

News and reviews

Glucose-dependent insulintropic polypeptide (GIP): anti-diabetic and anti-obesity potential?

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Abstract

Glucose-dependent insulintropic polypeptide (GIP or gastric inhibitory polypeptide) is a gastrointestinal hormone, which modulates physiological insulin secretion. Due to its insulintropic activity, there has been a considerable increase of interest in utilising the hormone as a potential therapy for type 2 diabetes. One of the difficulties in attempting to harness the insulintropic activity of GIP into an effective therapeutic agent is its short biological half-life in the circulation. However, recent years have witnessed the development of a substantial number of designer enzyme-resistant 'super GIP' molecules with potent insulintropic and anti-diabetic properties. In addition, observations in transgenic GIP receptor deficient mice indicate that GIP directly links overnutrition to obesity, therein playing a crucial role in the development of obesity and related metabolic disorders. The present review aims to highlight the rapidly emerging potential therapeutic applications of GIP, and especially, enzyme-resistant GIP analogues.

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1. Introduction

Glucose-dependent insulintropic polypeptide (GIP) is a 42 amino acid gastrointestinal hormone synthesised and secreted by enteroendocrine K-cells (Buchan et al., 1978). Following postprandial release into the circulation, the primary role of GIP is to modulate glucose-dependent insulin secretion (Pederson, 1994). In addition to enhancing insulin release, GIP stimulates proinsulin gene transcription and translation (Fehmann and Goke, 1995; Wang et al., 1996). GIP also stimulates the growth, differentiation, proliferation and survival of pancreatic β -cells (Pospisilik et al., 2003; Trumper et al., 2001), and it further acts as a β -cell mitogenic and anti-apoptotic factor (Trumper et al., 2002).

As well as its actions on insulin secretion, GIP exerts various extrapancreatic effects, which further enhance its glucose-lowering ability. Thus, GIP has been shown to inhibit hepatic glucose production (Elahi et al., 1986) and to promote glucose uptake in isolated mouse dia-

phragm muscle (O'Harte et al., 1998a). Functional GIP receptors have also been identified on adipocytes (Yip et al., 1998), where GIP has been shown to stimulate glucose transport (Eckel et al., 1979), increase fatty acid synthesis (Oben et al., 1991) and stimulate lipoprotein lipase activity (Knapper et al., 1995). As a consequence of these biological properties, GIP has recently come under increasing investigation as a potential therapeutic agent for the treatment of diabetes, obesity and related metabolic disorders (Gault et al., 2003a; Holst, 2002; Kieffer, 2003; Meier et al., 2002).

2. Anti-diabetic potential of GIP

2.1. Difficulties associated with therapeutic use of GIP

The two major difficulties associated with attempting to utilise GIP as a potential therapeutic agent are: (1) its rapid degradation in the bloodstream and (2) the apparent resistance of type 2 diabetic subjects to the action of the 'native' hormone.

Immediately after the secretion or exogenous administration of GIP, the native hormone is rapidly

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cleaved (biological half-life of approximately 3–5 min) at the amino-terminus by the ubiquitous enzyme, dipeptidylpeptidase IV (DPP IV), to produce the truncated metabolite, GIP(3–42), as illustrated in Fig. 1 (Kieffer et al., 1995; Mentlein et al., 1993). GIP(3–42) although initially shown to be non-insulinotropic in the perfused rat pancreas (Brown et al., 1981), is now believed to function as a GIP receptor antagonist *in vivo* (Gault et al., 2002a). Furthermore, any intact GIP remaining in the circulation is rapidly filtered in the glomerulus and degraded by renal capillary peptidases, including DPP IV (Mentlein et al., 1993). Involvement of the kidneys in the removal of GIP has been demonstrated in patients suffering from chronic renal failure (Sirinek et al., 1984), as well as by reduced clearance of GIP in nephrectomised rats (Jorde et al., 1981). However, demonstration that DPP IV is the major enzyme involved in degradation (Deacon et al., 2001) indicates that strategies that prevent DPP IV action, such as the use of DPP IV inhibitors (Holst and Deacon, 1998), or enzyme-resistant analogues of GIP (Gault et al., 2003a), can greatly improve the potential therapeutic efficacy of the hormone.

The difficulty of possible GIP resistance derives from early observations of a reduced incretin effect in type 2 diabetes (Perley and Kipnis, 1967). Several studies have since shown blunted early insulin responses to GIP infusion in type 2 diabetic patients, albeit with conflicting degrees of β -cell resistance (Elahi et al., 1994; Jones et al., 1987; Nauck et al., 1986, 1993). These studies have employed infusion conditions designed to produce circulating concentrations in the physiological rather than

the therapeutic range. Moreover, due to the lack of specific antisera (Deacon et al., 2000), the concentrations of active GIP in these infusion studies may well have been greatly overestimated. It is also clear that compromised insulinotropic activity in type 2 diabetes is not confined to GIP, but represents a global defect in insulin secretion, also extending to the sister incretin hormone glucagon-like peptide-1 (GLP-1) (Kjems et al., 2003; Ward et al., 1984). Pancreatic β -cell sensitivity to GIP in type 2 diabetes improves with glyburide treatment and any speculated mutations of GIP receptors are rare (Almind et al., 1998; Kubota et al., 1996). It is also evident that any hypothesised ‘post-receptor’ defect in the β -cell GIP signalling machinery (Vilsboll et al., 2002) can be effectively overcome by enzyme-resistant analogues of GIP (Gault et al., 2002b, 2003b,c; Hinke et al., 2002; O’Harte et al., 1998b, 1999, 2000, 2002).

