0013-7227/01/$03.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 86(9):4382–4389

A Meta-Analysis of the Effect of Glucagon-Like Peptide-1 (7–36) Amide on *Ad Libitum* Energy Intake in Humans

C. VERDICH, A. FLINT, J.-P. GUTZWILLER, E. NÄSLUND, C. BEGLINGER, P. M. HELLSTRÖM, S. J. LONG, L. M. MORGAN, J. J. HOLST, AND A. ASTRUP

Research Department of Human Nutrition, Centre for Food Research (C.V., A.F., A.A.), The Royal Veterinary and Agricultural University, DK-1958 Frederiksberg C, Denmark; Division of Surgery, Karolinska Institute (E.N.), Danderyd Hospital, SE-182 88 Daderyd, Sweden; School of Biological Science (S.J.L., L.M.M.), University of Surrey, Guildford GU2 5XH, United Kingdom; Division of Gastroenterolgy (J.-P.G., C.B.), University Hospital, CH-4031 Basel, Switzerland; Department of Gastroenterology and Hepatology (P.M.H.), Karolinska Hospital, SE-171 76 Stockholm, Sweden; and Department of Medical Physiology, The Panum Institute (J.J.H.), University of Copenhagen, DK-2200 Copenhagen N, Denmark

Seven studies have now been published pertaining to the acute effect of iv administration of glucagon-like peptide-1 (7–36) amide on *ad libitum* energy intake. In four of these studies energy intake was significantly reduced following the glucagon-like peptide-1 infusion compared with saline. In the remaining studies, no significant effect of glucagon-like peptide-1 could be shown. Lack of statistical power or low glucagon-like peptide-1 infusion rate may explain these conflicting results.

Our aim was to examine the effect of glucagon-like peptide-1 on subsequent energy intake using a data set composed of subject data from previous studies and from two as yet unpublished studies. Secondly, we investigated whether the effect on energy intake is dose dependent and differs between lean and overweight subjects.

Raw subject data on body mass index and *ad libitum* energy intake were collected into a common data set (n = 115), together with study characteristics such as infusion rate, duration of infusion, *etc.* From four studies with comparable protocol the following subject data were included if available: plasma concentrations of glucagon-like peptide-1, subjective appetite measures, well-being, and gastric emptying rate of a meal served at the start of the glucagon-like peptide-1 infusion.

Energy intake was reduced by 727 kJ (95% confidence interval, 548–908 kJ) or 11.7% during glucagon-like peptide-1 infusion. Although the absolute reduction in energy intake was higher in lean (863 kJ) (634–1091 kJ) compared with overweight subjects (487 kJ) (209–764 kJ) ($P = 0.05$), the relative reduction did not differ between the two groups (13.2% and 9.3%, respectively). Stepwise regression analysis showed that the glucagon-like peptide-1 infusion rate was the only independent predictor of the reduction in energy intake during glucagon-like peptide-1 (7–36) amide infusion ($r = 0.4$, $P < 0.001$). Differences in mean plasma glucagon-like peptide-1 concentration on the glucagon-like peptide-1 and placebo day (n = 43) were related to differences in feelings of prospective consumption ($r = 0.40$, $P < 0.01$), fullness ($r = 0.38$, $P < 0.05$), and hunger ($r = 0.26$, $P = 0.09$), but not to differences in *ad libitum* energy intake. Gastric emptying rate was significantly lower during glucagon-like peptide-1 infusion compared with saline. Finally, well-being was not influenced by the glucagon-like peptide-1 infusion.

Glucagon-like peptide-1 infusion reduces energy intake dose dependently in both lean and overweight subjects. A reduced gastric emptying rate may contribute to the increased satiety induced by glucagon-like peptide-1. (*J Clin Endocrinol Metab* 86: 4382–4389, 2001)

THE INTESTINAL HORMONE glucagon-like peptide-1 (GLP-1), released in response to food intake, has been proposed to act as a regulator of postprandial satiety (1, 2). In animal studies, acute administration of GLP-1 directly into the cerebrospinal fluid has been shown to reduce subsequent food intake (3, 4).

The acute effect of iv GLP-1 administration to humans has been studied by several groups (1, 5–10). In four of these studies GLP-1 was found to produce a significant, and relatively large (10–32%), reduction in energy intake compared with saline (1, 6, 8, 9). In all of the remaining studies energy intake tended to be lowered following GLP-1 infusion (0.1–7%) (5, 7, 10). Differences in infusion rate, duration of infusion before the *ad libitum* meal, preload, or subject characteristics might explain these inconsistent findings.

