in women pointing to interference of this protein with the chemoreflex response to hypoxia [20]. Accordingly, chronic mountain sickness, a syndrome characterized by excessive erythropoiesis and hypoventilation in highlanders mainly affects male subjects [21].

**REVERSAL OF SLEEP APNEA BY CARBAMYLATED EPO IN THE CHRONIC INTERMITTENT HYPOXIA MODEL**

In the present issue of the Journal, Andrade et al. [8] produce a coherent set of findings documenting that cEPO has a dramatic effect on SA in the chronic intermittent hypoxia model in the rat (Fig. 1). Indeed, this EPO-derived molecule abolished the augmented ventilatory response to hypoxia, normalized the number of apneas during sleep, and improved hypertension. These results are hypothesis-generating and qualify cEPO as a potential drug for SA in humans. However, we should be aware of the limitations of this carefully conducted experimental study. First, as previously remarked, the chronic hypoxia model does not replicate the main characteristics of human OSA and the number of apnea and hypopnea episodes (apnea–hypopnea index) during intermittent hypoxia in the present study was modest (just about eight episodes per hour). Second, the study design did not contemplate randomization and was purely sequential (baseline, exposure to hypoxia, exposure to hypoxia, and cEPO) without a parallel control group maintained at room air in the same environmental conditions. Third, no biomarker of inflammation and oxidative stress were measured either systematically or in the carotid body. Even though the anti-inflammatory and antioxidant effects of cEPO are well established, because the several disparate effects of the parent molecule, EPO [22], the hypothesis that the beneficial effect of cEPO on SA depends on the anti-inflammatory and antioxidant effect of this compound remains undemonstrated. Obvious limitations notwithstanding, the magnitude of the effect of cEPO makes likely that the drug effectively ameliorated the respiratory disturbance triggered by chronic intermittent hypoxia. cEPO is a molecule that was characterized by biologically more than two decades ago and tested in...
The left panel summarizes mechanisms underlying the respiratory disturbance induced by intermittent hypoxia in the rat. The right panel shows the putative interference of carbamylated EPO with inflammation/oxidative stress at level of the carotid body (1) and the subsequent mitigation of carotid body hyper-reflexia (2), the improvement in the respiratory disturbance (3), and the ensuing attenuation of sympathetic activity and BP surges. EPO, erythropoietin; BP, blood pressure.

FIGURE 1

Where we go from here? The study by Andrade et al. [8] suggests that EPO-derived molecules acting upon the βcR receptor deserve attention and further testing in experimental models. It was shown that EPO administration attenuates intermittent hypoxia-induced cognitive deficits in a murine model of SA [25]. A meta-analysis documented that EPO levels in patients with SA are coherently higher than in control subjects [26]. Recombinant human–EPO at a low dose (5000 IU intravenously) affects the ventilatory response to low oxygen in healthy individuals [20]. Investigating the effect of EPO in EPO-naïve end-stage kidney disease patients with SA may perhaps be a useful step toward advancing knowledge in this important research area. Treating adequately OSA remains an unmet clinical need. Investigators of the field should take the challenge of further testing EPO-derived compounds for the treatment of SA can pay dividends.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES


