Potential Therapies for Obstructive Sleep Apnea

Subjects: Otorhinolaryngology

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Obstructive sleep apnea syndrome (OSAS) is characterized by intermittent hypoxia (IH) during sleep due to recurrent upper airway obstruction. The derived oxidative stress (OS) leads to complications that do not only concern the sleep-wake rhythm but also systemic dysfunctions.

Keywords: obstructive sleep apnea syndrome ; OSAS ; OSA ; oxidative stress

1. Introduction

Obstructive sleep apnea syndrome (OSAS) affects from 9% to 39% of the adult population, with a higher incidence in males and the elderly, and is the most common form of respiratory sleep disorder [1][2][3][4]. It is characterized by recurrent, complete, or partial upper airway obstruction due to their collapse, with consequent hypopnea or apnea, leading to hypoventilation and chronic intermittent hypoxemia (IH) and increasing blood carbon dioxide partial pressure [5]. The OSAS consequences do not only concern excessive daytime sleepiness; they also independently favor the development of cardiovascular pathologies as an independent risk factor for hypercholesterolemia and hypertension, obesity, diabetes, and neuropsychological diseases such as depression [6][7][8][9][10][11][12]. Therefore, OSAS patients have higher cardiovascular-related morbidity compared with non-OSAS ones [13].

The diagnosis of OSAS follows the diagnostic criteria codified by the American Academy of Sleep Medicine (AASM) after the exclusion of other pathologies that may be the cause of the apnea/hypopnea events [14]. Furthermore, it is possible to make a diagnosis of OSAS when one is faced with anamnestic data, collected by interviewing the patient or those who sleep with him, with reported episodes of falling asleep when awake, excessive daytime sleepiness, non-refreshing sleep, tiredness, or insomnia, breathing, snoring, wheezing, choking, loud snoring, and at least 5 episodes of apnea, hypopnea, or breathing-related awakenings per hour in polysomnography. Alternatively, even in the absence of anamnestic data, it is possible to diagnose OSAS when polysomnography shows 15 or more apneas, hypopneas, or awakenings related to respiratory events per hour with evidence of respiratory effort in all or part of them in polysomnography [1]. To measure the degree of OSAS, the polysomnographic apnea-hypopnea index (AHI) is used [14][15]. Depending on the severity of the disease, treatment options include surgical interventions, lifestyle modifications, continuous positive airway pressure (CPAP), oral appliances such as mandibular advancement, and hypoglossal nerve stimulation [16][17][18]. However, the OSAS diagnosis and treatment currently do not take into consideration what happens at the molecular and cellular level, which instead causes systemic complications related to OSAS.

2. Potential Therapies

2.1. Antioxidants

There are many potentially beneficial molecules for patients with OSAS, but most of them have not been tested on humans. Manganese superoxide dismutase is protective against cortical neuron oxidative damage by IH in mouse models [19]. Adiponectin also proved to be useful in counteracting mitochondrial damage in the genioglossus muscle of OSAS mice [20].

In addition, ROS scavenger administration with Endavarone in mouse models of IH has been tested, showing a significant reduction in cognitive impairment associated with increased brain expression of phosphorylated-cAMP response element-binding (p-CREB) [21].

The molecules tested in humans have not been studied in courts large enough to give indications for their use. OS is an imbalance between reactive oxygen species (ROS) production and antioxidant capacity. Vitamin C and N-acetylcysteine (NAC) have shown interesting results in the reduction of OS in OSAS [7], and NAC reduces OS in OSAS through the

reduction of peroxidized lipids and the increase in glutathione. Surprisingly, patients who received it continuously also had improvements in sleep parameters [22]. Vitamin C, on the other hand, proved to be effective in improving the endothelial function of OSAS patients in a study that took as its reference the diameter of the brachial artery, an indirect indicator of endothelial function [23]. Lastly, Leptin is both a drug capable of reducing free radicals, OS, and atherosclerosis in patients with OSAS [24].

To date, the only confirmed antioxidant therapy is CPAP itself, which has shown to be able to reverse many of the molecular alterations observed in vivo, such as eNOS, nitro-tyrosine, and NF-kB in the endothelium and circulating TNF-α [25].

