

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800

Open access books available

122,000

International authors and editors

135M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.

For more information visit www.intechopen.com



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

Teresa Cobo, Emilio Macías, Covandonda Álvarez,
Alberto Álvarez-Suárez, Felix de Carlos,
Jose A. Vega and Juan Cobo

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/65438>

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 airways 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-hypopnea 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

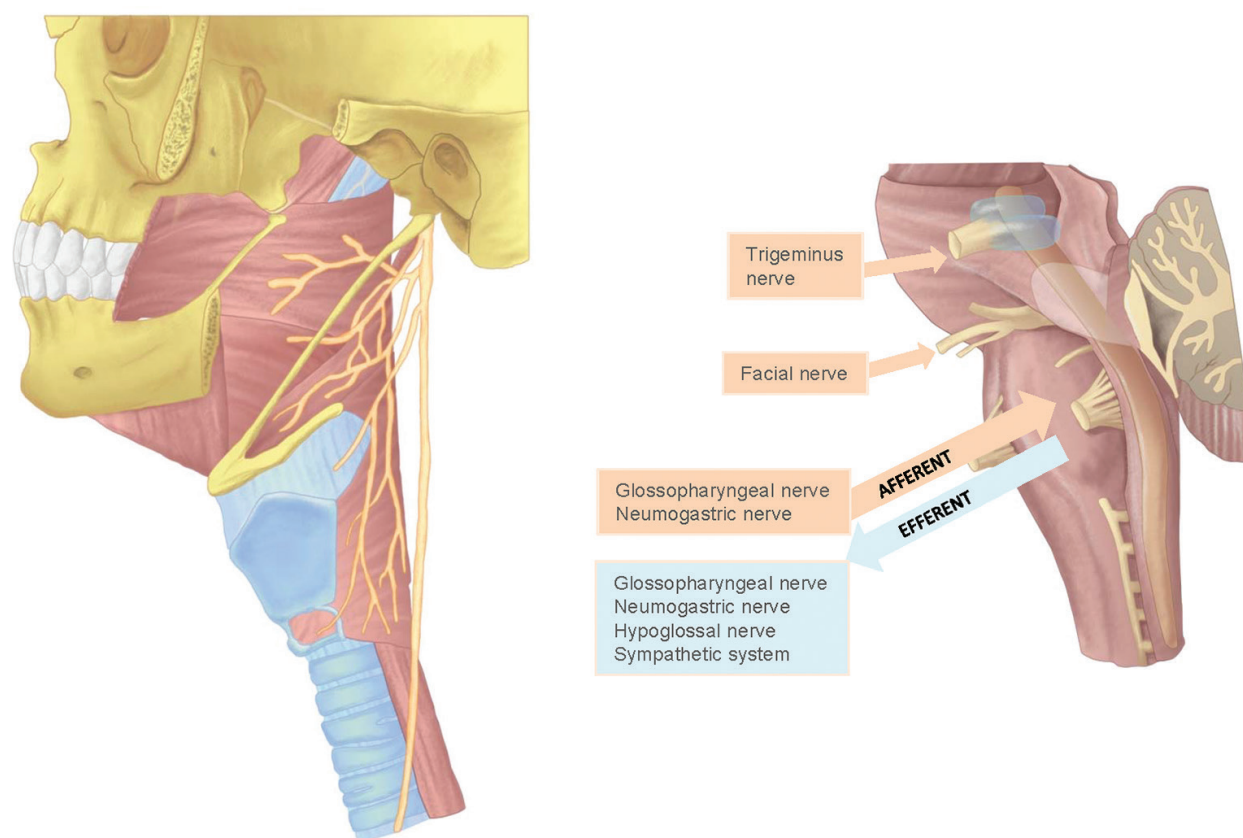


Figure 1. Schematic representation of the afferent and efferent innervation of the upper air ways. The mucosa of the nasopharynx, oropharynx, and laryngopharynx are primarily supplied by the trigeminal (maxillary division, V2), glossopharyngeal (IX), and vagus (X) cranial nerves, respectively, with a 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]).

