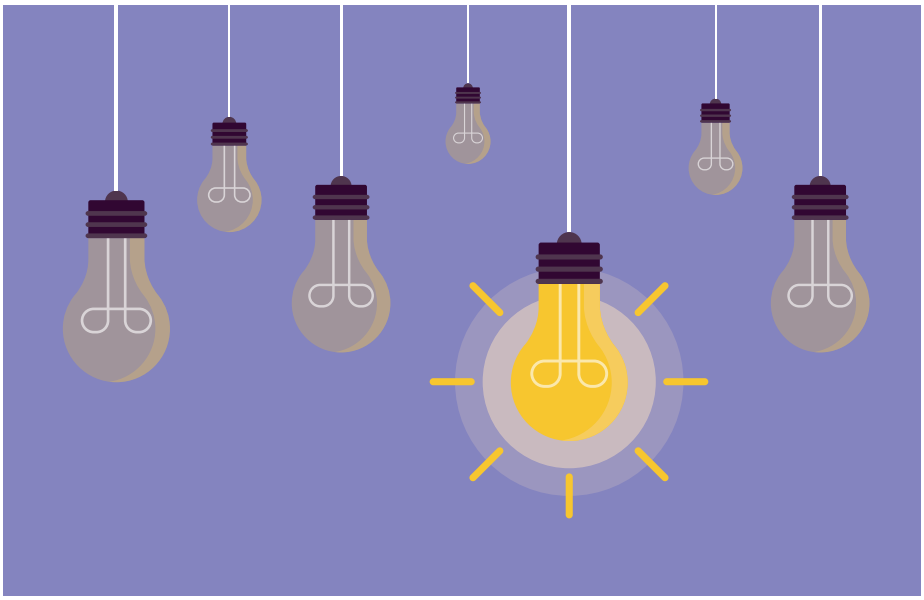
Milestone 9



Illuminating the incretin effect

The idea that the intestine produces factors following nutrient ingestion that stimulate the release of substances from the pancreas to modulate blood glucose levels first emerged in the early 1900s, and, in 1932, Jean La Barre coined the name 'incretin'. The 1960s witnessed formal proof of the existence of a gut hormonal mechanism that stimulated insulin secretion — plasma insulin levels following oral intake of glucose were shown to be greater than those observed when glucose was given intravenously, referred to as the 'incretin effect' — and the search for incretins began.

The first significant incretin to be identified was the duodenal glucose-dependent insulinotropic polypeptide, GIP. In 1973, Dupre et al. demonstrated that infusion of GIP in combination with glucose into healthy humans led to potentiation of insulin secretion and improvement of glucose tolerance. However, 10 years later, Ebert et al. reported that incretin activity was preserved after removal of GIP from rat gut extracts, indicating that GIP was probably not the exclusive incretin.

Attention then turned to glucagon. In addition to the pancreas, the glucagon gene is expressed in the intestine. Although the glucagon gene encodes a proglucagon that exhibits tissue-selective processing, glucagon-like peptides (GLPs) were found to be liberated in both tissues. Furthermore, the intestine contained GLP1 in at least two forms, 31 and 37 residues long (GLP1(1–37) and GLP1(7–37)).

"In 1987, key papers from the laboratories of Habener and Holst implicated GLP1 as a regulator of insulin secretion"

In 1987, key papers from the laboratories of Habener and Holst implicated GLP1 as a regulator of insulin secretion. Drucker et al. synthesized GLP1(1–37) and GLP1(7–37) and examined their effects on cAMP formation (which promotes insulin secretion), insulin mRNA levels and insulin release in a rat islet insulinoma cell line. GLP1(7–37) was found to be a more potent insulinotropic peptide than GLP1(1–37), exerting a greater increase in cAMP levels, insulin mRNA transcripts and insulin release. Further, Mojsov et al. studied the effects of synthetic GLP1 on insulin secretion in the isolated perfused rat pancreas. Low concentrations of GLP1(7–37) potently stimulated insulin secretion, while even high concentrations of GLP1(1–37) had no effect. Providing yet further evidence of the insulinotropic activity of GLP1, Holst et al. isolated naturally occurring GLP1 from pig small intestinal mucosa, which corresponded to proglucagon 78–107. This isolated natural peptide, as well as a synthetic proglucagon 78–107 fragment, dose-dependently and potently increased insulin secretion in the perfused pig pancreas.

Together, these studies laid the foundations for further exploration of the role of intestinal GLP1 in glucose homeostasis. In addition to augmentation of glucose-stimulated insulin secretion, GLP1 is now known to exert multiple effects, including inhibition of pancreatic glucagon secretion, gastric emptying and food intake, while stimulating β-cell proliferation.

In type 2 diabetes, which is characterized by hyperglycaemia resulting from defects in insulin secretion and action, the incretin effect is typically diminished. Although the secretion of GLP1 may be reduced and GIP secretion is largely normal, the effect of GLP1 is preserved whereas the effect of GIP is severely impaired. This preserved effect of GLP1 inspired attempts to treat type 2 diabetes with GLP1.

However, the clinical utility of the GLP1 peptide itself is limited by an extremely short half-life, due to rapid degradation by dipeptidyl peptidase 4 (DPP4) in human serum, as noted by Mentlein et al. and Kieffer et al. in 1993 and 1995, respectively. To address this, two solutions emerged that have given rise to two major classes of antidiabetic drugs: inhibitors of DPP4 and analogues of GLP1 protected against DPP4-mediated degradation (Milestone 22). Today, incretin hormone-based treatments represent widely and successfully used therapeutic agents in the management of type 2 diabetes.

Sarah Crunkhorn Senior Editor, *Nature Reviews Drug Discovery*

CREDIT: TOMMY

Milestone studies

Drucker, D. J. et al. Glucagon-like peptide I stimulates insulin gene expression and increases cyclic AMP levels in a rat islet cell line. *Proc. Natl Acad. Sci. USA* **84**, 3434–3438 (1987) | Mojsov, S., Weir, G. C. & Habener, J. F. Insulinotropin: glucagon-like peptide I (7-37) co-encoded in the glucagon gene is a potent stimulator of insulin release in the perfused rat pancreas. *J. Clin. Invest.* **79**, 616–619 (1987) | Holst, J. J. et al. Truncated glucagon-like peptide I, an insulin-releasing hormone from the distal gut. *FEBS Lett.* **211**, 169–174 (1987)

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