To our knowledge, only one study has been performed in which appetite has been measured in subjects given GLP-1 over a longer period of time (11). In this study, GLP-1 was administered to six type II diabetic patients by a continuous sc infusion over a period of 48 h, during which food intake was fixed. There was, however, a tendency to a reduction in hunger and prospective consumption and an increase in satiety during the GLP-1 infusion (11). These findings suggest that continuous administration of GLP-1 to type II diabetics might serve two treatment purposes: 1) to increase insulin secretion and hereby improve blood glucose regulation (11–14); and 2) to reduce food intake and to aid intended weight loss.

The aim of the present study was 1) to examine the overall effect of GLP-1 on energy intake on the basis of a data set composed of subject data from the seven previously published studies as well as from two as yet unpublished studies, and 2) to investigate whether the effect on energy intake is dose dependent and/or differs between lean and overweight

Abbreviations: BMI, Body mass index; CI, confidence interval; GLP-1, glucagon-like peptide-1 (7–36) amide; NIDDM, noninsulin-dependent diabetes mellitus; VAS, visual analog scale.

subjects. Furthermore, the relationship between differences in mean plasma concentration of GLP-1 and subjective sensations of hunger, prospective food consumption, and fullness were assessed using raw data from three of the studies with comparable protocols (1, 6, 10). Finally, data on gastric emptying rate from two of these studies (6, 10) were also included in the analysis.

Materials and Methods

Selection of studies

A Medline search was performed to identify all studies pertaining to the effect of iv GLP-1 infusion on subsequent food intake in humans. The following search words were used in combination: GLP-1 or glucagon-like peptide-1 and energy intake or food intake or appetite or satiety from 1966 to 2000. From this search 67 studies pertaining to humans were found. Six studies were selected as being suitable for the present meta-analysis (1, 5–9). One study involving GLP-1 administration was excluded because it differed markedly from the other studies. In this study, GLP-1 was administrated sc to type II diabetics during a 48-h period with fixed energy intake (11). Data from two unpublished studies performed by Christoph Beglinger *et al.* (unpublished results) and one study performed at our own institute (10) were included in the analysis.

Design of selected studies

All of the selected studies were randomized cross-over studies with iv infusion of either GLP-1 or placebo during an *ad libitum* meal. In one of the studies a 5% glucose solution was given as placebo (8) whereas saline was given in the remaining studies. The duration of infusion before the *ad libitum* meal varied from 0 to 240 min. In two of the studies infusion was stopped for 30 min before the *ad libitum* meal and resumed at the beginning of the meal (1, 10), whereas in the other studies the infusion was not disrupted. In the study where the *ad libitum* meal was served at the beginning of the infusion all subjects were fasting before the meal (5). In six studies a fixed preload meal (1.4–3.0 MJ) was served 4–6 h before the *ad libitum* meal (Refs. 1, 6, 7, 9, and 10; Beglinger *et al.*, unpublished results). In the last study, subjects were asked to eat their usual breakfast at home (8). In addition, 36 subjects followed a weight-maintaining standardized diet for 2 days before the examination (1, 10). The rate of infusion per kilogram of body weight was equal for all subjects within all studies, except one (10). In this study, subjects were given 0.75 pmol fat free mass $(kg)^{-1}/min^{-1}$, corresponding to a mean infusion rate of 0.5 pmol kg^{-1} min^{-1} (range, 0.45–0.52 pmol/kg^{-1}·min^{-1}). In this meta-analysis the mean infusion rate was used in replacement for the infusion rate calculated for each subject.

Collection of data

A letter was sent to the corresponding author of the seven relevant articles informing them about our plans for a meta-analysis and asking them to contribute to this by delivering raw data on the following variables: body mass index (BMI) and *ad libitum* energy intake on the placebo day and on the GLP-1 day.

The four studies by Näslund *et al.* (5, 6) and Flint *et al.* (1, 10) were selected for further analysis, as they followed comparable protocols with infusion lasting 3–4 h. In these studies appetite measures were assessed by the use of visual analog scales (VAS) throughout the infusion. Furthermore, plasma concentrations of GLP-1 were assessed in the same laboratory in three of the studies (1, 6, 10), and gastric emptying rate was assessed in three of the studies (5, 6, 10). From these studies raw data on gastric emptying, plasma GLP-1 concentration, and VAS scores were collected into a separate data file, together with the rest of the data material from these studies, to investigate the effect of GLP-1 infusion rate and GLP-1 plasma concentrations on gastric emptying, *ad libitum* energy intake, and VAS scores for appetite measures (hunger, fullness, prospective food consumption).

