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PERSPECTIVE

'Inflammation, nitro-oxidative stress and altered autonomic outflow in obstructive sleep apnoea: an assault on homeostasis'

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The carotid body (CB) acts as a chemoreceptor which, when stimulated by arterial hypoxia, hypercapnia or acidosis, releases transmitters which stimulate sensory afferents that signal to the nucleus tractus solitarius (NTS). Acting through the rostral ventrolateral medulla (RVLM), this initiates a chemoreflex, stimulating autonomic efferents that orchestrate compensatory cardiorespiratory responses. Unfortunately, chronic intermittent hypoxia (CIH), which occurs in obstructive sleep apnoea (OSA), subverts the beneficial homeostatic function of this chemoreflex, causing increases in basal and hypoxia-induced transmitter release by the CB and sensitizing the cardiorespiratory centres it acts through. This causes a chronic sympathetic overdrive, contributing to the pathophysiological consequences of OSA such as heart failure, resistant hypertension and insulin resistance.

The CB expresses multiple cytokines (e.g. TNF-α, IL-1β, IL-6) and their receptors and can be activated by increases in these and other blood-borne inflammatory mediators, causing a compensatory anti-inflammatory response mediated through sympathetic efferents (Katayama et al., 2022). In the current issue of the *Journal of Physiology*, a review by Rodrigo Iturriaga, a pioneer in the chemoreception field, discusses the evidence that inflammatory mechanisms reinforce CIH-induced hypersensitivity of the chemoreflex. He proposes that CIH causes excessive activation of the CB chemoreflex and the resulting sympathetic overactivity by increasing nitro-oxidative stress and expression of inflammatory pathways in the CB and brainstem (Iturriaga, 2023). Much of the evidence supporting this proposal comes from animal studies that evaluated the effects on the CB and brainstem of recurrent intervals of intermittent hypoxia imposed for periods of days to weeks.

Notably, Iturriaga describes work by his laboratory showing that 21 days of CIH increased protein 3-nitrotyrosine (3-NT) levels in rat CB, indicative of nitro-oxidative stress. The development 3-NT labelling paralleled an increasing responsiveness of the CB to hypoxia, and both effects were prevented by administration of the antioxidant ascorbic acid. CIH also elevated the expression of TNF-α and IL-1β in the CB. This followed, and required, the occurrence of nitro-oxidative stress. Further work from this laboratory demonstrated that ibuprofen treatment prevented the CIH-induced rise in CB cytokine levels and the baseline overactivation of the chemosensory reflex, without diminishing oxidant stress or the exaggerated response to hypoxia. Thus, inflammatory stimuli can cause basal chemoreflex hypersensitivity.

The initial observation that CIH increased CB activity through a ROS-dependent mechanism was made by Prabhakar's group (Peng & Prabhakar, 2003). More recently, this laboratory demonstrated that 30 days of CIH increased oxidant stress in rat CB, brainstem and adrenal medulla by upregulating the expression of NOX2 and decreasing the expression of SOD2; these effects were due to increases and decreases, respectively, in the expression of HIF-1α and HIF-2β. They also demonstrated that the cardiorespiratory effects of the resulting hypersensitivity of the CB chemosensory reflex persisted for at least 30 days after CIH discontinuation, as did elevated oxidant stress in the CB and adrenal medulla, and that this was due to the persistent down-regulation of antioxidant gene expression associated with increased DNA methylation (Prabhakar et al., 2023). As Iturriaga notes, whether this mechanism causes permanent chemoreflex hypersensitivity remains an important unknown.

The observation that oxidant stress increases both basal and hypoxia-induced CB activity dovetails nicely with accumulating evidence that hypoxia stimulates the CB, at least in part, by causing a rise in reactive oxygen species (ROS). This acts by inhibiting one or more types of K^+ channels, causing membrane depolarization, a rise in intracellular [Ca^{2+}], and transmitter release. Interestingly, cytokines also depress K^+ currents in glomus cells (Shu et al., 2007) through a yet unknown mechanism.

The last point to highlight in Iturriaga's review is the hypothesis that neuroglia may influence chemoreflex hyperactivity, particularly in prolonged hypoxia, as occurs in OSA. CIH produces repetitive and enhanced chemosensory inputs from CBs to the NTS leading to plastic changes in cardiorespiratory neural circuits, which cause potentiated chemoreflex responses, long-term potentiation and arterial hypertension (Iturriaga, 2023). CIH also causes oxidative stress and neuroinflammation in the brainstem which could be due to enhanced chemosensory input to the NTS and RVLM and/or to the effect of recurrent hypoxia–reoxygenation on cardiorespiratory centres. While the first pathway seems to be involved in the process, as denervation of the carotid sinus nerve partially prevents central activation (Iturriaga, 2023), the activation of the second pathway and the possible role of astroglia remains to be confirmed. Astrocytes are the most abundant type of glial cells in the brain and, like CB glomus cells, express many neurotransmitters and K^+ channels, and are vulnerable to oxidative stress and pro-inflammatory cytokines. In addition to being involved in respiratory rhythm generation, astrocytes sense physiological decreases in PO_2 and participate in the control of ventilation, as shown in unanaesthetized animals with denervated

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peripheral oxygen chemoreceptors (Angelova et al., 2015). Pharmacological analysis of astroglial Ca^{2+} responses and ATP release suggests that, like CB glomus cells, inhibited mitochondrial respiration and increased ROS production underlie astroglial oxygen sensitivity (Angelova et al., 2015). Their potential contribution to the enhanced chemosensory reflex following sustained and intermittent hypoxia is unknown. However, brain PO_2 swings may develop because of CIH, and may activate production of ROS, release of ATP and cause increased activity of sympathoexcitatory neurons, sustained elevation of sympathetic drive, and cardiovascular disease.

The observations described in this review show that it is clearly of great clinical interest to better understand how the hyperactivated chemoreflex in OSA is sustained over the long term, how it correlates with the severity of sympathetically mediated cardiovascular disease, and how glial dysfunction affects the whole process.

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Additional information

Competing interests

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Author contributions

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Supporting information

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