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Incretin

To be or not to be—an incretin or enterogastrone?

M Horowitz, M A Nauck

Glucagon-like peptide 1 does not comfortably fulfil the criterion of a gut derived factor responsible for an enhanced meal related insulin response; it appears logical to add the definition of a “physiological incretin hormone”

Incretin hormones are gut derived peptides that augment the insulin releasing action of hyperglycaemia. In his seminal review, based on the 1978 Claude Bernard lecture, delivered at the European Association for the Study of Diabetes Meeting, Werner Creutzfeldt defined the term incretin as “an endocrine transmitter produced by the gastrointestinal tract which is: (a) released by nutrients, especially carbohydrates and (b) stimulates insulin secretion in the presence of glucose if exogenously infused in amounts not exceeding blood levels achieved after food ingestion”.¹ At that time, the best characterised incretin candidate was glucose dependent insulinotropic polypeptide (GIP), although there was evidence that GIP was not the only incretin.^{1–3} An incretin role for GIP was established, along the lines of Creutzfeldt’s definition,¹ by intravenous infusion in healthy subjects, both alone and in combination with glucose, and demonstrating that the insulinotropic

property of GIP was dependent on a permissive rise in blood glucose.² Subsequent experiments, performed under more physiological conditions, with plasma GIP and glucose concentrations mimicking the postprandial state, confirmed these observations.⁴ That relatively uncomplicated infusion experiments had the capacity to predict the physiological role of GIP with regard to its effects on insulin secretion is testimony to the fact that, metabolically speaking, GIP is apparently devoid of additional actions which have the potential to confound such experiments.⁵

The situation with glucagon-like peptide 1 (GLP-1) is far less straightforward. The GLP-1/glucose infusion experiment results in effects similar to those observed with GIP,⁶ and GLP-1, accordingly, fulfils the definition of an incretin hormone, as put forward by Creutzfeldt.¹ However, studies which have evaluated the effects of GLP-1 on the metabolic response to a meal, by

infusing physiological or pharmacological amounts of GLP-1,⁷ or interfering with endogenous GLP-1 action with the well characterised GLP-1 antagonist exendin(9–39),^{8–10} have revealed a complex pattern of GLP-1 actions. In particular, as a result of its effect on slowing gastric emptying substantially, exogenous GLP-1 attenuates the postprandial rise in glycaemia, leading to lesser substrate (glucose) mediated insulin secretion and an overall reduction, rather than an increase, in the insulin secretory response to a meal.^{7–11–12} In other words, inhibition of gastric emptying by exogenous GLP-1 outweighs its direct insulinotropic effects. This was highlighted in a recent study demonstrating that intravenous erythromycin, as a result of its prokinetic properties, abolishes the deceleration of gastric emptying induced by exogenous GLP-1 in healthy subjects and that this is associated with a marked reduction in its glucose lowering effect.¹² Furthermore, the GLP-1 antagonist exendin(9–39) increases, rather than lowers, the insulin response to a meal.¹³ Based on these observations it is clear that GLP-1 does not comfortably fulfil the criterion of a gut derived factor responsible for an enhanced meal related insulin response; furthermore, it appears logical to add the definition of a “physiological incretin hormone” to that provided by Creutzfeldt,¹ and assigning such a role to GLP-1 appears inappropriate based on current data.¹¹

In their important study in the current issue of *Gut*, Schirra and colleagues¹⁴ have introduced a new approach to evaluation of the incretin role of GLP-1 in healthy subjects (*see page 243*). They used intraduodenal administration