Statistics

The traditional meta-analysis is made exclusively on summary data that are published in original articles. Typically, the aim of a meta-analysis is to create a systematic overview of the effect of a specific treatment (for instance, the effect of *ad libitum* intake of low-fat diets on body weight) (15). In this type of meta-analysis the original studies are randomized, placebo-controlled intervention studies, including an intervention group that receives the treatment of the study and a control group either receiving placebo or a conventional treatment. However, studies investigating the physiological effect of a short-term intervention such as the effect of GLP-1 infusion on the subsequent *ad libitum* energy intake are typically performed as cross-over studies where the subject serves as their own control. The essential parameters in a meta-analysis are the mean and the 95% confidence interval (CI) for the mean difference in the outcome measure between the intervention and the control group. These measures are then weighted according to the size of the study, and an overall mean and 95% CI for all studies is then estimated. When the study is designed as a randomized, placebo-controlled intervention, the mean and the CI for the difference between the two intervention groups is easily estimated from the mean and the CI of the outcome measure for each of the two groups. However, to include cross-over studies in a meta-analysis one needs to include the mean and CI of the within-subject differences between the two treatments. The effect of the treatment is typically tested using a paired sample *t* test. Most often, however, mean and CI for the outcome measure is reported separately for the two interventions whereas CI for the within-subject difference between the two treatments is not reported in the article, and cannot be calculated from the reported data. Therefore, when performing a meta-analysis including cross-over studies one will need either raw data for all subjects or summary measures of the within-subject differences between the two treatments. Because we were able to obtain raw data from all studies, we decided to perform only an analysis on individual subject data, that is creating a large data set including raw data from all subjects and examining these data as data from a single study using study-specific circumstances such as infusion rate, duration of infusion, size of test meal, or pre load as covariates together with BMI. One of the studies included in this meta-analysis examined the dose-response relationship between GLP-1 infusion rate and reduction in energy intake compared with the placebo. The subjects in this study were subjected to one control infusion of 5% glucose solution and three intervention infusions of GLP-1 of 0.325, 0.75, and 1.50 $pmol/kg^{-1}$ ·min^{-1}. When including data from this study into the meta-analysis, the same subject and the same control measurements are included three times and the fact that these are repeated measurements was not taken into account. However, because the aim of the present analysis was to examine the dose-response relationship between GLP-1 infusion rate and reduction in *ad libitum* energy intake, it is obvious that relevant information would be lost if we excluded some of the data. Therefore, we chose to include data from all three infusion rates in the primary analysis, but to repeat the analysis using only data from either the high, medium, or low infusion rate. All statistical procedures in the present meta-analysis were performed using SPSS 10.0 for Windows (SPSS, Inc., Chicago, IL). The relationship between GLP-1 infusion rate and change in *ad libitum* energy intake compared with the control was tested using bivariate correlation analysis (using Pearson coefficient of correlation) and stepwise linear regression. Data pertaining to the effect of GLP-1 infusion rate or GLP-1 plasma concentration on subjective appetite measures, gastric emptying rate, and reported well-being were analyzed in the same manner.

Subjects

All subjects were male. In five of the studies only healthy lean subjects (BMI, 20.1–26.9 kg/m^2) were included (Table 1). Of the remaining four studies, three included only healthy overweight subjects (BMI, 30.0–51.1 kg/m^2), whereas one study was performed on 12 lean and overweight type II diabetics (BMI, 24.2–36.3 kg/m^2). For the purpose of examining the effect of GLP-1 on lean and overweight subjects separately, BMI was used to divide the subject data into two groups: BMI less than 25 and BMI 25 or greater. One lean subject suffering from type II diabetes was found to have a higher energy intake (1.3 MJ greater) on the day of GLP-1 infusion compared with the placebo day. Data from this subject was included in the overall data analysis, but excluded when analyzing overweight and lean separately, because the inclusion of this subject in the lean group could lead to a false conclusion when comparing the sensitivity toward the hormone between lean and overweight subjects.

TABLE 1. Characteristics of nine randomized cross-over trails investigating the effect of iv GLP-1 infusion on *ad libitum* energy intake

Author, yr (Ref.)	No.	BMI (kg/m^2)	Infusion rate $pmol/kg^{-1}\cdot min^{-1}$	Duration of infusion prior to *ad libitum* meal (min)	Difference in *ad libitum* energy intake (kJ)
Flint *et al.*, 1998 (1)	19	22.9 (0.3)	0.83	240	−528 (150)
Näslund *et al.*, 1998 (5)	6	35.7 (1.8)	0.75	0	−15 (176)
Näslund *et al.*, 1999 (6)	8	45.5 (2.3)	0.75	240	−520 (164)
Long *et al.*, 1999 (7)	10	23.2 (0.6)	1.2	40	−417 (243)
Gutzwiller *et al.*, 1999 (8)	16	23.3 (0.2)	0.375	60	−452 (225)
			0.75	60	−739 (281)
			1.5	60	−2179 (299)
Gutzwiller *et al.*, 1999 (9)	12	29.0 (1.2)	1.5	60	−1046 (401)
Flint *et al.*, 2001 (10)	17	33.6 (0.6)	0.50[a]	240	−87 (176)
Beglinger *et al.*, unpublished data	12	22.8 (0.2)	0.9	60	−559 (313)
Beglinger *et al.*, unpublished data	15	22.5 (0.5)	0.9	60	−925 (313)

