Hidden Gems

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Shining a light into the past for the articles that continue to shape our diabetes clinical practice today

This issue: McIntyre N, Holdsworth CD, Turner DS (1965) Intestinal factors in the control of insulin secretion. *J Clin Endocrinol Metab* **25**: 1317–24

By the mid-20th century it was evident that insulin secretion was stimulated more by oral intake of glucose than by intravenous infusion in animals. This article by McIntyre et al describes an early experiment designed to confirm this finding in humans and to identify the mechanism behind it. The authors' explanation was that "a humoral substance is released from the jejunal wall during glucose absorption which acts by stimulating the release of insulin from the pancreatic islet cells." This conclusion formed the basis for the discovery of incretin hormones and the later manufacture of two new classes of antidiabetes drug: glucagon-like peptide-1 analogues and dipeptidyl peptidase-4 inhibitors.

Historical context

Following the discovery of insulin in 1921, a fairly simple model of blood glucose regulation initially developed. Digestion of carbohydrate and the subsequent absorption of glucose into the portal and then systemic circulation stimulated the beta-cells to produce insulin, completing a feedback loop. A direct effect of plasma glucose on insulin secretion was confirmed; however, out of keeping with this simple model was the finding from animal studies that oral administration of carbohydrate appeared to stimulate higher insulin levels than intravenous administration of a similar dose.

Several mechanisms might have explained this finding. It was possible that glucose absorbed from the gut somehow stimulated insulin production on its way through the liver via the portal circulation. It was not certain initially that the pancreas was the only organ to secrete insulin, so a hepatic source was possible. It was also postulated that an undiscovered capillary connection between the duodenum and the pancreas allowed glucose to travel directly to the gland without dilution via the systemic circulation. Such a direct, localised effect might plausibly stimulate insulin secretion more effectively. But another explanation was that a different hormone, secreted most probably from the gut wall in response to ingested carbohydrate, produced a separate and additional stimulant effect on the beta-cells. It was suggested as early as 1902, a time when the pancreas was suspected to be the seat of blood glucose regulation but insulin remained undiscovered, that a hormone arising from the gut might influence this organ (Bayliss and Starling, 1902).

Just 4 years later, Moore (1906) showed through a case series that a duodenal extract from pigs could reduce blood glucose levels in humans. The extraction techniques were fairly basic, involving in the first stage a "broad blunt knife" and then a sausage machine before chemical treatments. Much later, La Barre and Still (1930) coined the term "incretin" for the postulated hormone. However, subsequent experiments by Loew et al (1940) failed to confirm the hypoglycaemic effects of intestinal extracts, and research into incretins was stalled until the mid-1960s.

The Hidden Gem

The current article signals a reawakening of interest in this avenue by the research community. McIntyre and colleagues designed an elegant experiment to measure the incretin effect in humans and to clarify the underlying mechanism. They compared the response of plasma glucose and insulin levels following intravenous and intrajejunal infusion of a fixed amount of glucose. They inserted a polyvinyl tube into the jejunum several inches distal to the duodenojejunal junction, beyond the point where the upper small bowel lies in close proximity to the pancreas. This would negate the effects of gastric emptying, which would have complicated a similar experiment involving oral carbohydrate administration, on the effect being studied. It would also determine whether the effect occurred independently of some unknown capillary connection, as the jejunum is anatomically free of the pancreas at this point.

This experiment was conducted initially in nine healthy volunteers. In addition, to exclude the effect of glucose passing through the liver, two patients with cirrhosis and functioning portacaval shunts were recruited to undergo the same procedure. The shunts had been created as end-to-side

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Box 1. Beneficial effects of incretin hormones in humans

- Glucose-dependent stimulation of insulin secretion
- Improved satiety through central nervous system-based mechanisms
- Delayed gastric emptying
- Reduction in gluconeogenesis
- Suppression of glucagon levels
- Increased insulin sensitivity
- Preservation of beta-cell mass

anastomoses following recurrent haemorrhage from oesophageal varices.

