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Development and therapeutic potential of incretin hormone analogues for type 2 diabetes

BRIAN D GREEN, NIGEL IRWIN, VICTOR A GAULT, FINBARR PM O'HARTE, PETER R FLATT

Abstract

The rising prevalence of type 2 diabetes and increasing burden of diabetic complications requires new approaches to diabetes therapy. An encouraging new approach for development of future anti-diabetic drugs is based on analogues of incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Both peptides reduce postprandial glucose by stimulating glucose-dependent insulin release and exert a number of other beneficial actions including trophic effects on the beta-cell. Efforts are currently focused on developing stable analogues of GLP-1 and GIP which are resistant to dipeptidylpeptidase IV mediated degradation and renal filtration. Thus, by increasing the half-life and potency of these incretins, they should become a new class of agents for the treatment of type 2 diabetes.

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Key words: GLP-1, GIP, incretin hormones, diabetes

Introduction

The 'enteroinsular axis' was a term coined by Unger and Eisentraut¹ to describe all the gut factors which contribute to enhanced insulin secretion following a meal. The insulinotropic action of incretin gut hormones, GLP-1 and GIP, form the greatest part of this effect. These physiological peptides are released from intestinal endocrine cells following feeding, and their glucose-lowering actions have fuelled speculation that they have therapeutic potential for type 2 diabetes. More recently, beneficial effects of GLP-1 and GIP on beta-cell growth and viability, differentiation and insulin biosynthesis have been reported also. This review considers the obstacles that have hindered development of GLP-1 and GIP into the clinic, and the steps which are being taken to overcome them.

Correspondence to: Dr Brian D Green
School of Biomedical Sciences, University of Ulster, Coleraine, BT52 1SA,
Northern Ireland.
Tel: +44 (0)28 7032 4313; Fax: +44 (0)28 7032 4965
E-mail: b.green@ulster.ac.uk

Table 1. An overview of functional characteristics of GLP-1 and GIP

	GLP-1	GIP
Released in response to a mixed meal	✓	✓
Lower blood glucose	✓	✓
Glucose-dependent stimulation of insulin secretion	✓	✓
Suppress glucagon secretion	✓	-
Enhance beta-cell survival	✓	✓
Stimulate beta-cell expansion	✓	✓
Extrapancreatic glucose-lowering actions	✓	✓
Suppress gastric acid secretion	-	✓
Inhibition of gastric emptying	✓	-
Inhibition of hepatic insulin extraction	-	✓
Enhance safety	✓	-
Reduce body weight	✓	-

Difficulties associated with current treatments of type 2 diabetes

Type 2 diabetes is characterised by two main defects; impairment of pancreatic beta-cell function, and insulin insensitivity of muscle and liver. Any optimal treatment strategy to tackle this disease should preferably address both of these defects, as well as the resultant hyperglycaemia. Dietary control is always the primary approach to type 2 diabetes, and reducing adiposity will enhance insulin sensitivity and improve glucose control.^{2,3} However, moderate or severe hyperglycaemia invariably requires drug intervention.^{4,5} Current therapies improve metabolic abnormalities by enhancing insulin secretion (sulphonylureas; meglitinides) or reducing insulin resistance (biguanides; thiazolidinediones). Additional treatments include α -glucosidase inhibitors (acarbose; miglitol) to reduce the rate of carbohydrate digestion and absorption, and anti-obesity agents (sibutramine; orlistat) to lower body weight.

All of the available agents are limited in efficacy by the progressive deterioration of beta-cell function that occurs throughout the natural history of type 2 diabetes. Thus, a future treatment that could prevent or reverse this gradual beta-cell decline would be a particularly advantageous addition to existing treatments.

The advantages of incretin hormone-based treatments for type 2 diabetes

Incretin hormones are nature's mediators of postprandial insulin secretion forming the basis of the so-called 'enteroinsular axis'.