Data are expressed as mean (SEM).
[a] Range 0.45–0.52 $pmol/kg^{-1}\cdot min^{-1}$ (SEM, 0.005).

Eleven overweight type II diabetics were include in the analysis with the overweight subjects.

Plasma concentrations of GLP-1

In three of the included studies (n = 44, but data are missing from one subject in Ref. 10) plasma concentrations of GLP-1 were assessed during the infusion using RIAs specific for both the C- and the N-terminal of the molecule as described previously (1, 6, 10). Here, we only include plasma concentrations assessed by the assay specific for the C-terminal. Two summary measures were calculated and incorporated in the analysis, namely the mean GLP-1 concentration during the time between the preload and the *ad libitum* meal and the mean concentration during the last hour before the *ad libitum* meal.

Gastric emptying

In three of the studies gastric emptying was assessed by adding 1.5 g acetaminophen to the preload meal (6, 10) or the *ad libitum* meal served at the beginning of the infusion (5). Blood samples were taken every 30 min during the following 3–5 h to assess the rate of absorption of acetaminophen, which is known to depend almost exclusively on the rate of gastric emptying (16, 17). For the purpose of the present meta-analysis, gastric emptying was estimated by incremental postprandial area under the curve (AUC) for plasma acetaminophen, incremental peak value (Δpeak), and time to peak for plasma concentrations of acetaminophen, as described previously (10).

Subjective ratings using VAS

From the three studies measuring plasma concentrations of GLP-1 during the infusion VAS scores for hunger, fullness, and prospective food consumption were included in the present analysis. Additional VAS scores for nausea from one study and well-being from another study (6, 10) were pooled into a common data set to assess possible side effects of GLP-1. For appetite ratings, the numeric difference between the measurement immediately after ingestion of the preload and immediately before the *ad libitum* meal, the Δ-value, was used as the only outcome measure. For side effects, a mean value for the same period was also included. As described above, in two of the studies the infusion was stopped for 30 min before the *ad libitum* meal. The differences in Δhunger, Δfullness, Δprospective food consumption, Δwell-being and mean well-being between the 2 test days were calculated as:

$$\Delta hunger_{GLP\text{-}1} - \Delta hunger_{placebo} \quad (A)$$

Negative values indicated a greater change in fullness, and positive values indicates a greater change in prospective food consumption and hunger during the intermeal period on the placebo day compared with the GLP-1 day.

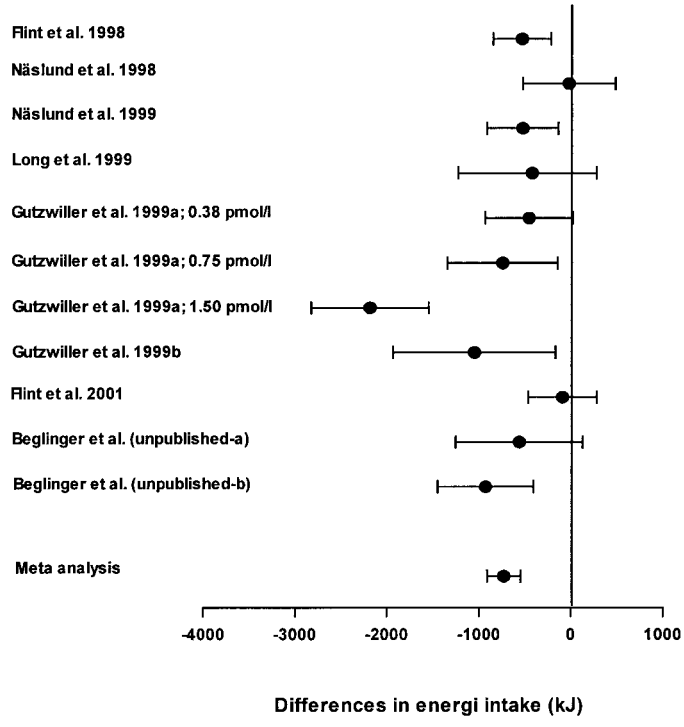


FIG. 1. The difference in *ad libitum* energy intake (kJ) between the placebo day and the day of GLP-1 infusion. Mean and 95% CI are shown for the original studies and for the meta-analysis.

