

Exendin-4 reduces fasting and postprandial glucose and decreases energy intake in healthy volunteers

C. MARK B. EDWARDS,¹ SARAH A. STANLEY,¹ RACHEL DAVIS,²
AUDREY E. BRYNES,² GARY S. FROST,² LEIGHTON J. SEAL,¹
MOHAMMAD A. GHATEI,¹ AND STEPHEN R. BLOOM¹

¹Endocrine Unit, and ²Department of Dietetics, Imperial College of Science,
Technology and Medicine, Hammersmith Hospital, London W12 0NN, United Kingdom

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Edwards, C. Mark B., Sarah A. Stanley, Rachel Davis, Audrey E. Brynes, Gary S. Frost, Leighton J. Seal, Mohammad A. Ghatei, and Stephen R. Bloom. Exendin-4 reduces fasting and postprandial glucose and decreases energy intake in healthy volunteers. *Am J Physiol Endocrinol Metab* 281: E155–E161, 2001.—Exendin-4 is a long-acting potent agonist of the glucagon-like peptide 1 (GLP-1) receptor and may be useful in the treatment of type 2 diabetes and obesity. We examined the effects of an intravenous infusion of exendin-4 (0.05 pmol·kg⁻¹·min⁻¹) compared with a control saline infusion in healthy volunteers. Exendin-4 reduced fasting plasma glucose levels and reduced the peak change of postprandial glucose from baseline (exendin-4, 1.5 ± 0.3 vs. saline, 2.2 ± 0.3 mmol/l, *P* < 0.05). Gastric emptying was delayed, as measured by the paracetamol absorption method. Volunteers consumed 19% fewer calories at a free-choice buffet lunch with exendin-4 (exendin-4, 867 ± 79 vs. saline 1,075 ± 93 kcal, *P* = 0.012), without reported side effects. Thus our results are in accord with the possibility that exendin-4 may be a potential treatment for type 2 diabetes, particularly for obese patients, because it acts to reduce plasma glucose at least partly by a delay in gastric emptying, as well as by reducing calorie intake.

glucagon-like peptide 1; glycemia; gastric emptying; type 2 diabetes

GLUCAGON-LIKE PEPTIDE 1 (GLP-1) is released from the intestine in response to nutrient ingestion (20). Exogenous administration to humans has a number of effects that result in a decrease in plasma glucose levels. It stimulates plasma insulin levels (20), suppresses glucagon levels (22), and delays gastric emptying (27, 45). There is some evidence that GLP-1 may also increase peripheral insulin sensitivity (4, 16), although this is controversial (30). GLP-1 has been shown to decrease food intake and body weight in rats when administered into the third cerebral ventricle (24, 42). A number of groups have looked at the effect of GLP-1 on satiety and food intake in humans, and it appears to parallel the effect seen in rats, although not always (11, 18, 23, 25). Recently, we infused the GLP-1 antag-

onist, exendin-(9–39), in humans and demonstrated that endogenous GLP-1 regulates plasma glucose levels (10), and its effects on plasma glucagon and gastric emptying appear to be physiological (10). GLP-1 has also been shown to have a physiological role in glucose homeostasis in the rat (21, 44), mouse (38), and baboon (5), although it appears that this is not always the case, as exogenous administration has little effect in the calf (9).

Exendin-4 is a 39-amino acid peptide isolated from the Gila monster salivary gland and acts as an agonist of the GLP-1 receptor (13, 40). Exendin-4 appears to have a considerably greater biological half-life than GLP-1 (14, 39, 46). We (10) have shown that the circulating half-life of the truncated exendin-4, exendin-(9–39), is 33 ± 4 min in humans; this compares with a half-life for the biologically active intact GLP-1 of 1–3 min in a number of species (6, 19, 32). Thus it would appear likely that exendin-4 has a longer circulating and biological half-life than GLP-1 in humans. Exendin-4 in vivo seems considerably more potent than GLP-1 (14, 28, 39, 46) and may have potential as a therapeutic agent for use in type 2 diabetes. A number of GLP-1 analogs have been tested in vitro and in vivo in both rats and mice (2, 20, 29, 34). They also appear to have greater plasma stability and a longer action than GLP-1, indicating a number of potential therapeutic agents acting at the GLP-1 receptor. Before investigation of exendin-4 in patients, its actions and possible side effects needed to be elucidated in healthy volunteers. Thus we infused exendin-4 into healthy volunteers to assess the effect on fasting and postprandial glucose and hormones, gastric emptying rate, and calorie consumption, as well as scores of nausea and satiety.