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

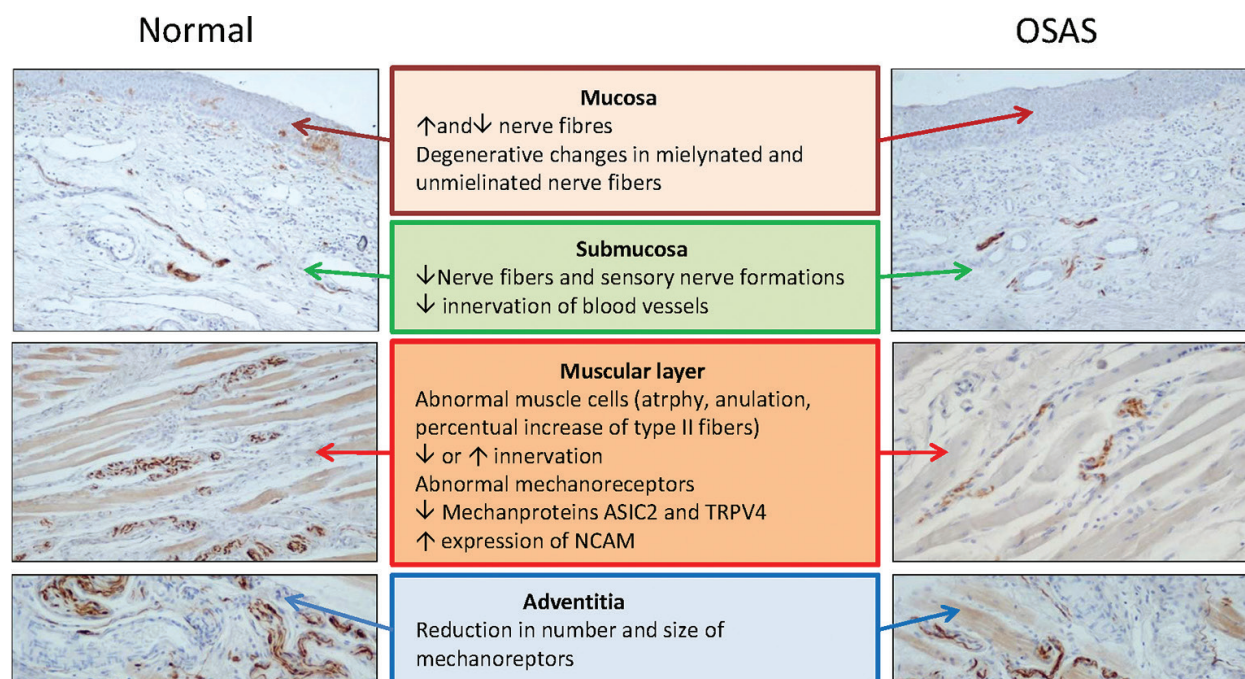


Figure 2. Main changes in nerves and muscles in OSAS patients in comparison with non-OSAS subjects. Data are based on the text and the figures are a courtesy of J.A. Vega.

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].

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.

Author details

Teresa Cobo^{1,2}, Emilio Macías^{1,2}, Covandonda Álvarez^{1,2}, Alberto Álvarez-Suárez³, Felix de Carlos², Jose A. Vega^{4*} and Juan Cobo^{1,2}

