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OBESITY

Could 13 amino acids combat obesity?

> Neurotensin serves a beneficial role of ensuring the efficient absorption of ingested fats

Neurotensin (NT), a 13-amino-acid peptide expressed in the brain and enteroendocrine cells, is a prognostic marker of future obesity according to new data published in *Nature*. The data also suggest that NT mediates lipid uptake in intestinal cells. Importantly, this mechanism is evolutionarily conserved. Moreover, humans with obesity have increased levels of pro-NT, an inactive precursor of NT, which is also associated with a doubling of the risk of future obesity.

"Neurotensin serves a beneficial role of ensuring the efficient absorption of ingested fats," explains Mark Evers, who led the study. "However, with the abundance of fats in current western diets, this could actually be contributing to increased obesity."

Jennie Vallis/NPG

Compared with wild-type littermates, $Nt^{-/-}$ mice fed a high-fat diet (HFD) had smaller fat depots, gained less body weight and had improved glycaemic parameters, such as insulin sensitivity and fasting levels of glucose and insulin. Hepatic steatosis and liver accumulation of triglycerides and cholesterol were also reduced in $Nt^{-/-}$ mice. Although NT can suppress food intake when injected into the rat brain, food intake, energy expenditure and activity were similar between $Nt^{-/-}$ and wild-type mice. Consequently, the team investigated if the uptake of lipids in intestinal cells was reduced.

In $Nt^{-/-}$ mice, faecal triglyceride content was increased and intestinal absorption of $^{13}C_{18}$-oleic acid was reduced, compared with $Nt^{+/+}$ mice. The phenotype seen in $Nt^{-/-}$ mice could also be replicated by administering a NT receptor inhibitor (SR48692) to wild-type mice; these mice gained less weight when fed a HFD than untreated mice.

The mechanism is dependent on phosphorylation of AMPK, which was increased in $Nt^{-/-}$ mice. Notably, phosphorylated AMPK levels were decreased in olive oil-treated $Nt^{+/+}$ mice, but returned to normal levels upon SR48692 administration.

The team also used *Drosophila melanogaster* to understand the physiological role of human NT, which confirmed many of the results found in mice. Human NT expressed in the *Drosophila* gut led to increased lipid and triglyceride accumulation, accompanied by a decrease in phosphorylated AMPK. The increased lipid droplet size could also be attenuated by knock-down of a *Drosophila* NT receptor orthologue.

Taken together, the results indicate that NT promotes lipid storage, which is useful from an evolutionary perspective in times of nutrient deprivation, but not so good with the high-fat diets we now consume.

Finally, using data from the Malmö Diet and Cancer Study cohort, the team found that in 4,632 middle-aged individuals, fasting plasma concentrations of pro-NT were significantly associated with obesity and insulin resistance ($P = 0.01$ and $P < 0.0001$, respectively). Moreover, non-obese individuals with the highest quartile of pro-NT plasma levels were twice as likely to develop obesity in the future (OR 2.05; 95% CI 1.38–3.06) compared with individuals in the lowest quartile.

"Increased fasting pro-NT levels strongly predicted the likelihood of future obesity, which was independent from baseline BMI, insulin resistance, age and sex," clarifies Evers, who hopes the measurement of NT levels could soon be used for clinical benefit. "There is already a commercial test to assess pro-NT levels, therefore, individuals who are at risk of future obesity could be tested and lifestyle or dietary changes instituted."

Evers and his team also want to look at the wider implications of elevated NT levels in obesity. "As NT is known to contribute to the increased proliferation of cancers ... one area that we are pursuing is whether increased NT may be one of the factors linking the increased incidence of certain cancers with obesity."

Although small, this 13-amino-acid protein might have large implications for the ever growing problem of obesity.

Tim Geach

ORIGINAL ARTICLE Li, J. *et al.* An obligatory role for neurotensin in high-fat-diet-induced obesity. *Nature* http://dx.doi.org/10.1038/nature17662 (2016)