of glucose which predictably led to GLP-1 secretion, an increase in blood glucose, and greater increments in plasma insulin and C peptide than an "isoglycaemic" intravenous glucose infusion. These experiments were then repeated with exendin(9–39), known to completely block the actions of exogenous, as well as endogenous GLP-1.^{8,9} Exendin(9–39) reduced the insulin secretory response to intraduodenal glucose by approximately 50%, demonstrating that GLP-1 secretion and action made a substantial contribution to insulin secretion in this setting. However, in interpreting these observations it is important to recognise the limitations inherent in the experimental paradigm employing an intraduodenal glucose infusion, rather than a carbohydrate containing meal (that is, in this situation any effect of GLP-1 on gastric emptying has been bypassed). Accordingly, Schirra and colleagues¹⁴ have overestimated the contribution of GLP-1 to postprandial insulin secretion and it still remains debatable whether GLP-1 is a "physiological incretin" at all.¹¹ As described above, the reason is that GLP-1 has two concurrent effects after a meal—that is, (a) retardation of gastric emptying and (b) glucose dependent stimulation of insulin secretion. With respect to the quantitative influence on postprandial insulin secretion, the inhibitory effect (via slowing gastric emptying) appears stronger than the stimulatory effect exerted directly on pancreatic B cells.^{7,11}

In addition to slowing gastric emptying, exogenous GLP-1 is known to inhibit gastric acid and pancreatic exocrine secretion in humans.¹⁵ The study by Schirra and colleagues¹⁴ provides persuasive evidence that endogenous GLP-1 modulates antro-pyloro-duodenal motility in both the fasted state and in response to small intestinal glucose infusion. The latter observation is of particular interest given that the major mechanism regulating gastric emptying of nutrients (that is, liquids and "liquefied" solids) is feedback inhibition triggered by receptors that are distributed throughout the small intestine.^{16,17} Animal studies indicate that the extent of small intestinal feedback is dependent on the length, and possibly the region, of small intestine that has been exposed, but the underlying neural/humoral mechanisms remain poorly defined.¹⁶ As a result of small intestinal feedback, gastric emptying of glucose is highly regulated; after a more rapid initial phase, overall duodenal delivery remains relatively constant at ~1.5–3 kcal/min.^{17,18} Phasic and tonic contractions localised to the pylorus probably play an important role in the

regulation of nutrient gastric emptying by acting as a brake,¹⁹ and the observed inhibition of the pyloric response to small intestinal glucose by exendin(9–39) is, accordingly, likely to be associated with more rapid gastric emptying of carbohydrate, although the latter was not measured in this,¹⁴ or a previous,¹³ study.

The effects of GLP-1 on gastric emptying/gastro-pyloro-duodenal motility and glucose induced insulin secretion have implications for an understanding of both the normal regulation of postprandial glycaemia and the potential pharmacological use of GLP-1 in the management of type 2 diabetes. In particular, it is now recognised, albeit relatively recently that: (a) the rate of gastric emptying of carbohydrate has a major influence on postprandial glycaemia^{18,20–23}; (b) the latter is probably the major determinant of "average" glycaemic control, as assessed by glycated haemoglobin, the traditional marker of the risk of diabetic complications²⁴; and (c) therapies which reduce postprandial glycaemia decrease glycated haemoglobin and have positive effects on the development of cardiovascular disease in both diabetic and non-diabetic subjects.²⁵ There is increasing evidence that postprandial hyperglycaemia per se represents an independent risk factor for cardiovascular disease in patients with, and without, diabetes.²⁵ Gastric emptying is central to blood glucose homeostasis, accounting for ~35% of the variance in the initial blood glucose response to 75 g oral glucose loads in cross sectional studies of healthy subjects¹⁸ and type 2 patients²²—even minor variations in gastric emptying of carbohydrate may have a profound effect on overall postprandial glycaemic and insulin responses.²⁰ Hence dietary or pharmacological interventions which result in a modest, and early, slowing of gastric emptying have the potential to minimise postprandial glycaemic excursions in healthy subjects and type 2 diabetics and, thereby, optimise glycaemic control.²¹ Pharmacological doses of GLP-1 also have a number of effects in addition to slowing of gastric emptying and stimulation of insulin secretion which are likely to be helpful in the management of type 2 diabetes, including inhibition of glucagon secretion, reduction in appetite and food intake, enhancement of glucose disposal and, possibly, stimulation of pancreatic β cell proliferation.^{26,27}