Results

Overall effect of GLP-1 on ad libitum energy intake

When pooling the 147 observations a mean reduction in *ad libitum* energy intake of 727 kJ (95% CI, 908–548 kJ) ($P < 0.001$) or 11.7% (95% CI, 8.1–15.3%) ($P < 0.001$) was seen during GLP-1 infusion compared with the control infusion (Fig. 1). The mean GLP-1 infusion rate for all observations was 0.89 $pmol/kg^{-1}\cdot min^{-1}$. The mean *ad libitum* energy intake during the placebo treatment was significantly higher in healthy lean subjects (n = 99; 6.4 MJ) (95% CI, 6.1–6.8 MJ) than in overweight subjects (n = 47; 3.7 MJ) (95% CI, 3.3–4.2 MJ) ($P < 0.001$). In lean subjects the mean infusion rate was 0.9 $pmol/kg^{-1}\cdot min^{-1}$, and the average reduction in *ad libitum*

intake was 863 kJ (95% CI, 634-1091 kJ) or 13.2% (95% CI, 9.7–16.7%) ($P < 0.001$ for both). In merely overweight subjects (n = 36) the mean infusion rate was 0.67 pmol/kg^{-1}·min^{-1}, and the reduction in *ad libitum* intake was, on average, 252 kJ (95% CI, 15–489 kJ) ($P < 0.04$) or 4.5% (95% CI, −5% to 14.0%) (NS). When including data from overweight type II diabetic subjects (n = 11) the mean infusion rate was 0.86 pmol/kg^{-1}·min^{-1}, and the reduction in *ad libitum* intake was, on average, 487 (95% CI, 764–209 kJ) ($P = 0.001$) or 9.3% (95% CI, 0.8–17.3%) ($P < 0.04$). Although a difference in *ad libitum* energy intake was found between lean and overweight subjects ($P = 0.05$), the percentage reduction in energy intake was similar between the two groups. Furthermore, when excluding the six subjects for whom the *ad libitum* meal was served at the beginning of the infusion (5) the mean difference in *ad libitum* energy intake was 556 kJ (95% CI, 247–865) ($P = 0.001$) or 10.5% (0.93–20.1%) ($P < 0.04$) for overweight subjects (n = 41), which was not significantly different from lean subjects. Both the absolute and the relative reduction in *ad libitum* energy intake was greater for overweight subjects with noninsulin-dependent diabetes mellitus (NIDDM) compared with merely overweight subjects ($P < 0.05$ for both).

Dose-response relationship

In the overall data set the reduction in *ad libitum* energy intake correlated with the GLP-1 infusion rate (Fig. 2A) (r = 0.40, $P < 0.001$). The analysis was repeated including data from only one of the three infusion rates applied to the subjects in the dose-response study by Gutzwiller *et al.* (8). The strength of the relationship remained when results obtained during medium and low infusion rates were excluded (r = 0.46, $P < 0.001$). However, it was reduced, but still significant, when the data obtained during the high infusion rate was excluded (r = 0.21, $P = 0.023$ when including data from a medium infusion rate, and r = 0.22, $P = 0.021$ when including data from a low infusion rate). The relationship between infusion rate and reduction in energy intake in lean subjects was similar to that seen in the overall data set (r = 0.42, $P < 0.001$) (Fig. 2B). In the group of merely overweight subjects no correlation was seen. However, when including data from overweight type II diabetics, the same correlation was seen in overweight subjects as in lean subjects (r = 0.47, $P = 0.001$) (Fig. 2B). By the SPSS procedure "curve fitting" it was tested whether the relationship between the GLP-1 infusion rate and reduction in energy intake was best described by a linear, logarithmic, inverse, or quadratic model. In the overall data set, as well as in lean subjects, the fit of the model was slightly improved by applying the quadratic model compared with the linear (Table 2). By stepwise linear regression analysis the GLP-1 infusion rate was found to be the only independent predictor of the reduction in energy intake, whereas BMI, duration of infusion, and duration of time between preload and *ad libitum* meal did not contribute any further. This was seen both in the overall data set and in the lean and overweight subjects. When repeating the analysis with residuals from the quadratic model describing the relationship between infusion rate and reduction in *ad libitum* intake (Table 2) as the dependent variable neither BMI, duration of infusion, or duration of time between preload and *ad libitum* meal turned out significantly in the stepwise regression analysis (data not shown). In six of the studies a fixed test meal was served several hours before the *ad libitum* meal. Stepwise regression showed no relationship between the size of the test meal and the reduction in subsequent *ad libitum* intake.