Abbreviations

DPP IV	dipeptidylpeptidase IV
FDA	Food and Drug Administration
GIP	Glucose-dependent Insulinotropic Polypeptide (also known as Gastric Inhibitory Polypeptide)
GLP-1	Glucagon-Like Peptide-1

Table 2. The advantages and disadvantages of incretin-based anti-diabetic therapies**Advantages**

- Physiological interaction with specific receptors on target cells
- Potent glucose-dependent and short-lived insulin-releasing action; therefore avoid the occurrence of hypoglycaemia
- Lower glucose levels by several other distinct mechanisms
- Exert proliferative and protective effects on the pancreatic beta-cell, improving cell mass and insulin biosynthesis
- Exert genotypic and phenotypic changes from pancreatic ductal tissues to beta-cell tissue

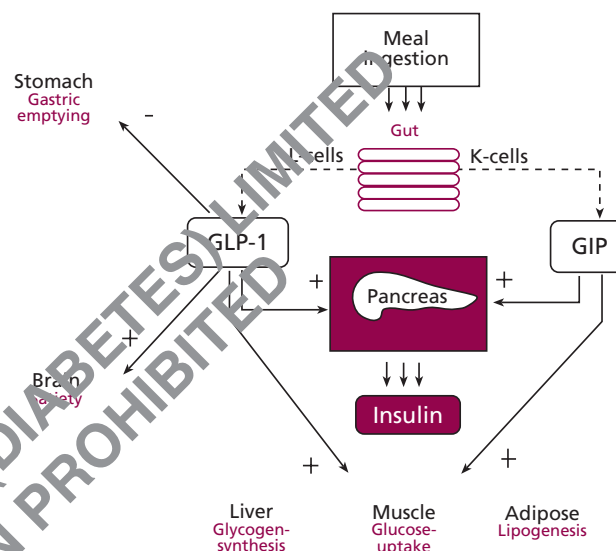
Disadvantages

- Not immediately suitable as an orally administered therapy
- Rapidly degraded by DPP IV*
- Suffer from renal filtration

* DPP IV = dipeptidylpeptidase IV

Figure 1. Biological actions of GLP-1 and GIP on organs and peripheral tissues

Following meal ingestion GLP-1 and GIP are released from intestinal L-cells and K-cells, respectively. GLP-1 and GIP lower glucose by stimulating insulin release from the endocrine pancreas and improve glucose uptake and utilisation in peripheral tissues (liver, muscle and adipose). In contrast to GIP, GLP-1 brings about feelings of satiety and fullness by interaction with its receptors in the brain. GLP-1 also exerts inhibitory effects on gastric emptying



Through a range of actions, incretins aid the physiological control of postprandial blood glucose (table 1). The glucose-dependent nature of the stimulation of insulin secretion by GLP-1 and GIP means that they are unlikely to lead to hypoglycaemic episodes as associated with other insulin-releasing agents used in the treatment of type 2 diabetes.^{6,7} This is one of the main attributes of incretin hormones that has led to the recent interest in both GLP-1 and GIP as potential therapies of type 2 diabetes.⁸

From the list of properties of GLP-1, there are many which represent advantages for the treatment of type 2 diabetes (table 2). Besides stimulating insulin release and glucose-uptake, which leads to the lowering of glucose levels in type 2 diabetic patients,⁸ GLP-1 also stimulates insulin gene-transcription, increases pancreatic beta-cell mass⁹ and protects against beta-cell apoptosis,⁹ which may compensate for the defective regulation of insulin secretion. In peripheral tissues, such as liver, skeletal, muscle, and adipose tissue, GLP-1 exerts many insulin-like anabolic actions (figure 1). These anabolic effects, such as promotion of glucose uptake, glycogenesis and lactate production,⁸ contribute to the removal of glucose from the circulation. Finally, as the development of type 2 diabetes is strongly linked with obesity, the association of GLP-1 with improved satiety and often some weight loss are of potential significance.¹⁰