SUBJECTS, MATERIALS, AND METHODS

Peptides. Exendin-4 was synthesized using fluorenylmethoxycarbonyl chemistry on an Advanced Chemtech 396MPS peptide synthesizer. The product comprised one major peak, which was purified to homogeneity by reversed-phase HPLC on a C₈ column (Phenomenex, Macclesfield, UK). Electro-

Address for reprint requests and other correspondence: S. R. Bloom, ICSM Endocrine Unit, Hammersmith Hospital, London W12 0NN, UK (E-mail: s.bloom@ic.ac.uk).

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pray mass spectrometry was used to confirm the identity of the peptide. The Limulus Amoebocyte Lysate assay test for pyrogen was negative, and the peptide was sterile on culture.

Subjects. Eight healthy subjects [1 male and 7 female, age 25.5 ± 1.4 (mean \pm SE) yr, body mass index 21.8 ± 0.7 kg/m²] participated in the study. Subjects gave informed, written consent, and ethical approval was obtained from the local Research Ethics Committee. The study was carried out in accordance with the principles of the Declaration of Helsinki. We had previously infused the exendin-4 fragment, exendin-(9–39), at 1,000 \times the concentration of exendin-4 infused here, without side effects (10). Subjects were taking no regular medication and had no allergies or abnormalities on physical examination and electrocardiogram. They had no evidence of abnormal renal function. Hemoglobin, fasting plasma glucose, and insulin levels were normal. Volunteers filled out a food diary for the 3 days before the first infusion to standardize intake before each infusion. Subjects refrained from alcohol and strenuous exercise for 24 h before infusion. All subjects were fasted of food and drink except water from 8:00 PM on the evening before each study day.

Protocol. Each subject was studied on two occasions with ≥ 1 wk between each study. On the morning of study, a cannula was inserted into a large forearm vein for collection of blood, and another was inserted into a vein in the opposite forearm for infusion of exendin-4 or saline. Subjects sat at a 45° angle throughout the studies. Subjects were infused with saline or exendin-4 in a randomized, double-blind manner; four received exendin-4 first and four saline first. Exendin-4 was diluted in saline and mixed with volunteer's plasma (5% by volume) to reduce adsorption to infusion tubing.

In pilot studies, we had infused exendin-4 up to a dose of 0.32 pmol \cdot kg⁻¹ \cdot min⁻¹ in the fasted state without side effects. However, dose-related side effects were noted on consumption of food. Exendin-4 (0.16 pmol \cdot kg⁻¹ \cdot min⁻¹) caused vomiting in most subjects, but only after prolonged infusion if subjects consumed food. Exendin-4 (0.1 pmol \cdot kg⁻¹ \cdot min⁻¹) caused nausea in some patients with no vomiting after prolonged infusion and consumption of food. No side effects were noted at concentrations below 0.1 pmol \cdot kg⁻¹ \cdot min⁻¹; thus, for the experiment detailed below, subjects were infused with exendin-4 at a dose of 0.05 pmol \cdot kg⁻¹ \cdot min⁻¹ or saline.

The infusions were started 1 h before a standard test breakfast (described as 0 min), which was consumed within 15 min. The standard test breakfast consisted of 75 g of hard-boiled eggs, 60 g of white bread, 10 g of butter, and 200 ml of fresh orange juice (400 kcal: 44% carbohydrate, 16% protein, and 40% fat). At 0 min, 1.5 g of paracetamol were also consumed to allow measurement of gastric emptying rate. Exendin-4 or saline infusion continued for a further 210 min.

