Chapter 2

Nerve and Muscle Changes in the Upper Airways of Subjects with Obstructive Sleep Apnea: Structural Basis for the Neurogenic Theory

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Abstract

Obstructive sleep apnea syndrome (OSAS) is a widely diffused disease associated with specific genetics, age, gender, craniofacial and upper airways anatomy, obesity, and endocrine conditions, but not with ethnicity profiles. The so-called neurogenic neurogenic theory of OSAS postulates that the collapse of the upper airways that characterize this disease is due to peripheral nerve degeneration that leads to muscle atrophy and collapse. This review attempts to summarize the structural and functional changes in both the sensory and motor innervation of the walls of the upper air ways in patients suffering from OSAS.

Keywords: peripheral neuropathy, nerve fibers, mechanoreceptors, skeletal muscles, obstructive sleep apnea syndrome

1. Introduction

Obstructive sleep apnea syndrome (OSAS) is a common chronic disease characterized by sleep fragmentation due to apnea-hypoapnea and repeated arousal [1]. OSAS afflicts 2–4% of the population and has a strong genetic component [2]. Moreover, age, gender, craniofacial structure and the anatomy of the upper airways (UA), endocrine conditions, and obesity, but not ethnicity, are associated with OSAS [3].

The collapse of UA during sleep is the major characteristic of OSAS [4]. Two primary theories have been proposed to explain the pathophysiology of OSAS: the obstructive theory, in which muscle hypertrophy leads to airway narrowing, and the neurogenic theory, which postulates that peripheral nerve degeneration due to vibratory stretch trauma, or systemic diseases, lead to muscle atrophy and collapse [5–7]. A progressive local neurogenic lesion caused by repeated microtrauma of snoring might be a potential contribution factor for UA collapsibility [8].

The UA size and resistance are tightly regulated by neural mechanisms that control muscles and reflexes. The sensory nerve endings in the mucosa and mechanoreceptors of UA walls respond to changes in different sensory modalities (light touch, temperature, pressure, pain, muscle stretch and proprioception, water and chemical stimuli). Sensory inputs from these structures continually streams toward the central nervous system, including respiratory centers, which control UA muscles via efferent motor neural outputs [9], thus adjusting the contraction of the UA muscles during sucking, swallowing, respiration, speech, and mastication, as well as gagging, vomiting, coughing, and snoring reflexes (**Figure 1**). The structural