2.2. Dipeptidylpeptidase IV (DPP IV) inhibition

Since the observation that DPP IV was the key enzyme responsible for the metabolism of GIP and GLP-1 (Kieffer et al., 1995), the use of DPP IV inhibitors to enhance the actions of incretin hormones has been proposed (Holst and Deacon, 1998). Several animal studies using a number of different DPP IV inhibitors have reported marked improvements of metabolism and glycaemic control in diabetes (Ahren et al., 2000; Balkan et al., 1999; Deacon et al., 2001, 2002; Pauly et al., 1999; Pederson et al., 1998a). Administration of the DPP IV inhibitor NVP-LAF237 with pioglitazone has also been

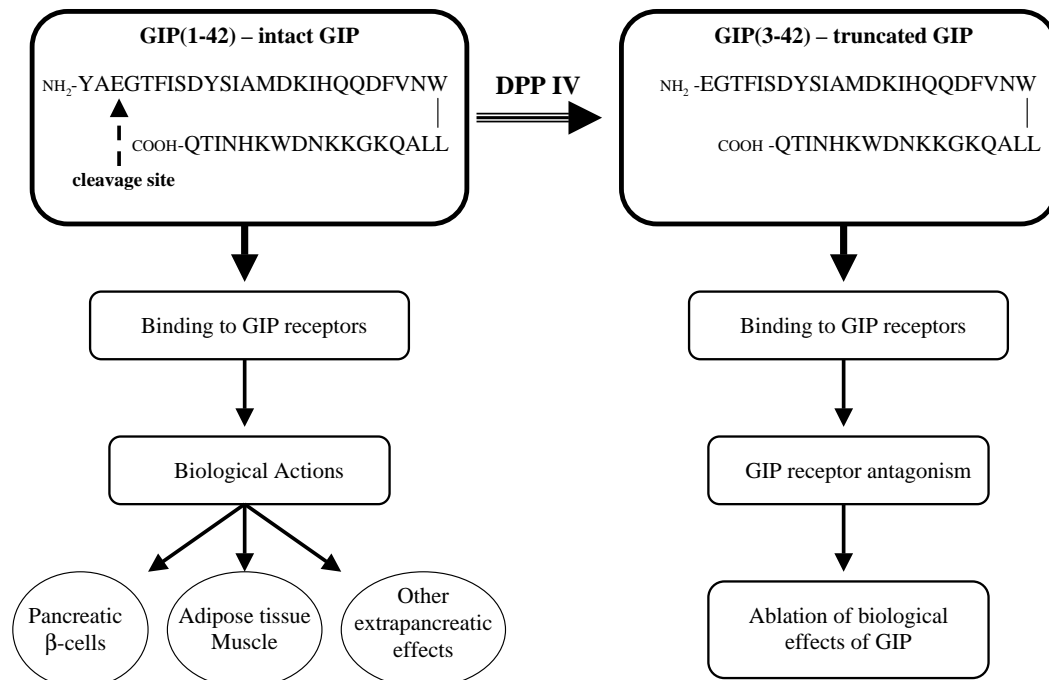


Fig. 1. Biological activity, sequence and cleavage site of GIP(1–42) by dipeptidylpeptidase IV (DPP IV) to produce the antagonist GIP(3–42).

shown to completely normalise glucose concentrations in adult obese Zucker rats (Burkey et al., 2002). In other studies, the DPP IV inhibitor FE 999011 delayed the onset of type 2 diabetes in Zucker diabetic rats (Sudre et al., 2002). Sustained improvements in glucose tolerance, insulin sensitivity, hyperinsulinemia and β -cell glucose responsiveness have also been demonstrated with the oral DPP IV inhibitor P32/98 in VDF (*falfa*) Zucker rats (Pospisilik et al., 2002a). Long-term treatment with P32/98 also improved hepatic and peripheral insulin sensitivity in this animal model (Pospisilik et al., 2002b), and stimulated β -cell survival and islet neogenesis in streptozotocin-induced diabetic rats (Pospisilik et al., 2003). Moreover, 2–3 times daily administration of NVP DPP728 over a 4 week study lead to improved metabolic control in type 2 diabetic subjects (Ahren et al., 2002).

