No Hypoglycemia After Subcutaneous Administration of Glucagon-Like Peptide-1 in Lean Type 2 Diabetic Patients and in Patients With Diabetes Secondary to Chronic Pancreatitis

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OBJECTIVE — Glucagon-like peptide 1 (GLP-1) is a proglucagon derivative secreted primarily from the L-cells of the small intestinal mucosa in response to the ingestion of meals. GLP-1 stimulates insulin secretion and inhibits glucagon secretion. It has previously been shown that intravenous or subcutaneous administration of GLP-1 concomitant with intravenous glucose results in hypoglycemia in healthy subjects. Because GLP-1 is also effective in type 2 diabetic patients and is currently being evaluated as a therapeutic agent, it is important to investigate whether GLP-1 may cause hypoglycemia in such patients. We have previously shown that GLP-1 does not cause hypoglycemia in obese type 2 diabetic patients with insulin resistance amounting to 5.4 ± 1.1 according to homeostasis model assessment (HOMA). In this study, we investigated diabetic patients with normal or close to normal insulin sensitivity.

RESEARCH DESIGN AND METHODS — Eight lean type 2 diabetic patients (group 1) aged 60 years (range 50–72) with BMI 23.1 kg/m^2 (20.3–25.5) and HbA_{1c} 8.0% (6.9–11.4) and eight patients with type 2 diabetes secondary to chronic pancreatitis (group 2) aged 52 years (41–62) with BMI 21.9 kg/m^2 (17.6–27.3) and HbA_{1c} 7.8% (6.2–12.4) were given a subcutaneous injection of 1.5 nmol GLP-1/kg body wt. Then, 15 min later, at the time of peak GLP-1 concentration, plasma glucose (PG) was raised to 15 mmol/l with an intravenous glucose bolus. HOMA (mean ± SEM) showed insulin resistance amounting to 1.9 ± 0.3 and 1.7 ± 0.5 in the two groups, respectively.

RESULTS — In both groups, PG decreased rapidly and stabilized at 7.5 mmol/l (range 3.9–10.1) and 7.2 mmol/l (3.1–10.9) in groups 1 and 2, respectively, after 90 min. Neither symptoms of hypoglycemia nor biochemical hypoglycemia were observed in any patient.

CONCLUSIONS — We conclude that a GLP-1–based therapy would not be expected to be associated with an increased risk of hypoglycemia in insulin-sensitive type 2 diabetic patients.

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Glucagon-like peptide 1 (GLP-1)(7–36) amide is an incretin hormone secreted primarily from the enteroglucagon-producing L-cells in the small intestine. In patients with type 2 diabetes, the effects of GLP-1 are remarkable (1). Thus, intravenous infusion of GLP-1 has been demonstrated to normalize fasting blood glucose completely, even in patients with long-standing disease and secondary failure of oral antidiabetic drugs (2). This is primarily due to the stimulation of insulin secretion and inhibition of glucagon secretion. The secretion of GLP-1 is related to the rate of gastric emptying, and in partially gastrectomized subjects, the plasma concentrations of GLP-1 after oral glucose or test meals may increase up to 10-fold compared with matched healthy subjects (1,3,4). Therefore, it was proposed that the excessive secretion of GLP-1, stimulated by rapid entry of nutrients into the intestine, could be responsible for the hyperinsulinemia and hence the reactive hypoglycemia often observed in this patient group (4,5). Indeed, intravenous or subcutaneous administration of GLP-1 combined with intravenous glucose, resulting in plasma concentrations of GLP-1 similar to those seen in partially gastrectomized subjects, has been shown to induce hypoglycemia in healthy subjects (6). On the other hand, it seems that subcutaneous administration of GLP-1 at 1.5 nmol/kg body wt (maximally tolerated dose) to type 2 diabetic patients with high BMI (31 kg/m^2 [27–38]) is without risk of hypoglycemia (7). In the same experiment, the subcutaneous GLP-1 injection induced biochemical hypoglycemia and symptoms of hypoglycemia in five of seven healthy, but obese, subjects. Obese type 2 diabetic patients are known to be insulin resistant. It is therefore of importance to investigate subgroups of diabetic patients without severe insulin resistance, e.g., lean type 2

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Abbreviations: DPP-IV, dipeptidyl peptidase IV; FPG, fasting plasma glucose; GLP-1, glucagon-like peptide 1; HOMA, homeostasis model assessment; iAUC, incremental area under the curve; PG, plasma glucose; RIA, radioimmunoassay; WHO, World Health Organization.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

diabetic patients and patients with diabetes secondary to chronic pancreatitis.

