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THEN AND NOW

The incretin hormones: from scientific discovery to practical therapeutics

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Abstract The incretins are gut hormones secreted in response to nutrient/carbohydrate ingestion and act on the pancreatic beta cell to amplify glucose-stimulated insulin secretion. Incretin hormone-based treatments for patients with type 2 diabetes represent a major advance in diabetes therapeutics. The ability of the incretin agents (glucagon-like peptide 1 [GLP-1] agonists and dipeptidyl peptidase IV [DPP-4] inhibitors) to improve glycaemia with a low associated risk of hypoglycaemia, together with beneficial/neutral effects on body weight, offers a significant advantage for both patients and treating clinicians. In this edition of 'Then and Now,' it is useful to look back 25 years and reflect upon the developments in this field since Nauck and colleagues published two seminal papers. In 1986 they first documented a reduced incretin effect in patients with type 2 diabetes (*Diabetologia* 29:46–52), and then in 1993 they demonstrated that, in patients with poorly controlled type 2 diabetes, a single exogenous infusion of an incretin (GLP-1) increased insulin levels in a glucose-dependent manner and normalised fasting hyperglycaemia (*Diabetologia* 36:741–744). In the ensuing 26 years, progress in the field of incretin hormones has resulted in a greater understanding of the relative roles of GLP-1 and glucose-dependent insulinotropic polypeptide secretion and activity in the pathogenesis of type 2 diabetes and the important recognition that native GLP-1 is quickly degraded by the ubiquitous protease DPP-4. This has led to the development of GLP-1 agonists that are resistant to degradation by DPP-4 and of selective inhibitors of DPP-4 activity as therapeutic agents. GLP-1 agonists (exenatide and liraglutide) and DPP-4 inhibitors (sitagliptin, vildagliptin, saxagliptin and linagliptin) currently represent effective treatment options for patients with type 2 diabetes. Several additional agents are in the pipeline, including longer acting DPP-4-resistant GLP-1 agonists. More exciting, however, is the increasing recognition that the incretin agents have numerous extra-glycaemic effects that could translate into potential cardiovascular and other benefits.

Keywords GIP · GLP-1 · Incretin hormones

Abbreviations

CNS	Central nervous system
DPP-4	Dipeptidyl peptidase IV
GIP	Glucose-dependent insulinotropic peptide
GLP-1	Glucagon-like peptide 1

Then

In their 1986 *Diabetologia* paper [1], Nauck et al described the results of an elegant study in which they studied beta cell secretory responses during an oral glucose tolerance test and an isoglycaemic clamp study. They found that, although immunoreactive glucose-dependent insulinotropic polypeptide (GIP) responses to an oral glucose load were not different between controls and diabetic patients, there was an impaired incretin effect in the face of normal GIP levels in patients with type 2 diabetes. They concluded that this reduced incretin effect may be explained by decreased

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sensitivity of the beta cells towards the stimulatory effect of GIP on insulin secretion. It is important to note that Nauck et al described the reduced incretin effect of GIP and not glucagon-like peptide 1 (GLP-1), because at that time GIP was the only incretin to have been identified and studied. However, in this 1986 paper, Nauck et al. did hypothesize that the reduced incretin effect they had observed in their diabetic patients could also be explained by hyposecretion or reduced effectiveness of as yet unidentified humoral or neural gut factors with incretin activity. This was confirmed in 1987, when GLP-1 was identified as an incretin hormone and shown to be more effective than GIP in stimulating insulin release on a molar basis, at an equivalent level of glycaemia [2]. In this study, performed in non-diabetic volunteers during an intravenous glucose load, GLP-1 greatly enhanced insulin release, reduced glucagon concentrations and significantly reduced peak plasma glucose concentrations, compared with a control saline infusion. By comparison, infusion of GIP at physiological levels was less effective in stimulating insulin release. This was confirmed by several others including Nauck and his colleagues who used human GIP (as opposed to porcine GIP used earlier) to demonstrate that in mild type-2 diabetes, GLP-1, in contrast to GIP, not only retains much of its effect to enhance insulin secretion, but in addition, lowers glucagon concentrations [3].