*Address all correspondence to: javega@uniovi.es

1 Orthodontics Area - Instituto Asturiano de Odontología, Oviedo, Spain

2 Department of Surgery and Medical-Surgical Specialties (Section of Odontology), University of Oviedo, Spain

3 Mechanical Engineering Area – Instituto Asturiano de Odontología, Oviedo, Spain

4 Department of Morphology and Cell Biology, SINPOS Group, University of Oviedo, Spain

References

- [1] Dempsey JA, Veasey SC, Morgan BJ, O'Donnell CP. Pathophysiology of sleep apnea. *Physiol Rev.* 2010; 90:47–112. DOI: 10.1152/physrev.00043.2008.
- [2] Paiva T, Attarian H. Obstructive sleep apnea and other sleep-related syndromes. *Handb Clin Neurol.* 2014; 119:251–271. DOI: 10.1016/B978-0-7020-4086-3.00018-7.
- [3] Ralls FM, Grigg-Damberger M. Roles of gender, age, race/ethnicity, and residential socioeconomics in obstructive sleep apnea syndromes. *Curr Opin Pulm Med.* 2012; 18: 568–573. DOI: 10.1097/MCP.0b013e328358be05.

- [4] Eckert DJ, Malhotra A. Pathophysiology of adult obstructive sleep apnea. *Proc Am Thorac Soc.* 2008; 5: 144–153. DOI: 10.1513/pats.200707-114MG.
- [5] Saboisky JP, Butler JE, Gandevia SC, Eckert DJ. Functional role of neural injury in obstructive sleep apnea. *Front Neurol.* 2012; 3: 95. DOI: 10.3389/fneur.2012.00095. eCollection 2012.
- [6] Tsai YJ, Ramar K, Liang YJ, Chiu PH, Powell N, Chi CY, Lung TC, Wen-Yang Lin W, Tseng PJ, Wu MY, Chien KC, Weaver EM, Lee FP, Lin CM, Chen KC, Chiang RP. Peripheral neuropathology of the upper airway in obstructive sleep apnea syndrome. *Sleep Med Rev.* 2013; 17:161–168. DOI: 10.1016/j.smrv.2012.05.005.
- [7] Saboisky JP, Butler JE, Luu BL, Gandevia SC. Neurogenic changes in the upper airway of obstructive sleep apnoea. *Curr Neurol Neurosci Rep.* 2015; 15:12. DOI: 10.1007/s11910-015-0537-1.
- [8] Friberg D, Ansved T, Borg K, Carlsson-Nordlander B, Larsson H, Svanborg E. Histological indications of a progressive snorer disease in an upper airway muscle. *Am J Respir Crit Care Med.* 1998; 157:586–593. DOI: 10.1164/ajrccm.157.2.96-06049.
- [9] Horner RL. Neural control of the upper airway: integrative physiological mechanisms and relevance for sleep disordered breathing. *Compr Physiol.* 2012; 2: 479–535. DOI: 10.1002/cphy.c110023.
- [10] Miller AJ. Oral and pharyngeal reflexes in the mammalian nervous system: their diverse range in complexity and the pivotal role of the tongue. *Crit Rev Oral Biol Med.* 2002; 13: 409–425. DOI: 10.1177/154411130201300505.
- [11] Woodson BT, Garancis JC, Toohill RJ. Histopathologic changes in snoring and obstructive sleep apnea syndrome. *Laryngoscope.* 1991; 101:1318–1322. DOI: 10.1002/lary.5541011211.
- [12] Lindman R, Stal PS. Abnormal palatopharyngeal muscle morphology in sleep-disordered breathing. *J Neuro Sci.* 2002; 195: 11–23. DOI: 10.1016/S0022-510X(01)00676-1.
- [13] Boyd JH, Petrof BJ, Hamid Q, Fraser R, Kimoff RJ. Upper airway muscle inflammation and denervation changes in obstructive sleep apnea. *Am J Respir Crit Care Med.* 2004; 170: 541–546. DOI: 10.1164/rccm.200308-1100OC.
- [14] Stål PS, Lindman R, Johansson B. Capillary supply of the soft palate muscles is reduced in long-term habitual snorers. *Respiration.* 2009; 77:303–310. DOI: 10.1159/000197975.
- [15] Kimoff RJ, Sforza E, Champagne V, Ofiara L, Gendron D. Upper airway sensation in snoring and obstructive sleep apnea. *Am J Respir Crit Care Med.* 2001; 164: 250–255. DOI: 10.1164/ajrccm.164.2.2010012.
- [16] Nguyen AT, Jobin V, Payne R, Beauregard J, Naor N, Kimoff RJ. Laryngeal and velopharyngeal sensory impairment in obstructive sleep apnea. *Sleep.* 2005; 28: 585–593.
- [17] Friberg D. Heavy snorer's disease: a progressive local neuropathy. *Acta Otolaryngol.* 1999; 119: 925–933.