The aim of the present study was to investigate whether hypoglycemia, as seen in healthy subjects after administration of high doses of GLP-1 and glucose, can also be elicited in subgroups of type 2 diabetic patients with close to normal insulin sensitivity.

RESEARCH DESIGN AND METHODS

Patients

We studied two groups of patients. One group (group 1) included eight lean type 2 diabetic patients (seven men and one woman) with a mean age 60 years (range 50–72), BMI 23.1 kg/m^2 (20.3–25.5), HbA_{1c} 8.0% (6.9–11.4), fasting plasma glucose (FPG) 10.2 mmol/l (7.6–12.0), and duration of diabetes 52 months (7–114). One of the patients in this group was treated with diet alone, whereas seven were treated with diet and oral antidiabetic drugs (sulfonylureas and/or biguanides). Three patients had a history of hypertension and were treated with ACE inhibitors. The remaining five patients in the group were without cardiovascular disease. All of the lean type 2 diabetic patients were diagnosed according to the criteria of the World Health Organization (WHO) (8,9). The second group (group 2) consisted of eight patients with type 2 diabetes, diagnosed according to WHO criteria (8,9), secondary to chronic pancreatitis. The eight patients in group 2 included five men and three women with a mean age of 52 years (range 38–62), BMI 21.9 kg/m^2 (17.6–27.3), HbA_{1c} 7.8% (6.2–12.4), FPG 9.2 mmol/l (6.0–13.8), and duration of diabetes 21.5 months (8–40). Diabetes was developed after the diagnosis of chronic pancreatitis was established, and none of the participants in this group had first-degree relatives with type 1 or type 2 diabetes. Four of the patients were treated with diet alone, whereas the remaining four were treated with diet and oral antidiabetic drugs (sulfonylureas and/or biguanides). All were without cardiovascular disease, except for one who had a history of hypertension and was treated with furosemide and diltiazem. All were without clinical or biochemical signs of acute inflammatory activity in the pancreas. Two of the patients had elevated levels of serum alkaline phosphatase, whereas serum albumin, prothrombin, and bilirubin were within normal limits. The etiology of chronic pancreatitis was judged to be alcoholism in six patients and idiopathic in two patients. None of the patients drank alcohol on a daily basis. The diagnostic criteria of chronic pancreatitis were according to Layer et al. (10), and all patients had reduced meal-stimulated duodenal concentration of lipase and amylase or reduced concentration of elastase in stool plus unequivocal morphologic changes of the pancreas shown at ultrasonography, computed tomography scan, or endoscopic retrograde cholangiopancreatography according to the Cambridge classification (11). Two patients were regularly treated with oral pancreatic enzyme supplementation because of steatorrhoea.

None of the patients in the two groups had impaired renal function (normal serum creatinine levels [<130 μmol/l] and no albuminuria) or proliferative retinopathy, and all patients were negative with regards to islet cell autoantibodies. None of the participants had more than two times the upper reference range for biochemical liver parameters (alanine and aspartate transaminases, alkaline phosphatase, bilirubin, albumin, and coagulation factor II, VII, and X).

All subjects agreed to participate after oral and written information. The study was approved by the Copenhagen County ethical committee in July 2000 (journal number in the committee: KA00087 m), and the study was conducted according to the principles of the Helsinki Declaration.

