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Review

Relationship Between Sleep Apnea and Cancer☆

Miguel Ángel Martínez-García,[a,d,*] Francisco Campos-Rodríguez,[b] Isaac Almendros,[c,d] Ramón Farré[c,d]

[a] Servicio de Neumología, Hospital Universitario y Politécnico La Fe, Valencia, Spain
[b] Servicio de Neumología, Hospital Valme, Sevilla, Spain
[c] Unidad de Biofísica y Bioingeniería, Facultad de Medicina, Universidad de Barcelona, Barcelona, Spain
[d] CIBER de Enfermedades Respiratorias (CIBERES), Madrid, Spain

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ABSTRACT

In the light of relationships reported between hypoxemia (tissue hypoxia) and cancer, Abrams et al. concluded in 2008 that sleep apnea-hypopnea syndrome (SAHS) and its main consequence, intermittent hypoxia, could be related with increased susceptibility to cancer or poorer prognosis of a pre-existing tumor. This pathophysiological association was confirmed in animal studies. Two large independent historical cohort studies subsequently found that the degree of nocturnal hypoxia in patients with SAHS was associated with higher cancer incidence and mortality. This finding has been confirmed in almost all subsequent studies, although the retrospective nature of some requires that they be considered as hypothesis-generating only. The relationship between sleep apnea and cancer, and the pathophysiological mechanisms governing it, could be clarified in the near future in a currently on-going study in a large group of melanoma patients.

Relación entre apnea del sueño y cáncer

Palabras clave:
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RESUMEN

En 2008, Abrams et al. publicaron que, habida cuenta de las anteriores relaciones encontradas entre la hipoxemia (hipoxia tisular) y el cáncer, el síndrome de apneas e hipopneas del sueño (SAHS) y su principal consecuencia, la hipoxia intermitente, podrían relacionarse con una mayor propensión a padecer cáncer o a un peor pronóstico de un tumor preexistente. Con esta base fisiopatológica y tras algunos estudios en animales que confirmaron esta asociación, 2 grupos independientes de investigación observaron en sendos estudios clínicos amplios de cohortes históricas que el grado de hipoxia nocturna aparecida en pacientes con SAHS se asociaba a una mayor incidencia y mortalidad por cáncer. Este dato ha sido confirmado por casi todos los estudios posteriores, si bien el carácter retrospectivo de todos ellos obliga a considerarlos tan solo como trabajos generadores de hipótesis. Un estudio puesto en marcha actualmente sobre un amplio grupo de pacientes con melanoma posiblemente arroje más luz en un futuro cercano sobre la existencia o no de esta relación y de los mecanismos fisiopatológicos que la gobiernan.

Introduction

The relationship between obstructive sleep apnea-hypopnea syndrome (SAHS) and cancer is set to become an exciting area of research in the near future, although at the moment the clinical basis is far from solid. Nevertheless, both physiopathological and animal studies conducted to date appear to bestow credibility on this relationship. From a clinical point of view, several studies have shown an association between SAHS (particularly when evaluated by hypoxemia) and cancer incidence and mortality, although their retrospective nature means that more in-depth studies will be required before a more definitive conclusion can be reached. Nevertheless, everything indicates that if this association is proven, it will be one of the most significant discoveries of the last 100 years, since both SAHS and cancer share common epidemiological

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* Corresponding author.
E-mail address: mianmartinezgarcia@gmail.com (M.Á. Martínez-García).

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characteristics: they are both highly prevalent, cause a significant social and healthcare burden, and are potentially treatable. The aim of this review is to present the findings reported to date on the relationship between SAHS and cancer, and the mechanisms supporting and clarifying the physiopathological hypothesis.

Physiopathological Aspects

Several physiopathological mechanisms have been uncovered suggesting that a relationship between SAHS and the transformation of healthy to malignant cells or the spread and growth of tumors may be biologically plausible. The 3 most significant mechanisms are oxidative stress,[1,2] a higher degree of systemic inflammation[3,4] (both usually compounded in these patients by concomitant obesity), and, possibly most importantly, the presence of intermittent hypoxemia (IH)[5] (and, in particular, the intermittent tissue hypoxia resulting from IH). The latter is probably the underlying cause of all these mechanisms (Fig. 1).

