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PERSPECTIVES

Should we be 'Doping' the peripheral chemoreceptors?

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The carotid body chemoreceptors are located bilaterally at the bifurcation of the common carotid artery and are primarily known for their ability to sense and respond to changes in the partial pressure of oxygen in arterial blood. As such, peripheral chemoreceptor hyperactivity has been widely studied in adults with sleep apnoea, who are exposed to multiple, acute hypoxic events during sleep. In response to intermittent falls in the arterial partial pressure of oxygen, patients with sleep apnoea present with increases in heart rate, blood pressure, sympathetic activity and ventilation (e.g. measures of *increased* carotid chemoreceptor sensitivity). This observed *upregulation* at the level of the carotid chemoreceptors in response to repeated activation is unlike the typical downregulation/desensitization responses seen in many other physiological systems.

In addition to hypoxia, a broad range of factors are now emerging as potent stimulators of carotid body afferent activity (e.g. hypercapnia, hypoglycaemia, hyperinsulinaemia, hypoperfusion). Thus it may not be surprising that carotid chemoreceptor hyperactivity was recently implicated in the pathophysiology of a variety of other cardiovascular and metabolic diseases, such as hypertension, heart failure, insulin resistance and diabetes. In this context, perhaps it is useful to think of these conditions as 'diseases of sympathoexcitation' or possibly carotid body-mediated sympathoexcitation.

Along these lines, therapies focused on desensitization of the carotid chemoreceptors have shown provocative and successful results in animal models. For example, carotid body denervation appears to prevent the development of hypertension and insulin resistance in a rodent model of overfeeding (Ribeiro *et al.* 2013) and can eventually improve cardiac function in models of heart failure (Del Rio *et al.* 2013). Yet, whether denervation is beneficial in long-term treatment of such disorders in humans is still an open question. This is especially true given not all (heart failure) patients respond to chemoreceptor-desensitizing therapies (van de Borne *et al.* 1996), nor do all patients respond positively to other types of invasive denervation procedures (Joyner, 2012). So how might we identify patients that are likely to respond to carotid body desensitization or even denervation?

In this edition of *The Journal of Physiology*, Niewinski and colleagues used systemic low-dose dopamine in young, healthy humans to lower afferent activity at the level of the peripheral chemoreceptors (Niewinski *et al.* 2014). Although such doses appear to have minimal impact on basal measures of heart rate, blood pressure, or minute ventilation in healthy adults, low-dose dopamine blunts peripheral chemoreceptor responsiveness to hypoxia as measured by changes in both ventilation and haemodynamic variables. Additionally, when the dopamine infusion was stopped, a transient rise in ventilation was observed – possibly due to release of an accumulating pool of neurotransmitters, given that the post-infusion increase in ventilation correlated with basal levels of carotid chemoreceptor sensitivity.

The practicality of low-dopamine as a long-term therapy for 'diseases of sympathoexcitation' is questionable. However, techniques used by Niewinski and colleagues in the present investigation could be important in identifying which patients respond to desensitization of the carotid chemoreceptors and are thus potential candidates for carotid body denervation (Niewinski *et al.* 2013). Since the present investigation is limited to young healthy adults, future studies will be necessary to examine the impact of low-dose dopamine on ventilatory and haemodynamic parameters in disease states known to exhibit increased chemoreceptor activation at baseline. Until then, it is unclear how much patient-to-patient variability exists, what benefit low-dose dopamine has over other clinical measures, and whether a clinical test could be developed using this approach. Furthermore, one must not forget that the carotid chemoreceptors are important in sensing and responding to a number of peripheral stimuli (e.g. hypoglycaemia, hyperinsulinaemia, hyperthermia, hypoperfusion). Thus, removal or desensitization may not only blunt sympathoexcitatory and ventilatory responses to hypoxia (thus impacting natural responses to this environmental stressor), but may impact human physiology in ways that are not fully realized (Johnson & Joyner, 2013). Finally, 'diseases of sympathoexcitation' are complex and have effects on multiple organ systems. Because of this, it is hard to imagine that modulation of carotid body afferent activity alone will be sufficient to treat and/or reverse most or all of them.

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Additional information

Competing interests

None declared.

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