Methods

All oral antidiabetic drugs were discontinued 3 days before the study, except for metformin, which was discontinued 7 days before the study. After an overnight fast (including water, coffee, and cigarettes) from 10:00 P.M., the subjects were studied in the recumbent position, with two cannulas, one inserted into the cubital vein for glucose infusion, and one inserted in the retrograde direction in the opposite dorsal hand vein for the collection of arterialized blood samples. The hand with the retrograde cannula was kept in a heating box (42°C) throughout the experiment. At time zero, GLP-1 was injected subcutaneously into the periumbilical region (GLP-1 at 1.5 nmol/kg body wt). The injected volume was 1.3 ml (range 1.26–1.40). We have previously shown (12) that peak GLP-1(7–36) amide concentrations occur ~15 min after subcutaneous injection. Therefore, at 15 min, plasma glucose (PG) was elevated to 15 mmol/l by an intravenous glucose (50% wt/vol) bolus administered within 1 min, calculated as follows: (15 mmol/l − FPG) × 35 mg glucose × body weight in kilograms. Arterialized blood was sampled 15, 10, and 0 min before and 10, 18, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 100, 105, 110, 120, and 135 min after GLP-1 administration. Recombinant human GLP-1(7–36) amide, supplied as a 3-ml 1.0 mg/ml liquid sterile formulation, with a peptide purity >99% by reverse-phase high-performance liquid chromatography, was a generous gift from BioNebraska (Now Restoragen, Lincoln, NE). Before injection, the dissolved peptide was mixed with 0.5 ml of human serum albumin (5% wt/vol human albumin, guaranteed to be free of hepatitis-B surface antigen, hepatitis-C virus antibodies, and human immunodeficiency virus antibodies; Statens Serum Institute, Copenhagen) and 0.5 ml sterile saline. Blood was distributed into fluoride tubes for bedside PG measurements. The tubes were centrifuged for 3 min at 10,000 rpm (room temperature) immediately, and PG was measured. Blood was distributed into lithium heparin and EDTA (6 mmol/l) tubes with aprotinin (Trasylol, 500 KIU/ml blood; Bayer, Leverkusen, Germany) and a specific dipeptidyl peptidase IV (DPP-IV) inhibitor (valine-pyrrolidide, 0.01 mmol/l final concentration; a gift from Drs. R.D. Carr and L.B. Christiansen, Novo Nordisk, Bagsværd, Denmark) for peptide and hormone analyses. Tubes were chilled immediately on ice and centrifuged for 20 min at 3,000 rpm and 4°C. Plasma for GLP-1 and glucagon analyses was stored at −20°C and plasma for insulin and C-peptide analyses was stored at −80°C until analysis.

During the experiments, the participating patients were observed continuously for possible side effects of GLP-1 and asked about their state of well-being and other subjective parameters such as dizziness, nausea, sweats, and the urge to defecate every 10 min the first 60 min after administration of GLP-1.

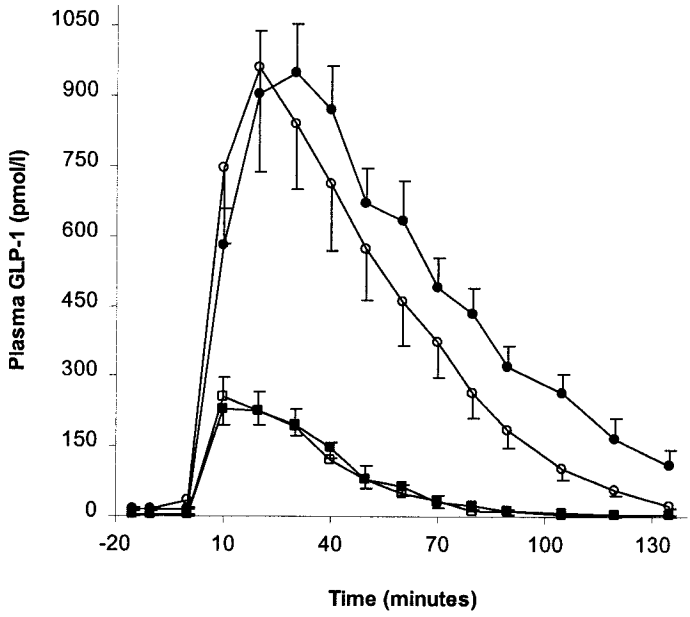

Figure 1—*Total plasma GLP-1 concentrations for lean type 2 diabetic patients (●) and patients with type 2 diabetes secondary to chronic pancreatitis (○) with COOH-terminally directed RIAs, and biologically active GLP-1 concentrations for lean type 2 diabetic patients (■) and patients with type 2 diabetes secondary to chronic pancreatitis (□) with NH_2-terminally directed RIAs. Data are means ± SEM. Time of GLP-1 injection = 0 min, and time of intravenous glucose bolus = 15 min.*