At 180 min, while the exendin-4 or saline infusion continued, the volunteers were presented with a free-choice buffet lunch. Subjects were asked to eat as much as they wanted of whatever they wanted. The choices consisted of chicken curry and plain boiled rice, fruit salad, and a variety of mini chocolate bars and fruit-flavored sweets and water as required. Food was provided in excess, such that all appetites could be satisfied and subjects would be unable to assess their own intake. Food was weighed pre- and postprandially to allow calculation of total caloric intake in response to infusion of exendin-4 or saline.

Subjects were asked to fill out visual analog scores to determine their degree of fullness (rated 0–10 from “as hungry as it is possible to be” to “as full as it is possible to be”) and nausea (rated 0–10 from “as unsick as it is possible to be” to “as sick as it is possible to be”). These were completed just

before the start of the infusion, just before the standard test breakfast, 60, 120, and 180 min after the start of the breakfast and at the start of the buffet lunch, and 30 and 60 min later. In addition, subjects were asked to inform the investigators of any symptoms.

Samples of exendin-4 infusate were collected before and after termination of the infusion for calculation of actual infusion rate. Blood samples were collected 20 min before the start of exendin-4 infusion and for 240 min after the standard test breakfast. Subjects were asked to complete food diaries for the 24 h after each infusion. During the infusions, subjects were attached to a cardiac monitor, and arterial blood pressure was measured regularly using a Critikon Dinamap vital signs indicator. Subjects were encouraged to relax by either reading or watching videotapes during the course of the studies.

Analytical methods. Blood was collected into heparinized tubes containing 5,000 kallikrein inhibitor units (0.2 ml) of aprotinin and centrifuged, and plasma was separated and stored at -20°C until analysis. Plasma glucose was measured using a YSI 2000 glucose analyzer. Plasma insulin, glucagon, GLP-1, and gastric inhibitory polypeptide (GIP) levels were measured using established radioimmunoassays (RIAs) (12, 22, 36). Plasma exendin-4-like immunoreactivity (exendin-4-LI) levels were measured using our recently described RIA for exendin-(9–39) (10), which used an antiserum raised against exendin-4. The assay standard was synthetic exendin-4, and the assay had a sensitivity of 1.2 pmol/l. Gastric emptying rate was assessed by measurement of plasma paracetamol levels with an enzymatic colorimetric assay with the use of an Olympus AU600 analyzer. Peak plasma paracetamol concentrations (C_{\max}) and time of C_{\max} (T_{\max}) were recorded.

Calculations. The decay curve of exendin-4-LI concentrations was converted to natural logarithms and plotted against time. The resulting straight line plot was used to derive the half-time of disappearance ($t_{1/2}$) for infused exendin-4-LI for each subject. The metabolic clearance rate (MCR) of exendin-4-LI was calculated for each volunteer from the steady-state concentration (CSS; taken as the value at t 210, the end of the infusion) and infusion rate at which this concentration was stable, where $\text{MCR} = \text{infusion rate} / \text{CSS}$. The apparent volume of distribution (VD) was calculated from the half-life and the CSS, where $\text{VD} = \text{MCR} \times t_{1/2} \times 1.44$.

Statistical analysis. All results are presented as means \pm SE. The incremental or decremental area under the curve (AUC) for glucose and each hormone was calculated using the trapezoidal rule. AUC values for postprandial glucose, insulin, glucagon, GLP-1, and GIP were calculated from 0 min immediately before consumption of the standard test breakfast to 180 min immediately before the buffet lunch, or earlier if stated. To assess an effect on fasting, AUC was calculated between -60 min, the time of initiation of the infusion, and 0 min; the absolute change between -60 and 0 min was also calculated. Comparisons of AUCs, peak postprandial plasma glucose levels, C_{\max} and T_{\max} of plasma paracetamol levels, absolute differences between the infusion groups, and food consumption between the exendin-4 and control studies were by paired t -test. Visual analog scores were compared by the Wilcoxon signed-rank test.

RESULTS

No side effects were reported by any subject with either exendin-4 (0.05 pmol \cdot kg⁻¹ \cdot min⁻¹) or saline in-

fusion. Exendin-4 infusion had no effect on blood pressure or pulse rate.

