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Peroxisome proliferation in POMC cells is associated with leptin resistance

Increased peroxisome proliferation in hypothalamic pro-opiomelanocortin (POMC) neurons might mediate leptin resistance, suggest Sabrina Diano and colleagues in *Nature Medicine*.

In the setting of leptin resistance, a feature of diet-induced obesity, high leptin levels do not decrease feeding; the central mechanisms underlying leptin resistance are not well understood.

In a previous study in mice, Diano and co-workers observed elevated levels of reactive oxygen species (ROS) in POMC neurons during satiety. They now report that raised ROS levels actively promote neuronal firing of POMC cells, which decreases feeding. Conversely, reduced ROS levels decrease POMC activation and thereby increase feeding.

In lean animals, leptin levels were positively correlated with ROS levels and POMC neuronal firing. However, this correlation was not found in mice with diet-induced obesity. An increased proliferation of peroxisomes in POMC neurons was found to be associated with high-fat feeding and could explain the decrease in ROS levels and increased food intake observed in obese mice. Of note, peroxisome proliferation in this context was mediated by PPARγ signaling, with PPARγ agonism increasing and PPARγ antagonism blocking proliferation.

Consistently high levels of ROS are likely to cause brain and peripheral tissue degeneration. As Diano points out, successful promotion of satiety by stimulation of POMC neuronal activity will lead to lower body weight but might also be deleterious to the brain and body.

Joana Osório

Original article Diano, S. *et al.* Peroxisome proliferation-associated control of reactive oxygen species sets melanocortin tone and feeding in diet-induced obesity. *Nat. Med.* doi:10.1038/nm.2421