A Novel, Long-Acting Agonist of Glucose-Dependent Insulinotropic Polypeptide Suitable for Once-Daily Administration in Type 2 Diabetes

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ABSTRACT

Glucose-dependent insulinotropic polypeptide (GIP) is a gastrointestinal hormone with a potentially therapeutic role in type 2 diabetes. Rapid degradation by dipeptidylpeptidase IV has prompted the development of enzyme-resistant N-terminally modified analogs, but renal clearance still limits in vivo bioactivity. In this study, we report long-term antidiabetic effects of a novel, N-terminally protected, fatty acid-derivatized analog of GIP, N-AcGIP(LysPAL37), in obese diabetic (ob/ob) mice. Once-daily injections of N-AcGIP(LysPAL37) over a 14-day period significantly decreased plasma glucose, glycated hemoglobin, and improved glucose tolerance compared with ob/ob mice treated with saline or native GIP. Plasma insulin and pancreatic insulin content were significantly increased by N-AcGIP(LysPAL37). This was accompanied by a significant enhancement in the insulin response to glucose together with a notable improvement of insulin sensitivity. No evidence was found for GIP receptor desensitization and the metabolic effects of N-AcGIP(LysPAL37) were independent of any change in feeding or body weight. Similar daily injections of native GIP did not affect any of the parameters measured. These data demonstrate the ability of once-daily injections of N-terminally modified, fatty acid-derivatized analogs of GIP, such as N-AcGIP(LysPAL37), to improve diabetes control and to offer a new class of agents for the treatment of type 2 diabetes.

Glucose-dependent insulinotropic polypeptide (GIP) secreted from intestinal K-cells in response to nutrient absorption is an important enteroinsular hormone capable of lowering blood glucose concentrations (Meier et al., 2002). In addition to enhancing insulin secretion, GIP has been shown to stimulate proinsulin gene transcription and translation (Wang et al., 1996), increase pancreatic β cell growth (Trumper et al., 2001), and inhibit pancreatic β cell apoptosis (Ehses et al., 2003). Since GIP also displays antihyperglycemic actions through extrapancreatic effects on muscle, adipose, and liver tissue (Yip et al., 1998), increasing attention has been devoted to its possible antidiabetic potential (Gault et al., 2003b). Moreover, because the insulinotropic actions of GIP are glucose-dependent (Bailey and Flatt, 1995), the risk of hypoglycemia, a major drawback with nonendogenous insulin-releasing drugs, is minimized (Collins, 2002). Accordingly, an important opportunity currently exists to generate a safe and efficient GIP-based pharmaceutical agent for the treatment of type 2 diabetes (O’Harte et al., 2000, 2002; Gault et al., 2002a, 2003a; Hinke et al., 2002).

Despite its antihyperglycemic properties, rapid degradation of GIP in the circulation poses a major obstacle in the realization of any possible therapeutic potential for GIP. Thus, GIP is rapidly metabolized by the ubiquitous enzyme dipeptidylpeptidase IV (DPP IV) to release the N-terminal dipeptide Tyr-Ala2, giving rise to the major degradation fragment GIP(3–42) (Kieffer et al., 1995). This N-terminally truncated peptide lacks biological activity and possibly serves as a GIP receptor antagonist in vivo (Gault et al., 2002c). Therefore, it is anticipated that the development of DPP IV resistant analogs of GIP would not only extend the biological half-life of the peptide but also curtail production of GIP(3–42), thereby alleviating possible GIP receptor antag-
onism. In addition to inactivation by DPP IV, GIP is also subject to rapid renal clearance (Meier et al., 2004b), thereby imposing further limitations on biological half-life and potential for type 2 diabetes therapy.