2.2. Non-Antioxidant-Based Therapy

Estrogen-related receptor-α (ERR-α) is downregulated in OSAS patients and its ligand-binding induces the expression of fast-type muscle fibers in palatopharyngeal muscles. The interaction between estrogens and ERR-α could be a therapeutic target to reverse the muscle remodeling typical of these patients [26]. They inhibit the overexpression of HIF-1α induced by chronic IH and improve the endurance and regeneration of the genioglossus muscle in OSAS animal models [27]. Estrogens, in particular 17β-estradiol (E2) and a resveratrol dimer (RD), have a protective action against OSAS by limitation of HIF-1α action.

A pilot study in OSAS patients evidenced that Desipramine reduced airway collapse. At the same time, its anti-inflammatory properties could be beneficial in counteracting the systemic effects of OSAS, but further clinical studies are needed on a larger scale to evaluate its application [28][29].

The use of sedatives in the treatment of OSAS appears to be counterintuitive. However, it has been hypothesized that trazodone may reduce the respiratory arousal threshold and upper airway obstruction. The first phenomenon occurred in an experimental group, while the second was not significant, and the magnitude of the threshold change was not sufficient to counteract the changes due to mechanical obstruction [30].

The Phase II Pharmacotherapy of Apnea by Cannabimimetic Enhancement (PACE) has shown encouraging preliminary results for Dronabinol. A reduction in the AHI, a reduction in the feeling of sleepiness, and good satisfaction in the treated patients have been observed [31].

Sildenafil involves the inhibition of cyclin guanosine monophosphate phosphodiesterase 5, resulting in an increase in cyclic guanosine monophosphate and NO. Its experimentation in a randomized controlled trial in which it was compared with a placebo, however, showed a worsening of the disease [32].

In a randomized trial, the combination of Atomoxetine, a norepinephrine reuptake inhibitor, and antimuscarinic Oxybutynin, taken before going to sleep, was shown to be able to reduce the severity of OSAS, and further studies on larger sample sizes are needed [33].

It is important to observe that many molecules have only been tested in mouse models, such as Astragaloside IV, which showed an improvement of hypoxia-induced endothelial function [34]; Tauroursodeoxycholic acid, against hepatic damage induced by HI [35]; Pitavastatin, showing a reversal of IH-induced myocardial hypertrophy, cardiac function, perivascular fibrosis and inflammatory indices [36]; Allopurinol also showed beneficial effects in mouse models of OSAS with a reduction of lipid peroxidation and an improvement in cardiac function [37]; and for all molecules, clinical trials are needed.

References

1. Epstein, L.J.; Kristo, D.; Strollo, P.J.J.r.; Friedman, N.; Malhotra, A.; Patil, S.P.; Ramar, K.; Rogers, R.; Schwab, R.J.; Weaver, E.M.; et al. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. J. Clin. Sleep Med. 2009, 5, 263–276.
2. Peppard, P.E.; Young, T.; Barnet, J.H.; Palta, M.; Hagen, E.W.; Hla, K.M. Increased prevalence of sleep-disordered breathing in adults. Am. J. Epidemiol. 2013, 177, 1006–1014.
3. Senaratna, C.V.; Perret, J.L.; Lodge, C.J.; Lowe, A.J.; Campbell, B.E.; Matheson, M.C.; Hamilton, G.S.; Dharmage, S.C. Prevalence of obstructive sleep apnea in the general population: A systematic review. Sleep Med. Rev. 2017, 34, 70–81.