In their second seminal *Diabetologia* paper, published in 1993 [4], Nauck et al demonstrated that, in the fasting state, exogenous GLP-1 infusion stimulates insulin and reduces glucagon secretion, and leads to a normalisation of plasma glucose concentrations even in patients with poorly-controlled type 2 diabetes with secondary failure after sulfonylurea treatment. Furthermore, its glucose-dependent effect to enhance insulin secretion limited the amount of insulin secreted when high doses of GLP-1 were administered at near-normal fasting plasma glucose concentrations.

Now

Moving on to the present, in the 26 years since the publication of the first of the two Nauck papers discussed above, our knowledge of incretin physiology has improved and the relative roles of GIP and GLP-1 secretion and activity in the pathophysiology of type 2 diabetes have been further clarified [5]. It is now well recognised that GLP-1 not only stimulates glucose-mediated insulin secretion, but also has beneficial effects on glucagon, gastric emptying and satiety—additional effects that GIP lacks [5]. Thus, although GIP was the first incretin to be identified and studied, it is now clear that its ability to stimulate glucose-dependent insulin secretion (even at supraphysiological levels) is impaired, even though its secretion is not impaired in patients with diabetes. Thus, its potential value as a therapeutic agent has greatly diminished [4, 5]. On the other hand, GLP-1 retains its enhancing effects on insulin secretion in patients with type 2 diabetes, independent of its plasma levels. In earlier studies there have been problems with the assay used to identify GLP-1 and with measuring total versus active GLP-1 levels. Thus, GLP-1 levels have variously been described as being normal, decreased or even increased in patients with diabetes [6]. Nauck et al recently performed a detailed analysis of the data from nine studies with 13 datasets and 406 participants (189 patients with type 2 diabetes, 217 healthy controls) [6]. They concluded that GLP-1 secretion is influenced by several factors, some of which (e.g. higher weight/BMI and high glucagon concentrations) predict lower GLP-1 responses, while other factors (e.g. older age, and higher fasting NEFA concentrations) are determinants of enhanced GLP-1 secretion. Thus, in a given individual, the ability to predict 'normal' or impaired GLP-1 responses will depend on the relative impact of the above factors, as well as the rate of gastric emptying on GLP-1 secretion. It is also important to note that GLP-1 is predominantly secreted from the L cells in the distal gut (ileum, colon/rectum), while GIP is secreted from the K cells in the proximal small intestine [6]. However, the ingestion of nutrient/glucose results in a very early rise in plasma GLP-1, much before nutrients have entered the lower gut. This suggests that GLP-1 is released from GLP-1-producing L cells, which are present in small numbers in the upper gut, rather than from the main source in the distal gut. It is also possible that neural factors are involved. In human studies, resections of the small intestine, as well as proctocolectomy, do not change overall GLP-1 responses, particularly not the early increment after oral glucose [7]. Furthermore, it is now known that a subset of enteroendocrine cells in humans co-express both GLP-1 and GIP. Thus, it is possible that there is simultaneous secretion of these hormones by gut nutrient stimulation [8]. In addition, GLP-1 secretion itself may be regulated in part by GIP secretion from the upper gut. In a recent study, Mentis et al demonstrated that in type 2 diabetes, GIP does not further amplify the insulin secretion and glucose-lowering effects of GLP-1 [9]. Surprisingly, GIP blunted the suppression of glucagon by GLP-1 [9]. Further research is ongoing into the molecular mechanisms/receptors responsible for GLP-1 and GIP secretion and their enteroendocrine effects.