In the past 6 years, a number of N-terminally modified analogs of GIP have been developed that exhibit profound resistance to DPP IV (O’Harte et al., 2000, 2002; Gault et al., 2002a, 2003a). Several of these, most notably those modified at Tyr1 of GIP with an addition of an acetyl, glucitol, pyroglycaminyl, or Fmoc adduct, exhibit enhanced activity at the GIP receptor in vitro (O’Harte et al., 1998, 2002; Gault et al., 2002a, 2003a). As a result of degradation resistance and enhanced cellular activity, these analogs display enhanced and protracted antihyperglycemic and insulin-releasing activity when administered acutely to animals with genetically-inherited obesity-diabetes (O’Harte et al., 2000, 2002; Gault et al., 2002a, 2003a). To increase potency and generate a long-acting GIP analog, possibly suitable for once-daily injection in diabetes, the problem of renal clearance needs to be overcome. We have designed, therefore, a novel analog of GIP, namely N-AcGIP(LysPAL37), based on the premise that fatty acid derivatization will counter renal clearance by promoting binding of the peptide to albumin. Such a strategy has been shown to prolong the half-life of insulin (Kurzthals et al., 1995) and the sister incretin glucagon-like peptide-1 (GLP-1) (Knudsen et al., 2000; Kim et al., 2003; Green et al., 2004).

The present study was designed to examine the ability of long-term treatment with N-AcGIP(LysPAL37) to counter the glucose intolerance and related features exhibited by obese diabetic (ob/ob) mice, a commonly employed animal model of type 2 diabetes (Bailey and Flatt, 1982). N-AcGIP(LysPAL37), native GIP, or saline as control were administered once daily by i.p. injection for 14 days prior to evaluation of glucose homeostasis, pancreatic β cell function, and insulin sensitivity. Furthermore, possible desensitization of GIP receptor action by prolonged exposure to elevated concentrations of N-AcGIP(LysPAL37) was examined. The results indicate significant antidiabetic potential for this second generation N-terminally acetylated GIP analog containing a C-16 palmitate group linked to Lys at position 37.

Materials and Methods

Animals. Obese diabetic (ob/ob) mice derived from the colony maintained at Aston University (Birmingham, UK) were used at 14 to 17 weeks of age. Animals were housed in an air-conditioned room at 22 ± 2°C with a 12-h light/dark cycle (8:00 AM–8:00 PM). Drinking water and standard rodent maintenance diet (Trouw Nutrition, Cheshire, UK) were freely available. All animal experiments were carried out in accordance with the UK Animals (Scientific Procedures) Act 1986. No adverse effects were observed following long-term administration of GIP or N-AcGIP(LysPAL37).

Synthesis, Purification, and Characterization of GIP and N-AcGIP(LysPAL37). Native GIP was sequentially synthesized on an Applied Biosystems automated peptide synthesizer (model 432 A; Applied Biosystems, Foster City, CA) using standard solid-phase Fmoc peptide chemistry as previously reported (O’Harte et al., 2002). N-AcGIP(LysPAL37) was sequentially synthesized in the same way but with the exception that the lysine residue at position 37 was conjugated to an Fmoc-protected C-16 palmitate fatty acid. The synthetic peptides were judged pure by reverse-phase high-pressure liquid chromatography on a Waters Millenium 2010 chromatography system (software version 2.1.5; Waters, Milford, MA) and subsequently characterized using matrix-assisted laser desorption ionization/time of flight mass spectrometry as described previously (Gault et al., 2002b). The molecular masses of GIP and N-AcGIP(LysPAL37) were 4982.4 and 5267.7 Da, respectively. These were within 1 to 2 Da of the theoretical masses, indicating successful peptide synthesis. Biological potency of both peptides was confirmed by acute in vivo tests (Fig. 1).

