METABOLIC DISEASE

GOAT inhibitors to battle the bulge?

Much research in the quest to develop a safe and highly effective obesity treatment has focused on deciphering the nutrient–hormone interactions that influence weight gain. The gastric peptide hormone ghrelin has been identified as a central player in this process, but strategies to target its active form, acyl ghrelin, have had limited success. Now, reporting in *Science*, Barnett and colleagues present a peptide inhibitor of ghrelin-O-acetyltransferase (GOAT) that blocks the formation of acyl ghrelin and reduces weight gain in mice fed a high-fat diet.

The inhibitor, GO-CoA-Tat, was designed to mimic and 'lock' a putative ternary complex formed between GOAT and its substrates octanoyl-CoA and ghrelin. To achieve this, amino acids 1–10 of ghrelin were linked with a non-cleavable bond to octanoyl-CoA and coupled to an 11-mer HIV Tat-derived sequence to promote membrane permeation.

GO-CoA-Tat specifically and directly interacted with GOAT in cell lines expressing GOAT and pro-ghrelin, and reduced acyl ghrelin formation. Intraperitoneal injection of GO-CoA-Tat in mice fed a high-fat diet resulted in a relative reduction of fat mass, but no difference in lean mass, compared with vehicle-treated or ghrelin-knockout mice. Serum levels of acyl ghrelin, glucose and insulin-like growth factor 1 were reduced, whereas the level of desacyl ghrelin remained unchanged.

To decipher the effect of GOAT inhibition on glucose homeostasis and insulin levels, isolated human pancreatic islet cells were challenged with glucose. Cells that were pretreated with GO-CoA-Tat had a significantly higher insulin response compared with untreated cells. *In vivo*, GO-CoA-Tat pretreatment of glucose-challenged wild-type mice, but not ghrelin-knockout mice, resulted in significantly higher serum insulin levels and a reduction in blood glucose. A small population of ghrelin-expressing cells were identified in pancreatic islets. Further analysis demonstrated a 20-fold reduction of the mRNA coding for uncoupling protein 2 (UCP2), a suppressor of insulin secretion, in pancreatic islet cells from mice treated with GO-CoA-Tat. These data point to a tissue-specific role for GOAT inhibition in suppressing UCP2 levels and in enhancing insulin release in response to glucose, providing a further link between acyl ghrelin, obesity and type 2 diabetes.

The authors point out that targeting the biosynthesis of acyl ghrelin can have several advantages over approaches to block its receptor. As acyl ghrelin formation can be blocked in the periphery, the drug does not need to cross the blood–brain barrier. Also, targeting an enzyme may be easier than targeting an abundant receptor. Furthermore, there has been concern that acyl ghrelin receptor antagonists can increase the level of acyl ghrelin. While peptide inhibitors have obvious limitations, synthetic derivatives of GOAT inhibitors like GO-CoA-Tat could be developed into a promising tool for the management of metabolic disorders.

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