4. Iannella, G.; Vicini, C.; Colizza, A.; Meccariello, G.; Polimeni, A.; Greco, A.; de Vincentiis, M.; de Vito, A.; Cammaroto, G.; Gobbi, R.; et al. Aging effect on sleepiness and apneas severity in patients with obstructive sleep apnea syndrome: A meta-analysis study. Eur. Arch. Oto-Rhino-Laryngol. 2019, 276, 3549–3556.
5. Flemons, W.W.; Buysse, D.; Redline, S. Sleep-related breathing disorders in adults: Recommendations for syndrome definition and measurement techniques in clinical research. Sleep 1999, 22, 667–689.
6. Lavie, L. Obstructive sleep apnoea syndrome—An oxidative stress disorder. Sleep Med. Rev. 2003, 7, 35–51.
7. Lira, A.B.; de Sousa Rodrigues, C.F. Evaluation of oxidative stress markers in obstructive sleep apnea syndrome and additional antioxidant therapy: A review article. Sleep Breath. 2016, 20, 1155–1160.
8. Mohit; Tomar, M.S.; Sharma, D.; Nandan, S.; Pateriya, A.; Shrivastava, A.; Chand, P. Emerging role of metabolomics for biomarker discovery in obstructive sleep apnea. Sleep Breath. 2022, 2, 1–8.
9. Young, T.; Palta, M.; Dempsey, J.; Skatrud, J.; Weber, S.; Badr, S. The Occurrence of Sleep-Disordered Breathing among Middle-Aged Adults. N. Engl. J. Med. 1993, 328, 1230–1235.
10. Nieto, F.J.; Young, T.B.; Lind, B.K.; Shahar, E.; Samet, J.M.; Redline, S.; D'Agostino, R.B.; Newman, A.B.; Lebowitz, M.D.; Pickering, T.G. Association of sleep-disordered breathing sleep apnea, and hypertension in a large community-based study. J. Am. Med. Assoc. 2000, 283, 1829–1836.
11. Li, J.; Thorne, L.N.; Punjabi, N.M.; Sun, C.K.; Schwartz, A.R.; Smith, P.L.; Marino, R.L.; Rodriguez, A.; Hubbard, W.C.; O'Donnell, C.P.; et al. Intermittent hypoxia induces hyperlipidemia in lean mice. Circ. Res. 2005, 97, 698–706.
12. Peppard, P.E.; Young, T.; Palta, M.; Skatrud, J. Prospective Study of the Association between Sleep-Disordered Breathing and Hypertension. N. Engl. J. Med. 2000, 342, 1378–1384.
13. Gozal, D.; Kheirandish-Gozal, L. Cardiovascular morbidity in obstructive sleep apnea: Oxidative stress, inflammation, and much more. Am. J. Respir. Crit. Care Med. 2008, 177, 369–375.
14. Kapur, V.K.; Auckley, D.H.; Chowdhuri, S.; Kuhlmann, D.C.; Mehra, R.; Ramar, K.; Harrod, C.G. Clinical practice guideline for diagnostic testing for adult obstructive sleep apnea: An American academy of sleep medicine clinical practice guideline. J. Clin. Sleep Med. 2017, 13, 479–504.
15. Punjabi, N.M.; Sorkin, J.D.; Katzel, L.I.; Goldberg, A.P.; Schwartz, A.R.; Smith, P.L. Sleep-disordered breathing and insulin resistance in middle-aged and overweight men. Am. J. Respir. Crit. Care Med. 2002, 165, 677–682.
16. Taheri, S.; Mignot, E. The genetics of sleep disorders. Lancet Neurol. 2002, 1, 242–250.
17. Hukins, C.A. Obstructive sleep apnea—Management update. Neuropsychiatr. Dis. Treat. 2006, 2, 309–326.
18. Lee, J.S.; Choi, H.; Lee, H.; Ahn, S.; Noh, G. Biomechanical effect of mandibular advancement device with different protrusion positions for treatment of obstructive sleep apnoea on tooth and facial bone: A finite element study. J. Oral Rehabil. 2018, 45, 948–958.
19. Shan, X.; Chi, L.; Ke, Y.; Luo, C.; Qian, S.; Gozal, D.; Liu, R. Manganese superoxide dismutase protects mouse cortical neurons from chronic intermittent hypoxia-mediated oxidative damage. Neurobiol. Dis. 2007, 28, 206–215.
20. Fiedorczuk, P.; Olszewska, E.; Rogalska, J.; Brzóska, M.M. Osteoprotegerin, Chitinase 3-like Protein 1, and Cardiotrophin-1 as Potential Biomarkers of Obstructive Sleep Apnea in Adults—A Case-Control Study. Int. J. Mol. Sci. 2023, 24, 2607.
21. Ling, J.; Yu, Q.; Li, Y.; Yuan, X.; Wang, X.; Liu, W.; Guo, T.; Duan, Y.; Li, L. Edaravone improves intermittent hypoxia-induced cognitive impairment and hippocampal damage in rats. Biol. Pharm. Bull. 2020, 43, 1196–1201.
22. Sadasivam, K.; Patial, K.; Vijayan, V.K.; Ravi, K. Antioxidant treatment in obstructive sleep apnoea syndrome. Indian, J. Chest Dis. Allied Sci. 2011, 53, 153–162.
23. Grebe, M.; Eisele, H.J.; Weissmann, N.; Schaefer, C.; Tillmanns, H.; Seeger, W.; Schulz, R. Antioxidant vitamin C improves endothelial function in obstructive sleep apnea. Am. J. Respir. Crit. Care Med. 2006, 173, 897–901.
24. MacRea, M.; Martin, T.; Zagrean, L.; Jia, Z.; Misra, H. Role of leptin as antioxidant in obstructive sleep apnea: An in vitro study using electron paramagnetic resonance method. Sleep Breath. 2013, 17, 105–110.
25. Peng, L.; Li, Y.; Li, X.; Du, Y.; Li, L.; Hu, C.; Zhang, J.; Qin, Y.; Wei, Y.; Zhang, H. Extracellular Vesicles Derived from Intermittent Hypoxia–Treated Red Blood Cells Impair Endothelial Function Through Regulating eNOS Phosphorylation and ET-1 Expression. Cardiovasc. Drugs Ther. 2020, 35, 901–913.
26. Chen, H.H.; Lu, J.; Guan, Y.F.; Li, S.J.; Hu, T.T.; Xie, Z.S.; Wang, F.; Peng, X.H.; Liu, X.; Xu, X.; et al. Estrogen/ERR-α signaling axis is associated with fiber-type conversion of upper airway muscles in patients with obstructive sleep apnea hypopnea syndrome. Sci. Rep. 2016, 6, 27088.