Effects of GIP and N-AcGIP(LysPAL37) in ob/ob Mice. Initially, extended biological activity of N-AcGIP(LysPAL37) was examined in fed ob/ob mice in comparison with N-AcGIP and native GIP. Over a 14-day period, groups of ob/ob mice received once-daily i.p. injections (5:00 PM) of saline vehicle [0.9% (w/v) NaCl], native GIP, or N-AcGIP(LysPAL37) (at 12.5 nmol/kg body weight/day). This dose was chosen on the basis of preliminary experiments that showed significant antihyperglycemic and insulinotropic activity of N-AcGIP(LysPAL37) over the range of 0.25 to 25 nmol/kg, when administered acutely with glucose (18 mmol/kg) (Fig. 1). Food intake and body weight were recorded daily from 5 days before commencement of the treatment regimes. Plasma glucose and insulin concentrations (10:00 AM) were monitored at 2- to 6-day intervals. At 14 days, pools of animals were used to evaluate i.p. glucose tolerance (18 mmol/kg) and insulin sensitivity (50 U/kg). In a separate series, two experimental protocols were used to examine the possibility of GIP receptor desensitization after 14 days of treatment. Acute metabolic effects of the usual injection of saline, GIP, or N-AcGIP(LysPAL37) were monitored when administered together with glucose (18 mmol/kg). In the second, acute effects of N-AcGIP(LysPAL37) given together with glucose were examined in all three groups of mice. All acute tests were commenced at 10:00 AM. At the end of the 14-day treatment period, pancreatic tissues were excised for measurement of insulin following extraction with 5 ml/g ice-cold acid ethanol (75% ethanol, 2.35% H2O, and 1.5% HCl). Whole blood was taken for determination of glycated hemoglobin. All other blood samples were collected from the cut tip of the tail vein of conscious mice into chilled fluoride/heparin-coated glucose microcentrifuge tubes (Sarstedt, Nümbrecht, Germany) at the times indicated in the figures. Blood samples were immediately centrifuged using a Beckman microcentrifuge (Beckman Coulter, Fullerton, CA) for 30 s at 13,000g. The resulting plasma was then aliquoted into fresh tubes and stored at −20°C prior to glucose and insulin determinations.

Biochemical Analyses. Plasma glucose was assayed by an automated glucose oxidase procedure (O’Harte et al., 2002) using a Beckman Glucose Analyzer II. Plasma and pancreatic insulin was assayed by dextran-charcoal radioimmunoassay as described previously (O’Harte et al., 2002). Glycated hemoglobin was determined using cation-exchange columns (Sigma Chemical, Poole, Dorset, UK) with measurement of absorbance (415 nm) in wash and eluting buffers using a VersaMax microplate spectrophotometer (Molecular Devices, Sunnyvale, CA).

Statistics. Results are expressed as mean ± S.E.M. Data were compared using the unpaired Student’s t test. Where appropriate, data were compared using repeated measures analysis of variance or one-way analysis of variance, followed by the Student-Newman-Keuls post hoc test. Incremental areas under plasma glucose and insulin curves (AUC) were calculated using a computer-generated program employing the trapezoidal rule (O’Harte et al., 2002) with baseline subtraction. Groups of data were considered to be significantly different if p < 0.05.

Results

Persistent Glucose Homeostatic Effects of N-AcGIP(LysPAL37). As shown in Fig. 2, administration of N-AcGIP(LysPAL37) decreased the glycemic excursion and glucose levels for up to 24 h after administration with glucose to fed ob/ob mice (32% reduction; p < 0.05). In comparison, the glucose homeostatic effects of N-AcGIP were relatively
short-lived (27% reduction at 1 h; \( p < 0.05 \)), and native GIP lacked any effect on circulating glucose at the time points studied. This supports a protracted biological half-life of N-AcGIP(LysPAL\(^{37}\)) and forms the basis of the once-daily injections.

**Effects of N-AcGIP(LysPAL\(^{37}\)) on Food Intake, Body Weight, Glycated Hemoglobin, and Nonfasting Plasma Glucose and Insulin Concentrations.** Administration of GIP or N-AcGIP(LysPAL\(^{37}\)) had no effect on food intake or body weight (Fig. 3, A and B). Plasma glucose and insulin concentrations were also unchanged by treatment with native GIP for 14 days (Fig. 4, A and B). In contrast, daily injection of N-AcGIP(LysPAL\(^{37}\)) resulted in a progressive lowering of plasma glucose, resulting in significantly \(( p < 0.05 \)) lowered concentrations at 14 days (Fig. 4A). At this time, glycated hemoglobin was also significantly \(( p < 0.01 \)) decreased in N-AcGIP(LysPAL\(^{37}\))-treated ob/ob mice (Fig. 4C). These changes were accompanied by a tendency toward elevated insulin concentrations, but these did not achieve statistical significance over the time frame studies (Fig. 4B).