Plasma exendin-4-LI was undetectable in the fasted state before infusion. The measured infusion rate of exendin-4 was $0.028 \pm 0.001 \text{ pmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, presumably less than the concentration in the syringe secondary to peptide adhesion to the infusion tubing. The plateau level of exendin-(9–39)-LI was $16.4 \pm 0.9 \text{ pmol/l}$. The course of exendin-4-LI disappearance followed first-order kinetics. The plasma half-life of exendin-4-LI was calculated to be $26 \pm 3 \text{ min}$. The mean MCR was $1.8 \pm 0.2 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, and the apparent volume of distribution was $64 \pm 7 \text{ ml/kg}$.

Exendin-4 decreased plasma glucose over the 60 min in the fasted state from 4.5 ± 0.1 to 4.0 ± 0.1 vs. saline 4.6 ± 0.1 to $4.5 \pm 0.1 \text{ mmol/l}$ (Fig. 1). The absolute decrease in plasma glucose level was significant (0.47 ± 0.05 vs. $0.10 \pm 0.04 \text{ mmol/l}$, $P < 0.005$); the decrease was also significant as measured by incremental AUC ($-60-0$: exendin-4 -13.7 ± 1.9 vs. saline $-3.9 \pm 1.9 \text{ mmol} \cdot \text{min} \cdot \text{l}^{-1}$, $P < 0.03$).

Plasma glucose levels were decreased by 35% with exendin-4 infusion for the 180-min postprandial period; however, this effect failed to reach statistical significance (AUC 0–180: exendin-4 100 ± 26 vs. saline $155 \pm 50 \text{ mmol} \cdot \text{min} \cdot \text{l}^{-1}$, $P = 0.21$; Fig. 1). The peak change from baseline of postprandial glucose for each individual was decreased with exendin-4 infusion (exendin-4 1.5 ± 0.3 vs. saline $2.2 \pm 0.3 \text{ mmol/l}$, $P < 0.05$) without change in the time of the peak.

There was no change in plasma insulin levels in the fasted state with exendin-4 infusion compared with saline [AUC $-60-0$: exendin-4 -160 ± 260 vs. saline $-230 \pm 140 \text{ pmol} \cdot \text{min} \cdot \text{l}^{-1}$, $P = \text{not significant (NS)}$]; Fig. 2). However, this effect was in the face of a reduction in plasma glucose that would be expected to be associated with a reduction in insulin if no insulinotropic agent was present. Plasma insulin was decreased by 23% with exendin-4 infusion for the 180-min postprandial period (AUC 0–180: exendin-4 $13,180 \pm 2,200$ vs. saline $17,140 \pm 1,530 \text{ pmol} \cdot \text{min} \cdot \text{l}^{-1}$, $P < 0.03$; Fig. 2). There was no effect of exendin-4

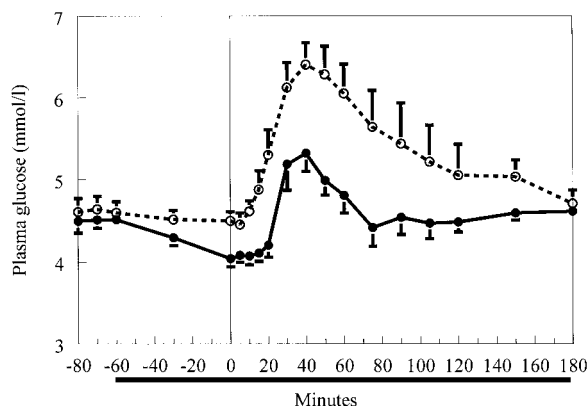


Fig. 1. Plasma glucose levels in response to infusion of exendin-4 ($0.05 \text{ pmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, ●, solid line) or saline (○, dotted line). A standard test breakfast was consumed at 0 min. Solid bar indicates time of infusion. Results presented are means \pm SE.