- [18] Mayer P, Dematteis M, Pépin JL, Wuyam B, Veale D, Vila A, Lévy P. Peripheral neuropathy in sleep apnea: a tissue marker of the severity of nocturnal desaturation. *Am J Respir Crit Care Med.* 1999; DOI: 159:213–219. 10.1164/ajrccm.159.1.9709051.
- [19] Donald F1, Esdaile JM, Kimoff JR, Fitzcharles MA. Musculoskeletal complaints and fibromyalgia in patients attending a respiratory sleep disorders clinic. *J Rheumatol.* 1996; 23:1612–1616.
- [20] Eckert DJ, Saboisky JP, Jordan AS, Malhotra A. Upper airway myopathy is not important in the pathophysiology of obstructive sleep apnea. *J Clin Sleep Med.* 2007; 3: 570–573.
- [21] Petrof BJ, Hendricks JC, Pack AI. Does upper airway muscle injury trigger a vicious cycle in obstructive sleep apnea? A hypothesis. *Sleep.* 1996; 19:465–471.
- [22] Svanborg E. Upper airway nerve lesions in obstructive sleep apnea. *Am J Respir Crit Care Med.* 2001; 164: 187–189. DOI: 10.1164/ajrccm.164.2.2105010c.
- [23] Svanborg E. Impact of obstructive apnea syndrome on upper airway respiratory muscles. *Respir Physiol Neurobiol.* 2005; 147: 263–272. DOI:10.1016/j.resp.2005.06.012.
- [24] Mihalj M, Lušić L, Đogaš Z. Reduced evoked motor and sensory potential amplitudes in obstructive sleep apnoea patients. *J Sleep Res.* 2016; 25: 287–295. DOI: 10.1111/jsr.12368.
- [25] Dematteis M, Pepin JL, Jeanmart M, Deschaux C, Labarre-Vila A, Levy P. Charcot-Marie-Tooth disease and sleep apnoea syndrome: a family study. *Lancet* 2001; 357: 267–272. DOI:10.1016/S0140-6736(00)03614-X.
- [26] Lüdemann P, Dziewas R, Soros P, Happe S, Frese A. Axonal polyneuropathy in obstructive sleep apnoea. *J Neurol Neurosurg Psychiatr.* 2001; 70: 685–687. DOI:10.1136/jnnp.70.5.685.
- [27] Dziewas R, Schilling M, Engel P, Boentert M, Hor H, Okegwo A, Ludemann P, Ringelstein EB, Young P. Treatment for obstructive sleep apnoea: effect on peripheral nerve function. *J Neurol Neurosurg Psychiatr.* 2007; 78: 295–297. DOI: 10.1136/jnnp.2006.102806.
- [28] Tahrani AA, Ali A, Raymond NT, Begum S, Dubb K, Mughal S, Jose B, Piya MK, Barnett AH, Stevens MJ. Obstructive sleep apnea and diabetic neuropathy: a novel association in patients with type 2 diabetes. *Am J Respir Crit Care Med.* 2012; 186: 434–441. DOI: 10.1164/rccm.201112-2135OC.
- [29] Aurora RN, Punjabi NM. Obstructive sleep apnoea and type 2 diabetes mellitus: a bidirectional association. *Lancet Respir Med.* 2013; 1: 329–338. DOI: 10.1016/S2213-2600(13)70039-0.
- [30] Boentert M, Knop K, Schuhmacher C, Gess B, Okegwo A, Young P. Sleep disorders in Charcot-Marie-Tooth disease type 1. *J Neurol Neurosurg Psychiatry.* 2013; 85: 319–325. DOI: 10.1136/jnnp-2013-305296.
- [31] Fujihara K, Kodama S, Horikawa C, Yoshizawa S, Sugawara A, Hirasawa R, Shimano H, Yachi Y, Suzuki A, Hanyu O, Sone H. The relationship between diabetic neuropathy and sleep apnea syndrome: a meta-analysis. *Sleep Disord.* 2013: 150371. DOI: 10.1155/2013/150371.