While many positive effects of DPP IV inhibitors on glycaemic control have been reported, the consequences of long-term interference in the metabolism of a substantial number of other peptide substrates for DPP IV are as yet unknown (Mentlein, 1999). For this reason, widespread DPP IV inhibition could prove problematic and as such, a more comprehensive evaluation of the potential adverse side effects must be carried out. One important advantage for the use of DPP IV inhibitors is the possibility that they can be administered orally, however, there has been recent uncertainty about their efficacy (Holst, 2003). Therefore, since information regarding the substrate specificity of DPP IV is well documented, a more attractive approach than widespread DPP IV inhibition concerns the synthesis of specific GIP analogues modified in the region around the enzyme cleavage site to impart DPP IV resistance (O'Harte et al., 1999).

2.3. Why develop enzyme resistant GIP analogues?

There are several key features that make GIP an alluring target for the development of enzyme-resistant analogues for diabetes therapy. First of all, GIP is the major physiological incretin (Gault et al., 2003d; Miy-

awaki et al., 1999; Pederson et al., 1998b; Tseng et al., 1999). Second, structural modification of GIP typically results in enhanced biological activity (Gault et al., 2002b, 2003b,c; Hinke et al., 2002; O'Harte et al., 1998b, 1999, 2000, 2002), whereas the opposite is true for many analogues of its sister incretin, GLP-1 (Burcelin et al., 1999; Deacon et al., 1998; Gallwitz et al., 2000; Siegel et al., 1999; Xiao et al., 2001). Third, unlike GLP-1, and administration of its analogues (Agero et al., 2002), GIP lacks any significant effects on gastric emptying and is, therefore, well tolerated by human subjects. Fourth, GIP only exerts stimulatory effects on plasma glucagon concentrations at normal glucose concentrations (Meier et al., 2003; Pederson and Brown, 1978), which becomes irrelevant when treating type 2 diabetes (Kreyman et al., 1987). Consequently, these striking attributes have rekindled growing interest towards 'super GIP' agonists as potential anti-diabetic agents (Gault et al., 2003a; Meier et al., 2002). Thus far, several reports investigating the *in vitro* biological activities of a variety of GIP fragments and analogues have been published (Gault et al., 2002c, 2003e; Hinke et al., 2001, 2003; Kuhn-Wache et al., 2000; Manhart et al., 2003; O'Harte et al., 1998b). Furthermore, the *in vivo* anti-diabetic potential of a family of designer human GIP analogues modified at positions Tyr¹ (Gault et al., 2002b; O'Harte et al., 1999, 2000, 2002) and Ala² (Gault et al., 2003b,c; Hinke et al., 2002) has been tested in animal models of type 2 diabetes and obesity.

2.4. Super GIP agonists

A number of novel Tyr¹-modified analogues of GIP have been developed and characterised (Gault et al., 2002b; O'Harte et al., 1999, 2002). These include, *N*-acetyl-GIP, *N*-glucitol-GIP, *N*-pGlu-GIP, *N*-palmitate-GIP and *N*-Fmoc-GIP, all of which display profound resistance to the enzymatic actions of DPP IV (see Table 1). This concurs with the recognised DPP IV substrate-binding specificity, which predicts the prerequisite of a free protonated α -amino group (Mentlein, 1999).

Table 1
Molecular and biological properties of N-terminally Tyr¹-modified human GIP analogues

Peptide	Molecular mass (Da)	Biological half-life (h)		Cyclic AMP EC ₅₀ (nM)	Maximal insulin response (% GIP max)
		DPP IV	Plasma		
GIP	4982.5	2.3	6.2	18.2	100 ± 3.1
<i>N</i> -acetyl-GIP	5027.0	>24	>24	1.8	127 ± 4.0
<i>N</i> -glucitol-GIP	5146.7	>24	>24	2.0	141 ± 8.1
<i>N</i> -pGlu-GIP	5094.9	>24	>24	2.6	118 ± 1.6
<i>N</i> -palmitate-GIP	5220.8	>24	>24	10.0	122 ± 3.3
<i>N</i> -Fmoc-GIP	5205.6	>24	>24	9.4	112 ± 2.5

Molecular masses were calculated using electrospray ionisation-mass spectrometry (ESI-MS). Biological half-lives were calculated by plotting the percentage of intact peptide remaining after incubation with DPP IV or human plasma ($n = 3$) versus incubation time. EC₅₀ values were calculated from cyclic AMP dose-response curves ($n = 3$) in human GIP-receptor transfected CHL cells. Maximal insulin response values in clonal pancreatic BRIN-BD11 cells ($n = 8$) were calculated relative to the maximal percentage GIP response. Values represent means ± SEM. Data taken from Gault et al. (2002d) and O'Harte et al. (1998b, 2000, 2002).

Masking the charge on the amino-terminal Tyr¹, for example, through acetylation, confers metabolic stability on the peptide resulting in a significant prolongation of its circulating half-life.