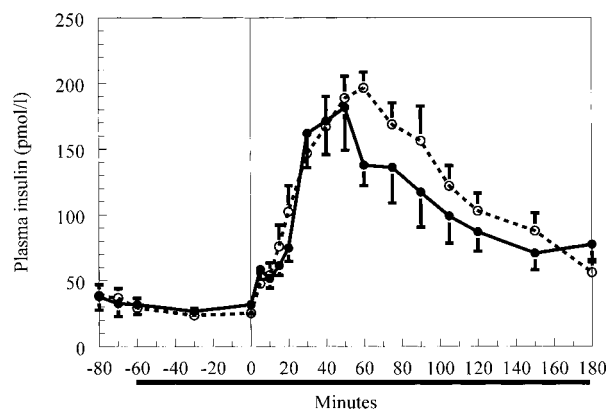


Fig. 2. Plasma insulin levels in response to infusion of exendin-4 ($0.05 \text{ pmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, ●, solid line) or saline (○, dotted line). A standard test breakfast was consumed at 0 min. Solid bar indicates time of infusion. Results presented are means \pm SE.

infusion on the average peak postprandial insulin level or on the time of the peak.

There was a tendency toward a decrease in plasma glucagon levels in the fasted (AUC $-60-0$: exendin-4 11 ± 20 vs. saline $55 \pm 39 \text{ pmol} \cdot \text{min} \cdot \text{l}^{-1}$, $P = \text{NS}$) and postprandial states, although this did not attain statistical significance (AUC 0–180: exendin-4 -95 ± 70 vs. saline $-13 \pm 158 \text{ pmol} \cdot \text{min} \cdot \text{l}^{-1}$, $P = \text{NS}$).

Exendin-4 decreased gastric emptying as measured by the paracetamol absorption test (T_{max} saline 79 ± 20 vs. exendin-4 $120 \pm 23 \text{ min}$, $P < 0.05$; Fig. 3). There was a tendency toward a decrease in C_{max} (saline 0.14 ± 0.02 vs. exendin-4 $0.1 \pm 0.02 \text{ mmol/l}$, $P = 0.07$).

Exendin-4 infusion reduced postprandial GLP-1 levels by 75% (AUC: exendin-4 210 ± 137 vs. saline $866 \pm 260 \text{ pmol} \cdot \text{min} \cdot \text{l}^{-1}$, $P < 0.05$; Fig. 4). Exendin-4 reduced GLP-1 greater than control in the fasted state (exendin-4 -4.3 ± 1 vs. saline $-0.7 \pm 1.4 \text{ pmol/l}$, $P < 0.02$; Fig. 4).

Exendin-4 reduced plasma GIP levels by 32%, although this effect failed to reach significance (AUC: exendin-4 $19,600 \pm 3,100$ vs. saline $28,700 \pm 5,600$

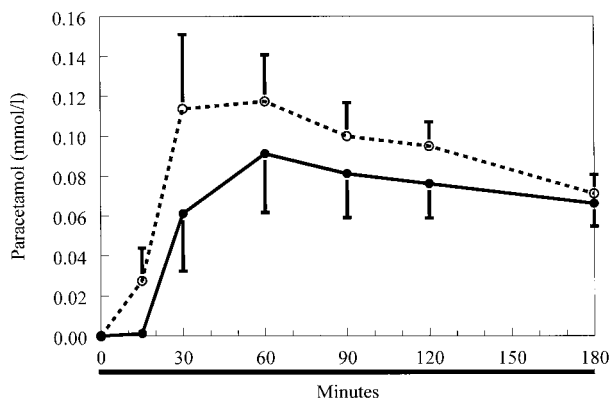


Fig. 3. Plasma paracetamol levels in response to infusion of exendin-4 ($0.05 \text{ pmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, ●, solid line) or saline (○, dotted line). 1.5 g of paracetamol together with a standard test breakfast were consumed at 0 min. Solid bar indicates time of infusion. Results presented are means \pm SE.

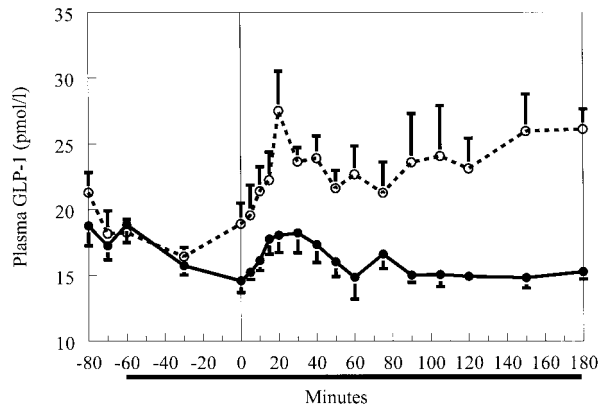


Fig. 4. Plasma glucagon-like peptide 1 (GLP-1) levels in response to infusion of exendin-4 ($0.05 \text{ pmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, ●, solid line) or saline (○, dotted line). A standard test breakfast was consumed at 0 min. Solid bar indicates time of infusion. Results presented are means \pm SE.