Oxidative Stress

The desaturation-reoxygenation pattern that defines IH is typical of SAHS. By increasing production of oxygen species (ROS), it constitutes an important stimulus in the activation of the oxidative stress system.[1,2] This leads to an imbalance between the production and degradation of certain oxidant/antioxidant products. This situation has been related with an increase in both acute and chronic mutagenesis, changes in cell function and structure, DNA damage, genome instability that may cause greater cell proliferation and neoplastic transformation. Oxidative stress has also been related with some transcription factors such as activator protein-1 (AP-1) and nuclear factor-kB (NF-kB) that have been associated with a greater propensity to develop cancer.[6]

Hypoxia-Induced Factor

All cells in the body have several mechanisms to compensate for situations of both continuous and intermittent hypoxia (such as seen in SAHS). One of the most powerful is the increased production of a key molecule, known as hypoxia-induced factor (HIF-1). HIF-1 orchestrates the regulation of genes that code for mediators that enable cells to adapt to situations of tissue hypoxia. It is composed of 2 subunits: HIF-1α and HIF-1ß. Of these, the α form plays a greater role in tissue hypoxia regulation.[7] It compensates hypoxia by triggering a series of mechanisms that activate the production of angiogenic molecules. The most important of these is vascular endothelial growth factor (VEGF), which regulates the formation of new collateral blood vessels for providing more oxygen to the hypoxic area or for avoiding areas of vascular obstruction.[8–14] While this is an important compensatory mechanism in cardiovascular diseases that involve hypoxic areas, it seems to have a deleterious effect in cancer patients. Tumors contain large hypoxic areas (with pO_2 <10 mmHg) that act as potent activators of HIF-1-mediated compensatory systems. These systems generate tumor neovascularization that provides cancer cells with an excellent mechanism for propagation and generation of distant metastases. Moreover, this neovascularization is produced in a scenario of abnormal, fragile vessels, so reoxygenation does not occur in the best of conditions.

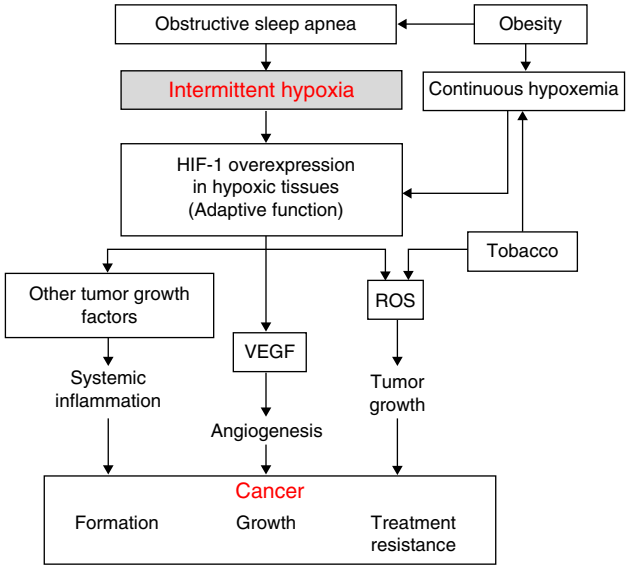

Fig. 1. Physiopathological hypothesis on the relationship between SAHS and cancer and the role of the most relevant confounding factors. HIF-1, hypoxia-induced factor; ROS, reactive oxygen species; VEFG, vascular endothelial growth factor.

Systemic Inflammation

In SAHS, inflammation is increased both locally and systemically.[15,16] The role of SAHS as a generator of systemic inflammation goes some way to explaining the possible association between SAHS and cancer. Oxidant/antioxidant imbalance and increased ROS have been related with a systemic increase in levels of proinflammatory substances such as tumor necrosis factor (TNF-α), interleukin (IL)-6, and IL-8, caused, as mentioned above, by the activation of transcription factors NF-kB and AP-1. The NF-kB factor is thought to be essential in the transcription of multiple genes associated with inflammation, arteriosclerosis, and cancer. IH appears to be the most important factor in the activation of this inflammatory element in SAHS patients.[15,16]

Obesity is very common among SAHS patients,[17] and has been related *per se* with several tumor types.[18–21] This means that obesity is a significant confounding factor in the analysis of the relationship between SAHS and cancer. Obesity-related inflammation, which may be described as chronic low grade inflammation generated by the fat cells themselves in response to excess calories and nutrients, appears to be the most important element in this relationship, and may be unrelated to the existence of SAHS.

Evidence From SAHS in Animal Models

Effects of Intermittent Hypoxia in Cancer

In an initial study,[22] IH mimicking the sequence occurring in SAHS was seen to double the rate of tumor growth in a melanoma model (Fig. 2). These results were confirmed in a second study,[23] which addressed the question of whether obesity in SAHS could mask to a certain extent the effects of IH in tumor outcome. In the absence of IH, the authors observed greater tumor growth in obese animals than in controls, as described previously.[18,24,25] However, exposure to IH in obese rats did not produce greater tumor growth than that already caused by the obesity itself. Plasma VEGF levels increased in all obese animals, whether exposed or not exposed to IH, and only in the slim animals exposed to IH. Moreover, circulating VEGF levels correlate closely with tumor size. This signaling protein, which has been proposed in various oncology studies as a possible marker for cancer prognosis,[26–28] may be of relevance in SAHS, since SAHS patients have higher circulating VEGF levels.[29–31]

A subsequent study was conducted to evaluate the metastatic capacity of melanoma in response to IH in two experimental metastasis models, one induced and one spontaneous.[32] In both models, IH was found to induce an increase in both number and size of