Mastering the metabolic mind

Research on the control of appetite and metabolism in the brain has uncovered a potential new target for combating type 2 diabetes. Xiaoqing Zhang *et al.*[1] report that, in mice, excess intake of nutrients activates hypothalamic expression of IκB kinase-β–nuclear factor-κB (IKK-β–NF-κB), a complex known for its role in immune regulation. This activation interferes with the correct signaling of the hormones insulin and leptin in a process involving stress on the endoplasmic reticulum (ER), which accumulates aberrantly folded proteins. Experimentally suppressing IKK-β or ER stress in the hypothalamus protected mice against obesity and glucose intolerance.

> "The work is compelling, but it's unclear whether this is a real physiological system —DJW

Gökhan S. Hotamisligil:

This work builds on the emerging therapeutic concept that agents that can alleviate chronic inflammation or ER stress carry the potential to manage leptin and insulin resistance in obesity or other metabolic conditions. Such agents are being pursued widely in the hope that they will be effective in treating type 2 diabetes. If these agents also reach the central nervous system, they could improve both insulin and leptin sensitivity. It is also possible that IKK-β inhibitors, other anti-inflammatory drugs, or chemical chaperones—such as 4-phenyl butyric acid (PBA) and taurine-conjugated ursodeoxycholic acid (TUDCA)—may facilitate the utility of leptin therapy against obesity, which, so far, has been disappointing.

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COMPETING INTERESTS STATEMENT

The author declares competing financial interests: details accompany the full-text HTML version of the paper at http://www.nature.com/naturemedicine/.

Get that hypothalamus working!

Dominic J. Withers:

This work dovetails with previous studies implicating the IKK-β–NF-κB system in insulin resistance in peripheral tissues in the face of obesity and overnutrition. The work is compelling, but it's unclear whether this is a real physiological system, as nutrient excess is not a facet of our evolutionary past.

In addition, although this system may operate through alterations in central nervous system insulin signaling, greater complexity is probably at work: previous work has shown that disruption of the insulin receptor in the relevant hypothalamic neurons barely affects body weight and that central insulin action may even boost fat mass.

Administration of high-dose salicylate into the third ventricle of the brain could provide a way to target IKK-β–NF-κB in the hypothalamus; such an experiment in mice would test the reasonable notion that this complex is a relevant therapeutic target.

Professor, Department of Medicine, University College, London, UK.

Jeremy Turner & Steve Bloom:

NF-κB is recognized as the master regulator of inflammatory responses, but that designation may not hold here, given that no cytokines were induced in these experiments. Infection and other states involving NF-κB activation are usually associated with loss of appetite and loss of weight—opposite to the effects observed here.

Will this work open a new therapeutic area for obesity? It could, but the practicalities of selectively targeting hypothalamic NF-κB signaling without causing major systemic, and potentially extremely deleterious, immunosuppression look very daunting.

Jeremy Turner, Senior Lecturer and Steve Bloom, Professor, Kennedy Institute of Rheumatology and Department of Investigative Medicine, Imperial College London, UK.

1. Zhang, X., Zhang, G., Zhang, H., Karin, M., Bai, H. & Cai, D. Hypothalamic IKK-β/NF-κB and ER stress link overnutrition to energy imbalance and obesity. *Cell* **135**, 61–73 (2008).