Gastric inhibitory polypeptide links overnutrition to obesity

A Ballinger

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 olive oil mixed with a meal inhibited gastric acid secretion and gas-tination to obesity and may be a potential target for antiobesity drugs.


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-homozygous mice (Gipr(-/-), Lep(ob)/Lep(ob)) generated by cross-breeding 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.
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.\(^6\) 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.\(^6\)

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.\(^1\) Therefore, inhibition of GIP signalling to treat obesity may carry the price of impaired glucose tolerance or possibly frank diabetes.

**Author’s affiliation**
A Ballinger, Digestive Disease Research Centre, St Bartholomew’s and the Royal London, Turner Street, London, UK; a.b.ballinger@qmul.ac.uk

**REFERENCES**