- [32] Aptel F, Khayi H, Pépin JL, Tamisier R, Levy P, Romanet JP, Chiquet C. Association of nonarteritic ischemic optic neuropathy with obstructive sleep apnea syndrome: consequences for obstructive sleep apnea screening and treatment. *JAMA Ophthalmol.* 2015; 133: 797–804. DOI: 10.1001/jamaophthalmol.2015.0893.
- [33] Wu Y, Zhou LM, Lou H, Cheng JW, Wei RL. The association between obstructive sleep apnea and nonarteritic anterior ischemic optic neuropathy: a systematic review and meta-analysis. *Curr Eye Res.* 2015; 7: 1–6. DOI: 10.3109/02713683.2015.1075221.
- [34] Levý P, Pépin JL, Dematteis M. Pharyngeal neuropathy in obstructive sleep apnea: where are we going? *Am J Respir Crit Care Med.* 2012; 185: 241–243. DOI: 10.1164/rccm.201111-1992ED.
- [35] Guilleminault C, Huang YS, Kirisoglu C, Chan A. Is obstructive sleep apnea syndrome a neurological disorder? A continuous positive airway pressure follow-up study. *Ann Neurol.* 2005; 58: 880–887. DOI: 10.1002/ana.20654.
- [36] Guilleminault C, Ramar K. Neurologic aspects of sleep apnoea: is obstructive sleep apnoea a neurologic disorder? *Semin Neurol.* 2009; 29: 68–71. DOI: 10.1055/s-0029-1237122.
- [37] Saboisky JP, Stashuk DW, Hamilton-Wright A, Carusona AL, Campana LM, Trinder J, Eckert DJ, Jordan AS, McSharry DG, White DP, Nandedkar S, David WS, Malhotra A. Neurogenic changes in the upper airway of patients with obstructive sleep apnea. *Am J Respir Crit Care Med.* 2012; 185: 322–329. DOI: 10.1164/rccm.201106-1058OC.
- [38] Friberg D, Gazelius B, Hökfelt T, Nordlander B. Abnormal afferent nerve endings in the soft palatal mucosa of sleep apnoics and habitual snorers. *Regul Pept.* 1997; 71: 29–36. DOI:10.1016/S0167-0115(97)01016-1.
- [39] De Bellis M, Pagni F, Ronchi S, Limonta G, Gorla S, Nicoletti G, Cucci M, Di Bella C, Vicini C. Immunohistochemical and histomorphometric study of human uvula innervation: a comparative analysis of non-snorers versus apneic snorers. *Sleep Breath.* 2012; 16: 1033–1040. DOI: 10.1007/s11325-011-0597-7.
- [40] Bassiouny A, Nasr S, Mashaly M, Ayad E, Qotb M, Atef A. Electron microscopy study of peripheral nerves in the uvulae of snorers and obstructive sleep apnoea patients. *J Laryngol Otol.* 2009; 123: 203–207. DOI: 10.1017/S0022215108002971.
- [41] Sunnergren O, Broström A, Svanborg E. Soft palate sensory neuropathy in the pathogenesis of obstructive sleep apnea. *Laryngoscope* 2011; 121: 451–456. DOI: 10.1002/lary.21371.
- [42] De Carlos F, Cobo J, Macías E, Feito J, Cobo T, Calavia MG, García-Suárez O, Vega JA. The sensory innervation of the human pharynx: searching for mechanoreceptors. *Anat Rec (Hoboken).* 2013; 296: 1735–1746. DOI: 10.1002/ar.22792.
- [43] De Carlos F, Cobo J, Macías E, Feito J, González M, Cobo T, Fernández-Mondragón MP, García-Suárez O, Vega JA. Reduced innervation in the human pharynx in patients with obstructive sleep apnea. *Histol Histopathol.* 2015; 30: 865–874. DOI: 10.14670/HH-11-593.