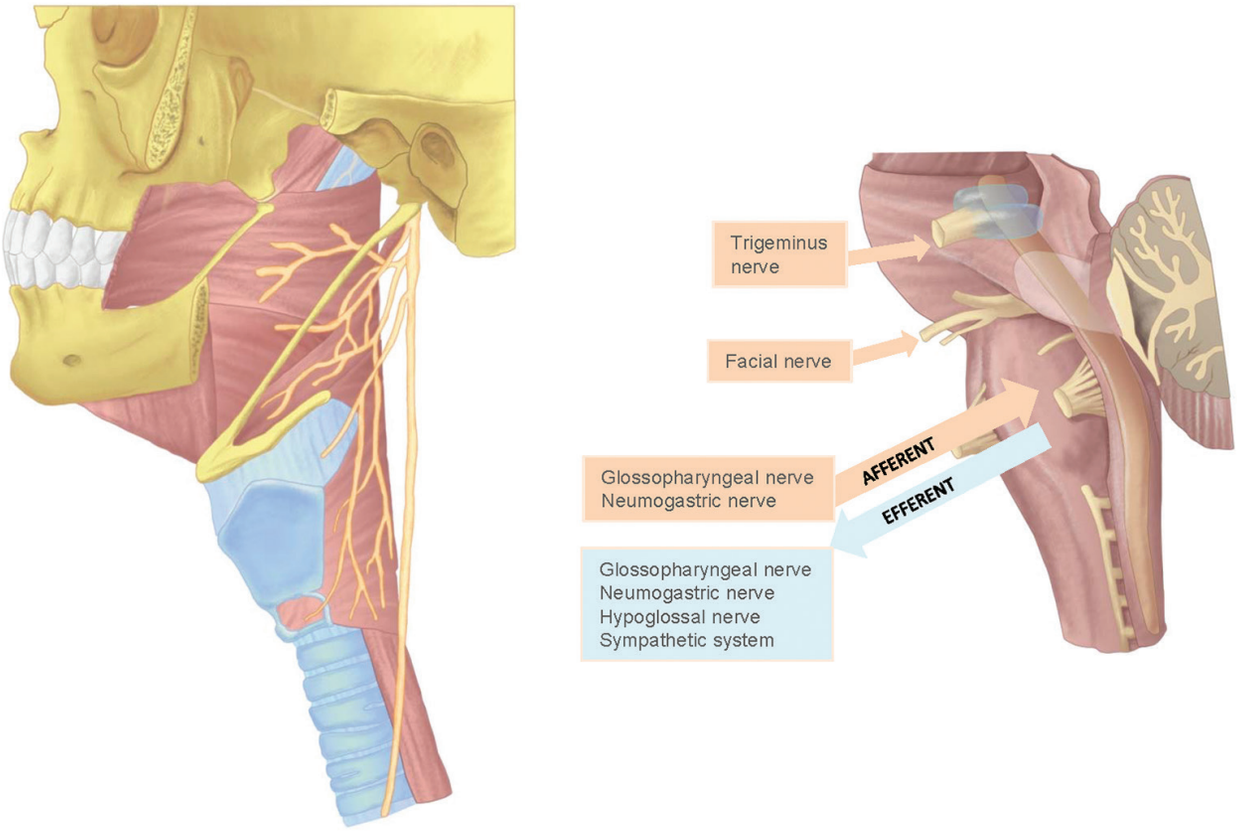

Figure 1. Schematic representation of the afferent and efferent innervation of the upper air ways. The mucosa of the nasopharynx, oropharynx, and laryngopharynx are primarily supplied by the trigeminus (maxillary division, V2), glossopharyngeal (IX), and vagus (X) cranial nerves, respectively, with a minimal contribution of the facial nerve (VII). The sensory neurons of these nerves are placed in the parent sensory ganglia and their central processes synapse within the trigeminal and tractus solitarius nuclei of the brain stem. These nuclei send the inputs to nuclei whose motoneurons are located in the pons trigeminal, facial, ambiguous, and hypoglossal nuclei, and in the anterior horn of the cervical spinal cord (C1-2). Axons from these motor neurons travel through cranial nerves V, VII, IX to XII, and the ansa cervicalis and form motor endplates that use acetylcholine for neurotransmission via nicotinic receptors to innervate innervating UA muscles (for a more detailed description of these muscles and nerves, see Massey [68]).

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support of these reflexes consists of sensory receptors connected with sensory nerve fibers, the central synaptic connections that almost always use interneurons, and the efferent pathway composed of the motoneurons, innervating the effector organ. The effector organ in a somatic reflex is the striated muscle innervated by the α-motoneurons [10].

2. The neurological theory of OSAS and the upper airways remodeling

In the last decade of twentieth century, Woodson et al. [11] hypothesized that the pathophysiologic events that lead to the development of airway instability may be secondary to modifications in neurologic control, airway morphology, or both. Changes in sensation, muscle structure, and physiological properties of UA have been reported in patients with OSAS; these changes are referred to as airway remodeling. But whereas the structural and functional properties of muscles of OSAS patients have been extensively analyzed [5, 12–14], the motor nerve fibers and motor endplates as well as the potential role of sensory nerve impairment in OSAS have not been sufficiently investigated [15, 16]. Furthermore, the available data are heterogeneous and sometimes contradictory, because of the heterogeneity of the UA muscles, the different nerves innervating these muscles and the UA mucosae, and the differences in the methods used.

The nerve and muscle characteristics of OSAS patients may result from complex interactions of vibratory stretch trauma, inflammation, and hypoxia [8, 15–20]. It has been proposed that the repeated mechanical trauma and/or hypoxemia associated with OSA may lead to sensory and motor impairment of upper airway structures [8, 21], or that local nerve lesions due to long-standing snoring vibrations could be the basis of OSAS or its progression [17, 22, 23]. But is the neuropathy of OSAS, the cause or a consequence of the disease? It is unknown to what extent chronic intermittent hypoxemia in OSAS causes damage to the motor and sensory peripheral nerve, but muscle action potential and sensory nerve action potential amplitudes are significantly reduced in the nerves outside UA in patients with OSAS suggesting that axonal damage exists in patients with OSAS to a greater extent than previously thought [24]. On the other hand, association between OSAS and sensory neuropathy, and nerve damage outside the UA [18, 25–27], type 2 or type 1A diabetic neuropathy, and axonal subtypes of Charcot-Marie-Tooth disease [28–31] has been also demonstrated. Of particular interest is the epidemiological association between OSAS and anterior ischemic optic neuropathy [32] although a concluding rapport cannot be established [33].