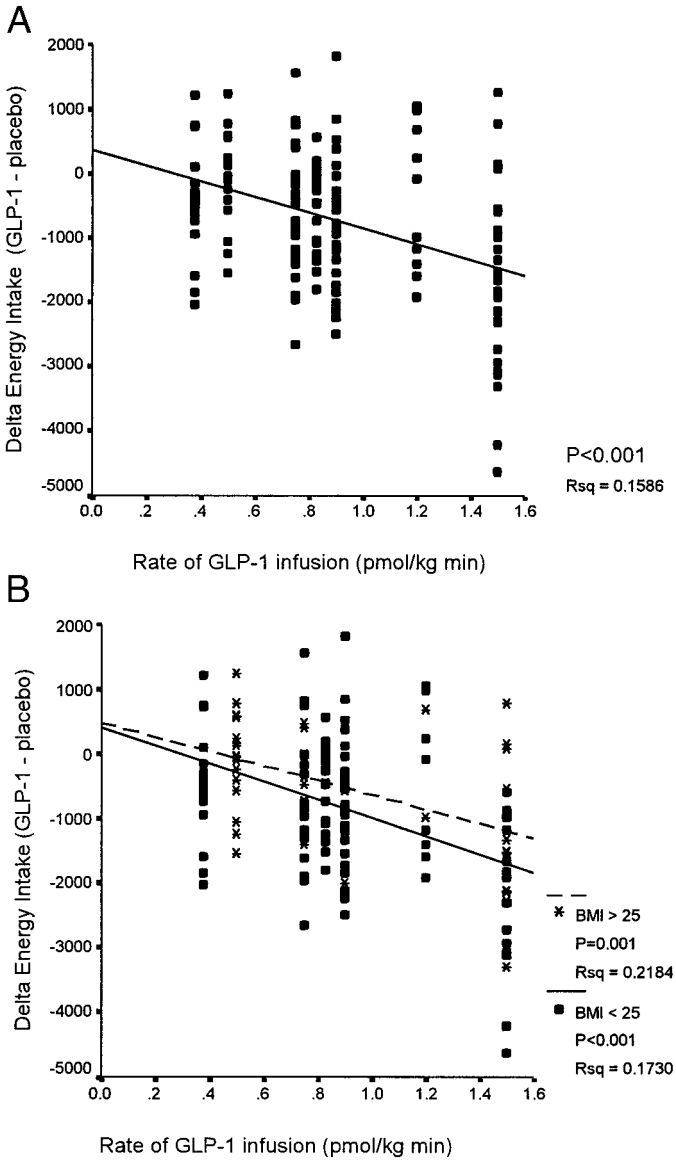


FIG. 2. The linear association between GLP-1 infusion rate (pmol/kg^{-1}·min^{-1}) and the reduction in *ad libitum* energy intake (kJ) on the day of GLP-1 infusion and compared with the control day. The association is shown for the overall data set (n = 147; A) and for the obese subjects (n = 47) and healthy lean subjects (n = 99; B).

Plasma GLP-1 concentration and appetite regulation

The relationship between plasma GLP-1 concentrations and subjective measures of appetite was examined in 42 subjects. No relationship was seen between the difference in *ad libitum* energy intake and mean GLP-1 concentration between the 2 test days (neither during the whole period be-

TABLE 2. Determinants of reduction in *ad libitum* energy intake on the day of GLP-1 infusion by stepwise regression analysis

Predicted equation	r^2	*P*
Difference in *ad libitum* energy intake [GLP-1 − placebo] (kJ) (all n = 147)		
$= -531 + 908 \times IR - 1090 \times IR^2$	0.18	<0.001
$= 362 - 1224 \times IR$	0.16	<0.001
Difference in *ad libitum* energy intake [GLP-1 − placebo] (kJ) (lean n = 99)		
$= -1104 + 2200 \times IR - 1881 \times IR^2$	0.23	<0.001
$= 398 - 1402 \times IR$	0.17	<0.001
Difference in *ad libitum* energy intake [GLP-1 − placebo] (kJ) (overweight n = 47)		
$= 311 - 721 \times IR - 198 \times IR^2$	0.22	<0.001
$= 478 - 1120 \times IR$	0.22	=0.001

ΔIR, Infusion rate (pmol/kg^{-1}·min^{-1}).

tween preload and the *ad libitum* meal or during the last hour before the *ad libitum* meal). On the other hand, the difference in GLP-1 concentration between the 2 test days correlated with the difference in Δfullness (r = −0.38 *P* = 0.013) and Δprospective food consumption (r = 0.40, *P* = 0.008) (Fig. 3, A and B) and tended to correlate with the difference in Δhunger (r = 0.26, *P* = 0.09) (Fig. 3C). Finally, no correlation was found between difference in *ad libitum* energy intake and Δfullness (r = 0.25 *P* = 0.09), Δprospective food consumption (r = 0.1, *P* = 0.5), or Δhunger (r = 0.1, *P* = 0.5).