The *in vitro* biological activity of the Tyr¹-modified analogues was assessed by their ability to stimulate cyclic AMP in human GIP-receptor transfected cells (Gremlich et al., 1995) and insulin release from clonal BRIN-BD11 cells (McClenaghan et al., 1996). All of the Tyr¹-modified analogues tested exhibited significantly increased potency in stimulating cyclic AMP production (2- to 10-fold increase in EC₅₀ values) and enhanced insulin releasing activity (1.1- to 1.4-fold) compared to the native peptide (Gault et al., 2002b; O'Harte et al., 1999, 2002). *N*-acetyl-GIP, *N*-glucitol-GIP and *N*-pGlu-GIP were possibly the most potent analogues judged on this basis.

In determining the *in vivo* anti-diabetic potential of the Tyr¹-modified analogues, obese diabetic *ob/ob* mice were employed. Characteristically, *ob/ob* mice exhibit hyperphagia, marked obesity, moderate hyperglycaemia and severe hyperinsulinemia (Bailey et al., 1982). All of

the Tyr¹-modified analogues significantly stimulated insulin secretion (2.0- to 2.5-fold) and lowered plasma glucose levels (1.4- to 1.9-fold) compared with native GIP (see Fig. 2). Again, *N*-acetyl-GIP, *N*-glucitol-GIP and *N*-pGlu-GIP appeared to be the most effective of these analogues. The magnitude of improvement in glycaemic excursion is notable (see Fig. 2(a)), especially given the severe insulin resistance and β -cell defect of the *ob/ob* syndrome (Bailey et al., 1982). Hence, the capacity of such analogues to act as 'super GIP' agonists and overcome the severe insulin resistance and β -cell defect (including weak response to native GIP) further supports the idea that such 'super GIP' molecules may offer remarkable potential as future therapeutic agents for the treatment of type 2 diabetes.

Likewise, a series of Ala²-substituted analogues of GIP has been developed and tested for their metabolic stability and anti-diabetic potential (Gault et al., 2003b,c; Hinke et al., 2002). While several of these analogues, including (Gly²)GIP, (Ser²)GIP and (D-Ala²)GIP exhibited significantly improved insulinotropic and antihyperglycaemic activity compared with native GIP (Gault et al., 2003b; Hinke et al., 2002), it is evident that their efficacy was not as impressive as that of the Tyr¹-modified analogues. However, together with other potential pancreatic and extrapancreatic effects, these novel 'super GIP' agonists provide the basis for exploration to bring to fruition the potential of GIP in the treatment of type 2 diabetes (see Fig. 3).

3. Anti-obesity potential of GIP

3.1. What is the evidence for GIP playing a role in obesity?

Although considerably less well researched than effects on insulin secretion and carbohydrate metabolism, there is increasing and compelling evidence that GIP plays a role in lipid metabolism and obesity. Early observations of elevated plasma GIP concentrations in type 2 diabetic patients (Creutzfeldt et al., 1978; Ebert et al., 1979; Elahi et al., 1984; Salera et al., 1982) and obese diabetic *ob/ob* mice (Flatt et al., 1983) prompted suggestions that GIP may play a key anabolic function in lipid metabolism (Marks, 1988).

Functional GIP receptors have since been identified on adipocytes (Yip et al., 1998), and a number of effects on lipid metabolism have been documented. For example, GIP is released by fatty acids, excessive fat intake chronically increasing plasma GIP concentrations and 24-h GIP profiles parallel plasma triglyceride levels (Elliott et al., 1993). Exogenous GIP administration increases chylomicron clearance (Wasada et al., 1981) and reduces postprandial circulating triglyceride levels

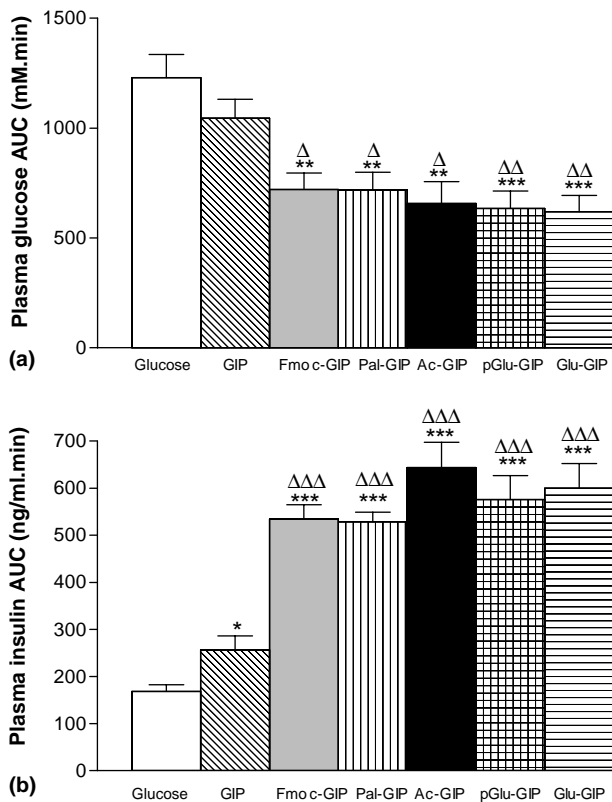


Fig. 2. Plasma glucose (a) and insulin (b) AUC values (0–60 min) of 18 h-fasted obese diabetic *ob/ob* mice after intraperitoneal injection of glucose alone (2 g/kg body weight) or in combination with either 25 nmol/kg GIP or Tyr¹-modified analogues. Values are means \pm SEM for 7–8 mice. * P < 0.05, ** P < 0.01, *** P < 0.001 compared to glucose alone. ΔP < 0.05, $\Delta\Delta P$ < 0.01, $\Delta\Delta\Delta P$ < 0.001 compared to GIP. Data taken from Gault et al. (2002b) and O'Harte et al. (2000, 2002).

