Hypertension in obesity: the role of hypothalamic inflammation

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In an article published in the June 2014 issue of *Nature Reviews Endocrinology* (*The pathophysiology of hypertension in patients with obesity*, *Nat. Rev. Endocrinol.* **10**, 364–376; 2014),¹ Vincent G. DeMarco and colleagues reviewed the potential mechanisms that can link obesity to hypertension, including dietary factors, metabolic, endothelial and vascular dysfunction, neuroendocrine imbalances, sodium retention, glomerular hyperfiltration, proteinuria, maladaptive immune and inflammatory responses, uric acid and altered incretin or dipeptidyl peptidase 4 activity, as well as the role of the gut microbiota in modulating these mechanisms.¹

However, we would like to add another potentially important mechanism that could contribute to hypertension in patients with obesity—hypothalamic inflammation. The hypothalamus is a key region of the brain that regulates the activity of the sympathetic nervous system (SNS). Studies published in the past 6 years suggest that obesity-associated hypertension depends on the activation of proinflammatory pathways such as those involving I κ B kinase (IKK)- β and nuclear factor κ B (NF- κ B) in pro-opiomelanocortin (POMC) neurons of the arcuate nucleus in the hypothalamus.^{2,3}

Purkayastha *et al.*² showed that virus-mediated gene delivery of constitutively active IKK- β to the mediobasal hypothalamus in mice caused hypertension even when the mice were fed normal chow. Mice with obesity induced by ingesting a high-fat diet were hypertensive, but inactivation of NF- κ B through mediobasal hypothalamic injection of a dominant negative form of

I κ B α in these mice led to a notable drop in blood pressure.² Humphreys *et al.*^{4,5} speculated that both α -melanocyte stimulating hormones (MSHs) and γ -MSHs, which are derived from POMC, regulate SNS outflow. They further suggested that if IKK- β and NF- κ B activation leads to increased processing of POMC into these peptides, it could cause hypertension via an increase in sympathetic activity, as obese mice deficient in melanocortin 4 receptor, in which MSH peptides cannot bind to the receptor, have normal blood pressure. These results suggest that the cause of the hypertension in animals with diet-induced obesity can be separated from the pathways mediating the obesity. Mechanistically, these studies indicate that hypothalamic inflammation is implicated in the pathogenesis of hypertension.

Also interestingly, Zhang *et al.*³ reported that overnutrition atypically activated hypothalamic IKK- β and NF- κ B, which might be partly attributable to increased endoplasmic reticulum stress in the hypothalamus. Although the mechanisms leading to hypothalamic IKK- β and NF- κ B activation are yet to be elucidated, Purkayastha *et al.*² showed that TNF stimulated the IKK- β and NF- κ B pathways in POMC neurons and elevated blood pressure via a central mechanism involving SNS activation. Similarly, Jang *et al.*⁶ demonstrated that leptin could also stimulate IKK- β and NF- κ B signalling in POMC neurons, which suggests that these molecules are the factors that could explain obesity-associated hypertension.

Therefore, hypertension in patients with obesity could be related to hypothalamic

inflammation via IKK- β and NF- κ B activation that can be induced by excess levels of TNF and leptin in patients with obesity. Further studies are necessary to evaluate the effect of the various cytokines that are increased in patients with obesity when IKK- β and NF- κ B are activated in the hypothalamus and to elucidate if targeting the IKK- β and NF- κ B pathways in the hypothalamus (including POMC neurons) is beneficial in the treatment of obesity-associated hypertension.

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Competing interests

The authors declare no competing interests.

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