Analyses

PG concentrations were measured during the experiments by a glucose oxidase method using a glucose analyzer (YSI 2300 STAT plus analyzer; Yellow Springs Instruments, Yellow Springs, OH).

Plasma insulin and C-peptide concentrations were measured using commercial AutoDELFIA time-resolved fluoroimmunoassay (Wallac Oy, Turku, Finland). The detection limits of the assays are 3 pmol/l for insulin and 17 pmol/l for C-peptide. The intra- and interassay coefficients of variation are 4.0–5.0% at 37–319 pmol/l and 4.8–5.4% at 78–718 pmol/l, respectively, for insulin and 2.0–8.0% at 423–2,726 pmol/l and 5.5–6.6% at 366–3,646 pmol/l for C-peptide. The cross-reactivities with intact and 32–33 split proinsulin in the C-peptide assay is 51.1 and 34.9%, respectively.

Plasma samples were assayed for GLP-1 immunoreactivity using radio immunoassays (RIAs), which are specific for each terminus of the GLP-1 molecule. Catalyzed by the ubiquitous enzyme DPP-IV, GLP-1 is cleaved almost immediately to form an inactive NH_2-terminally truncated molecule, GLP-1(9–36) (13,14). COOH-terminal measurements therefore reflect the amount of peptide injected (i.e., the sum of the intact peptide plus the primary metabolite), whereas NH_2-terminal assays measure the resulting concentration of intact surviving GLP-1. COOH-terminal immunoreactivity of GLP-1 was measured as described previously by Orskov et al. (15) against standards of synthetic GLP-1(7–36) amide [proglucagon(78–107) amide], using antiserum no. 89390, the cross-reaction of which is <0.01% with COOH-terminally truncated fragments and 83% with GLP-1(9–36) amide. The detection limit is 1 pmol/l. NH_2-terminal immunoreactivity was measured using antiserum no. 93242 (16), which cross-reacts ~10% with GLP-1(1–36) amide and <0.1% with both GLP-1(8–36) amide and GLP-1(9–36) amide. The assay has a detection limit of 2 pmol/l. For both assays, intra- and interassay coefficients of variation were <6% and <15%, respectively, at 40 pmol/l.

The glucagon assay is directed against the COOH terminus of the glucagon molecule (antibody code no. 4305) and therefore measures glucagon of mainly pancreatic origin. The detection limit of the assay is ~1 pmol/l, and the intra-assay coefficient of variation is <6% in the range between 10 and 25 pmol/l (17).

A quantitative assessment of insulin resistance was made by comparing the subjects' fasting insulin and FPG using homeostasis model assessment (HOMA) (18). The formula is as follows: insulin resistance = (FI × FPG)/22.5, where FI is fasting insulin (μU/ml) and FPG is in mmol/l.

Statistical analysis and calculations

All results are presented as the mean ± SEM or followed by the range in parentheses. The significance of difference between glucose and glucagon concentrations within the groups was evaluated using Wilcoxon's test for pair differences. Significance of differences for insulin and C-peptide concentrations and insulin–to–C-peptide ratios between the groups were evaluated using two-factor ANOVA, and for insulin resistance, they were evaluated using the Mann-Whitney rank-sum test for unpaired data. The level of statistical significance was set at $P < 0.05$.

RESULTS

— HOMA (18) showed insulin resistance amounting to 1.9 ± 0.3 and 1.7 ± 0.5 in the lean type 2 diabetic patients (group 1) and in the patients with diabetes secondary to chronic pancreatitis (group 2), respectively. No statistical significant difference could be shown between the two groups.