**Effects of N-AcGIP(LysPAL\(^{37}\)) on Glucose Tolerance.** Consistent with effects on glycated hemoglobin, treatment of ob/ob mice for 14 days with N-AcGIP(LysPAL\(^{37}\)) resulted in a significant improvement in glucose tolerance (Fig. 5A). Plasma glucose concentrations throughout the test and the overall 0- to 60-min AUC values were decreased \(( p < 0.01 \) to \( p < 0.001 \)). This was accompanied by increased insulin concentrations during the latter stages \(( p < 0.05 \)) and a greater \(( p < 0.01 \) overall AUC insulin response (Fig. 5B). In contrast, daily administration of native GIP had no effect on glucose tolerance or the plasma insulin response to glucose compared with control ob/ob mice receiving saline injections for 14 days (Fig. 5).

**Effect of N-AcGIP(LysPAL\(^{37}\)) on Insulin Sensitivity.** Insulin sensitivity of the three groups of mice after 14 days of treatment is shown in Fig. 6. Compared with ob/ob receiving daily injections of saline or native GIP, N-AcGIP(LysPAL\(^{37}\)) prompted a significant improvement of insulin sensitivity. Both the individual glucose concentrations and 0- to 60-min AUC values were significantly different \(( p < 0.05 \)) from the other two groups. In contrast, daily treatment with native GIP did not affect the characteristic insulin resistance of ob/ob mice (Fig. 6).
Evaluation of GIP Receptor Desensitization. As shown in Fig. 7, treatment of ob/ob mice with N-AcGIP(LysPAL\textsuperscript{37}) for 14 days did not prevent the ability of the peptide to significantly moderate the glycemic excursion \( (p < 0.01) \) and enhance plasma insulin concentrations \( (p < 0.01) \) when administered acutely with i.p. glucose. In contrast, the responses of ob/ob mice to acute administration of native GIP were almost identical in mice receiving treatment with GIP or saline for 14 days (Fig. 7). To further substantiate the lack of GIP receptor desensitization following chronic treatment with N-AcGIP(LysPAL\textsuperscript{37}), the acute effects of the analog, administered with glucose, were examined in each of the three groups after 14 days of treatment with N-AcGIP(LysPAL\textsuperscript{37}), native GIP, or saline (Fig. 8). Apart from lower basal values in the former group, the glucose and insulin responses were identical, with similar 0- to 60-min AUC measures for both plasma glucose and insulin concentrations.

Effects of N-AcGIP(LysPAL\textsuperscript{37}) on Pancreatic Insulin Content. Treatment of ob/ob mice for 14 days with native GIP or N-AcGIP(LysPAL\textsuperscript{37}) did not affect pancreatic weight compared with saline-treated controls (Fig. 9A). Similarly, pancreatic insulin content was similar in the GIP- and saline-treated groups. However, daily administration of N-AcGIP(LysPAL\textsuperscript{37}) significantly increased \( (p < 0.01) \) insulin content compared with each of the other groups (Fig. 9B).

Discussion

In common with the sister incretin hormone GLP-1 (Meier and Nauck, 2004), great effort has been devoted in recent years to generate stable long-acting analogs of GIP for potential use in the therapy of type 2 diabetes (Gault et al., 2003b,c). This approach supposes that selected GIP analogs can overcome any defect of GIP action in diabetes. The prospect for this is encouraging in that the once-postulated specific defect in GIP stimulation of insulin secretion in diabetes (Nauck et al., 1993) is now recognized to represent one aspect of a generalized pancreatic \( \beta \) cell dysfunction that extends to many secretagogues including incretin hormones (Kjems et al., 2003; Meier et al., 2003b). Additionally, DPP IV-resistant N-terminally modified analogs of GIP have been shown to induce a protracted insulin response in both animals and humans with type 2 diabetes (O’Harte et al., 2000, 2002; Gault et al., 2002a, 2003a; Lindsay et al., 2002).

In the present study, we have examined the ability of a second generation N-terminally modified GIP analog to counter aspects of the ob/ob syndrome in mice (Bailey and Flatt, 1982). The analog N-AcGIP was chosen for secondary modification by fatty acid derivatization to extend half-life and bioavailability by binding to albumin, thereby decreasing renal filtration. N-AcGIP has already been shown to exhibit profound DPP IV resistance, enhanced ability to stimulate cyclic AMP production, and insulin secretion in vitro.
together with substantial antihyperglycemic and insulin-releasing action in ob/ob mice in vivo (O’Harte et al., 2002). Further modification of GIP to carry a C-16 palmitate fatty acid at the \(\text{H9280}\)-amino group of the naturally occurring Lys at position 37 has been shown to conserve these attributes (O’Harte et al., 2004). At the same time, \(\text{N-AcGIP(LysPAL37)}\) exhibits extended action in acute tests, making it suitable for exploration as a possible once-daily treatment using animal models of diabetes.