$\text{pmol} \cdot \text{min} \cdot \text{l}^{-1}$, $P = 0.1$). There was no effect of exendin-4 on fasting plasma GIP levels.

Exendin-4 reduced food intake at the buffet lunch by 19% (exendin-4 867 ± 79 vs. saline $1,075 \pm 93$ kcal, $P = 0.012$; Fig. 5A), with all eight subjects reducing their caloric intake (range 2–41%; Fig. 5B). Addition of

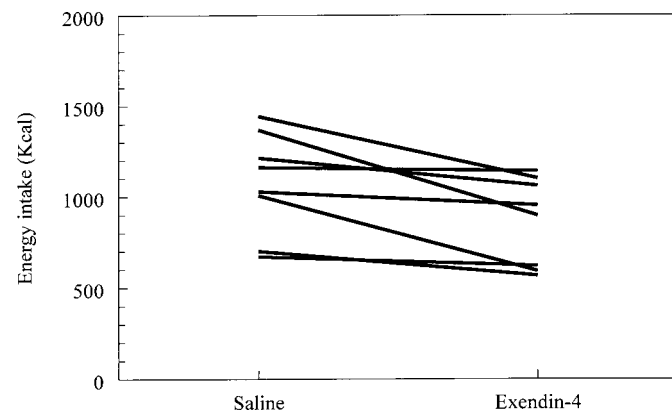
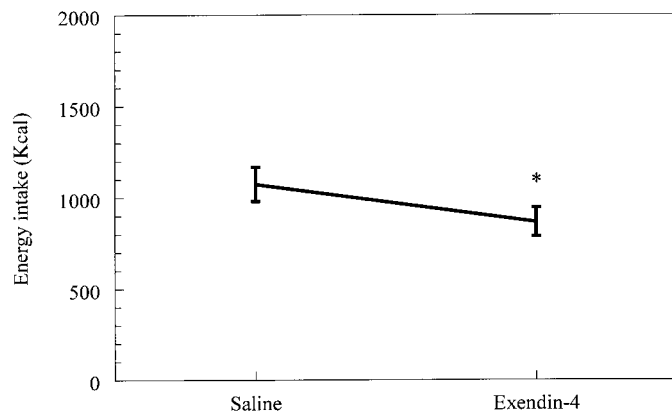


Fig. 5. A: mean (\pm SE; $*P = 0.012$) energy consumed at a free-choice buffet lunch in response to infusion of exendin-4 ($0.05 \text{ pmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) or saline. B: results presented for all 8 individuals.

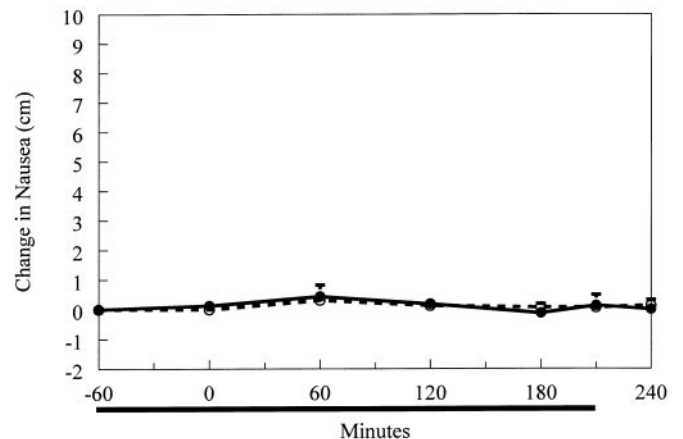
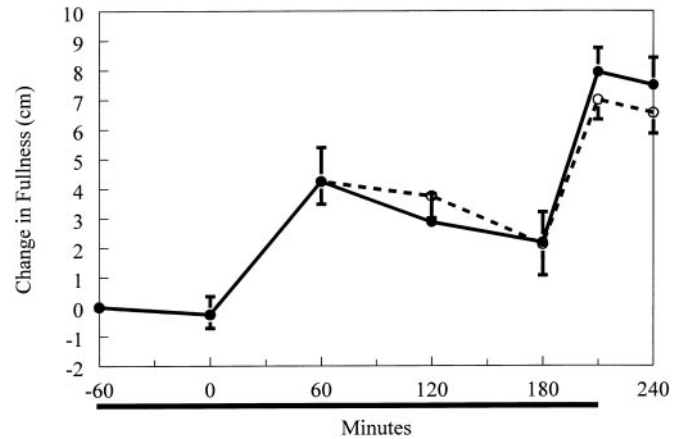


