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EDITORIAL

(Mal)adaptative responses of arterial chemoreceptors: O_2-dependent and -independent mechanisms

Silvia V. Conde
iNOVA4Health, NOVA Medical School, Faculdade de Ciências Médicas, Universidade NOVA de Lisboa, Lisboa, Portugal

Email: silvia.conde@nms.unl.pt

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The discovery of the carotid bodies (CBs) by von Haller dates back to the 18th century (Gonzalez et al., 1994). This small organ was initially considered as an autonomic ganglion, a gland or a paraganglion until the seminal histological studies by De Castro in the 1920s, during which the idea emerged that CBs could be sensory organs capable of detecting chemical substances in the blood (Gonzalez et al., 1994; 2010). However, it was through the functional studies of Jean-François Heymans and his son, Corneille Heymans, Nobel Prize-winning scientist in 1938, that the role of the carotid body in cardiorespiratory homeostasis was demonstrated (De Castro, 2009; Kumar & Parbhakar, 2012).

Today, a century after the CB's sensory functions were postulated, it is widely accepted that the CB is a sensor of arterial gases such as O_2 and CO_2, also detecting pH and temperature (Gonzalez et al., 1994; Kumar & Parbhakar, 2012). But while many advances in the classical field of arterial O_2, CO_2 and pH sensing have been achieved, the most impressive ones are probably related to the non-canonical roles of the CB. In the last decades, the CB has been described as a polymodal organ capable of responding to numerous stimuli, such as hypoglycaemia or pro-inflammatory cytokines (Kumar & Parbhakar, 2012; Sacramento et al., 2020) and research within the CB field has gained attention with the finding that its dysfunction is involved in the development or maintenance of highly prevalent diseases, such as sleep apnoea, essential hypertension, hypertension associated with obstructive sleep apnoea, chronic heart failure and metabolic diseases.

This special issue of *The Journal of Physiology* contains papers based on presentations that explored the breadth and depth of the CB's role in the initiation and progression of respiratory and cardiometabolic diseases given at the XXI meeting of the International Society for Arterial Chemoreception (ISAC) in Lisbon, Portugal (27–30 June 2022). The papers focus on the adaptive and maladaptive responses of arterial chemoreceptors to O_2-dependent and O_2-independent mechanisms, namely their impact on respiratory, cardiovascular and metabolic homeostasis. Interestingly, some of the papers are a collaborative work between several researchers in the chemoreceptor field who provide different and integrative points of view, and they will certainly be a valuable reference source for years to come.

Obstructive sleep apnoea (OSA) is the most common sleep-related breathing disorder, being associated with increased cardiovascular risk and with several comorbidities. In this series of papers, Bonsignore et al. (2023) review in an elegant manner the results of clinical studies from the European Sleep Apnoea Database (ESADA) group that associate OSA with arterial blood pressure and hypertension, with cardioembolic risk in patients with OSA and atrial fibrillation, with glycaemic control deregulation, with dyslipidaemia, with chronic kidney disease, and with cancer. While they conclude that the effects of chronic intermittent hypoxia (CIH), one of the hallmarks of OSA, on OSA severity and comorbidities were confirmed by the ESADA studies, they highlight that the combined effects of CIH and sleep fragmentation should be studied further. Moreover, they state that intense research is ongoing and will provide new markers of OSA severity and high cardiovascular risk.

Going deep into the mechanisms by which OSA is associated with hypertension, Prabhakar et al. (2023) discuss the role of the CBs in heightened sympathetic tone and hypertension in rodent models treated with CIH, and the underlying cellular, molecular and epigenetic mechanisms. They suggest that in rodents, reactive oxygen species generation by non-transcriptional and transcriptional mechanisms involving dysregulated hypoxia-inducible factor (HIF)-1 and HIF-2 and epigenetic mechanisms are crucial for CB activation by CIH promoting sympathetic activation and hypertension. Moreover, they present evidence that a hyperactive CB chemoreflex causes irregular breathing, with apnoea and hypopnoea in mice with genetic deletion of haem oxygenase (HO)-2, suggesting that a hyperactive CB chemoreflex causes OSA. Nevertheless, it remains to be established to what extent the mechanisms described contribute to cardiovascular morbidities in OSA patients and if *HO-2 null* mice also exhibit sleep fragmentation and arousals, other hallmark characteristics of OSA.