GIP too has many similar benefits other than its physiological glucose-dependent insulinotropic actions (table 1). For example, GIP stimulates proinsulin gene transcription and translation.⁸ GIP also stimulates cellular proliferation and inhibits apoptosis of

insulin producing cells,⁸ thus avoiding the risk of potential beta-cell exhaustion. It has been proposed also that GIP may exert some effects on insulin extraction¹¹⁻¹³ compensating for the reduced insulin secretion associated with type 2 diabetes. In addition, GIP has been shown to inhibit hepatic glucose production⁸ and to promote glucose uptake and metabolism in muscle⁸ (figure 1). Also, GIP unlike GLP-1 does not slow gastric emptying which may be a useful attribute in determining its therapeutic tolerability.¹⁴ Functional GIP receptors have been identified on adipocytes and shown to stimulate glucose transport and lipoprotein lipase activity.⁸ An effect of GIP on glucagon secretion is evident at euglycaemia and thus probably inconsequential in diabetic patients.¹⁵ As a consequence of these diverse biological actions, the incretin hormones are coming under increasing investigation as potential multi-functional antidiabetic agents.

Obstacles in bringing incretin hormone-based therapies to the clinic

Unfortunately, the potential benefits that GIP and GLP-1 could bring to type 2 diabetes therapy are limited by biological degradation and renal elimination *in vivo* (table 2). GLP-1 and GIP are swiftly inactivated by degradation at the N-terminus (figure 2) by the aminopeptidase enzyme, DPP IV; EC.3.4.14.5, present in blood and tissues.¹⁶ DPP IV actively cleaves amino terminal dipep-

tides from peptides that contain penultimate Pro, Ala or hydroxyproline residues.⁸ Accordingly, the amino-terminal dipeptides are removed from GLP-1 and GIP (His⁷-Ala⁸ and Tyr¹-Ala², respectively) to leave non-insulinotropic peptides.⁸ In fact, GLP-1(9-36)amide and GIP(3-42) may be specific antagonists of their respective receptors, acting in opposition to the intact GLP-1 and GIP.^{17,18} The rapid degradation of circulating GLP-1 and GIP by DPP IV (t_{1/2} 3–5 minute) makes their therapeutic use problematic. Furthermore, as with many peptides in the circulation, GLP-1 and GIP are rapidly cleared from the bloodstream by renal filtration (t_{1/2} < 10 minutes).¹⁹

The peptide nature of GLP-1 and GIP makes them most suitable for injection. However, oral administration, where GLP-1 is conjugated to zinc²⁰ or encapsulated in a buccal tablet²¹ has shown promise. Furthermore, the use of inhaled 'intrapulmonary' insulin has shown promise of late as an effective alternative to subcutaneous injection. A similar approach may be effective with stable incretin analogues. Indeed, the application of other modes of drug delivery, such as transcutaneous patches, warrants further investigation. Capsules containing genetically engineered cells to secrete GLP-1 have been proposed for *in situ* peptide delivery.²²

Strategies to prolong and enhance incretin hormone actions

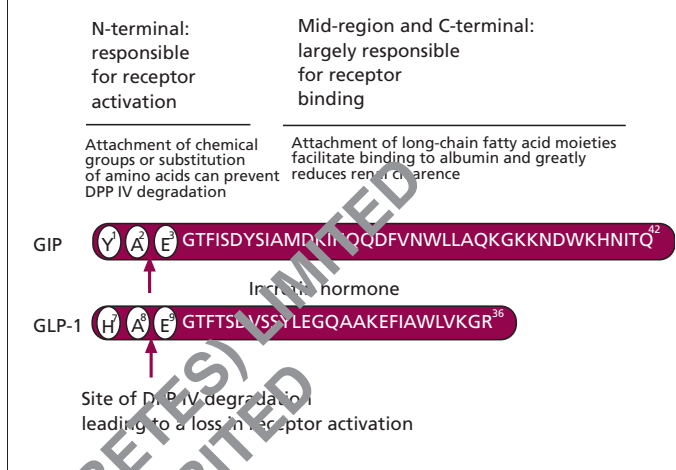
Several different strategies for peptide engineering have been applied to prolong and enhance the actions of incretin hormones. Logically the most direct way of tackling the degradation caused by DPP IV is N-terminal modification of GLP-1 or GIP near or adjacent to the cleavage site (figure 2). N-terminal modification of GLP-1 (at His⁷, Ala⁸, Glu⁹) or GIP (at Tyr¹, Ala²) has been successful in generating DPP IV resistant peptides with potent or 'super' potent biological activity.⁸ In fact, the generation and characterisation of a series of analogues have established that strategic modifications to the N-termini of either GLP-1 or GIP lead to the inhibition or even complete prevention of DPP IV-mediated degradation.⁸