Fig. 6. Change in subjective feelings of fullness (A) and nausea (B) in response to infusion of exendin-4 ($0.05 \text{ pmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, ●, solid line) or saline (○, dotted line), measured from visual analog scores on a scale from 0 to 10. A standard test breakfast was consumed at 0 min. Solid bar indicates time of infusion. A free-choice buffet lunch was consumed at 180 min. Results presented are means \pm SE.

the food intake at lunch to that of the evening gave a total voluntary food intake for the day 21% less after exendin-4 (exendin-4 $1,694 \pm 192$ vs. saline $2,152 \pm 207$ kcal, $P = 0.023$). Food intake on the following day was not different between the two infusions ($P = 0.81$).

There was no difference in the sensations of fullness or nausea reported by the volunteers between the two infusions at any point (Fig. 6).

DISCUSSION

We have shown that exendin-4 infusion caused a significant decrease in fasting plasma glucose levels, although not into the hypoglycemic range. It reduced postprandial glucose excursions after a standard test breakfast by approximately one-third, and the peak rise in plasma glucose was also decreased.

It is now well documented that long-term improvement in glycemic control is of benefit to patients with type 2 diabetes (43). However, it is a matter of some debate whether reduction of peak plasma glucose levels or average plasma glucose, or both, is particularly important. Exendin-4 infusion appears to decrease

both parameters, at least in healthy subjects. The reduction in postprandial plasma glucose appears to be mediated, at least in part, by a delay in gastric emptying. It seems most likely that the decrease in postprandial plasma insulin levels that we found with exendin-4 was secondary to the fall in glucose caused by this delay in gastric emptying.

The cause of the exendin-4-induced drop in fasting plasma glucose is difficult to interpret. There was no statistically significant effect of exendin-4 on plasma glucagon levels, in contrast to the effect of GLP-1, which potently suppresses glucagon (10, 22). Similarly, there was no significant effect of exendin-4 on fasting plasma insulin levels. Given that the fasting plasma glucose level was lower with exendin-4 infusion, it would be expected that insulin be suppressed and glucagon stimulated compared with saline infusion. The fact that this did not occur implies that exendin-4 was having an insulinotropic effect and was suppressing plasma glucagon in the fasted state, although the effect was apparently of insufficient magnitude to be significant. In addition, it is possible that a small and transient effect on plasma insulin and/or plasma glucagon levels did occur, which we did not see with the limited number of sampling points in the fasted state. Such effects have been reported with GLP-1 (31, 33).

Plasma GLP-1 levels were greatly decreased in the postprandial state, and there also appeared to be a decrease in the fasted state. It has been suggested that a minimal delivery rate of nutrients into the duodenum is necessary for release of GLP-1 (37). The delay in gastric emptying caused by exendin-4 in our study may have caused duodenal nutrient delivery to decrease to such an extent that very little endogenous GLP-1 was released. Levels of the other incretin hormone, GIP (7), showed a tendency to decrease; this could also be secondary to the delay in gastric emptying. Why fasting plasma GLP-1 levels were reduced is not explained by this mechanism. An alternative explanation is that exogenous administration of exendin-4 causes a reduction in or downregulation of endogenous production of GLP-1 from the L-cell. A similar effect has been noted with infusion of exogenous GLP-1-(7-37), causing a reduction in mean levels of endogenous GLP-1-(7-36) amide, although this effect failed to reach significance (41).