Administration of \(\text{N-AcGIP(LysPAL37)}\) to young adult ob/ob mice by daily i.p. injection resulted in a progressive lowering of plasma glucose concentrations and a significant decrease of glycated hemoglobin by 14 days. This was associated with a substantial improvement of glucose tolerance. Importantly, food intake and body weight were unchanged during the study, ruling out the possibility that improvement of glucose homeostasis was merely the consequence of body weight loss. These observations also indicate that \(\text{N-AcGIP- (LysPAL37)}\) was not associated with body weight gain and did not exert any untoward toxic actions affecting feeding over the study period. This is in harmony with recent studies showing that GIP, unlike the sister incretin GLP-1, does not inhibit gastric emptying (Meier et al., 2003a). Daily administration of native GIP to ob/ob mice for 14 days had no effect on any of the parameters measured, consistent with the very short half-life of the native GIP in vivo (Holz et al., 1993).

As expected, a key component of the beneficial action of \(\text{N-AcGIP(LysPAL37)}\) concerned the stimulation of insulin secretion. Thus, although native GIP is a weak stimulus to insulin secretion in ob/ob mice at the age studied, plasma and pancreatic insulin concentrations were raised in ob/ob mice receiving the novel fatty acid-derivatized analog. This is consistent with the action of GIP as a promoter of proinsulin gene expression (Wang et al., 1996) and exemplifies the increased potency reported for N-terminally modified GIP analogs in animal models of diabetes (O’Harte et al., 2000, 2002; Gault et al., 2002a, 2003a; Hinke et al., 2002). Furthermore, the insulin response to glucose was significantly enhanced in ob/ob mice receiving \(\text{N-AcGIP(LysPAL37)}\). This ability to augment or restore pancreatic \(\text{H9252}\) cell glucose responsiveness in diabetes has been similarly observed with GLP-1 (Holz et al., 1993). As with observations on glycemic control, none of these attributes were reproduced by daily injections of native GIP.

Results of insulin sensitivity tests conducted after 14 days of treatment indicate that the improvement of diabetic status

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**Fig. 5.** Effects of daily \(\text{N-AcGIP(LysPAL37)}\) administration on glucose tolerance and plasma insulin response to glucose. Tests were conducted after 14 daily injections of \(\text{N-AcGIP(LysPAL37)}\) (12.5 nmol/kg/day), native GIP (12.5 nmol/kg/day), or saline vehicle (control). Glucose (18 mmol/kg) was administered by i.p. injection at the time indicated by the arrow. Plasma glucose and insulin AUC values for 0 to 60 min postinjection are shown in the right panels. Values are mean ± S.E.M. for eight mice. \(\star, p < 0.05; \star\star, p < 0.01; \star\star\star, p < 0.001\) compared with control. \(\Delta, p < 0.05; \Delta\Delta, p < 0.01; \Delta\Delta\Delta, p < 0.001\) compared with native GIP.
achieved in ob/ob mice with N-AcGIP(LysPAL37) was not solely due to the potentiation of insulin secretion. Thus, these animals also exhibited a significant improvement of insulin sensitivity compared with the GIP- or saline-treated groups. Given that hyperinsulinemia is generally believed to down-regulate insulin receptor function, this suggests that N-AcGIP(LysPAL37) may exert other compensatory effects. Further study is necessary to evaluate this aspect, but possibilities include inhibition of counterregulatory hormones and effects on extrapancreatic sites such as muscle, adipose tissue, and liver (Yip et al., 1998).