- [44] Akay M, Leiter JC, Daubenspeck JA. Reduced respiratory-related evoked activity in subjects with obstructive sleep apnea syndrome. *J Appl Physiol*. 2003; 94: 429–438. DOI: 10.1152/jappphysiol.00018.2001.
- [45] Larsson H, Carlsson-Nordlander B, Lindblad LE, Norbeck O, Svanborg E. Temperature thresholds in the oropharynx of patients with obstructive sleep apnea syndrome. *Am Rev Respir Dis*. 1992; 146: 1246–1249. DOI: 10.1164/ajrccm/146.5_Pt_1.1246.
- [46] Hagander L, Harlid R, Svanborg E. Quantitative sensory testing in the oropharynx: a means of showing nervous lesions in patients with obstructive sleep apnea and snoring. *Chest*. 2009; 136: 481–489. DOI: 10.1378/chest.08-2747.
- [47] Grippo A, Carrai R, Romagnoli I, Pinto F, Fanfulla F, Sanna A. Blunted respiratory-related evoked potential in awake obstructive sleep apnoea subjects: a NEP technique study. *Clin Neurophysiol*. 2011; 122: 1562–1568. DOI: 10.1016/j.clinph.2011.01.005.
- [48] Afifi L, Guilleminault C, Colrain IM. Sleep and respiratory stimulus specific dampening of cortical responsiveness in OSAS. *Respir Physiol Neurobiol*. 2003; 136: 221–234. DOI: 10.1016/S1569-9048(03)00084-3.
- [49] Donzel-Raynaud C, Redolfi S, Arnulf I, Similowski T, Straus C. Abnormal respiratory-related evoked potentials in untreated awake patients with severe obstructive sleep apnoea syndrome. *Clin Physiol Funct Imaging*. 2009; 29: 10–17. DOI: 10.1111/j.1475-097X.2008.00830.x.
- [50] Eckert DJ, Lo YL, Saboisky JP, Jordan AS, White DP, Malhotra A. Sensori-motor function of the upper airway muscles and respiratory sensory processing in untreated obstructive sleep apnea. *J Appl Physiol*. 2011; 111: 1644–1653. DOI: 10.1152/jappphysiol.00653.2011.
- [51] Vakulin A, Catcheside PG, Baulk SD, Antic NA, van den Heuvel CJ, Banks S, McEvoy RD. Auditory evoked potentials remain abnormal after CPAP treatment in patients with severe obstructive sleep apnoea. *Clin Neurophysiol*. 2012; 123: 310–317. DOI: 10.1016/j.clinph.2011.07.004.
- [52] Edstrom L, Larsson H, Larsson L. Neurogenic effects on the palatopharyngeal muscle in patients with obstructive sleep apnoea: a muscle biopsy study. *J Neurol Neurosurg Psychiatr*. 1992; 55: 916–920.
- [53] Smirne S, Iannaccone S, Ferini-Strambi L, Comola M, Colombo E, Nemni R. Muscle fibre type and habitual snoring. *Lancet*. 1991; 337: 597–599.
- [54] Ferini-Strambi LJ, Smirne S, Moz U, Sferrazza B, Iannaccone S. Muscle fibre type and obstructive sleep apnea. *Sleep Res Online* 1998; 1: 24–27.
- [55] Series F, Simoneau JA, St Pierre S. Muscle fiber area distribution of musculus uvulae in obstructive sleep apnea and non-apneic snorers. *Int J Obes Relat Metab Disord*. 2000; 24: 410–415.
- [56] Sauleda J, Garcia-Palmer FJ, Tarraga S, Maimo A, Palou A, Agusti AG. Skeletal muscle changes in patients with obstructive sleep apnoea syndrome. *Respir Med*. 2003; 97: 804–810. DOI: 10.1016/S0954-6111(03)00034-9.

