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Review

Central and peripheral factors contributing to obstructive sleep apneas

Jan-Marino Ramirez[a,*], Alfredo J. Garcia III[a], Tatiana M. Anderson[a], Jenna E. Koschnitzky[a], Ying-Jie Peng[b], Ganesh K. Kumar[b], Nanduri R. Prabhakar[b]

[a] Center for Integrative Brain Research, Seattle Children's Research Institute, Department of Neurological Surgery and Pediatrics, University of Washington School of Medicine, Seattle, WA, USA
[b] Center for Systems Biology of O_2 Sensing, Institute for Integrative Physiology, University of Chicago, Chicago, IL, USA

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ABSTRACT

Apnea, the cessation of breathing, is a common physiological and pathophysiological phenomenon. Among the different forms of apnea, obstructive sleep apnea (OSA) is clinically the most prominent manifestation. OSA is characterized by repetitive airway occlusions that are typically associated with peripheral airway obstructions. However, it would be an oversimplification to conclude that OSA is caused by peripheral obstructions. OSA is the result of a dynamic interplay between chemo- and mechanosensory reflexes, neuromodulation, behavioral state and the differential activation of the central respiratory network and its motor outputs. This interplay has numerous neuronal and cardiovascular consequences that are initially adaptive but in the long-term become major contributors to morbidity and mortality. Not only OSA, but also central apneas (CA) have multiple, and partly overlapping mechanisms. In OSA and CA the underlying mechanisms are neither "exclusively peripheral" nor "exclusively central" in origin. This review discusses the complex interplay of peripheral and central nervous components that characterizes the cessation of breathing.

1. Introduction

Obstructive Sleep Apnea (OSA) is a major health issue worldwide affecting 3–7% of adult men and 2–5% of adult women (Young et al., 2002) with the incidence increasing because of the dramatic rise in obesity (Bhattacharjee et al., 2012). Weight change predicts the incidence of OSA, and a 10% increase in weight is associated with a 32% increase in the apnea/hypopnea index (Peppard et al., 2000a). Furthermore, OSA is an important contributor to the morbidity and mortality associated with obesity (Gozal and Kheirandish-Gozal, 2009; Tuomilehto et al., 2012). OSA is defined as the cessation of breathing caused by the repetitive, episodic collapse of the pharyngeal airway due to an obstruction or increased airway resistance. The first modern description of OSA was by Burwell and colleagues (1956) but was documented much earlier (Bickelmann et al., 1956; Bray, 1994; Lavie, 1984). OSA is distinguished from central apnea (CA), which is primarily caused by the cessation of the central respiratory network. CA is highly prevalent in congestive heart failure but is also present in normal subjects (Eckert et al., 2009a).

The distinction between each form of apnea, however, is not straightforward. OSA (Fig. 1) as well as CA is the result of complex interactions between the peripheral and central nervous system (Eckert et al., 2009a). These interactions lead to short-term and long-term changes that contribute to the evolution of OSA and CA. Consequences of these disorders include excessive daytime somnolence, neurocognitive impairment, and increased risk for accidents related to sleep deprivation (Gozal et al., 2012; Gozal and Kheirandish-Gozal, 2012; Jordan and White, 2008; Kim et al., 1997; Young et al., 1997). In addition to these neurological consequences, the number of apneas that patients experience is positively correlated with an increased risk of hypertension (Peppard et al., 2000b). Other serious cardiovascular morbidities include increased risk for stroke, coronary artery disease, and heart failure (Phillips, 2005).

Mechanistically, increased sympathetic activity, endothelial dysfunction, and systemic inflammation as well as oxidative stress are all contributors to myocardial damage and hypertension (Baguet et al., 2012). Thus, the airway obstruction in OSA as well as CA is the beginning of a complex series of events that affect numerous central and peripheral neuronal and cardiovascular mechanisms (Eckert et al., 2009a; Gozal et al., 2013; Jordan and White, 2008; Leung and Bradley, 2001; Meier and Andreas, 2012; Susarla et al., 2010). Some of the long-term consequences of

* Corresponding author. Tel.: +1 206 884 8188; fax: +1 206 884 1210.
E-mail addresses: nino1@uw.edu, nino.ramirez@seattlechildrens.org (J.-M. Ramirez).

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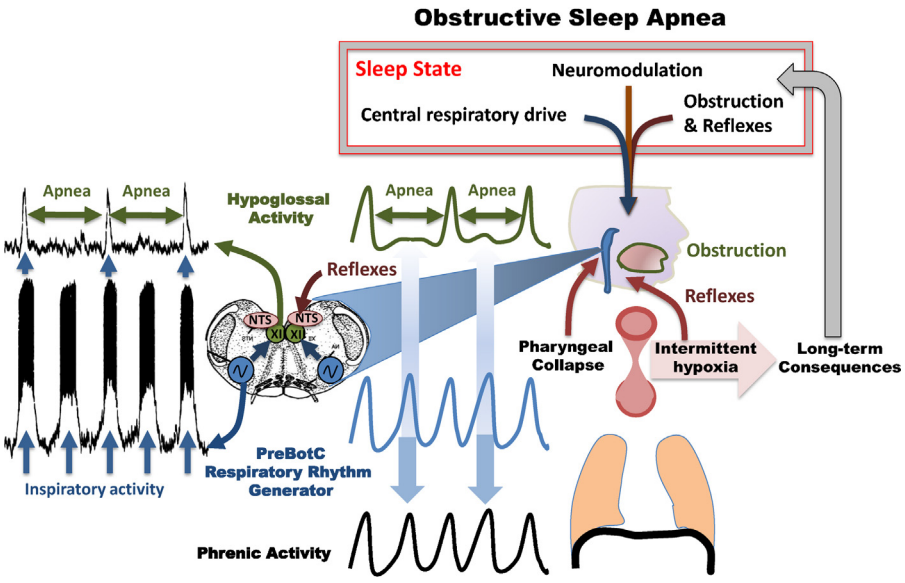