Irrespective of knowledge of the full range of actions contributing to the antihyperglycemic effect of N-AcGIP(LysPAL37), a currently envisaged problem of long-term treatment with stable analogs of GIP or GLP-1 concerns desensitization of hormone receptor action (Delmeire et al., 2004). Although this has been observed during prolonged exposure of pancreatic β cells to GIP during culture in vitro (Tseng et al., 1996), there was no evidence that treatment with N-AcGIP(LysPAL37) for 14 days compromised the glucose-lowering or insulin-releasing actions of N-AcGIP(LysPAL37) in any way. Thus, the antidiabetic actions of

Fig. 6. Effects of daily N-AcGIP(LysPAL37) administration on insulin sensitivity. Tests were conducted after 14 daily injections of N-AcGIP(LysPAL37) (12.5 nmol/kg/day), native GIP (12.5 nmol/kg/day), or saline vehicle (control). Insulin (50 U/kg) was administered by i.p. injection at the time indicated by the arrow. Plasma glucose AUC values from baseline for 0 to 60 min postinjection are shown in the right panels. The starting values for saline, GIP, and N-AcGIP(LysPAL37) were 16.3 ± 2.0, 15.7 ± 1.7, and 13.9 ± 2.4 mM, respectively. Values are mean ± S.E.M. for eight mice. *, p < 0.05; **, p < 0.01 compared with control. Δ, p < 0.05 compared with native GIP.

Fig. 7. Retention of glucose homeostatic and insulin releasing activity of N-AcGIP(LysPAL37) and native GIP after daily injection for 14 days. Glucose (18 mmol/kg) was administered by i.p. injection alone or in combination with either N-AcGIP(LysPAL37) or native GIP (both at 25 nmol/kg) at the time indicated by the arrow. Plasma glucose and insulin AUC values for 0 to 60 min postinjection are shown in the right panels. Values are mean ± S.E.M. for eight mice. *, p < 0.05; **, p < 0.01 compared with glucose alone. Δ, p < 0.05; ΔΔ, p < 0.01 compared with native GIP.
N-AcGIP(LysPAL$_{37}$) were clearly evident when the analog was administered acutely together with glucose. Furthermore, the acute effects of N-AcGIP(LysPAL$_{37}$) in such experiments were identical in groups of ob/ob mice receiving N-AcGIP(LysPAL$_{37}$), native GIP, or saline injections for 14 days.

Such data clearly indicate that prolonged exposure to N-AcGIP(LysPAL$_{37}$) does not induce and possibly overcomes inherent GIP receptor desensitization in ob/ob mice. Given the high circulating concentrations of GIP in these obese diabetic rodents (Flatt et al., 1983, 1984), it is tempting to link β cell refractoriness to GIP evident in ob/ob mice and reported in some individuals with clinical diabetes (Ebert et al., 1979) to simple receptor desensitization at the hands of inappropriate secretion and metabolism of GIP. This is supported by the recent observation that the insulin response to i.v. bolus injection of GIP was effectively preserved in patients with type 2 diabetes, whereas continuous i.v. infusion induced a poor response (Meier et al., 2004a). However, present appreciation of the role of circulating GIP in clinical diabetes is far from complete. This is due to lack of specificity of radioimmunoassays for active as opposed to the predominant inactive metabolite GIP(3–42). However it is quite reasonable to consider that the latter truncated form of GIP as a receptor antagonist (Gault et al., 2002c) might actively contribute to the reported down-regulation of GIP receptor function on pancreatic β cells in diabetes.

In conclusion, these studies indicate that once-daily inject-
tion of N-AcGIP(LysPal)\(^{37}\) to ob/ob mice for 14 days results in a significant amelioration of diabetes and associated metabolic disturbances. Such effects are independent of changes in feeding and body weight. The anti-diabetic actions appear to be mediated by enhancement of both pancreatic \(\beta\) cell function and insulin sensitivity, although other possible extrapancreatic actions may exist. Development of antibodies against analogs of naturally circulating peptides such as N-AcGIP(LysPal)\(^{37}\) is also likely to be minimized by the minor structural changes undertaken, as evidenced by the use of insulin analogs (Bolli, 2003) Overall, these novel observations provide strong encouragement for the development of long-acting fatty acid-derivatized N-terminally modified analogs of GIP, such as N-AcGIP(LysPal)\(^{37}\), for the once-daily treatment of type 2 diabetes.

References