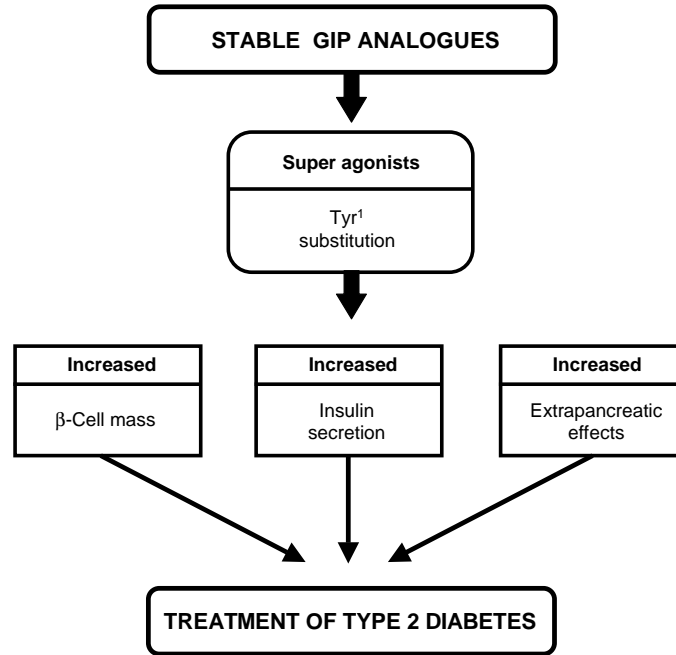


Fig. 3. Therapeutic potential of novel DPP IV resistant ‘stable GIP’ agonists for the treatment of type 2 diabetes. Enzyme resistant analogues of GIP possessing enhanced agonist activity increase insulin secretion, β-cell mass and glucose-responsiveness. Together with potential extrapancreatic effects, ‘super GIP’ agonists exert potent glucose-lowering actions, making them attractive anti-diabetic agents.

(Ebert et al., 1991). GIP augments insulin-stimulated glucose transport via increased adipocyte insulin sensitivity (Starich et al., 1985) and increases fatty acid synthesis in adipose tissue explants (Baba et al., 2000; Beck and Max, 1983; Hauner et al., 1988; Oben et al., 1991). GIP has also been shown to reduce glucagon-stimulated lipolysis (Dupre et al., 1976) and to stimulate the syn-

thesis and secretion of lipoprotein lipase in rat adipose tissue explants (Eckel et al., 1979, 1981;Knapper et al., 1993, 1995).

Additionally, epidemiological evidence clearly shows a link between overnutrition and obesity (Bray and Popkin, 1998). Furthermore, substantial early evidence in the obese diabetic *ob/ob* mouse model, points to a

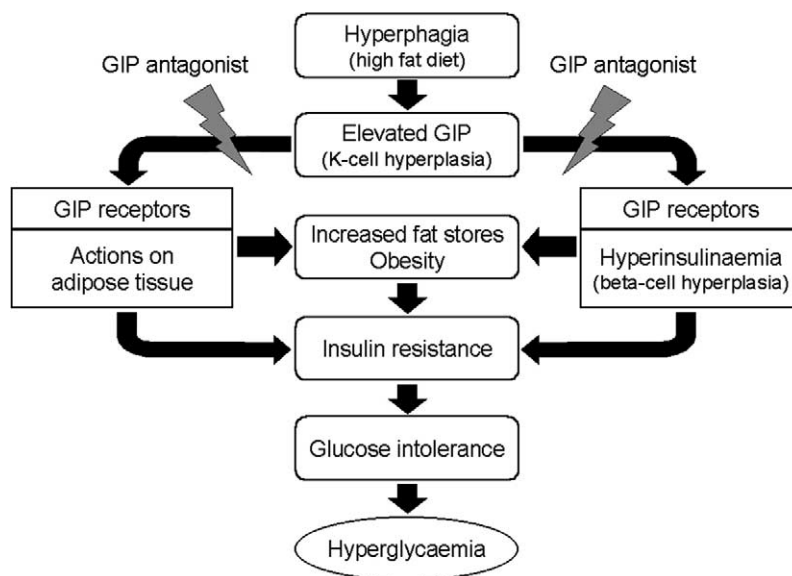


Fig. 4. Scheme illustrating how GIP directly links overnutrition to obesity, hyperinsulinemia, insulin resistance and type 2 diabetes. Functional ablation of GIP moderated pathways by GIP receptor antagonism is expected to decrease deposition of fat stores, prevent hyperinsulinemia and associated β-cell hyperplasia, and ameliorate both insulin resistance and glucose intolerance.

clear link between hyperphagia, high-fat diet, K-cell hyperplasia, increased cellular and circulating GIP concentrations (Bailey et al., 1986; Flatt et al., 1983, 1984). These observations demonstrate that GIP is a key molecule linking overnutrition to obesity. Therefore, strategies targeting the ablation of GIP action may well decrease fat deposition (see Fig. 4).