GLP-1 analogues modified at His⁷, such as desamino-GLP-1, (D-His⁷)GLP-1, N-Me-GLP-1 and N-pyroglutamyl GLP-1, are often highly resistant to degradation by DPP IV, but in most cases suffer losses in biological activity.⁸ GLP-1 analogues modified at Ala⁸, such as (D-Ala⁸)GLP-1, (Ser⁸)GLP-1, (Aib⁸)GLP-1, (Val⁸)GLP-1 and (Abu⁸)GLP-1, are usually resistant to DPP IV degradation with similar or improved biological activities.⁸ Finally, GLP-1 analogues modified at Glu⁹, such as (Asp⁹)GLP-1, (Ala⁹)GLP-1, (Pro⁹)GLP-1, (Phe⁹)GLP-1 and (Tyr⁹)GLP-1 display varying degrees of resistance to DPP IV and varying degrees of biological activity.⁸ Synthetic GLP-1 analogues of particular note, which possess improved antihyperglycaemic activity compared with native GLP-1, are (Val⁸)GLP-1 and (Pro⁹)GLP-1.⁸

GIP analogues modified at Tyr¹ such as N-acetyl, N-glucitol, N-pGlu, N-Fmoc displayed remarkable resistance to DPP IV inactivation.^{23,24} This concurs with the well-established DPP IV binding specificity, predicting the requirement of a free protonated α -amino group.²⁵ Tyr¹ modification of native GIP thus masks this

Figure 2. Regions targeted for structural modification of incretin hormone

The major incretin hormones (GLP-1 and GIP) possess similar peptide structures which can be either modified, N-terminally to prevent DPP IV degradation, or C-terminally to circumvent renal filtration



potential binding site resulting in metabolically stable peptide analogues. All the aforementioned Tyr¹ modified GIP analogues significantly stimulated insulin secretion and lowered plasma glucose concentrations compared with native GIP in the type 2 ob/ob mouse model. Hence, these Tyr¹ modified GIP analogues act as 'super' GIP agonists and are able to overcome the severe insulin resistance and beta-cell defect. A series of Ala² substituted analogues of GIP has also been developed and their antidiabetic potential assessed in animal models of type 2 diabetes.⁸ Several of these GIP analogues including; (Ser²)GIP, (Gly²)GIP and (DAIa²)GIP exhibited significantly improved antihyperglycaemic and insulinotropic activity compared to native GIP. However, it was evident that their efficacy was not as impressive as the Tyr¹ modified GIP analogues.

Certain modifications can have opposite effects on GLP-1 and GIP. For example, N-terminal extension of GLP-1 with glucitol, acetyl or pyroglutamyl groups reduced receptor binding, cAMP production and insulin secretion.⁸ Identical modifications of GIP led to analogues with enhanced bioactivity and improved antihyperglycaemic performance *in vivo*.⁸ Interestingly, parallel substitutions of proline for Glu⁹ of GLP-1, or Glu³ of GIP have led to biological properties which are entirely different to native peptides. (Pro⁹)GLP-1 appears to be a novel and DPP IV stable GLP-1 agonist,⁸ while (Pro³)GIP is a specific and potent functional antagonist of the GIP receptor.⁸ A recent report directly assessed how an equivalent Ala⁸/Ala² modification affected the bioactivities and DPP IV stabilities of GLP-1 and GIP.²⁶ This noted that (Abu⁸)GLP-1 is a GLP-1 analogue with profound resistance to DPP IV and similar glucose-lowering and insulin-releasing activities to native GLP-1. In contrast, (Abu²)GIP has slightly improved resistance to DPP IV but suffers detrimental losses in biological activity.²⁶