The effect of GLP-1 on gastric emptying rate

The studies from which data on gastric emptying was obtained were all performed on overweight subjects (n = 31). In the pooled data set, Δpeak and incremental AUC for acetaminophen were reduced ($P < 0.001$ for both), and time to peak was increased ($P < 0.01$) on the day with GLP-1 infusion compared with the placebo day. As seen in Table 3, the reduction in peak and incremental AUC was much higher in the studies using 0.75 pmol/kg^{-1}·min^{-1} compared with the study using 0.50 pmol/kg^{-1}·min^{-1}, suggesting a nonlinear relationship between infusion rate and reduction in gastric emptying rate. In the 24 subjects for whom plasma GLP-1 concentrations had been assessed, the difference in mean plasma GLP-1 concentration on the two interventions was related to both the percentage reduction in Δpeak (r = 0.65 for the quadratic model, r = 0.63 for the linear model, *P* = 0.001 for both) and incremental AUC (r = 0.77 for the quadratic model, r = 0.71 for the linear model, $P < 0.001$ for both) (Fig. 4, A and B) but not to differences in time to peak.

No correlation was seen between the reduction in Δpeak and AUC acetaminophen and the reduction in *ad libitum* intake during GLP-1 infusion. This was tested using only the data from Flint *et al.* (10) and Näslund *et al.* (6) (n = 25). In the last study (5), the *ad libitum* meal was served as a preload, and subsequently the emptying rate for this meal was assessed. Therefore, it would not give any meaning to include this in the analysis.

Side effects of GLP-1 infusion

In two of the studies VAS scores on either well-being or feelings of nausea were included. Neither in the separate studies nor in the pooled data set (n = 25) were there any signs of side effects of the GLP-1 infusion.

Discussion

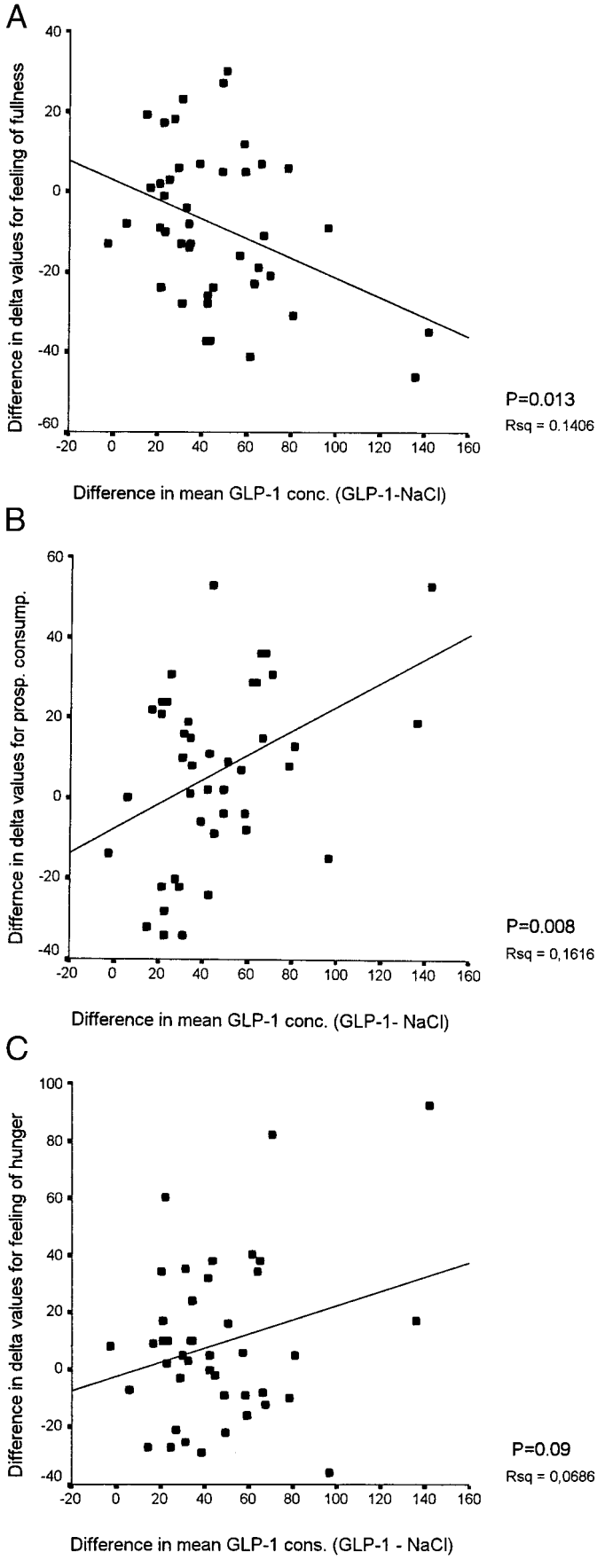
The present meta-analysis is the first combined analysis of data from previous studies of the effect of iv GLP-1 infusion on appetite regulation, gastric emptying, and well-being in humans. From this meta-analysis it is evident that GLP-1 infusion inhibits *ad libitum* energy intake and that the effect is dose dependent, as previously indicated in the study by Gutzwiller *et al.* (8).

