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LETTERS TO THE EDITOR

The use of resveratrol in the treatment of obstructive sleep apnea and cancer: a commentary on common targets

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We are writing regarding the possible effects of resveratrol on both obstructive sleep apnea (OSA) and cancer biology by common inflammatory and hypoxia signaling pathways.

OSA is characterized by repeated events of total or partial obstruction of the upper airway that last 10 or more seconds during sleep[1] and is a prevalent sleep disorder.[2] These episodes result in intermittent hypoxia, elevation of oxidative stress, and higher levels of proinflammatory cytokines, especially interleukin 6 (IL-6), tumor necrosis factor α (TNF-α), and C-reactive protein. Cardiovascular diseases and obesity are associated with this sleep disorder.[3] Inflammation is not only important in OSA but is also a feature of cancer, and its chronicity tends to aggravate tumorigenesis and worsen tumor prognosis.[4]

Resveratrol is a nonsteroidal polyphenolic phytoalexin present in several plants, such as red grapes, blueberries, and peanuts, and in food/beverages derived from these natural resources.[5,6] The possible applications of resveratrol have been widely explored and include anti-inflammatory, antioxidant, antitumor, and estrogenic-modulator properties.[5,6]

Considering that inflammatory and hypoxia signaling pathways are essential characteristics of both OSA and cancer biology, treatment with resveratrol should be evaluated in individuals presenting both these conditions concurrently. To date, studies and clinical trials have largely been focused on the use of resveratrol as an alternative approach in cancer treatments.

One way in which resveratrol can regulate inflammatory cascades is through the estrogen pathway; it selectively binds to the estrogen receptor α, modulating the recruitment of coregulators that bind to the *IL6* gene locus, thereby inhibiting its expression.[7] A study by Lian et al with a rat model of chronic induced hypoxia (resembling OSA) showed positive effects of resveratrol via the nuclear factor erythroid 2-related factor 2 (NRF2) pathway by decreasing levels of IL-6 and TNF-α in serum and alveolar lavage and reducing apoptosis in lung cells.[8] The upregulation of antioxidant genes by NRF2 is already a well-known mechanism of this transcription factor.[9] Singh et al, using *in vitro* and *in vivo* models of breast cancer, reported that resveratrol acted against this type of tumor by enhancing *NRF2* expression. Even in combination with 17β-estradiol, resveratrol blocked estrogen-mediated proliferation and diminished the development of the breast tumor.[9]

In breast tumors, resveratrol has been shown to affect mitogen-activated protein kinase (MAPK)-3/MAPK1 (known as ERK1/2) signaling by inhibiting enhancer of zeste 2 polycomb repressive complex 2 subunit (EZH2) expression. Although this pathway is not fully understood, EZH2 is important for the proliferation of estrogen-dependent breast tumors and its expression is upregulated upon exposure to 17β-estradiol. The suppression of both EZH2 mRNA and protein levels suggests an antiproliferative role of resveratrol in this cancer.[10]

In addition to estrogen-dependent tumors, resveratrol exerts effects on androgen receptor (AR)-dependent cell tumors, which is an intrinsic characteristic of some prostate cancers. It can downregulate *AR* transcription by binding to a specific c-Jun region in DNA and decrease AR activity by blocking phosphoinositide 3-kinases.[11] In an animal model, resveratrol was able to contain prostate tumor development by downregulating insulin-like growth factor-1 and the MAPK signal pathway and up-regulating estrogen receptor beta.[12]

Individuals with long-term OSA present chronic intermittent hypoxia. Carreras et al showed that induced-intermittent hypoxia in mice contributes to alterations in metabolism and to a more intense inflammatory activity response via M1 macrophagess,[13] which produces proinflammatory cytokines, nitric oxide, and reactive oxygen intermediates.[14] At the same time, M2 macrophages were reduced in the animals.[13] This scenario may contribute to insulin resistance induced by intermittent hypoxia. Resveratrol successfully reversed the situation in the experimental condition, normalizing the levels of M1/M2 macrophages and reducing inflammation in adipose tissue.[13] It is worth noting that the proinflammatory cytokines TNF-α and IL-1β produced by macrophages can lead to estrogen receptor α phosphorylation in breast cancer cells.[15]

Two systematic reviews and a meta-analysis by Koushki et al analyzed separately the effects of resveratrol supplementation on inflammatory[16] and oxidative stress markers[17] in randomized clinical trials. The results showed that this substance reduced the levels of the proinflammatory cytokines TNF-α and high-sensitivity C-reactive protein, but not IL-6.[16] Regarding antioxidant properties, data only corroborated the effect of resveratrol on total antioxidant capacity but not on the oxidative indicators catalase, glutathione reductase, or superoxide dismutase.[17]

The authors pointed out that further studies are still necessary due to the heterogeneity of the identified studies.

Cross talk between the inflammatory and hypoxia signaling pathways can occur. We suggest that these pathways and the respective aforementioned factors—IL-6, IL-1β, TNF-α, C-reactive protein, macrophages, NRF2, 17β-estradiol, estrogen receptor α, nitric oxide, reactive oxygen intermediates, catalase, glutathione reductase, or superoxide dismutase—should be evaluated in clinical trials to investigate the effects of resveratrol on patients with OSA. Although resveratrol has been explored in intermittent hypoxia models, there are currently no active clinical trials aiming to examine the use of resveratrol in the treatment of OSA (according to a search of the ClinicalTrials.gov database; https://clinicaltrials.gov/).

It is important that future studies of the use of resveratrol in the treatment of OSA and different types of cancer (especially hormone-dependent types) consider obesity and cardiovascular diseases as cofactors, as they share some signaling pathways with OSA. We hypothesize that resveratrol may help to mitigate chronic inflammation and minimize the effects of intermittent hypoxia in patients with OSA. Resveratrol may prove to be a useful coadjutant intervention in OSA alongside current treatments, such as continuous positive airway pressure therapy, surgeries, oral appliances, and behavioral treatment to help improve the management of this sleep-related breathing disorder.[18]

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