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Commentary

Cardiovascular sequelae of sleep apnea: In your brain and in your gut

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Epidemiological studies have clearly established a bidirectional link between sleep apnea and hypertension: sleep apnea patients are more likely to develop hypertension compared to control individuals, and among hypertensive subjects, the proportion of patients with sleep apnea is exaggerated compared to the normotensive population [1]. Animal research helped to understand this link and explored the underlying mechanisms. Exposures to intermittent hypoxia (IH) in a laboratory setting conveniently reproduce the cycles of arterial oxygen desaturation/re-oxygenation, and rapidly (within a few days of exposure) induces arterial hypertension in rodent models [2]. Furthermore, the development of arterial hypertension is critically dependent from activation of arterial chemoreceptors (that are localized in the carotid bodies - CB) as demonstrated following CB denervation. Later experiments went into deeper details, providing functional and molecular insights. IH enhances the tonic activity of CB, and increases the response evoked by abrupt hypoxic exposure [3]. This elevation of CB activity enhances the activity of the sympathetic nervous system, leading to altered vascular functions, a key element for the development of hypertension. In the animal models, the elevated CB activity also increases the hypoxic ventilatory response, and contributes to more instabilities of the respiratory control system, as shown by higher frequency of sigh and apneas during sleep [4]. This model is pretty smart, and data gathered by physiologists nicely fit with the clinical feature encountered in sleep apnea patients, providing the elements to explain the links between sleep apnea and arterial hypertension patients.

Then came the microbiota, and the gut is calling for a parallel story. Gut bacteria exchange nutrients and metabolites with their host and provide the enzymatic machinery to breakdown complex dietary fibers and carbohydrates in reactions that synthesize short chain fatty acids (such as butyrate, propionate and acetate) or lactate. These products have potent physiological influences on the host's physiology [5]. In spontaneous hypertensive rats, or in angiotensin II-induced hypertension, the populations of gut bacteria have a determinant role. In these models, the hypertensive animals demonstrate reduced microbial species richness, and increased ratio of *Firmicutes*/*Bacteroidetes* (F:B) - populations that account for the majority of gut bacteria [6]. Oxygen levels are important determinants of the gut microbiota composition, and cumulative evidences indicate that following exposure to intermittent hypoxia the gut microbiota is altered, also with an increased F:B ratio [7]. More impressively, transplantation of fecal content from hypertensive rats to naïve rats leads to the development of hypertension, this also occurs following fecal transplantation from hypertensive human donors to germ-free mice [8]. In Long-Evans rats, IH and high fat diet are necessary to induce hypertension, this also coincides with alterations of the F:B ratio, with a parallel decrease of bacteria producing short chain fatty acids and increased of bacteria producing lactate. In this model, the hypertensive phenotype can be replicated by fecal transplants of IH + fat-diet donors [9].

It is clear that these data have the potential to challenge the CB-centered view linking intermittent hypoxia and hypertension: we have some work to do to fit this new player in our old and comfortable storyline.

The study of Lucking et al. [10] addresses this issue with an original approach calling to the rescue the guinea pigs, whose CB are mostly insensitive to hypoxia. This can be viewed as "negative control experiment" that avoids the common pitfalls encountered in other models in which the carotid bodies are inactivated by surgical denervation, a delicate procedure that can induce plasticity in the central nervous system and compensatory responses from accessory chemoreceptors. After exposure to IH for a few days the guinea pigs do not develop hypertension, have no signs of elevated CB responses to hypoxia or sympathetic activation, and the stability of the breathing pattern actually increases. However, the authors also report a tachycardia and signs of depressed baroreflex control. These data strengthen the hypothesis that there is an obligatory role played by the CB for the establishment of hypertension during IH exposure. In the absence of the CB activity, the gut microbiota responded to the IH exposure with an overall reduced fauna richness, as observed in the other models of hypertension. However, and in striking contrast with these previous models, the relative abundance of *Firmicutes* decreases while *Bacteroidetes* increase after IH exposure. It is striking that the absence of hypertension in this animal model coincides with a small decrease of the F:B ratio, while this ratio clearly increases after exposure to IH in animals with normal CB functions [7], or in other models of hypertension [6,8]. The authors rightfully note that increased *Bacteroidetes* also accounts for decreased arterial blood pressure in hypertensive mice [11].

This study [10] strengthens the CB-centered view linking sleep apnea and hypertension, and in the same time suggests that gut microbiota is an essential element that respond to the CB/sympathetic system activation to induce hypertension. There is no doubt that this intriguing set of data establishes a new landmark in a rapidly evolving field, and if future studies confirm the CB > sympathetic system>microbiota>hypertension axis, new therapeutic avenues based on control of the microbiota

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populations could help reduce the burden of cardiovascular diseases in sleep apnea patients.

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