The results showed that, compared with intravenous glucose infusion, intrajejunal infusion produced a smaller rise in plasma glucose levels. This is perhaps unsurprising, as the administration of glucose into the venous circulation is likely to raise plasma levels more directly. However, the authors also demonstrated substantially higher levels of plasma insulin following intrajejunal infusion. This finding was incompatible with the original model of blood glucose regulation, in which insulin was secreted in direct response to plasma glucose alone. The effect was confirmed both in healthy subjects and in those with cirrhosis.

Why it still shines today

The incretin effect was a key physiological discovery of the 20th century, opening the door to novel pharmacological treatments for diabetes mellitus. The subsequent quest for the authors' "humoral substance" led to the discovery of the natural incretin glucose-dependent insulinotropic polypeptide in 1970 (Brown and Pederson, 1970). The isolation of glucagon-like peptide-1 (GLP-1) took much longer, as it required a whole new generation of techniques based on recombinant DNA technology. Kieffer and Habener (2013) give a fascinating account of the history of these discoveries.

GLP-1 was isolated initially from lizard venom and was found to be potently insulinotropic. Pharmacological manufacture followed, with the licensing of the injectable drugs exenatide in 2005, liraglutide in 2009 and lixisenatide in 2013.

The natural enzyme dipeptidyl peptidase-4 (DPP-4) was found to rapidly metabolise GLP-1, leading to a further avenue of drug discovery based on inhibition of this breakdown. The oral DPP-4 inhibitors (sitagliptin, saxagliptin, vildagliptin, linagliptin and alogliptin) promote the effects of natural GLP-1.

People with diabetes do not simply lack sufficient insulin, they also lack the regulatory mechanism that tailors insulin secretion to insulin requirement. Older insulin secretogogue drugs such as sulphonylureas, as well as injected insulin itself, meet this requirement in a way that is decidedly blunt compared with the physiological state. The short-acting sulphonylureas (and the even shorter-acting meglitinides) are administered with meals in an attempt to stimulate insulin secretion tailored to carbohydrate intake and thereby avoid postprandial elevations in blood glucose. But with standard doses administered prior to meals of different sizes within the individual, and with variable timing of the drugs in relation to requirement, they can at best produce only a vague replication of physiological insulin profiles. It is unsurprising, therefore, that these drugs put people at risk of hypoglycaemia and weight gain, as there is an inevitable mismatch between insulin availability and requirement.

Natural incretins are depleted in people with type 2 diabetes. Replacing them and promoting their effects using GLP-1 analogues and DPP-4 inhibitors not only stimulates the secretion of insulin but also enables its production to be tailored to carbohydrate intake. Stimulation of insulin secretion is glucose-dependent and "switches off" when blood glucose levels reach the fasting range. This is important for both patients and clinicians. The drugs on their own do not significantly increase the risk of hypoglycaemia unless the person is also taking a sulphonylurea, meglitinide or insulin. This freedom reduces the need for self-monitoring of blood glucose and may be safer for those who drive cars or other vehicles.

Incretins were found to have other beneficial effects for people with diabetes (see *Box 1*), including an overall reduction in caloric intake through improved satiety and delayed gastric emptying. They cause a reduction in gluconeogenesis through suppression of glucagon levels, increased insulin sensitivity and preservation of beta-cell mass due to reduced apoptosis. Through these effects, blood glucose levels may be safely reduced without risk of weight increase. Whilst the DPP-4 inhibitors are weight-neutral, GLP-1 analogues may actually reduce weight, an effect that is small on average but very significant in some people.

It is still too early to say how much long-term cardiovascular risk and other complications of diabetes are reduced by these two new classes of drug. Concerns over a raised risk of pancreatitis are the subject of ongoing investigation. These issues should be resolved in the foreseeable future.

The history of the discovery of the incretin effect, traceable to the first observations in 1906 and leading to the marketing of the first licensed GLP-1 analogue, exenatide, a century later was made possible by the resurgence of interest in the phenomenon described in this article. ■

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