Exendin-4 has been reported to be insulinotropic (46); however, in this study we found a small decrease in postprandial plasma insulin, although not to the extent of the plasma glucose. The delay in gastric emptying would be expected to decrease plasma insulin as well as the plasma glucose. Small changes in plasma glucose are usually associated with relatively larger changes in plasma insulin. The small postprandial decrease in plasma glucose found here would thus be expected to have a larger effect on plasma insulin. The observation that the decrease in insulin was smaller than the decrease in glucose suggests that exendin-4 was having an insulinotropic effect in our study; however, the many potentially compensating factors made it impossible to quantify the magnitude of the effect (8).

This study was not designed to assess whether exendin-4 was affecting peripheral insulin sensitivity or having an insulin-like effect in either the fasting or the postprandial state; however, such an effect cannot be ruled out.

Pharmacokinetics of exendin-4 in humans were assessed. The MCR of exendin-4-LI at $1.8 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ is similar in magnitude to the normal glomerular filtration rate. The volume of distribution is similar to total body water volume and does not suggest that exendin-4 is extensively tissue bound. The relatively long half-life and the MCR being similar to the glomerular filtration rate suggest that the peptide is stable and that its main clearance is renal. No endogenous plasma exendin-4-LI was detectable by RIA before the onset of infusion.

Overall, the effects of exendin-4 on plasma glucose and insulin are similar to those reported for GLP-1 in a number of studies (3, 10, 16, 22, 26), except that exendin-4 appears considerably more potent than GLP-1 and has a half-life in the circulation considerably longer than that of GLP-1. However, it should be noted that the plateau plasma concentration of exendin-4-LI in this study is 16 pmol/l , not dissimilar to the concentration of bioactive GLP-1 that produces similar effects on plasma glucose and insulin (41); the proportion of exendin-4-LI that is bioactive in our study is unknown. The observation that twice the concentration of exendin-4 infused here caused side effects may suggest that exendin-4 has a narrow therapeutic range.

Infusion of exendin-4 also caused a highly significant decrease in caloric consumption, amounting to 19% for the free-choice buffet meal, and this was apparently long lasting, with a 21% decrease in food intake when the lunch and intake for the rest of the day were combined. All eight subjects decreased their caloric consumption with exendin-4 infusion and in the absence of any symptoms or signs of nausea.

A number of recent studies have assessed the effects of GLP-1 infusion on caloric intake (11, 17, 18, 23, 25, 41). In the first published study, a 12% reduction of caloric intake was found with infusion of GLP-1 at a rate of $50 \text{ pmol} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ to healthy volunteers, well over 10 times the concentration of exendin-4 that we infused here (11). Those authors also found a decrease in subjective feelings of hunger, although those effects were not large. Two other groups have also demonstrated a decrease in caloric intake with infusion of GLP-1 (18, 25). This is contrasted with one report showing no effect of GLP-1 on energy intake or scores of satiety with infusion of GLP-1 at a rate of $1.2 \text{ pmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ (23). However, that infusion of GLP-1 was short, and there was a tendency for a reduction in both caloric intake and satiety scores. More recently, these findings have been confirmed in patients with type 2 diabetes (17, 41).

Overall, our findings of a reduction in caloric intake are consistent with those previously found with GLP-1, although exendin-4 appears to be at least an order of

magnitude more potent. The delay in gastric emptying found with exendin-4 may be one mechanism; however, a direct satiety effect cannot be ruled out.

A number of studies have now been published concerning the use of exendin-4 in vivo. It has been demonstrated that exendin-4 reduces plasma glucose in mice, rats, and monkeys (14, 39, 46). Peripheral exendin-4 has also been shown to reduce food intake and body weight in lean and obese Zucker rats (1, 35). We have found that infusion of exendin-4 into healthy volunteers was well tolerated and, similar to the results found in animal studies, caused a reduction in fasting and postprandial glucose, a delay in gastric emptying, and a long-lasting reduction in food intake.

Taken together, these findings are in line with the possibility that exendin-4, given to produce concentrations similar to those found here, may be a potential treatment particularly likely to benefit obese patients with type 2 diabetes.

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