- [57] Molina FD, Santos FC, Falleiros LR Jr, Goloni-Bertollo EM, Felisbino SL, Justulin LA Jr, Maniglia JV, Taboga SR. Microscopical evaluation of extracellular matrix and its relation to the palatopharyngeal muscle in obstructive sleep apnea. *Microsc Res Tech*. 2011; 74: 430–439. DOI: 10.1002/jemt.20927
- [58] Stål PS, Johansson B. Abnormal mitochondria organisation and oxidative activity in palate muscles of long-term snorers with obstructive sleep apnea. *Respiration*. 2012; 83: 407–417. DOI: 10.1159/000336040.
- [59] Series F, Cote C, Simoneau JA, Gelinias Y, St Pierre S, Leclerc J, Ferland R, Marc I. Physiologic, metabolic, and muscle fiber type characteristics of musculus uvulae in sleep apnea hypopnea syndrome and in snorers. *J Clin Invest*. 1995;95: 20–25. DOI: 10.1172/JCI117640.
- [60] Series F, Wang W, Similowski T. Corticomotor control of the genioglossus in awake OSAS patients: a transcranial magnetic stimulation study. *Respir Res*. 2009; 10: 74. DOI: 10.1186/1465-9921-10-74.
- [61] Saboisky JP, Butler JE, McKenzie DK, Gorman RB, Trinder JA, White DP, Gandevia SC. Neural drive to human genioglossus in obstructive sleep apnoea. *J Physiol*. 2007; 585: 135–146. DOI: 10.1113/jphysiol.2007.139584.
- [62] Vuono IM, Zanoteli E, de Oliveira AS, Fujita RR, Pignatari SS, Pizarro GU, de Cássia Pradelle-Hallinan ML, Moreira GA. Histological analysis of palatopharyngeal muscle from children with snoring and obstructive sleep apnea syndrome. *Int J Pediatr Otorhinolaryngol*. 2007; 71: 283–290. DOI: 10.1016/j.ijporl.2006.10.019.
- [63] Berger G, Gilbey P, Hammel I, Ophir D. Histopathology of the uvula and the soft palate in patients with mild, moderate, and severe obstructive sleep apnea. *Laryngoscope*. 2002; 112: 357–363. DOI: 10.1097/00005537-200202000-00028.
- [64] Mezzanotte WS, Tangel DJ, White DP. Influence of sleep onset on upper-airway muscle activity in apnea patients versus normal controls. *Am J Respir Crit Care Med*. 1996; 153: 1880–1887. DOI: 10.1164/ajrccm.153.6.8665050.
- [65] Fogel RB, Malhotra A, Giora P, Edwards JK, Beauregard J, Shea SA, White DP. Genioglossal activation in patients with obstructive sleep apnea versus control subjects. *Am J Respir Crit Care Med*. 2001; 164: 2025–2030. DOI: 10.1164/ajrccm.164.11.2102048.
- [66] Gonzalez-Forero D, Portillo F, Sunico CR, Moreno-Lopez B. Nerve injury reduces responses of hypoglossal motoneurons to baseline and chemoreceptor-modulated inspiratory drive in the adult rat. *J Physiol*. 2004; 57: 991–1011. DOI: 10.1113/jphysiol.2003.059972.
- [67] Goldshtein E, Tarasiuk A, Zigel Y. Automatic detection of obstructive sleep apnea using speech signals. *IEEE Eng Med Biol Mag*. 2011; 58: 1373–1382. DOI: 10.1109/TBME.2010.2100096.
- [68] Massey BT. Physiology of oral cavity, pharynx, and upper esophageal sphincter. *GI Motility Online*. 2006; DOI: 10.1038/gimo2.