27. Zhou, J.; Liu, Y. Effects of genistein and estrogen on the genioglossus in rats exposed to chronic intermittent hypoxia may be HIF-1α dependent. Oral Dis. 2013, 19, 702–711.
28. Jaffuel, D.; Mallet, J.P.; Dauvilliers, Y.; Bourdin, A. Is the muscle the only potential target of desipramine in obstructive sleep apnea syndrome? Am. J. Respir. Crit. Care Med. 2017, 195, 1677–1678.
29. Taranto-Montemurro, L.; Sands, S.A.; Edwards, B.A.; Eckert, D.J.; White, D.P.; Wellman, A. Is the muscle the only potential target of desipramine in obstructive sleep apnea syndrome? Reply. Am. J. Respir. Crit. Care Med. 2017, 195, 1678–1679.
30. Eckert, D.J.; Malhotra, A.; Wellman, A.; White, D.P. Trazodone increases the respiratory arousal threshold in patients with obstructive sleep apnea and a low arousal threshold. Sleep 2014, 37, 811–819.
31. Carley, D.W.; Prasad, B.; Reid, K.J.; Malkani, R.; Attarian, H.; Abbott, S.M.; Vern, B.; Xie, H.; Yuan, C.; Zee, P.C. Pharmacotherapy of apnea by cannabimimetic enhancement, the PACE clinical trial: Effects of dronabinol in obstructive sleep apnea. Sleep 2018, 41, zsx184.
32. Roizenblatt, S.; Guilleminault, C.; Poyares, D.; Cintra, F.; Kauati, A.; Tufik, S. A double-blind, placebo-controlled, crossover study of sildenafil in obstructive sleep apnea. Arch. Intern. Med. 2006, 166, 1763–1767.
33. Taranto-Montemurro, L.; Messineo, L.; Sands, S.A.; Azarbarzin, A.; Marques, M.; Edwards, B.A.; Eckert, D.J.; White, D.P.; Wellman, A. The combination of atomoxetine and oxybutynin greatly reduces obstructive sleep apnea severity a randomized, placebo-controlled, double-blind crossover trial. Am. J. Respir. Crit. Care Med. 2019, 199, 1267–1276.
34. Zhao, F.; Meng, Y.; Wang, Y.; Fan, S.; Liu, Y.; Zhang, X.; Ran, C.; Wang, H.; Lu, M. Protective effect of Astragaloside IV on chronic intermittent hypoxia-induced vascular endothelial dysfunction through the calpain-1/SIRT1/AMPK signaling pathway. Front. Pharmacol. 2022, 13, 920977.
35. Hou, Y.; Yang, H.; Cui, Z.; Tai, X.; Chu, Y.; Guo, X. Tauroursodeoxycholic acid attenuates endoplasmic reticulum stress and protects the liver from chronic intermittent hypoxia induced injury. Exp. Ther. Med. 2017, 14, 2461–2468.
36. Inamoto, S.; Yoshioka, T.; Yamashita, C.; Miyamura, M.; Mori, T.; Ukimura, A.; Matsumoto, C.; Matsumura, Y.; Kitaura, Y.; Hayashi, T. Pitavastatin reduces oxidative stress and attenuates intermittent hypoxia-induced left ventricular remodeling in lean mice. Hypertens. Res. 2010, 33, 579–586.
37. Williams, A.L.; Chen, L.; Scharf, S.M. Effects of allopurinol on cardiac function and oxidant stress in chronic intermittent hypoxia. Sleep Breath. 2010, 14, 51–57.