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AUTONOMIC NERVOUS SYSTEM

Zapping fat in WAT

> "activation of WAT-innervating TH$^+$ neurons triggers noradrenaline release and breakdown of local fat stores"

White adipose tissue (WAT) stores fat that can be hydrolysed and released as free fatty acids to be metabolized in times of energy shortage. Leptin, a hormone secreted by WAT, acts on the hypothalamus and in other brain areas to regulate energy balance, by promoting the release of fat stores from adipocytes and reducing food intake. However, how leptin mediates the release of fat from WAT has been unclear. Now, Domingos and colleagues show in mice that the activity of sympathetic neurons innervating WAT leads to lipolysis.

The authors 'cleared' inguinal fat pads from mice to make them transparent for examination using optical projection tomography. This technique revealed bundles of neurons in the WAT, and microdissection and immunostaining of these bundles showed that around one-half of the neurons expressed tyrosine hydroxylase (TH), a marker of sympathetic neurons. *In vivo* multiphoton microscopy of fat pads in which adipocytes and TH$^+$ cells were fluorescently labelled showed that TH$^+$ axons make synapse-like contacts — or 'neuro–adipocyte junctions' — with WAT cells.

To investigate the effects of activating these TH$^+$ neurons on adipocytes, the authors optogenetically activated TH$^+$ neurons in the WAT of these mice. This led to increased levels of noradrenaline and phosphorylated hormone-sensitive lipase (pHSL; the active form of an enzyme involved in lipolysis) in WAT, suggesting that activation of WAT-innervating TH$^+$ neurons triggers noradrenaline release and breakdown of local fat stores. Strikingly, optogenetic activation of these neurons that was repeated every day for 4 weeks on one side of these animals led to a reduction of inguinal WAT (assessed using MRI) on the ipsilateral but not the contralateral (non-stimulated) side.

Next, the authors found that systemic administration of leptin led to increased noradrenaline and pHSL levels in the fat pads of wild-type mice. The leptin-induced increase in WAT pHSL levels was abolished in fat pads that were denervated by surgical nerve crush, but not in contralateral fat pads with intact innervation. Moreover, diphtheria toxin injected into the WAT of mice expressing the diphtheria toxin receptor specifically in TH$^+$ cells also prevented the leptin-induced increase in pHSL levels on the ipsilateral but not the contralateral (toxin-free) side. Therefore, the local sympathetic innervation of WAT is necessary for the lipolysis-stimulating effects of leptin.

Systemic administration of the β-adrenergic agonist isoproterenol led to increased HSL phosphorylation in WAT, confirming previous work indicating that β-adrenergic transmission stimulates lipolysis. The authors then set out to determine whether β-adrenergic signalling mediates the response to leptin in WAT. Indeed, compared with wild-type animals, mice lacking dopamine β-hydroxylase (an enzyme necessary for the synthesis of adrenaline and noradrenaline) showed smaller increases in WAT pHSL levels following a single dose of leptin, and decreased weight loss in response to 2 days of treatment with leptin. Furthermore, mice lacking all isoforms (β1–β3) of β-adrenergic receptors exhibited diminished — although not completely absent — leptin-induced HSL phosphorylation and weight loss responses. Therefore, β-adrenergic signalling mediates some — but not all — of the effects of leptin on WAT.

Together, the results of this study show that leptin promotes the activity of sympathetic neurons that directly innervate WAT and regulate local lipolysis.

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ORIGINAL RESEARCH PAPER Zeng, W. *et al.* Sympathetic neuro–adipose connections mediate leptin-driven lipolysis. *Cell* **163**, 84–94 (2015)