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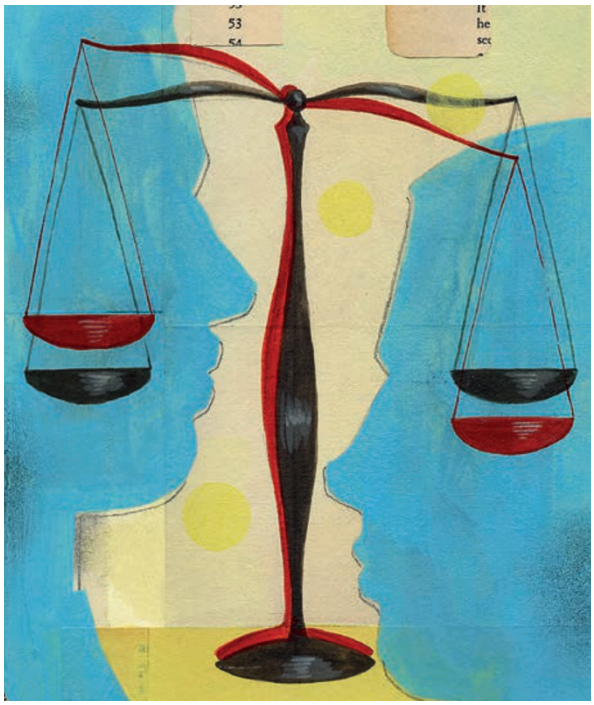
OBESITY

Neurotensin inhibition prevents weight gain

The development of novel anti-obesity therapies, capable of maintaining long-term weight loss without side effects, remains a global priority. Now, writing in *Nature*, Li, Evers and colleagues report that inhibition of the intestinal peptide neurotensin (NT) prevents the metabolically deleterious effects of a high-fat diet (HFD) in mice.

NT is a 13-amino-acid peptide located in enteroendocrine cells of the small intestine, where it is released by fat ingestion to facilitate fatty acid absorption. High levels of a stable NT precursor fragment, pro-NT, have previously been associated with increased risk of diabetes, cardiovascular disease and death, although a role for NT as a causative factor in these diseases is unknown.



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To further investigate the action of NT, Evers and colleagues studied NT-deficient ($Nt^{-/-}$) mice fed a HFD for 22 weeks. They found that body weights and fat deposits of $Nt^{-/-}$ mice were significantly lower than those of wild-type mice. This resulted in attenuated development of obesity-associated insulin resistance, with $Nt^{-/-}$ mice displaying lower levels of fasting plasma glucose and insulin, greater insulin sensitivity and faster glucose clearance. Furthermore, hepatic steatosis, liver triglyceride (TG) and cholesterol accumulation were significantly decreased in $Nt^{-/-}$ mice, and the size and inflammatory infiltration of adipocytes in their epididymal fat pads was reduced.

The beneficial metabolic effects observed in $Nt^{-/-}$ mice were not due to effects on feeding behaviour or energy expenditure but were a result of decreased intestinal lipid absorption. Importantly, there was no sign of steatorrhoea in mice deficient in NT.

Similarly, inhibition of NT activity with SR48692 — a selective antagonist of the NT receptor NTR1 — decreased intestinal fatty acid absorption in wild-type mice following olive oil gavage. In addition, treatment of wild-type mice with oral SR48692 for 13 weeks significantly attenuated body weight gain on a HFD.

Further studies in mice revealed that NT may be acting through suppression of activity of 5′-AMP-activated protein kinase (AMPK), a key fuel-sensing enzyme and critical regulator of metabolism. Indeed, levels of phosphorylated AMPK (pAMPK) were increased in the proximal intestinal mucosa of $Nt^{-/-}$ mice compared to that of wild-type mice. In addition, decreased intestinal pAMPK levels observed in wild-type mice subjected to olive oil gavage were prevented by SR48692 pretreatment.

Consistent with the findings in mice, expression of human full-length NT cDNA in *Drosophila* midgut enteroendocrine cells increased lipid accumulation and total body TG levels. These effects were enhanced on a HFD and were mediated by decreased gut AMPK activation.

Finally, analysis of fasting plasma concentrations of pro-NT from 4,632 middle-aged people from the population-based Malmö Diet and Cancer Study Cardiovascular Cohort revealed elevated plasma concentrations of pro-NT in obese and insulin-resistant individuals; and in non-obese individuals, high levels of pro-NT denoted a doubling of the risk of developing obesity later in life.

In summary, these findings demonstrate a key role of NT in HFD-induced obesity, highlighting NT as a prognostic marker of future obesity and a potential anti-obesity therapeutic target.

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ORIGINAL ARTICLE Li, J. *et al.* An obligatory role for neurotensin in high-fat-diet induced obesity. *Nature* **533**, 411–415 (2016)