3.2. Novel insights from GIP receptor deficient mice

Considerable support for the hypothesis that GIP not only affects glucose homeostasis but also plays a key role in the development of obesity has recently been demonstrated using GIP receptor deficient ($GIPR^{-/-}$) mice (Miyawaki et al., 2002). $GIPR^{-/-}$ mice not only manifested glucose intolerance and diminished insulin secretion (Miyawaki et al., 1999) but were resistant to the development of obesity when placed on a high-fat diet (Miyawaki et al., 2002). In contrast, normal wild-type control mice exhibited elevated GIP levels, increased weight gain (35% increase compared to $GIPR^{-/-}$ mice), hyperinsulinemia, and insulin resistance, when placed on the same high-fat diet. In agreement with other studies (Woods et al., 1981) there was no significant difference in food intake between both groups, clearly demonstrating that there is little if any direct effect of GIP on feeding behaviour.

Further convincing support for a role of GIP in obesity is derived from observations in double homozygous mice generated by the crossbreeding of $GIPR^{-/-}$ mice and genetically obese (Lep^{ob}/Lep^{ob}) mice (Miyawaki et al., 2002). Genetic ablation of GIP receptor expression resulted in decreased body weight gain and significant amelioration of both adiposity and insulin resistance compared with control Lep^{ob}/Lep^{ob} mice. Thus even though hyperphagia of *ob/ob* mice is driven by leptin deficiency (Friedman and Halaas, 1998), these results in $GIPR^{-/-}$ *ob/ob* mice clearly demonstrate that GIP directly links overnutrition to obesity. As GIP encourages the efficient deposition of ingested fat, the gene encoding GIP can be regarded as 'metabolically thrifty', thus enabling GIP to play a crucial role in the development of obesity due to chronic overnutrition. Therefore, the GIP receptor represents a new potential strategic target for the development of novel anti-obesity agents.

3.3. GIP receptor antagonists as potential anti-obesity agents?

Obesity is a serious and ever increasing problem facing the developing world (Schurgin and Siegel, 2003). Knowledge of the mechanisms underlying the disease and the success of current therapeutic strategies are far from complete. Thus pharmaceutical companies have a huge craving to unearth new and more effective molec-

ular targets to deal with the increasing health threat posed by obesity. Since GIP is a key promoter of hyperinsulinemia and β -cell hyperplasia (Bailey et al., 1986; Flatt et al., 1983) and ablation of GIP signaling prevents obesity (Miyawaki et al., 2002), there is increasing awareness that GIP receptor antagonists could be utilised to treat obesity (Gault et al., 2003a; Holst, 2002; Kieffer, 2003). In addition to moderating the development of obesity, GIP receptor antagonism should also improve insulin resistance, which is the major driving force behind glucose intolerance, hyperglycaemia and progressive β -cell dysfunction in diabetes (Fig. 4; Bailey and Flatt, 2003). Moreover, since $GIPR^{-/-}$ mice remained healthy, attenuating the action of GIP would seem to be a safe and effective methodology.