Possibly the most important advance in the field of incretin biology since the publication of the Nauck papers is the finding that native GLP-1 is quickly degraded by the ubiquitous protease dipeptidyl peptidase IV (DPP-4) [10]. This discovery, more than any other, has led to the therapeutic translation of the basic science of incretin biology and the development of GLP-1 agonists resistant to degradation by DPP-4 and of selective inhibitors of DPP-4 activity as therapeutic agents. An important practical distinction between the DPP-4-resistant GLP-1 agonists and DPP-4

inhibitors is the fact that GLP-1 agonists have to be injected subcutaneously, while the DPP-4 inhibitors are all oral agents. Given a choice, most patients would prefer oral agents over injectable agents. On the other hand, subcutaneous injection of GLP-1 agonists results in far more potent stimulation of insulin secretion than is obtained after oral ingestion of DPP-4 inhibitors, which result in supraphysiological levels of endogenous GLP-1 levels as opposed to pharmacological levels with GLP-1 agonists [5, 10, 11]. This translates into far more effective glucose lowering with the GLP-1 agonists. It is important to note that although DPP-4 inhibition results in a systemic increase in active GLP-1 levels, recent animal data suggest that the glycaemic effects of DPP-4 inhibition might also involve local intestinal inhibition of DPP-4 activity, activation of incretin receptors, reduced liberation of bioactive peptides and increased vagus nerve activity [12]. In addition, unlike DPP-4 inhibitors, the GLP-1 agonists slow gastric emptying, increase satiety and promote modest weight loss [5, 10, 11]. It is possible that these differences are due to the DPP-4 inhibitors blocking the degradation of peptides such as GIP and neuropeptide Y, which exert opposite effects on gastric motility and the central nervous system (CNS) control of appetite [5].

Another practical issue with DPP-4 inhibitors is whether these agents are effective in patients with poorly controlled type 2 diabetes who have a longer duration of disease and possibly have reduced GLP-1 secretion. In these patients, raising GLP-1 levels to supraphysiological levels with DPP-4 inhibitors (as opposed to pharmacological levels) may not be enough to lower blood glucose levels. However, a recent placebo-controlled study [13] demonstrated that the DPP-4 inhibitor vildagliptin significantly improved glycaemia (with a lower incidence of hypoglycaemia) in patients with type 2 diabetes with long-standing disease (~15 years) and poor glycaemic control (HbA_{1c} ~8.4% [68 mmol/mol]) on large doses of insulin (~80 units daily). The effects on glycaemia were even more pronounced in older patients (aged >65 years). When these patients were followed (in an open-label manner) for 1 year, the improved glycaemic control was sustained, as was the reduction in the incidence of hypoglycaemic events [14]. Although these data are promising, larger studies with longer duration of treatment with DPP-4 inhibitors are needed to evaluate whether efficacy is sustained in the longer term. Additionally, there is a need for longitudinal studies in patients with impaired glucose tolerance/type 2 diabetes to document whether GLP-1 secretion/activity really does decline over time.

Finally, the most promising aspects of incretin hormone-based treatment are the extra-glycaemic effects of these agents (Fig. 1). Several clinical studies have documented improved beta cell function after treatment with the incretin agents. But, what is more important is their beneficial effects on beta cell regeneration/function (mainly seen in pre-clinical studies), which have the potential to translate into better preservation of beta cell function and maybe even stabilisation/reversal of the diabetic disease process. The improved effects of the incretins on the beta cell have also been implicated in the remission of diabetes, seen in many patients who undergo bariatric surgery procedures. In the extreme, the enhanced effect of GLP-1 to promote

