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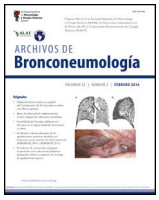

Editorial

Sleep and the Microbiome: A Two-Way Relationship☆

Sueño y microbioma: una relación bidireccional

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The gut microbiome is a polymicrobial ecosystem that coexists with the human body and acts symbiotically with it. This system can be modified in different situations associated with both everyday life and various pathological situations. In recent decades, it has become clear that many respiratory illnesses affect the quantity and quality of sleep among patients. In addition to the obvious case of respiratory diseases during sleep, sleep is also adversely affected in patients with lung cancer[1] and in those with chronic obstructive pulmonary disease[2] and obesity-hypoventilation syndrome.[3] The aim of this editorial is to analyze the existing evidence on the relationship between sleep disturbances (fragmentation and circadian rhythm) and the gut microbiome, and the consequences this can have in patients.

Restricted and Fragmented Sleep

Although revealing data are available, the relationship between sleep restriction and alteration of the gut microbiome is not entirely clear. While Benedict et al. showed that a short period (2 nights) of sleep restriction was associated with changes in the gut microbiome in 9 healthy adults,[4] a study carried out in 11 healthy adults showed that periods of 5 days of sleep restriction (4 h per night) followed by nights of recovery were not associated with changes in the richness, diversity or composition of the gut microbiome.[5] However, better quality sleep, as assessed by the Pittsburgh Sleep Quality Index questionnaire, was associated with higher proportions of the phyla *Verrucomicrobia* and *Lentisphaerae*[6] in healthy adults.

In contrast, sleep fragmentation (SF), a much more common situation in clinical settings, clearly contributes to the phenotypic consequences of obstructive sleep apnea syndrome plus inflammation and oxidative stress that lead to metabolic and vascular changes,[7] even in the absence of sleep restriction. In fact, studies in mouse models showed that SF is associated with both significant changes in the structure of the gut microbiome, and metabolite alterations in feces.[8] An increase in intestinal permeability was also observed when "fecal water" from animals submitted to SF, prepared from the soluble fraction of the gut microbiome, was applied to a monolayer of colonic cells. These same authors found that the administration of fecal pellets from mice subjected to SF to germ-free mice was associated with the development of the same systemic manifestations as SF animals, despite the fact that their sleep had not been disturbed.[8] These metabolic changes seem to be mediated by changes in the receptors of fatty acids in the intestine. For example, treatment with a selective free fatty acid receptor 4 agonist reverses the increase in food intake and weight gain and decreases the inflammation in visceral white adipose tissue and insulin resistance associated with SF.[9] Increased systemic levels of lipopolysaccharide-binding protein, a marker of low-grade endotoxemia, was also independently associated with body mass index, insulin resistance, and severity of obstructive sleep apnea syndrome in children.[10] These studies show that the metabolic alterations associated with SF can be the result of simultaneous changes in the gut microbiome. However, there is much less evidence on how changes in the gut microbiome affect sleep. A study in mice treated with inactivated *Lactobacillus brevis* SBC8803 for 4 weeks showed shorter periods of non-REM phase during sleep, as well as longer periods of wakefulness during the second half of the night, and a tendency to increase the total amount of time spent in non-REM sleep during the day.[11] In addition, a study by Thompson et al. showed that a diet rich in probiotics, lactoferrin, and milk fat globule membrane in a murine animal model increased the amount of *Lactobacillus rhamnosus* in feces and improved sleep quality, by facilitating non-REM sleep consolidation and enhancing REM sleep rebound, after stressor exposure.[12]

Alteration of the Circadian Rhythm

An altered circadian rhythm is associated with changes in the gut microbiome, particularly in the presence of another stressor. Both Voigt et al.[13] and Bishehsari et al.[14] showed in a murine model that combining a change in the light/dark cycle with a diet high in fat and sugar or alcohol was associated with alterations in the gut microbiome.

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Thaiss et al. evaluated the diurnal oscillation of the composition of the gut microbiome[15] by subjecting a group of mice to a light/dark cycle that shifted by 8 h over a 3-day period, after which the animals returned to the original light/dark cycle. This cycle was repeated every 3 days for 4 weeks. A taxonomic analysis of the composition of the microbiota every 6 h in the mice with jet lag showed that these animals had a reduced number of bacterial taxonomic units. Moreover, the dysbiosis worsened after 16 weeks of study. The same authors conducted a similar study in 2 healthy volunteers. A taxonomic stool analysis was made 1 day before the time change, during the jet lag (variation of 8–10 h) and after recovery (2 weeks after landing). Gut microbiome samples obtained during jet lag showed a higher relative representation of *Firmicutes*, that was reversed after jet lag resolved. These studies, then, suggest that the alteration of the circadian rhythm is associated with alterations in the gut microbiome. In a recent study, a simulation of night shift work in a murine model showed significant changes in the gut microbiome that induced metabolic alterations, such as insulin resistance.[16]

We should also mention, of course, that the gut microbiome exerts multidimensional influences on many, if not all, brain functions and, consequently, changes that occur in the microbiome are likely to affect the quality and quantity of sleep.[17,18]

In conclusion, there is evidence of a two-way relationship between sleep disorders and changes in the gut microbiome that induces potential metabolic, cardiovascular, and neurocognitive changes in the patient. Although these implications appear to be clearer in obstructive sleep apnea,[19] the possibility exists that sleep disturbances associated with other prevalent respiratory diseases can play a negative role in the evolution of patients, especially those with comorbidities, and this may be fruitful area for further investigation.

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