Gastric inhibitory polypeptide links overnutrition to obesity

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Obesity and diabetes are two of the most prevalent health conditions in industrial nations. Recent studies suggest that a gut derived peptide, gastric inhibitory polypeptide (GIP), may be involved in the pathogenesis of type 2 diabetes and obesity induced by overnutrition. The “thrifty genotype” hypothesis suggests that those who are prone to obesity have been favoured by natural selection in the past because they possess genes that promote the efficient storage of ingested food as body fat for use in periods of undernutrition. However, with the sedentary lifestyle and year round plentiful food supply of modern society, the tendency is to accumulate fat. Miyawaki et al have shown that GIP directly links overnutrition to obesity and may be a potential target for antiobesity drugs.

GIP was initially discovered and named for its gastric inhibitory properties. In 1886, Ewald and Boas showed that olive oil mixed with a meal inhibited both gastric emptying and acid secretion. In 1930 Kosaka and Lim proposed that this mixture liberated a chemical from the small intestine and went on to show that gastric acid secretion and gastric emptying could be inhibited by intravenously infused extracts of intestines. It is released from the duodenum and jejunum in response to ingestion of a meal containing glucose or fat and potentiates glucose induced insulin secretion, so GIP is also referred to as glucose dependent insulinotropic polypeptide. It has since also been shown that under physiological conditions in humans, GIP has a negligible effect on gastric acid secretion. The important role of GIP as an incretin hormone is demonstrated in GIP receptor knockout mice who show normal glucose tolerance after intraperitoneal administration of glucose and glucose intolerance accompanied by impaired insulin secretion after oral administration of glucose. The physiological role of GIP in the fasting state seems to be less important: fasting blood glucose and plasma insulin concentrations are the same in GIP receptor knockout and wild-type mice.

In the present study, mice fed a high fat diet for 43 weeks demonstrated a 35% increase in body weight compared with wild-type, indicating that the absence of GIP receptor primarily affects basal metabolism. The energy parameters only differed in the light phase when mice have low spontaneous motor activity indicating that the absence of GIP receptor directly links overnutrition to obesity and it is a potential target for anti-obesity drugs.


Secretion of gastric inhibitory polypeptide (GIP), a duodenal hormone, is primarily induced by absorption of ingested fat. Here we describe a novel pathway of obesity promotion via GIP. Wild-type mice fed a high-fat diet exhibited both hypersecretion of GIP and extreme visceral and subcutaneous fat deposition with insulin resistance. In contrast, mice lacking the GIP receptor (Gipr(−/−)) fed a high-fat diet were clearly protected from both the obesity and the insulin resistance. Moreover, double-homzygous mice (Gipr(−/−), Lep(ob)/Lep(ob)) generated by crossbreeding Gipr(−/−) and obese ob/ob (Lep(ob)/Lep(ob)) mice gained less weight and had lower adiposity than Lep(ob)/Lep(ob) mice. The Gipr(−/−) mice had a lower respiratory quotient and used fat as the preferred energy substrate, and were thus resistant to obesity. Therefore, GIP directly links overnutrition to obesity and it is a potential target for anti-obesity drugs.

The GIP receptor is a seven transmembrane G protein coupled receptor belonging to the secretin/vasoactive intestinal polypeptide family. The GIP receptor signaling prevents obesity.
polypeptide family of receptors. It is expressed in various tissues including pancreatic islets, stomach, brain, and adipose tissue. GIP has a direct effect on adipocytes and has been shown to dose dependently stimulate lipoprotein lipase activity, fatty acid synthesis, and fatty acid incorporation into adipose tissue. 4 11 Acyl CoA:diacylglycerol transferase 1 (Dgat1) catalyses the final step of triglyceride synthesis and mice deficient in this enzyme are resistant to obesity. Expression of Dgat1 was significantly reduced in adipocytes from GIP receptor knockout mice compared with controls and the authors suggest that loss of peripheral GIP actions in GIP receptor knockout mice may contribute to the increased fat oxidation in these mice. 2

The authors propose a model for over-nutrition in which excessive fat intake leads to hypersecretion of GIP, increased nutrient uptake into fat cells resulting in obesity, and in turn insulin resistance and hyperinsulinaemia. Although GIP receptor knockout mice are insulin sensitive they are glucose intolerant after oral glucose loading. 11 Therefore, inhibition of GIP signalling to treat obesity may carry the price of impaired glucose tolerance or possibly frank diabetes.

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