Basal plasma GLP-1 concentrations were between 7 and 25 pmol/l and 1 and 3 pmol/l, measured as COOH- and NH_2-terminal GLP-1, respectively, in both groups. COOH-terminal GLP-1, representing the intact peptide plus the primary metabolite, increased rapidly after subcutaneous injection, and peak concentrations amounting to 949 ± 105 pmol/l in group 1 and 960 ± 220 pmol/l in group 2 occurred after 30 and 20 min, respectively (Fig. 1). Plasma concentrations were still supraphysiological at the end of the experiment (group 1: 109 ± 33 pmol/l; group 2: 24 ± 6 pmol/l). Intact GLP-1 (NH_2-terminal) also increased rapidly after subcutaneous injection, and peak concentrations were seen at 10 min and amounted to 228 ± 34 pmol/l in group 1 and 256 ± 42 pmol/l in group 2 (Fig. 1). The concentration of intact GLP-1 (NH_2-terminal) returned to basal levels at 120 and 105 min in the two groups, respectively. The mean incremental area under the curves (iAUCs) for intact and total GLP-1 amounted to 10,142 min × pmol/l (range 5,225–

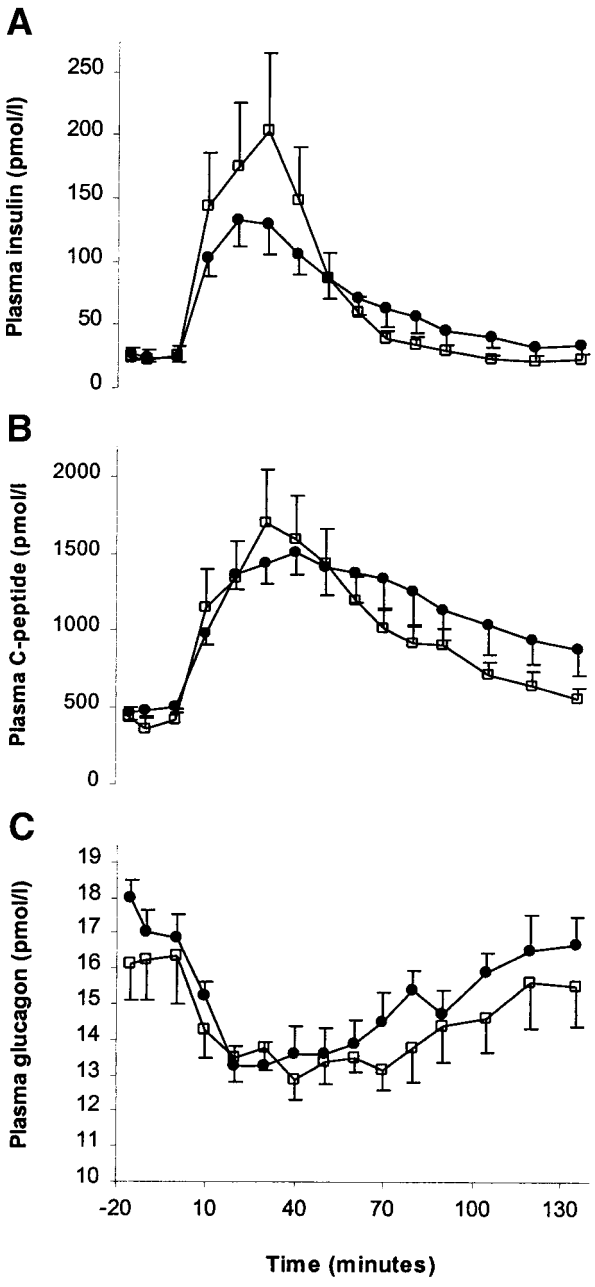

Figure 2—*Plasma insulin* (A)*, C-peptide* (B)*, and glucagon concentrations* (C) *for lean type 2 diabetic patients* (●) *and patients with type 2 diabetes secondary to chronic pancreatitis* (□)*. Data are means ± SEM. Time of GLP-1 injection = 0 min, and time of intravenous glucose bolus = 15 min.*

19,125) and 68,831 min × pmol/l (42,690–104,758), respectively, in group 1 and 10,035 min × pmol/l (2,745–20,845) and 53,415 min × pmol/l (25,520–105,008) in group 2. No statistical significant differences of total or intact GLP-1 concentrations could be shown between the two groups.