Thus, there is a large body of evidence that UA neuromuscular abnormalities are frequent in OSAS patients, and these altogether support the neurogenic theory of OSAS [5–7, 34]. In recent years, multiple studies have demonstrated altered UA sensory input and abnormal UA motor function in patients with OSAS using a variety of neurophysiological and histological approaches [5, 7, 35–37], and impaired neural function is at least partly reversible with treatment for sleep apnea [27].

3. Nerve changes in OSAS

Consistent with the above data, studies on the innervation of the palate-pharyngeal region in OSAS patients have revealed both increased and decreased number of nerves in the mucosa

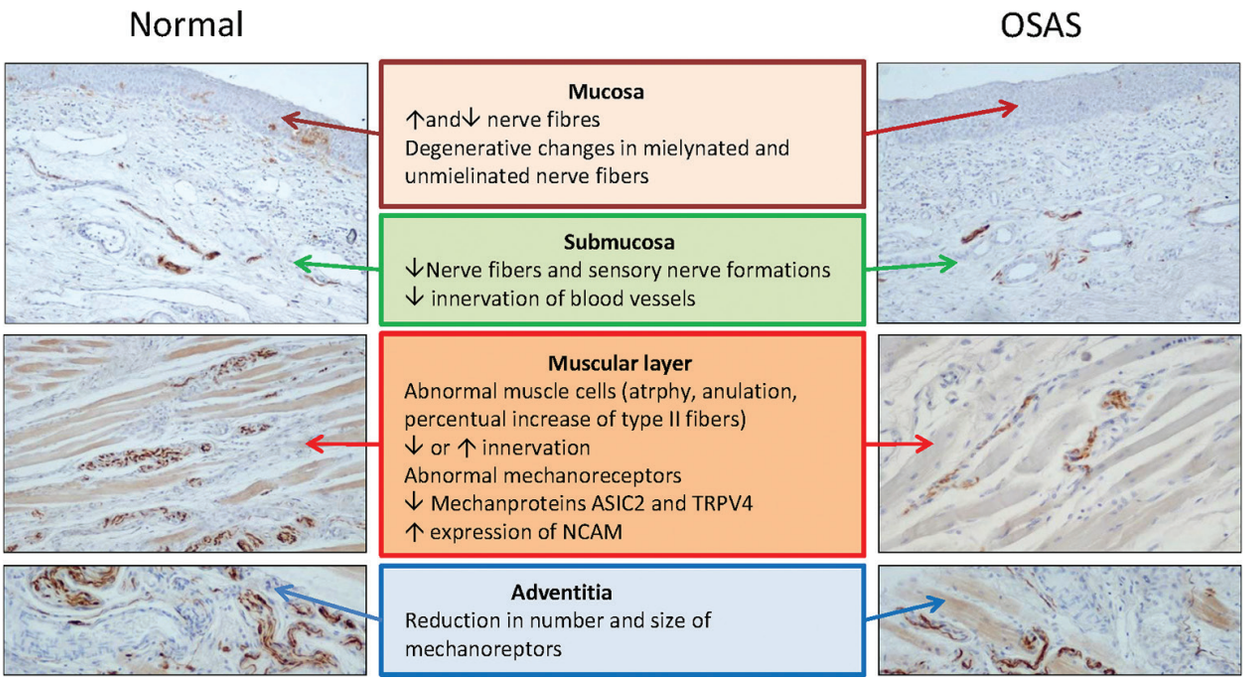

Figure 2. Main changes in nerves and muscles in OSAS patients in comparison with non-OSAS subjects. Data are based on the text and the figures are a courtesy of J.A. Vega.

and muscles [8, 13, 38, 39], as well as degenerative changes in myelinated and unmyelinated nerve fibers [40], and the degree of sensory neuropathy in UA correlates with the degree of OSAS (**Figure 2**) [41].

3.1. The afferent system: functional and structural data

If the anatomically deeper motor axons are affected by UA vibration, sensory afferents closer to the airway surface should also be impaired thus impairing normal inputs for reflex mechanisms which contribute to the upper airway function. Nevertheless, the evidence supporting sensory nerve impairment in OSA is less convincing than that for motor nerves.

