NEUROENDOCRINOLOGY

Stress fuels obesity

In the hypothalamus, neuropeptide Y (NPY) neuron circuits control feeding and energy homeostasis. Non-hypothalamic neurons can also produce NPY, but the role of these neurons in feeding is unclear. Research in *Cell Metabolism* now uncovers a previously unknown NPY neuron system that is activated by the combination of stress and calorie-dense food.

"Although it is known that stress and consumption of high-calorie food can cause obesity, the actual mechanism on how central pathways mediate this effect was unclear," explains corresponding author Herbert Herzog. "Using a NPY–GFP reporter mouse line, we noticed that while under stress conditions the expression of GFP is mainly found upregulated in the arcuate nucleus of the hypothalamus; the expression of NPY was also strongly enhanced in the central amygdala (CeA) when stress was combined with a high-fat diet (HFD)."

As previously shown, mice that were fed a HFD and subjected to stress conditions (HFDS) showed a significant obese phenotype compared with control mice. Notably, mice deficient in *Npy* in the CeA showed attenuated obesity in response to HFDS. Moreover, overexpression of NPY in the CeA increased the obese phenotype associated with HFDS. In addition, DREADD (designer receptors exclusively activated by designer drugs) technology was used to show that activation of NPY neurons in the CeA caused mice to consume more food.

Interestingly, HFDS-induced obesity was associated with impaired insulin inhibitory effects on NPY neurons located in the CeA. Mice with CeA NPY neurons that were engineered to be deficient in *Insr* showed increased HFDS-induced obesity, suggesting that insulin has an important role in regulating stress-induced food intake.

"We have now uncovered a previously unknown feeding stimulatory pathway that is specifically activated under conditions of chronic stress combined with high-caloric food," concludes Herzog. "One of the main aims of future research is to determine the downstream neuronal network (or networks) and the involved control mechanisms that might be potential targets for intervention to prevent accelerated obesity development."

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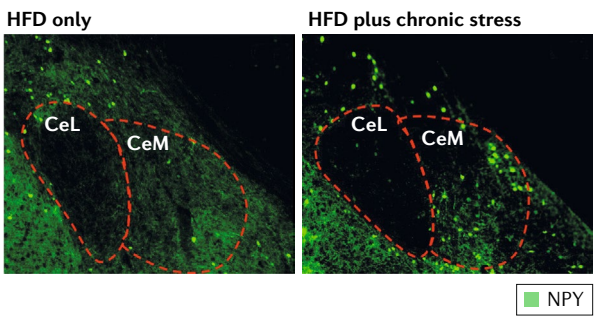

Neuropeptide Y (NPY) expression (green) in the central amygdala (CeA) under high-fat diet (HFD) and HFD and stress conditions. CeL, lateral CeA; CeM, medial CeA. Image courtesy of Herbet Herzog, Garven Institute of Medical Research.

AGEING

Regulating metabolism and ageing — the role of PI3K

The insulin–insulin-like growth factor 1 (IGF1) signalling pathway is a key regulator of metabolism. However, in a phenomenon known as the insulin paradox, loss-of-function mutations in the genes that encode the proteins involved in this pathway have beneficial effects on the metabolic profile of aged animals and can extend lifespan. The mechanisms underlying this effect are unclear. Now, a new study suggests that enhanced β-adrenergic signalling (a result of the inactivation of the p110α isoform of PI3K, which is activated downstream of the insulin and IGF1 receptors), explains the insulin paradox.

Previous work had suggested that deletion of p110α had beneficial effects in aged mice, and adipose tissue is known to be a key organ in metabolism and ageing. "We therefore inactivated p110α specifically in the adipose tissue by conditional gene targeting using adiponectin–Cre mice," explains author Lazaros Foukas.

The researchers were able to demonstrate that the deletion of p110α resulted in enhanced β-adrenergic signalling, which had a beneficial metabolic effect in aged mice despite also resulting in insulin resistance. "Enhanced adrenergic signalling resulted in elevated glucose uptake by brown adipose tissue as well as in increased thermogenic energy expenditure, thus maintaining normal glucose homeostasis and reducing age-related fat accumulation," explains Foukas.

β3-adrenergic receptor agonists have been tested as potential treatments for obesity, but have generally shown a lack of efficacy. "The potentiating effect of p110α inhibition on adrenergic signalling, demonstrated in the present study, suggests that p110α

OBESITY

Mapping leptin-responsive neurons in the hypothalamus

Leptin, which binds to the leptin receptor in the arcuate nucleus of the hypothalamus, is a satiety signal that controls food intake and energy expenditure. The genes and regulatory elements involved in the leptin response in arcuate neurons need to be characterized to develop effective therapeutics for obesity. However, owing to the gene regulatory elements being cell type-specific, identifying leptin receptor-specific neurons is technically challenging.

Now, Nadav Ahituv and colleagues have established a comprehensive map of genes and regulatory elements in leptin-responsive neurons. "We found that this map was consistent with the transcriptional activity of these neurons and leads to the identification of leptin-responsive genes and enhancers," explains Ahituv. The authors also show that this map can provide a blueprint for identifying and testing the relevance of variants that have been associated with human obesity through genome-wide association studies (GWAS).

In their study, which was the product of a long-time collaboration between Ahituv's group and Christian Vaisse's group, the authors set out to determine whether genetic variants predisposing to human obesity affect gene regulatory regions that are active in specialized neuronal populations that are essential for the regulation of body weight. "The hypothalamus is a complex brain structure composed of numerous different cell types," adds Fumitaka Inoue, the lead author of this study. "This complexity makes separating hypothalamic cells from one another for subsequent genomic analyses extremely complex."