Fig. 1. Mechanisms of obstructive apneas. Left panel: Upper trace: integrated extracellularly recorded hypoglossus activity obtained simultaneously with an intracellular recording from an inspiratory neuron located within the pre-Bötzinger complex (lower trace). The recordings were obtained in an isolated transverse slice preparation shown in the schematic. The preparation contains the functionally active pre-Bötzinger complex (blue), the nucleus tractus solitaries (NTS, pink), which in the intact animal would receive reflex inputs. Contained within the slice is also the hypoglossal nucleus (XII, green), which in the intact animal would innervate the genioglossus muscle. Note the XII activity is not always phase-locked with the pre-Bötzinger complex resulting in XII apneas that are uncoupled from the respiratory rhythm generator located within the pre-Bötzinger complex. (Figure modified from Ramirez et al., 1996). The actual data shown on the left panel inspired the middle panel, which schematically illustrates how the rhythmically active pre-Bötzinger complex (blue trace) could continue to activate the phrenic activity (black trace) resulting in diaphragmatic activity, while activity in the XII becomes uncoupled resulting in a cessation of XII activity (green trace, apnea). The right panel illustrates the anatomical components contributing to an airway occlusion: A decreased activity in the genioglossus (tongue in the schematic) and continued activity in the diaphragm (schematically drawn beneath the lung) will lead to the negative pressure that results in a pharyngeal collapse. The bilaterally organized pre-Bötzinger complex isolated in the transverse slice preparation, which was obtained from the lower brainstem (medulla – schematically shown in blue). The airway occlusion is the result of sleep state, neuromodulation, central respiratory drive, reflexes and the airway obstruction. These contributors are altered by long-term consequences of the intermittent hypoxia that is caused by repetitive pharyngeal collapses. For more details see text.

OSA, such as hypertension, often persist even after obstructions are eliminated or prevented through surgery or continuous positive airway pressure (CPAP) (Alchanatis et al., 2001; Vanderveken et al., 2011). Moreover, after surgical removal of the anatomical obstructions, or after treatment with CPAP, patients often remain refractory and shift toward the generation of central apneas (Boyd, 2009; Eckert et al., 2009b; Susarla et al., 2010).

In this review we use OSA as a template to discuss the complex interactions between factors that contribute to apnea pathogenesis. The first key concept we hope to convey is that OSA results from the convergence of multiple peripheral and central nervous system factors, not a single factor in isolation. The second concept is that many of the peripheral and central nervous system changes associated with OSA are initially reversible, and possibly even adaptive, but they become detrimental and irreversible during disease progression.

2. Airway obstruction and the importance of hypoglossal activity

Various anatomical abnormalities can contribute to the airway obstructions associated with OSA. Thus surgical procedures to remove these obstructions need to be adapted to the individual pattern and type of airway obstruction (Bhattacharjee et al., 2010; Sher et al., 1996). Obstructions can include macroglossia, adenotonsillar hypertrophy, increased nasal resistance, pharyngeal edema, and craniofacial abnormalities such as micrognathia and retrognathia (Bhattacharjee et al., 2010; Enoz, 2007; Lam et al., 2010; Prabhat et al., 2012; Shott and Cunningham, 1992; Verbraecken and De Backer, 2009; White, 2005; Won et al., 2008). Craniofacial factors are particularly important for pediatric OSA (Gozal, 2000). However, alone none of these anatomical determinants is sufficient to cause an airway occlusion.

Under normal conditions airflow is facilitated by a central respiratory drive to the upper airways (Fig. 1). Of critical importance are the hypoglossal (XII) motoneurons that innervate the genioglossus muscle via the medial branch of the hypoglossal nerve. The genioglossus muscle is the largest extrinsic muscle of the human tongue (Abd-El-Malek, 1938; Saboisky et al., 2007; Takemoto, 2001). Innervation of the genioglossus is very complex and many types of phasic and tonic motor units originating in the hypoglossal motor nucleus contribute to the genioglossus contraction (Haxhiu et al., 1992; Hwang et al., 1983; Saboisky et al., 2007). The XII motoneurons phasically activate the genioglossus muscle during each inspiration (Fig. 1), and some activity is maintained during expiration (Akahoshi et al., 2001; Fogel et al., 2001; Otsuka et al., 2000; Saboisky et al., 2010; Sauerland and Harper, 1976).

Overall, however, respiratory drive increases genioglossus muscle tone preferentially during inhalation, resulting in a contraction that pulls the tongue forward (Brouillette and Thach, 1979) and enlarges the upper airways (Bailey and Fregosi, 2004; Fuller et al., 1999; Mann et al., 2002; Oliven et al., 2001; Sokoloff, 2000). This mechanism largely prevents airway collapse during wakefulness. Indeed during wakefulness, electromyography (EMG) activity of the genioglossus is enhanced in OSA patients when compared to controls (Fogel et al., 2001; Mezzanotte et al., 1992), an adaptation that seems to compensate for the increased upper airway resistance and compliance that characterizes OSA patients (Malhotra and White, 2002; Randerath, 2007; Saboisky et al., 2007). However, during sleep or while anesthetized, the central respiratory drive to the genioglossus muscle weakens, and, as a consequence, anatomical obstructions can occlude the airway during inhalation