OBESITY

New therapeutic promise for leptin

> long-term (6 weeks) treatment of obese wild-type mice with leptin neutralizing antibodies was associated with a 10% reduction in food intake

The adipokine leptin is thought to act by decreasing food intake, which led to the development of leptin therapies for the treatment of obesity. However, these treatments have mostly failed, owing to the presence of high circulating levels of leptin and leptin resistance in most patients with obesity. A study in *Cell Metabolism* now presents a novel strategy that could revive the leptin axis as a therapeutic target.

First, the researchers show that acute high-fat diet (HFD) feeding of wild-type mice can upregulate leptin expression in adipose tissue depots and increase circulating plasma levels of leptin. Furthermore, an inducible adipocyte-specific leptin transgenic mouse (Alep-TG) fed a long-term HFD showed accelerated weight gain and decreased glucose tolerance and insulin sensitivity compared with littermate controls. These findings suggest that increasing leptin levels in the context of obesity can result in pathological changes and that a leptin-reduction approach might warrant further investigation.

"We used three separate approaches to reduce leptin levels — a CRISPR–Cas9 based approach, a classic approach using a floxed leptin locus and an antibody-based approach that neutralizes leptin action," describes corresponding author Philipp Scherer.

Importantly, the CRISPR–Cas9-based model enabled inducible depletion of leptin specifically from mature adipocytes in adult mice (Cas9-sgLeptin mice). The researchers observed that circulating levels of leptin were decreased 2 days after induction of adipocyte leptin depletion and remained at low levels for 8 weeks. Moreover, Cas9-sgLeptin mice were resistant to diet-induced obesity and showed improved metabolic parameters compared with littermate controls.

The second Cre-*loxP* based approach involved the generation of an adult mouse with one copy of *Lep* eliminated (ALepflox-HZ mice), causing a partial (~50%) deficiency in circulating levels of leptin. Interestingly, ALepflox-HZ mice were also resistant to weight gain induced by HFD and had improved glucose tolerance and insulin resistance compared with littermate controls.

The third approach involved partially reducing circulating levels of leptin in obese mice by administering neutralizing leptin-specific antibodies. Antibody injections were performed every other day for 2 weeks and body weight and food intake were measured at the time of each injection. Compared with vehicle-injected control mice, mice with partially decreased leptin levels showed reduced food intake, decreased weight gain and improvements in glucose tolerance, adaptive thermogenesis and hepatic steatosis.

"In all three cases, the results were identical and we achieved a high degree of leptin sensitization by lowering leptin levels in circulation, as well as also achieving further insulin sensitization," says Scherer.

To find further evidence of restored leptin sensitivity in obese mice, the researchers examined gene expression in the mediobasal hypothalamus (MBH) brain region in Alep-TG mice. Expression of *Pomc* and *Agrp* (encoding key neuroendocrine factors involved in feeding behaviour) were decreased in Alep-TG mice compared with control mice. In addition, all three leptin-reduced mouse models showed improvements in the MBH brain region compared with control mice.

Notably, live intravital imaging of POMC-hrGFP::LepR-cre::tdtomato mice showed that HFD feeding blunts the acute leptin-induced depolarization of POMC neurons expressing leptin receptor. This effect could be rescued by treating the mice with leptin neutralizing antibodies.

Importantly, long-term (6 weeks) treatment of obese wild-type mice with leptin neutralizing antibodies was associated with a 10% reduction in food intake, with no loss of treatment effectiveness over time.

"We are currently exploring leptin neutralizing antibodies in the context of peripheral leptin sensitivity (that is, in areas other than the hypothalamus) as well as for certain cancers in preclinical models," explains Scherer. "Soon, we hope to take the antibody into an exploratory phase I clinical study to explore the translatability by testing weight loss and insulin sensitizing effects in humans."

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