Table 3. Development and structures of GLP-1 and GIP peptides for type 2 diabetes therapeutics

Development name	Product name	Structure	Status	Company
AC-2993	Exenatide	Exendin-4(1-39) (unmodified)	30/04/05 PDUFA	Amylin/ Eli Lilly
AC-2993 LAR (long-acting release)	Exenatide LAR	Modified long-acting Exendin-4(1-39) No structural information available	Phase II	Amylin/ Eli Lilly/Alkermes
NN2211	Liraglutide	GLP-1 plus - Lys ²⁶ contains a hexadecanoyl fatty acid chain on its ε-amino group - Lys ³⁴ replaced with Arg ³⁴	Phase II	NovoNordisk
CJC-1131	CJC-1131	GLP-1 plus - Gly ²⁷ replaced with Lys ³⁷ - Lys ³⁷ contains a reactive chemical linker on its ε-amino group - Ala ⁸ replaced with D-Ala ⁸	Phase II	Conjuchem Inc.
Albugon	Albugon	Recombinant GLP-1-albumin protein	Preclinical trials	Human Genome/ Glaxo-SmithKline
LY315902	LY315902	GLP-1 plus - Lys ³⁴ contains an octanoyl fatty acid chain on its ε-amino group - Lys ²⁶ replaced with Arg ²⁶ - His ⁷ replaced with des-His ⁷	Preclinical trials	Eli Lilly
ZP10A	ZP 10A	Exendin-4(1-39) plus - N-terminally extended with a His - C-terminally extended with 6 Lys residues	Phase II	Zealand/Aventis
BIM51077	BIM51077	GLP-1 analogue No structural information available	Phase I	Roche/Ipsen
GLP-1-I.N.T.	GLP-1-I.N.T.	GLP-1 analogue No structural information available	Preclinical trials	Transition Therapeutics/Novo Nordisk
GLP-1-Tf	GLP-1-Tf	GLP-1 fused to the serum protein transferrin (Tf)	Preclinical trials	Biorexis
N-GIP	N-GIP	N-terminally modified GIP	Preclinical trials	Diabetica

It has been demonstrated, however, that in addition to DPP IV stability another hurdle may need to be surmounted to obtain GLP-1 and GIP preparations that are suitable for once-daily administration. The importance of the kidneys in the final elimination of GLP-1 and GIP has recently been underlined.¹⁹ A successful strategy in delaying such renal filtration has been to attach long-chain fatty acid molecules to GLP-1, a process known as acylation. Acylation of peptides facilitates their binding to plasma proteins, such as albumin, and thus minimises their elimination by the kidney. A number of GLP-1 peptides are currently undergoing pharmaceutical drug evaluation (table 3).

LY315902 is an acylated analogue with an octanoyl fatty acid chain and a half-life of 3–6 hours.²⁷ Acylated GLP-1 analogues in Phase II clinical trials such as Liraglutide (NN2211; NovoNordisk) and CJC-1131 (Conjuchem Inc.) (table 3) have demonstrated activities and half-lives greatly in excess of eight hours.²⁷ Liraglutide contains a hexanoyl fatty acid group attached to the ε-amino group of Lys²⁶, whilst Lys³⁴ is replaced with arginine. CJC-1131 contains a reactive chemical linker attached to the ε-amino group of Lys³⁴, and in addition Ala⁸ is replaced with D-Ala.⁸ This molecule binds to albumin in the circulation. Other