Due to its rapid degradation by dipeptidyl peptidase IV, GLP-1 has a half life of only ~5 minutes in humans, and this has impeded its development as an antidiabetic agent.²⁸ Hence there is considerable interest in the relatively

recent development of longer acting GLP-1 receptor agonists, such as exendin-4 (exenatide),²⁹ and GLP-1 analogues, such as liraglutide,³⁰ which have been shown to lead to significant improvements in average glycaemic control in patients with type 2 diabetes. (Exenatide has recently been approved for use in the USA.) The relative contribution of different mechanism(s) by which these drugs improve glycaemic control, including effects on gastric and small intestinal motility, are at present poorly defined. Nor is it known whether an effect to delay gastric emptying has implications for the substantial number of type 2 diabetic patients in whom gastric emptying is already abnormally slow.²¹ Nevertheless, it is implicit that such properties of GLP-1 and incretin mimetics will have positive and, potentially negative, effects in patients. Accordingly, it would be appropriate to extend the observations of Schirra and colleagues¹⁴ to evaluate the actions of incretin based antidiabetic medications in type 2 diabetic patients.

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Authors' affiliations

M Horowitz, University of Adelaide, Endocrine and Metabolic Unit, Royal Adelaide Hospital, Adelaide, South Australia 5005, Australia

M A Nauck, Internist/Gastroenterology/Endocrinology, Diabetology (DDG), Diabeteszentrum Bad Lauterberg, Kirchberg, Bad Lauterberg im Harz, Germany

Correspondence to: Professor M Horowitz, Department of Medicine, North Terrace, Royal Adelaide Hospital, Adelaide, South Australia 5005, Australia; michael.horowitz@adelaide.edu.au

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Pancreatic cancer

Anticipating disaster: the genetics of familial pancreatic cancer

M M Lerch

To be born into a family with familial pancreatic cancer, an inheritable, autosomal dominant disorder, has various implications for an individual's life—and none is fortunate. The prospects just turned even darker because of "anticipation", the phenomenon that successive generations are affected by an inheritable disorder at a progressively earlier age. An up to date study shows that "anticipation" is also operative in familial pancreatic cancer, meaning that affected children die approximately 10 years earlier than their affected parents

One of the definitions *The Oxford English Dictionary* offers for the word "anticipation" is: the action of looking forward to something. This is clearly the opposite of what individuals experience who have the misfortune of being born into a family that is burdened with the risk of an inheritable disorder. In genetics, "anticipation" describes the phenomenon that successive generations within a family are affected by an inherited disorder at either a progressively earlier age or with progressively greater severity. For example, if the malignant melanoma that affected your father at the age of

50 years was one of the inheritable variety, you have a good chance as a daughter or a son of this patient to develop malignant melanoma at the age of 30–35 years,¹ provided you have inherited the gene that places you at risk. Genetic "anticipation" therefore implies, indeed, nothing to look forward to. When the respective inheritable disorder is not one for which the offspring of an affected founder can be tested because no genetic assay is yet available or when a cure for this disorder is neither available nor within sight, "anticipation" feels like rolling dice with the devil for those at risk.

The phenomenon has been reported in families affected by Huntington's chorea,² familial leukaemias,³⁻⁵ and also certain types of lymphomas.⁶⁻⁸ If the diagnosis in question were to be pancreatic cancer, in which long term survival is close to zero even after technically successful surgery and no genetic test exists for most families, "anticipation" would truly spell disaster.

This is the question a consortium of two recruiting centres based in the UK (EUROPAC) and Germany (FaPaCa) have put to the test in a study⁹ that appears in the present issue of *Gut* (see page 252). For a number of years, both registries have been actively searching for kindreds affected by familial pancreatic cancer¹⁰ and other inherited disorders of the pancreas^{11,12} and have pooled their impressive resources of 1223 patients at risk for pancreatic cancer from 106 familial pancreatic cancer kindreds for the purpose of this trial.

For the uninitiated or the statistically naïve, the question of "anticipation" in this setting would be straightforward: all you have to do is compare the age of onset in the 80 available child-parent pairs of the study and, provided the parents were older than the children when pancreatic cancer was diagnosed, the difference in age will tell you the extent of anticipation. That approach alone however would likely be fraught with error because of recruitment bias and the way affected families are generally identified. As the sporadic variety of pancreatic cancer is much more