OBESITY

A two-pronged attack

Current pharmacotherapies for obesity have limited efficacy, typically producing a maximum sustained weight loss of less than 10%, and their use is limited by adverse effects. Reporting in *Nature Chemical Biology*, Day and colleagues have shown that a rationally designed single peptide that targets two key pathways in glucose homeostasis might provide a novel therapeutic strategy for obesity.

The signalling system of the gut hormone glucagon-like peptide 1 (GLP1) — which stimulates insulin secretion from the pancreas in response to food intake, thereby promoting blood glucose regulation — is already targeted by GLP1 receptor (GLP1R) agonists for the treatment of type 2 diabetes. Although signalling by glucagon, another metabolic hormone, through the glucagon receptor (GCGR) is classically seen as antagonizing the effects of insulin, some studies have indicated that sustained GCGR activation has lipolytic and thermogenic effects.

The authors of this study sought to harness these beneficial effects of glucagon signalling while circumventing any potential diabetogenic effects of this approach by simultaneously activating GLP1Rs. Starting with the native glucagon peptide, they used structural information to aid the synthesis of a set of peptide chimeras that were designed to be co-agonists of GCGR and GLP1R. The biological effects of the modifications were assessed by monitoring the ability of the peptides to activate the two receptors in cell-based assays. Part of the design rationale aimed to address the obstacles to long-term glucagon therapy, including the poor solubility and stability of this hormone. This was achieved by incorporating unnatural amino acids to provide resistance to cleavage by the endogenous enzyme dipeptidyl-peptidase 4, by adding a peptide bridge to stabilize the secondary structure, and by conjugation with poly(ethylene glycol) (that is, PEGylation) to increase the half-life.

Two PEGylated peptides were selected for further study. A single subcutaneous injection of either of these compounds to diet-induced obese (DIO) mice significantly decreased their food intake, causing a reduction in fat mass and therefore body weight within 1 week. Similarly encouraging results were seen in long-term (1 month) experiments: once-weekly administration of one of the peptides reduced body weight by ~28% in DIO mice, although cumulative food intake was statistically unchanged by treatment and the effects seemed to result predominantly from increased energy expenditure. Long-term treatment also reduced circulating levels of glucose and insulin, suggesting improved glucose homeostasis and increased insulin sensitivity, as well as decreasing total cholesterol levels and improving lipid profiles.

In GLP1R-knockout mice, the treatment still caused some reduction in body weight and fat mass, showing that glucagon agonism contributed to these effects independently of the GLP1 pathway. Importantly, blood glucose levels in these mice were increased by treatment with the co-agonist, highlighting the necessity of simultaneously targeting GLP1R to avoid the deleterious effects of GCGR activation while retaining the therapeutic benefit.

This study shows the possibility of selectively combining, in a single peptide, the lipolytic effects of glucagon with the glucose-regulating properties of GLP1, potentially providing a new approach to therapy for obesity and, by association, type 2 diabetes.

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