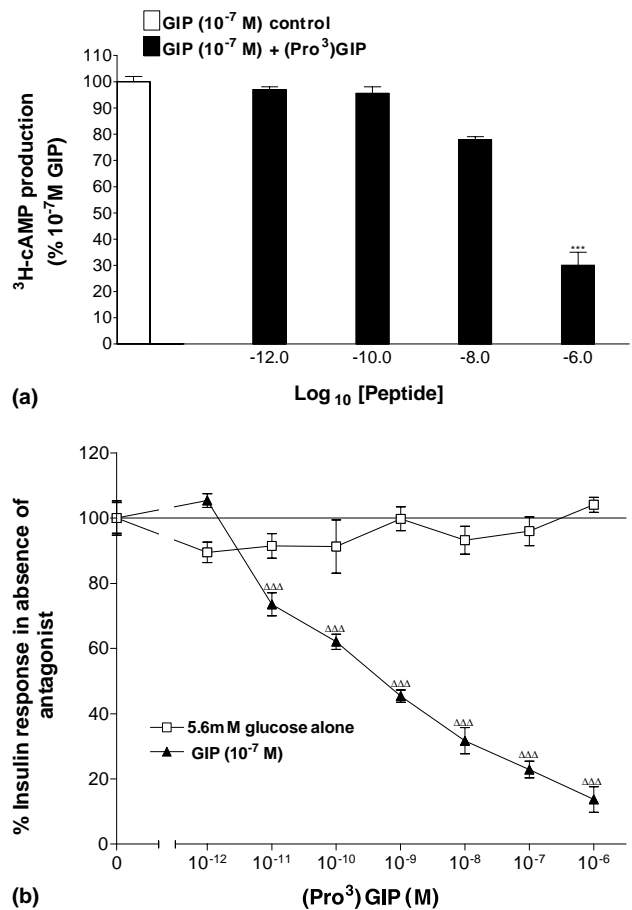


Fig. 5. (a) GIP receptor transfected Chinese hamster lung (CHL) cells were incubated with (Pro³)GIP (10⁻¹²–10⁻⁶ M) in the presence of native GIP (10⁻⁷ M). (Pro³)GIP inhibited GIP-induced cyclic AMP formation by up to 70 ± 3%. (b) Clonal pancreatic BRIN-BD11 cells were incubated with (Pro³)GIP (10⁻¹²–10⁻⁶ M) in the absence and presence of native GIP (10⁻⁷ M). (Pro³)GIP antagonised GIP-stimulated insulin secretion by up to 86%. Data are shown as percentage of GIP response recorded in the absence of (Pro³)GIP. ****P* < 0.001 compared with GIP (10⁻⁷ M) control. $\Delta\Delta\Delta P$ < 0.001 compared with 5.6 mM glucose control. Data taken from Gault et al. (2003d).

Several attempts have been made to ablate GIP signaling based on either immunoneutralisation of GIP (Ebert et al., 1979, 1983; Ebert and Creutzfeldt, 1982) or immunoneutralisation of the GIP receptor (Lewis et al., 2000). Numerous GIP receptor antagonists derived from either fragments of the full-length hormone (GIP(3–42) and GIP(7–30)amide) or amino acid substituted enzyme-resistant analogues have also been developed including ((Pro³)GIP) (Gault et al., 2002d, 2003d; Tseng et al., 1996, 1999). Although each of these approaches has resulted in some success, of particular note is the recently described GIP receptor antagonist, (Pro³)GIP (Gault et al., 2002d, 2003d).

3.4. (Pro³)GIP as a stable GIP receptor antagonist

(Pro³)GIP is a novel synthetic GIP analogue with a single proline substitution at position Glu³ (Gault et al., 2002d). Substitution of the N-terminal Glu³ in GIP with a proline residue renders the peptide completely resistant to the actions of DPP IV (half-life >24 h in vitro compared with 2.3 h for native GIP). However, unlike modifications at Tyr¹ or Ala², (Pro³)GIP only very weakly stimulates cyclic AMP production when applied

to GIP receptor transfected cells. Additionally, it effectively inhibits cyclic AMP formation (up to $70 \pm 3\%$ at 10^{-6} M) in cells exposed to stimulatory GIP (Fig. 5(a)). (Pro³)GIP also has no effect on GLP-1-stimulated cyclic AMP formation, consistent with its specificity for the GIP receptor (Gault et al., 2003d). In clonal pancreatic BRIN-BD11 cells, (Pro³)GIP acts as a potent inhibitor of GIP-induced insulin secretion with up to 86% maximal inhibition (Fig. 5(b)). Yet again, the inhibitory effect of (Pro³)GIP is specific as it does not affect GLP-1-stimulated insulin secretion (Gault et al., 2003d).

Acute administration of (Pro³)GIP to obese diabetic *ob/ob* mice in vivo has been shown to abolish GIP-stimulated insulin release (Gault et al., 2002d). Furthermore, although chronic treatment with a GIP receptor antagonist could improve β -cell responsiveness and insulin resistance through alleviation of obesity, acute administration of (Pro³)GIP actually worsened both the glycaemic and insulinotropic excursions to intraperitoneal glucose (Fig. 6). This may well be due to blockade of the permissive effects of high concentrations of endogenous GIP on glucose-induced insulin release (Flatt et al., 1983, 1984), as well as extrapancreatic actions on non-islet β -cells (O'Harte et al., 1998a).