The mucosal sensory function is impaired at multiple UA sites in OSAS [16]. Focal degeneration of myelinated and nonmyelinated nerve fibers, affecting Schwann cells and axons in the soft palate and uvula have been demonstrated in OSAS patients [11, 40]. In these UA zones, increase in the density of epithelial afferent nerve endings (based on the expression of substance P and calcitonin gene-related peptide) was also observed which is indicative of nerve lesion [38]. On the other hand, the afferent information from UA muscles is important in regulating the masticatory force and oromotor behaviors, but also in the response of important reflexes related to speech, swallowing, cough, vomit, or normal breathing [10, 42]. Patients with OSAS show a significant reduction in the density of nerve fibers in the submucosa as well as morphological abnormalities in mechanosensory corpuscles. Importantly, the muscle innervation of nerve fibers expressing ASIC2 and TRPV4 (regarded as two putative mechanoproteins) is also reduced in these subjects [43].

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In addition, and consistently with the above-mentioned pathological findings, UA sensory function has been shown to be impaired in OSAS during wakefulness [13, 15, 16, 44], specially patients with OSAS have altered vibration and cold detection thresholds [45, 46]. The respiratory-related evoked potentials (RREPs) during wakefulness in OSA revealed a reduction in the amplitude but not the latency of the early RREP components [44, 47] reflecting sensory processing is reduced in the OSA patients [48]. Other studies revealed no changes [49–51].

3.2. The efferent system: functional and structural data

Data regarding the changes in motor nerves during OSAS are scarce. Motor neuron lesions and/or direct damage in the muscles [17, 41] as well a decrease [39, 43] or increase [13] in the number of nerve fibers have been reported. But most studies have focused directly on muscles.

4. Muscle changes in OSAS

Structural changes in skeletal muscles have been studied primarily in the uvula muscles and the palatopharyngeal muscle, and the reported changes are very heterogeneous. They include focal muscle atrophy and muscle bundle disruption [11, 52], prevalence of angulated muscle fibers, increased and/or reduction of muscle fibers diameter and variation in fiber type grouping [14, 23, 53–57], atrophic and hypertrophic muscle fibers [8, 52, 58], changes in mitochondria content [14], enzymatic changes [56], and increased neural cell adhesion molecule expression by muscle cells [13].

Another characteristic of the UA muscles is the high percentage disproportion of glycolytic fast twitch of type II muscle fibers compared with non-OSA control subjects [12, 14, 55, 59–62], a difference that may represent an adaptive response to mechanical strain and/or neuronal activity. In this way, the over expression of N-CAM is suggestive of collateral nerve sprouting, reflected in the hyperinnervation that present these muscles [13]. Vascular enlargement, fibrosis, edema, inflammatory cells, and infiltration have also been reported. There is also increased fat in and around the muscles of the UA in patients with OSA [63].

However, all these changes in muscle fibers are not a major contributing factor to OSAS pathogenesis in most patients [20].

In addition to the structural changes, the UA muscles also show electrophysiological changes in OSAS. Patients with OSA have higher levels of multiunit electromyographic activity (EMG) recorded in the UA muscles compared to healthy control subjects presumably secondary to neurogenic remodeling. This is characterized by chronic partial denervation of muscle fibers, with reinnervation of the orphaned muscle fibers by collateral sprouting of surviving motor axons [13, 60, 64–66]. The apparent increase in drive was ascribed to a neural compensation for a narrow UA.

Recent investigations using single motor unit techniques have shown that the motor unit potentials of upper airway muscles in OSA patients are larger in area, longer in duration, and

more complex [7, 23, 37]. These changes could contribute to the increased multiunit EMG in OSAS. However, the presence of denervation and subsequent axonal sprouting may lead to changes in fine motor control such as speech [67].

5. Concluding remarks and future perspectives

The involvement of the peripheral nervous system and muscles in the pathogenesis of OSAS is now accepted. Nevertheless, large have been reported presumably due to the methodological differences used to evaluate both the pathological and functional changes in UA of patients suffering from OSAS. So, whereas some researchers found decrease in the density of nerve fibers [39, 40, 43] some others have found increased numbers of nerve fibers in the mucosa and muscles [13, 38]. These discrepancies can be related to the zones of the UA sampled or the muscles analyzed. And more importantly, no specific markers for sensory or motor nerve fibers were used in these studies. Another important aspect is the studies about the state of motor end-plates in OSAS. Thus, further studies are required to elucidate the role of upper airway sensory and motor impairment in modulating disease progression or severity.

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