Subjective side effects of GLP-1 were described by 7 (4 patients in group 1 and 3 patients in group 2) of the 16 patients, who reported an impaired state of well-being, light to moderate nausea, sweating, and/or the urge to defecate 10–40 min after the subcutaneous GLP-1 injection. All side effects diminished rapidly, and after 40 min all of the patients felt well, with no side effects at all.

Time courses of insulin and C-peptide concentrations are presented in Fig. 2*A* and *B*. After injection of GLP-1, an increase in insulin and C-peptide concentrations was seen, and injection of the glucose bolus 15 min later augmented the insulin and C-peptide responses further. Peak insulin and C-peptide concentrations occurred on the average 10 and 30 min, respectively, after intravenous glucose in group 1 and 20 min after intravenous glucose in group 2. Mean peak concentrations of insulin and C-peptide were 132 ± 21 and 1,509 ± 148 pmol/l, respectively, in group 1 and 203 ± 62 and 1,697 ± 353 pmol/l, respectively, in group 2. Insulin concentrations reached basal levels in both groups and stayed there for the last 15 min of the experiment, whereas C-peptide concentrations were still supra-basal but approaching basal levels in both groups at the end of the experiment. The iAUCs for insulin and C-peptide constituted 6,184 min × pmol/l (range 11,767–1,630) and 94,125 min × pmol/l (45,034–184,388), respectively, in group 1 and 7,029 min × pmol/l (812–13,587) and 87,410 min × pmol/l (16,590–141,909) in group 2. No statistical significant differences of insulin and C-peptide concentrations could be shown between the two groups. Insulin–to–C-peptide ratios for both total areas under the curve and iAUCs were calculated to evaluate differences in insulin clearance. The mean ratios amounted to 0.059 ± 0.006 and 0.066 ± 0.008, respectively, in group 1 and 0.067 ± 0.008 and 0.075 ± 0.008, respectively, in group 2. No statistically significant differences between the two groups were found.

As illustrated in Fig. 2*C*, plasma glucagon concentrations decreased after subcutaneous administration of GLP-1 to sub-basal values in both groups. In group 1, we observed a statistically significant fall from a basal value of 17.3 pmol/l (range 15–19.3) in the fasting state to a nadir of 12.5 pmol/l (10–15) ($P = 0.01$) at 29 min (20–60) after the subcutaneous GLP-1 injection. In group 2, we observed a statistically significant fall from 16.2 pmol/l (range 11.7–21.3) to a nadir of 12.1 pmol/l (10–15) ($P = 0.01$) at 45 min (20–80) after the injection. From the nadir levels and for the remainder of the experiment, the concentrations of glucagon slowly, but statistically significantly, increased to the end values of 15.5 pmol/l (range 10–20) ($P = 0.02$) and 16.4 pmol/l (13–19) ($P = 0.02$) in groups 1 and 2, respectively. We observed no statistically significant difference in basal values, nadir values, or end values between the two groups.

FPG was 10.2 mmol/l (range 9.0–11.7) and 9.2 mmol/l (6.0–13.8) in groups 1 and 2, respectively (Fig. 3). At 3 min after the intravenous glucose bolus, PG had increased to 15.2 mmol/l (range