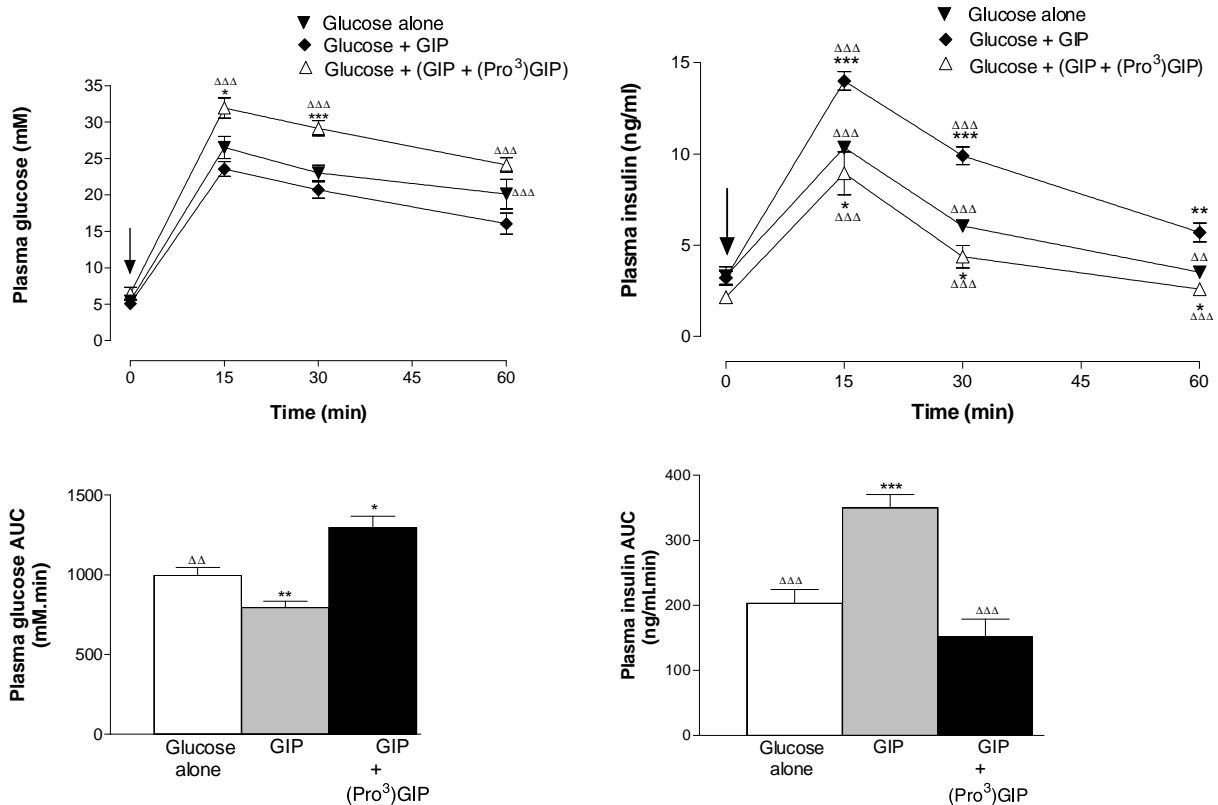


Fig. 6. Plasma glucose and insulin responses of 18-h fasted *ob/ob* mice after intraperitoneal administration of glucose alone (2 g/kg) or in combination with either native GIP (2×25 nmol/kg) or native GIP (25 nmol/kg) plus (Pro³)GIP (25 nmol/kg). The time of injection is indicated by the arrow (0 min). Plasma glucose and insulin AUC values are given for 0–60 min post-injection. Values are means \pm SEM for 8 mice. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ compared to glucose alone. $\Delta\Delta P < 0.01$, $\Delta\Delta\Delta P < 0.001$ compared to GIP. Data taken from Gault et al. (2002d).

3.5. Other benefits and challenges of GIP receptor antagonists

Novel GIP receptor antagonists may not only be useful in attempting to treat obesity, but may prove useful in elucidating the full spectrum of physiological actions of GIP. Exploitation of (Pro³)GIP in acute feeding studies in *ob/ob* mice has demonstrated that GIP is the major physiological incretin accounting for approximately 80% of nutrient-induced enteroinsular pancreatic β -cell stimulation (Gault et al., 2003d). Use of such antagonists could clearly help our understanding of extrapancreatic effects of GIP and its relative contribution to the enteroinsular axis in humans. However, due to the wide distribution of GIP receptors, administration of GIP receptor antagonists to specific target tissues could prove difficult. Furthermore, possible side effects through widespread ablation of GIP signalling could occur. For example, GIP ablation may well raise circulating triglyceride levels, which along with other things, could heighten the risk of coronary heart disease.

4. Conclusions

Despite its discovery 35 years ago, the physiological importance of GIP and the potential of GIP receptor agonists/antagonists for the treatment of diabetes and obesity are only now becoming appreciated. Problems of short circulating half-life can be overcome by the use of DPP IV inhibitors, or design of stable enzyme-resistant analogues of GIP. Analogous to the actions of sulphonylureas, 'super GIP' agonists may be useful for the treatment of diabetes, by acting largely through the stimulation of insulin secretion. Unlike sulphonylureas, the stimulatory effects of GIP are glucose dependent and are unlikely to exhaust pancreatic β -cells. Similar to metformin and insulin sensitizers, GIP antagonists may be effective in diabetes therapy due to improvement of insulin resistance. However, in the case of GIP antagonism, this effect is mediated through anti-obesity action. Such an approach may be effective, therefore, in preventing the development and progression of diabetes in obese individuals as well as the treatment of obesity per se. Although the current excitement about GIP has taken many years to develop, realisation of a GIP-based therapy for obesity and diabetes may come much quicker than we expected.

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