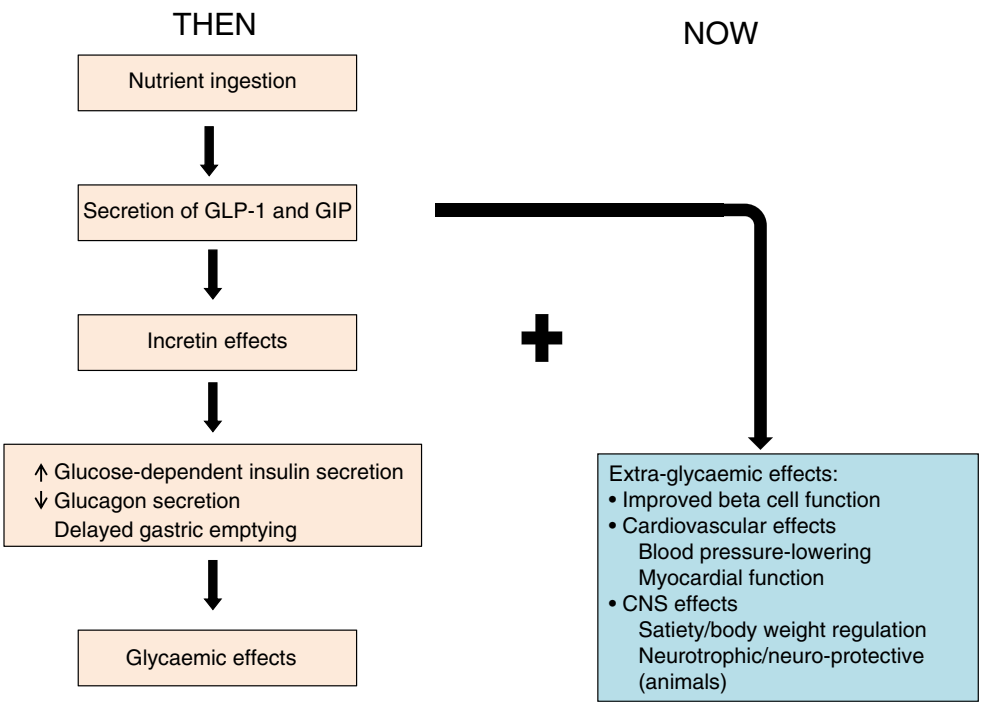

Fig. 1 Glycaemic and extra-glycaemic effects of the incretin hormones

postprandial insulin secretion after Roux-en-Y bypass surgery may also result in the hyperinsulinaemic hypoglycaemia seen in some individuals [15]. It is important to note that different bariatric surgery procedures result in distinct anatomical rearrangement of the normal proximal–distal gut axis with differences in levels of gut hormones and remission of diabetes. In addition to the gastrointestinal effects of the incretins, the cardiovascular effects have attracted a great deal of attention. Reduced blood pressure and improved lipids and endothelial/myocardial function have been seen in pre-clinical and clinical studies and have the potential to improve cardiovascular outcomes. Recent data from animal models suggest that some cardioprotective and vasodilatory actions of GLP-1(7–36) are independent of the known GLP-1 receptor and are mediated, at least in part, by its metabolite GLP-1(9–36) [16]. Even more intriguing than the effects of the incretins on cardiovascular disease are the effects on the CNS. GLP-1 receptors are widely expressed in the CNS and, although their stimulation is classically related to regulation of appetite and satiety, recent pre-clinical data suggest a neuroprotective/neurotrophic function of GLP-1 and, perhaps, the potential for halting/reversing neurodegenerative CNS disorders like Alzheimer's disease [17].

The incretin hormones have now established their role as effective glucose-lowering agents. Whether they will fulfil their potential extra-glycaemic effects described above will depend on the results of well-designed, long-term studies. In the meantime, it is important to monitor the long-term safety of the incretin agents as regards pancreatitis, C cell hyperplasia and medullary thyroid cancer [18]. However, the enormous progress we have made in the field of incretin-hormone biology in the 26 years from Then (in 1986) to Now (in 2012) gives hope for a bright future for those with type 2 diabetes.

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Duality of interest S. Mudaliar is a consultant for Bristol-Myers-Squibb, AstraZeneca and Boehringer Ingleheim; is on the Speakers Bureau of Bristol-Myers-Squibb, AstraZeneca and Boehringer Ingleheim and has received research grant support from Bristol-Myers-Squibb, AstraZeneca and Amylin paid to the Veterans Medical Research Foundation. R. R. Henry is a consultant for Boehringer Ingelheim, Eli Lilly, Merck and Novo Nordisk; is on the Advisory Board of Amylin, Boehringer Ingelheim, Merck and Novo Nordisk and has received research grant support from Amylin, Bristol-Myers-Squibb, Boehringer Ingelheim, Eli Lilly, Merck, Novo Nordisk and AstraZeneca.