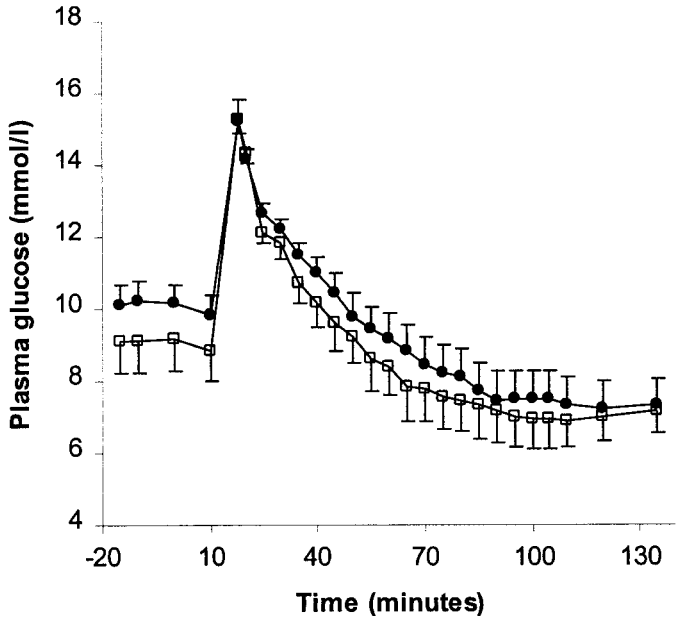

Figure 3—*PG concentrations in lean type 2 diabetic patients (●) and in patients with type 2 diabetes secondary to chronic pancreatitis (□). Data are means ± SEM. Time of GLP-1 injection = 0 min, and time of intravenous glucose bolus = 15 min.*

12.3–17.3) mmol/l in group 1 and 15.3 mmol/l (14.0–16.1) in group 2. During the initial 17 min after the PG peak (at 18 min), the PG decreased rapidly to 11.5 mmol/l (range 10.2–12.9) and 10.8 mmol/l (7.7–13.2) in groups 1 and 2, respectively. At 50 min after subcutaneous administration of GLP-1, the PG returned to the starting point in both groups. PG was stabilized 90 min after the GLP-1 injection at 7.5 mmol/l (range 3.9–10.1) and 7.2 mmol/l (3.1–10.9) in groups 1 and 2, respectively. From these time points, PG remained stable throughout the experiment in both groups.

The one patient (a patient in group 2) with the lowest PG (2.9 mmol/l at 100 min after the GLP-1 injection) experienced no symptoms of hypoglycemia and the PG concentration spontaneously increased to 3.4 mmol/l 10 min later. At the end of the experiment, at 135 min after the GLP-1 injection, this patient's PG had spontaneously increased to 5 mmol/l. None of the patients experienced symptoms of hypoglycemia, and biochemical hypoglycemia (with PG concentrations ≤2.5 mmol/l) was not observed.

CONCLUSIONS — The present study reveals that subcutaneous administration of the highest therapeutically relevant dose of GLP-1 in combination with intravenous glucose to lean type 2 diabetic patients and patients with diabetes secondary to chronic pancreatitis (patients with close to normal insulin sensitivity) does not provoke hypoglycemia.

We have earlier shown that a high dose of subcutaneous GLP-1 in combination with intravenous glucose does indeed induce hypoglycemia in overweight healthy subjects with normal glucose tolerance and does not induce hypoglycemia in overweight patients with type 2 diabetes (7). Other studies have also shown that GLP-1 induces hypoglycemia in lean healthy subjects (6,12,19). To determine whether insulin resistance explains the absent reactive hypoglycemic induction in the overweight type 2 diabetic patients, we studied two groups of type 2 diabetic patients with close to normal insulin sensitivity: lean type 2 diabetic patients (group 1) and patients with diabetes secondary to chronic pancreatitis (group 2). HOMA analyses of the participants' insulin resistance showed that both groups had essentially normal insulin resistance (1.9 ± 0.3 and 1.7 ± 0.5 in groups 1 and 2, respectively) (18), significantly lower than the values found in the earlier-studied obese type 2 diabetic subjects (5.4 ± 1.1; $P < 0.01$) (7). Because earlier experiments, using the exact same methods, have shown that subcutaneous administration of GLP-1 causes biochemical hypoglycemia and clear symptoms of hypoglycemia in healthy subjects (7), we found it irrelevant and unethical to assign a control group of matched healthy lean control subjects.