attempts to acylate GLP-1 with palmitate (16 carbon chain fatty acid) produce analogues with moderate activities, but with greatly reduced bioavailability.⁸ A similar strategy to prolong half-life by binding to larger proteins is used by GLP-1 analogues currently in pre-clinical trials namely Albugon (Human Genome/Glaxo-SmithKline) and GLP-1-Tf (Biorexis) (table 3). Although there is little structural information available, Albugon appears to be GLP-1 with recombinant albumin fused to it, and GLP-1-Tf appears to be GLP-1 with the serum protein transferrin fused to it. The potential to prolong the action of GIP by applying similar strategies is currently unknown, with only one palmitate derivatised GIP analogue (N-palmitate-GIP) reported to date.⁸ As shown in table 3, other GLP-1 analogues in clinical trials include ZP10 (Zealand/Aventis; Phase II) and BIM51077 (Roche/Ipsen; Phase I). Exenatide (Amylin/Eli Lilly), which is otherwise known as exendin-4(1-39) or AC-2993 is a DPP IV resistant GLP-1 receptor agonist isolated from the saliva of the Gila Monster lizard. Exenatide has an approximate structural similarity to GLP-1 and mimics its biological actions *in vivo*. Exenatide has been accepted for drug review by the FDA and the Prescription Drug User Fee Act (PDUFA) goal date is in April

2005. A longer-acting formulation of Exenatide, known as Exenatide LAR (long-acting release), is now in Phase II clinical trials.

Current pharmaceutical perspective of long-acting incretin analogues

The first of the GLP-1 analogue based pharmaceuticals are expected to reach the market in 2006. Clinical trials for GLP-1 mimetics are now reaching/completing Phase III (table 3). Exenatide, a twice-daily administered compound is predicted to arrive first on the market* shortly followed by Liraglutide, a once-daily administered compound. In addition, LY307161, a GLP-1 analogue developed by Eli Lilly & Co. has shown effective glucose lowering properties when administered once daily for 21 days to type 2 diabetic subjects.²⁸ Furthermore, CJC-1331 a GLP-1 molecule which is covalently bound to albumin has shown early promise in clinical trials.²⁹

The data from clinical trials indicate that there is a dosage problem associated with Liraglutide administration. High-dose levels (> 0.75 mg) of Liraglutide induce side effects of nausea, vomiting, dizziness and headaches. Side effects can be minimised by using doses of 0.75 mg or less, however the glucose-lowering efficacy at this concentration is disappointing.³⁰ Nausea and vomiting are likely to be the result of the potent effects of GLP-1 on inhibiting gastric emptying.⁸ Exenatide requires lower doses than Liraglutide but is administered twice daily, as opposed to, once daily.³⁰ It is hoped that Phase III trials will resolve problems of dosage, dose regimen and accompanying side effects for both Liraglutide and Exenatide.

The pharmaceutical potential of GIP has yet to be realised despite its discovery over 35 years ago. Substantial basic and pre-clinical studies have now been completed, identifying structurally modified forms of GIP as potentially attractive drug candidates.⁹ N-terminal GIP analogues (Diabetica Ltd) are under investigation (table 3). To date, only one fatty acid derivatised analogue of GIP has been produced and reported, namely N-palmitate-GIP,⁹ and the potential usefulness of strategies to prevent renal clearance for longer-acting preparations needs to be assessed. As GIP does not inhibit gastric emptying in man,¹⁴ adverse gastric side effects exhibited by longer-acting GLP-1 analogues, such as nausea and vomiting, may not be shared by longer-acting GIP agonists. The ability of GIP to reduce hepatic insulin extraction¹³ and thereby increase basal insulin may also be advantageous. Structural modification of GIP also typically results in increased bioactivity,⁹ whereas the opposite is true for similar GLP-1 analogues. This could clearly help address the relatively greater potency of GLP-1 reported in a number of studies.³¹ Thus, although a consequence of generalised beta-cell failure and not a specific or genetic defect, there are several reports where the insulin response to GIP is impaired in humans with type 2 diabetes.³²⁻³⁴ However, recent studies suggest that insensitivity of the beta-cell to GIP in these subjects appears to be a consequence of continuous intravenous injection and is not shared by therapeutic bolus injection.³⁵ Thus, the GIP receptor may represent a particularly attractive target for the development of enzyme-resis-

tant 'super' GIP agonists for type 2 diabetes therapy. Single administration of N-glucitol-GIP to type 2 diabetic subjects resulted in an enhanced and protracted insulinotropic effect without any adverse reaction.³⁶ However, the results of more extensive and detailed clinical studies are awaited with interest.

