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PERSPECTIVES

Hitting the wall: glycogen, glucose and the carotid bodies

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Do the carotid bodies sense blood glucose?

The classic view of the carotid bodies holds that they are the main peripheral sensory system that responds to hypoxia (Kumar & Prabhakar, 2012). When stimulated by low partial pressures of oxygen in the arterial blood, type 1 glomus cells release traditional neurotransmitters and gaseous signalling substances. These signals then stimulate afferent nerves which ultimately evoke reflex increases in minute ventilation driven by the brainstem respiratory centres. Conflicting evidence suggests this same sensory system might or might not be stimulated by low levels of blood glucose. In an effort to explore these discrepant findings, Holmes and colleagues from the Kumar laboratory (Holmes *et al.* 2014) performed a series of experiments where they carefully manipulated glucose and oxygen levels in isolated carotid bodies and recorded afferent nerve discharge. They found little evidence that low glucose *per se* acutely affects carotid nerve firing. However, in a novel series of observations, they demonstrated that glycogen depletion in type 1 glomus cells could lead to a pattern of transient increases in afferent discharge followed by what might be described as carotid body failure. This means that some combination of both low glucose and glycogen depletion in the carotid bodies is required to alter chemoreceptor function and depending on the timing, afferent responses might be either amplified or suppressed.

Experimental *vs.* real life hypoglycaemia?

Collectively, these findings might explain some of the discrepant results on the effects of glucose on the carotid body obtained in isolated and cellular preparations. However, do they explain observations in dogs and humans consistent with the idea that the carotid bodies participate in counter-regulatory responses to hypoglycaemia (Koyama *et al.* 2000; Wehrwein *et al.* 2010)? In these studies either carotid body resection (in dogs) or inhibition of the carotid bodies with hyperoxia (in humans) blunted a broad range of hormonal responses to hypoglycaemia generated using hyperinsulinaemic clamps. However, the extent to which hyperinsulinaemia mimics 'real life' conditions is subject to discussion, considering that under many circumstances like starvation, or 'hitting the wall' during prolonged exercise, hypoglycaemia occurs in a background of very low insulin levels. This topic is further complicated by emerging evidence in both humans and animals that insulin *per se* might stimulate the carotid bodies (Ribeiro *et al.* 2013; Limberg *et al.* 2014). Hypoglycaemia and insulin are also difficult to study in integrative models because of their profound effects in key regulatory areas of the hypothalamus and brainstem.

However, there are a number of provocative observations in humans that are of particular interest given the findings reported by Holmes and colleagues (Holmes *et al.* 2014). For example, prolonged severe caloric restriction in humans blunts the hypoxic ventilatory response (HVR) without attenuating the ventilatory response to carbon dioxide (Doekel *et al.* 1976). This suggests the carotid bodies are selectively influenced by severe caloric restriction. Under these circumstances does glycogen depletion within the carotid bodies contribute to the blunted HVR? Is there some minimal level of insulin required for normal carotid body function? Could ketone bodies or other circulating metabolites or hormones that rise during starvation inhibit carotid body function? Might the effects of caloric restriction be bimodal and would there be a period of increased chemoreceptor sensitivity in the first day or two of starvation followed by the observed blunting of the response as starvation continues?

While interesting, this final possibility is clearly worth further study based on observations from more acute manipulations of diet and exercise. There can be increased ventilation during exercise after acute glycogen depletion (Heigenhauser *et al.* 1983). This observation is at least superficially consistent with the observations of Holmes and colleagues that showed a period of neural hyper-responsiveness as carotid body glycogen is depleted prior to carotid body failure (Holmes *et al.* 2014). By contrast, breath holds following prolonged exercise suggest the opposite might be true and are more consistent, perhaps, with a reduction or inhibition of the HVR (Lindholm & Gennser, 2005).

The challenge of translation

All of the information and ideas mentioned thus far also highlight the challenge of integrating ideas about the carotid bodies as multimodal sensors of things other than oxygen from various experimental models to the human condition. Starvation and prolonged exercise can lead to blood glucose values in the ~3 mM range (Coyle *et al.* 1983), which is much higher than the concentrations used by Holmes *et al.* 2014. Additionally, little is known about what starvation or prolonged exercise might do to glycogen stores in the carotid body and how other metabolites or hormones associated with 'natural' forms of hypoglycaemia might influence the behaviour of the carotid bodies. Finally, how the carotid bodies respond to hypoxia is subject to both short and long term adaptive responses and patients with intermittent hypoxia from obstructive sleep apnoea frequently exhibit hyperglycaemia and hyperinsulinaemia (Limberg *et al.* 2014). How might these factors acting together over time influence carotid body responses to both hypoxia and glucose or other metabolic signals?

In summary, the provocative data from Holmes and colleagues show that creative studies on the integrated actions of the carotid bodies have a long way to go until they hit either a metabolic or – more importantly – intellectual wall.

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Additional information

Competing interests

None declared.