We used subcutaneous injections with the highest dose of GLP-1 that can be given by this route without pronounced side effects (12). Thus, this is probably close to the highest dose that can be administered therapeutically. As expected (12), 7 of 16 patients experienced temporary subjective side effects to GLP-1, such as light to moderate nausea and/or sweating. The plasma levels of both intact and total GLP-1 were grossly elevated after the subcutaneous injections, and the plasma level of total GLP-1 remained elevated above physiological levels (12) throughout the period of investigation in both groups, whereas intact GLP-1 reached basal values 120 and 105 min after the injection in groups 1 and 2, respectively. The lack of hypoglycemic reactions in the patients was, therefore, not due to inadequate levels of GLP-1 in the investigational period. GLP-1 injected alone in the fasting state is not likely to elicit hypoglycemia because of the glucose dependency of the insulin response to GLP-1 (20). Even in diabetic subjects with high FPG, only a very small reduction in blood glucose can be elicited after subcutaneous administration of GLP-1 in the fasting state (21). Therefore, experimentally, we brought up blood glucose to high levels at the time for maximal concentration of GLP-1, mimicking the injection of a large therapeutic dose of GLP-1 followed by ingestion of carbohydrates. The earlier-reported hypoglycemic reaction in healthy subjects (7) was interpreted to reflect the greatly enhanced insulin secretion induced by GLP-1 and the relatively long inactivation time of insulin's effect on glucose disposal, even after normoglycemia had been reached.

As mentioned above, no hypoglycemic reaction was reported among overweight type 2 diabetic patients (7). The possible contributors to the absence of hypoglycemia in obese insulin-resistant type 2 diabetic patients was judged to be a combination of impaired insulin response and increased insulin resistance. One could imagine, therefore, that groups of patients characterized predominantly by impaired insulin secretory capacity but with near-normal insulin sensitivity, including lean type 2 diabetic patients and patients with pancreatogenic diabetes,

still would run the risk of hypoglycemia in a GLP-1–based antidiabetic therapy, in view of the powerful insulinotropic and hypoglucagonotropic action of GLP-1. Both groups in the present study responded with a marked increase in insulin secretion in response to GLP-1 plus glucose, but the rate of secretion, as judged by the iAUCs for C-peptide, amounted to only ~40% of that reported earlier for healthy subjects (7). Thus, it seems that an impaired insulin secretory capacity is more important than insulin resistance with respect to the proneness to develop hypoglycemia after subcutaneous administration of GLP-1 in combination with intravenous glucose. In some studies, GLP-1 has been found to enhance insulin-mediated glucose transport in adipose and muscle tissues and to reduce glucose production in the liver (i.e., to enhance the insulin sensitivity) (22–25), and a recent study by Egan et al. (26) concluded that GLP-1 has insulinomimetic properties per se in insulin-resistant states. Our study suggests that regained insulin sensitivity (e.g., from weight loss or GLP-1 therapy) does not render the patient sensitive to the hypoglycemic effects of GLP-1.

We observed a significant increase in glucagon concentration at the end of the experiment in both groups ($P = 0.02$), but it is unlikely that elevated glucagon levels protect against GLP-1–induced hypoglycemia in the present experiment because GLP-1 caused a marked and apparently normal suppression of the secretion of glucagon (7).

Our results suggest that a GLP-1–based therapy for type 2 diabetes will not be associated with an increased risk of hypoglycemia, even in patients with preserved or restored insulin sensitivity, because the present groups of patients were characterized by a predominantly impaired insulin secretory capacity and close to normal insulin sensitivity. Nevertheless, GLP-1 has trophic actions on pancreatic β-cells and also promotes differentiation of β-cells from progenitor duct cells (27). Therefore, prolonged GLP-1 therapy may improve the insulin secretory capacity, and such patients might then run the risk of GLP-1–induced hypoglycemia, which, on the other hand, should be amendable by reducing the dose of GLP-1. On the basis of several studies, we conclude that treatment with GLP-1 is not likely to elicit hypoglycemia in type 2 diabetic patients. However, the new long-acting GLP-1 analogs still need to be studied with the risk of hypoglycemia in mind.

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