DPP IV inhibition

An alternative to DPP IV resistant GLP-1/GIP analogues would be to use specific inhibitors of DPP IV, which are now in various stages of development. These could in the future be used, alone to enhance physiological incretin action, or may be combined with native GLP-1 or GIP. One advantage of this approach lies in the possibility of oral administration of such agents. Numerous studies have shown improved glycaemic control following administration of various DPP IV inhibitors in animal models of type 2 diabetes.³⁷⁻³⁹ More importantly however, patients with type 2 diabetes have shown marked improvements in metabolic control following administration of such compounds.⁴⁰ However, the widespread actions of DPP IV and the lack of specificity of DPP IV inhibitors complicate their potential long-term therapeutic use. DPP IV is known to be involved in the metabolism of a number of hormones including neuropeptide Y, peptide YY, growth hormone releasing hormone, glucagon-like peptide-2 and a number of chemokines.²⁵ DPP IV inhibitors in pharmaceutical development include p32/98 (Probiobdrug AG, Halle/Saale, Germany), NVP-DPP728 (Novartis, New Jersey, USA), LAF 237 (Novartis New Jersey, USA), MK-0431 (Merck, Rahway, New Jersey, USA) and K579 (Kyowa Hakko Kogyo Co, Shizuoka-ken, Japan).⁴¹

Future potential of GIP receptor antagonists

A great deal of interest now surrounds the potential of specific GIP antagonists for therapy of obesity and related metabolic disease. One such antagonist is (Pro³)GIP, a metabolically stable, DPP IV resistant and specific GIP receptor antagonist.⁸ Substantial evidence in obese diabetic (ob/ob) mice, points toward a link between hyperphagia, high-fat diet, K-cell hyperplasia and increased circulating GIP concentrations.^{42,43} This would suggest GIP is a key molecule linking hyperphagia to obesity. The potential of selectively preventing GIP receptor signalling has been indicated by Miyawaki and co-workers.⁴⁴ GIP receptor deficient (GIPR^{-/-}) mice were shown to be resistant to the onset of obesity when placed on a high-fat diet compared with controls. In addition, double homozygous mice generated from the cross breeding of GIPR^{-/-} mice and ob/ob mice demonstrated a 23% reduction in body weight gain compared to the genetically obese control animals.⁴⁴ Thus, as the hyperphagia of ob/ob mice is driven by leptin deficiency it was clearly evident that GIP directly links overnutrition to obesity. In addition to controlling the onset of obesity, GIP receptor antagonism should also improve insulin resistance, a major stimulus behind the worsening glucose intolerance of type 2 diabetes. Further studies are clearly warranted

*Approved by FDA, April 2005, to be launched in USA June 2005 as BYETTA (www.byetta.com)



Key messages

- Molecular modifications to the N-terminus of GIP or GLP-1 can confer resistance to degradation by the enzyme DPP IV
- Molecular modifications of GIP and GLP-1 can enhance insulin-secreting potency for potential use as anti-diabetic agents
- Acylation (attachment of long-chain fatty acid moieties) to GLP-1 or GIP further prolongs biological action by conjugation to blood proteins and delaying renal filtration
- Other N-terminal modifications generate stable and specific 'antagonists' of the GIP or GLP-1 receptors, namely (Pro³)GIP and (Lys⁹)GLP-1, respectively
- 'Knock-out' of the GIP receptor protects against the development of obesity and insulin resistance
- GIP receptor antagonism using stable analogues such as (Pro³)GIP represents a potential new approach to counter obesity-related disease

to evaluate the potential of GIP receptor antagonists and their applicability to human obesity-diabetes.

Conclusion

GLP-1 and GIP are incretin hormones with proven beneficial effects for blood glucose control, and a wide-range of analogues have been produced for potential therapy of type 2 diabetes. As a result of enhanced bioavailability and stability to DPP IV degradation these incretin hormone analogues represent a novel class of drug compounds. GLP-1 has come the furthest in terms of progressing to the clinic and several drug candidates are now in the mid- to late-phases of clinical trials. GIP-based compounds have yet to be exploited, but show great promise in late preclinical studies.

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