References

1. Nauck M, Stöckmann F, Ebert R, Creutzfeldt W (1986) Reduced incretin effect in type 2 (non-insulin-dependent) diabetes. Diabetologia 29:46–52
2. Kreymann B, Williams G, Ghatei MA, Bloom SR (1987) Glucagon-like peptide-1 7–36: a physiological incretin in man. Lancet 2:1300–1304
3. Nauck MA, Heimesaat MM, Orskov C, Holst JJ, Ebert R, Creutzfeldt W (1993) Preserved incretin activity of glucagon-like peptide 1 [7–36 amide] but not of synthetic human gastric inhibitory polypeptide in patients with type-2 diabetes mellitus. J Clin Invest 91:301–307
4. Nauck MA, Kleine N, Ørskov C, Holst JJ, Willms B, Creutzfeldt W (1993) Normalisation of fasting hyperglycaemia by exogenous glucagon-like peptide 1 (7–36 amide) in type 2 (non-insulin-dependent) diabetic patients. Diabetologia 36:741–744
5. Nauck MA (2011) Incretin-based therapies for type 2 diabetes mellitus: properties, functions, and clinical implications. Am J Med 124(1 Suppl):S3–S18
6. Nauck MA, Vardarli I, Deacon CF, Holst JJ, Meier JJ (2011) Secretion of glucagon-like peptide-1 (GLP-1) in type 2 diabetes: what is up, what is down? Diabetologia 54:10–18
7. Nauck MA, Siemsglüss J, Orskov C, Holst JJ (1996) Release of glucagon-like peptide 1 (GLP-1 [7–36 amide]), gastric inhibitory polypeptide (GIP) and insulin in response to oral glucose after upper and lower intestinal resections. Z Gastroenterol 34:159–166
8. Mortensen K, Christensen LL, Holst JJ, Orskov C (2003) GLP-1 and GIP are colocalized in a subset of endocrine cells in the small intestine. Regul Pept 114:189–196
9. Mentis N, Vardarli I, Köthe LD et al (2011) GIP does not potentiate the antidiabetic effects of GLP-1 in hyperglycemic patients with type 2 diabetes. Diabetes 60:1270–1276
10. Drucker DJ, Nauck MA (2006) The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. Lancet 368:1696–1705
11. Chia CW, Egan JM (2008) Incretin-based therapies in type 2 diabetes mellitus. J Clin Endocrinol Metab 93:3703–3716
12. Waget A, Cabou C, Masseboeuf M et al (2011) Physiological and pharmacological mechanisms through which the DPP-4 inhibitor sitagliptin regulates glycemia in mice. Endocrinology 152:3018–3029
13. Fonseca V, Schweizer A, Albrecht D, Baron MA, Chang I, Dejager S (2007) Addition of vildagliptin to insulin improves glycaemic control in type 2 diabetes. Diabetologia 50:1148–1155
14. Fonseca V, Baron M, Shao Q, Dejager S (2008) Sustained efficacy and reduced hypoglycemia during one year of treatment with vildagliptin added to insulin in patients with type 2 diabetes mellitus. Horm Metab Res 40:427–430
15. Salehi M, Prigeon RL, D'Alessio DA (2011) Gastric bypass surgery enhances glucagon-like peptide 1-stimulated postprandial insulin secretion in humans. Diabetes 60:2308–2314
16. Ban K, Noyan-Ashraf MH, Hoefer J, Bolz SS, Drucker DJ, Husain M (2008) Cardioprotective and vasodilatory actions of glucagon-like peptide 1 receptor are mediated through both glucagon-like peptide 1 receptor-dependent and -independent pathways. Circulation 117:2340–2350
17. Li Y, Duffy KB, Ottinger MA et al (2010) GLP-1 receptor stimulation reduces amyloid-beta peptide accumulation and cytotoxicity in cellular and animal models of Alzheimer's disease. J Alzheimers Dis 19:1205–1219
18. Drucker DJ, Sherman SI, Bergenstal RM, Buse JB (2011) The safety of incretin-based therapies—review of the scientific evidence. J Clin Endocrinol Metab 96:2027–2031