Following the concept that oxidative stress is associated with OSA, and trying to find links between OSA and hypertension, Iturriaga (2023) has examined the contribution of nitro-oxidative stress and inflammatory mechanisms to the hyperactivation of the hypoxic chemoreflex, peripherally at the CB and centrally at the brainstem. Additionally, he provides evidence that persistence of autonomic and cardiorespiratory alterations is contingent upon glial-related neuroinflammation triggered by heightened CB chemosensory afferent input. Notably, although denervation of the carotid sinus nerve partly prevents central activation, the involvement of a second pathway and the potential role of astroglia in this process require further confirmation (Iturriaga, 2023), highlighting the need for more insights into these mechanisms and on the progression of cardiorespiratory OSA complications. The relevance and importance of this topic of research was clearly confirmed in the Perspectives article by Rocher and Aaronson (2023), discussing the paper by Iturriaga (2023), who highlight the enormous clinical interest in gaining a deeper understanding of the mechanisms sustaining the prolonged hyperactivation of the chemoreflex in OSA, its correlation with the severity of sympathetically mediated cardiovascular disease, and the impact of glial dysfunction on the entire process.

Another paper in this series relating OSA and cardiovascular outcomes, by Arnaud et al. (2023), focuses on CIH-induced cardiovascular and renal dysfunction. In this collaborative paper from laboratories in different countries, the authors explored several factors driving the transition from adaptation to maladaptation to CIH, such as sex, age,

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and the intensity and duration of CIH on cardio – hypertension, atrial fibrillation and heart failure – and renal dysfunction, and focused on the mechanisms such as sympathovagal imbalance, oxidative stress, inflammation, dysregulated HIF-1α transcriptional responses and resultant pro-apoptotic endoplasmic reticulum stress, calcium dysregulation and mitochondrial dysfunction driving myocardial injury and failure. Moreover, they provide several insights into the indirect and direct effects of CIH in the kidney that contribute to hypertension and later to chronic kidney disease. The authors postulate that the intermittent pattern of exposure to hypoxia (and reoxygenation) is the main driver of maladaptive signalling mechanisms and highlight the need for personalized approaches in the treatment of OSA patients due to heterogeneity in the exposure to CIH, relating to intensity and duration.

And last but not least, the paper by Conde et al. (2023) discusses the origins of sleep disordered breathing (SDB), and particularly OSA, the most recurrent form of SDB. Knowing that SDB increases the risk of obesity, diabetes, depression and anxiety disorders and that the same health issues are risk factors for SDB, they examine the cause or consequence of SDB and of SDB-related comorbidities. They discuss and emphasize how obesity, dysmetabolism and stress are key to the pathophysiology of SDB and how sex, behaviour and pre-existing conditions influence the manifestations of these problems. The authors highlight the growing body of evidence indicating that the arterial chemoreceptors are important sensors of key metabolic and endocrine signals associated with stress and dysmetabolism and propose that these organs play a key role in the process.

In addition to the CB being involved in OSA–CIH associated comorbidities, CB hypersensitivity and hypertonicity have been described, in the last decades, as being involved in other diseases that run with sympathetic overactivation, including hypertension and heart failure. The paper by Felippe et al. (2023) reviews in a concise manner the pathophysiological mechanisms behind CB hypersensitivity and hypertonicity in these diseases, referring also to the mechanisms in OSA. Interestingly, the authors point out some commonalities and potential differences in the mechanisms leading to CB abnormalities in these two cardiovascular diseases, exploring the impact of CB hypoperfusion, CB neurotransmitter and signalling pathways, CB sensing of circulating factors and other factors that modulate CB activity (Krüppel-like factor 2). The authors emphasize the need for a better understanding of CB pathophysiology for clinical interventions, and in a section dedicated to future perspectives, they discuss possible future clinical interventions and criteria for assessing and recruiting patients with CB hyperactivity.

In conclusion, this series of papers in *The Journal of Physiology* clearly highlight the contribution of CB dysfunction to cardiorespiratory and metabolic disturbances, highlighting the O_2-dependent and -independent mechanisms. Nevertheless, more investigations are certainly needed to untangle the complex associations between all these mechanisms and factors contributing, both peripherally and centrally, to maladaptive arterial chemoreceptor function and to establish new methodologies to correctly target these pathologies.

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Additional information

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