Fat feeding facilitates hot bodies, but is resistance futile?

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A high-fat diet (HFD) results in metabolic dysregulation and cardiometabolic abnormalities which contribute to the development of obesity and cardiovascular disease. The aetiology of this relationship is complex and multi-factorial, but a growing body of evidence suggests that the adipose-derived hormone leptin plays an important role in this process (Sáinz et al. 2015). Leptin levels are positively correlated with body weight as plasma leptin increases with weight gain, is elevated in obese individuals, and decreases with weight loss. Leptin has several important actions in the central nervous system (CNS), particularly in the hypothalamus where it acts on nuclei involved in regulating appetite/energy balance. Acutely, HFD promotes increased leptin release, reductions in appetite, and increases in energy expenditure via activation of the sympathetic nervous system. With prolonged exposure to a HFD and development of obesity, leptin levels rise (hyperleptinaemia) while the sensitivity of select tissues to leptin is diminished (Sáinz et al. 2015). Interestingly, the selectivity of this ‘leptin resistance’ is such that mechanisms which curb appetite and increase energy metabolism are down-regulated. Conversely, the sensitivity of neurons that modulate sympathetic outflow to the heart and kidneys remains normal. Thus, HFD, hyperleptinaemia and selective leptin resistance perpetuate obesity via dysregulation of appetite and energy metabolism and facilitate cardiometabolic disease in part via sustained activation of the sympathetic nervous system.

It is well established that leptin modulates hypothalamic neural circuits related to appetite regulation and autonomic outflow. However, it is currently unknown if leptin signalling plays any role in modulating the function of sensory cells/tissues outside the CNS, and if so, if this signalling is altered in response to hyperleptinaemia. The carotid body chemoreceptors (CBCs) represent an intriguing organ in which to explore the effects of hyperleptinaemia outside the CNS because of their well-known role in regulating autonomic and ventilatory function and their emerging role in the regulation of blood glucose. Previous studies have shown that functional leptin receptors are expressed in the CBCs, that administration of exogenous leptin increases ERK1/2 and Fra-1/2 immunoreactivity within glomus cells (Messinger et al., 2012), and that leptin facilitates the hypoxic ventilatory response (Polotsky et al. 2016). These studies offer a valuable perspective on the potential modulatory role of leptin in areas other than the CNS and suggest that hyperleptinaemia could potentially affect ventilation, autonomic outflow and metabolic regulation in part via actions on the CBCs.

Recent studies indicate that hyperinsulinaemia in lean and obese animals causes an enhanced CB chemoreflex and attendant autonomic dysregulation (Ribeiro et al. 2013). An important aspect of these findings is that chemoreflex activity was higher in obese animals fed a HFD compared to lean animals despite comparable degrees of hyperinsulinaemia. These findings suggest that hyperinsulinaemia alone does not explain CBC hyperactivity with a HFD and that another unknown factor must be involved. Given the known effects of acute leptin administration on CB function and the elevated leptin levels observed in animals on a HFD, it is reasonable to hypothesize that chronic hyperleptinaemia may play an important role in CBC hyperactivity associated with HFD. With that said, if leptin resistance develops in CBCs as it does in the CNS then a role for hyperleptinaemia in the maintenance of CBC hyperactivity observed in HFD animals could be ruled out. Until recently, no studies have addressed how HFD affects carotid body sensitivity to leptin or more ‘traditional’ stimuli such as hypoxia.

In this issue of The Journal of Physiology, Ribeiro et al. (2018) explore the effects of a HFD on leptin sensitivity in the CBCs and address signalling pathways which may be altered by HFD. Using a combination of sophisticated in vivo and ex vivo techniques, Ribeiro et al. measured ventilation and CBC activity in HFD animals and assessed the response to exogenous leptin alone and in combination with hypoxaemia. The authors make the novel observations that tonic baseline ventilation and CBC activity are increased in animals fed a HFD, but that the normal increase in ventilation and CBC activity that occurs in response to exogenous leptin is abolished. These observations were complemented by additional experiments demonstrating that release of adenosine from the CBs in response to exogenous leptin is blunted in HFD animals.

The findings of Ribeiro et al. (2018) affirm previous findings of CBC hyperactivity in animals fed HFD and suggest that leptin resistance associated with HFD develops in sensory tissues outside of the CNS. The implications of these findings are that hyperleptinaemia does not directly contribute to the maintenance of CBC hyperactivity and related autonomic dysfunction associated with HFD. Previous studies indicate that leptin infusion is sufficient to augment the hypoxic ventilatory response and cause hypertension in lean mice, an effect that is abolished by resection of the carotid sinus nerve (Polotsky et al. 2016). Thus, there is certainly support for the idea that leptin mediates CBC plasticity. The findings of Ribeiro et al. (2018) do not preclude the possibility that hyperleptinaemia contributes to enhanced CBC activity/sensitivity during the initial stages of HFD which persists after the development of leptin resistance; however, further studies using leptin receptor antagonists during HFD are needed to support this supposition. Thus, while selective leptin resistance in the CNS plays a key role in the development of metabolic dysregulation and obesity associated with HFD, the significance of chronic hyperleptinaemia and leptin resistance in the CBCs remains to be determined.

References


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**Competing interests**

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