It is well documented that obesity may be associated with a reduction of the postprandial GLP-1 response (18–21). Although the present analysis shows a somewhat lesser absolute reduction in energy intake following similar GLP-1 infusion rate in overweight compared with lean subjects, this difference is mainly due to the fact that the overall *ad libitum* intake was lower in obese subjects. Furthermore, from the stepwise regression analysis it is seen that BMI is not an independent determinant of the effect of GLP-1 and that the linear coefficient for reduction of energy intake during GLP-1 infusion is 1.4 MJ per pmol/kg^{-1}·min^{-1} in lean and 1.1 MJ per pmol/kg^{-1}·min^{-1} in overweight subjects, which would indicate that the sensitivity is equal in the two subject groups. Finally, the difference between lean and overweight subjects was somewhat reduced when excluding data from the study, in which the *ad libitum* meal was served at the beginning of the infusion. In this study, *ad libitum* energy intake was similar on the 2 test days (5). It is not possible to conclude whether this finding is related to GLP-1 being increasingly effective with time.

Both the absolute and the relative reduction in energy intake seemed to be greater in overweight subjects with NIDDM compared with merely overweight subjects. This finding might indicate a greater sensitivity to the satiating effect of GLP-1 in NIDDM. However, the observations made in NIDDM patients originated from the same study (9), and it is, therefore, not possible to distinguish a possible effect of the diabetes status from the effect of the study.

Although a linear relationship was shown between reduction in the *ad libitum* energy intake and GLP-1 infusion rate in both the whole group and the two subgroups the quadratic model was found to fit the data better, suggesting that the effect of increasing the GLP-1 dose is greater at a high rate than at a low rate of infusion. Thus, this observation might also indicate a rather weak effect at the more "physiological" levels of GLP-1.

From the pooled data set describing the relationship between plasma concentrations of GLP-1 and appetite mea-



sures, it was clear that increased plasma levels of GLP-1 reduced the feelings of hunger and prospective food consumption and increased the feeling of fullness. However, no relationship was seen between the differences in plasma GLP-1 concentration and *ad libitum* intake on the 2 test days. This might be explained by a large intraindividual variation in *ad libitum* energy intake, which might also explain the lack of correlation between differences in *ad libitum* energy intake and differences in subjective feelings of appetite reported by VAS scores, or that other, unmeasured factors were more important in determining energy intake.

The gastric emptying rate was reduced during GLP-1 infusion in all the three studies from which data on gastric emptying were included. The percentage reduction in emptying rate was much more pronounced during the high infusion rate (0.75 pmol/kg^{-1}·min^{-1}) compared with the lower dose (0.50 pmol/kg^{-1}·min^{-1}), and the percentage reduction in emptying rate increased with increasing plasma GLP-1 levels. The procedure for assessing gastric emptying by adding acetaminophen to the preload differed slightly between the studies using the high and the low infusion rate. In the study using the low infusion rate (10) acetaminophen was added to yogurt, whereas in the two studies using the high infusion rate it was added to a glass of water, which the subjects drank during or at the end of the preload (5, 6). However, as shown recently by Näslund *et al.* (16), acetaminophen dissolved in water and given with a meal follows the same emptying pattern as a solid phase marker. The relation between increase in mean plasma GLP-1 induced by the GLP-1 infusion and the concomitant reduction in peak and AUC for plasma acetaminophen (Fig. 4, A and B) seems to reflect a nonlinear dose-response relationship, even though it could be argued that clustering of the data might lead to false conclusions, and that differences in study design might be a confounder. However, this finding of a dose-response relationship between GLP-1 infusion rate and reduction in gastric emptying is supported by previous findings in lean subjects (22).

In contrast to what might be expected, no correlation was seen between the reduction in gastric emptying and *ad libitum* energy intake during treatment with GLP-1. However, this analysis was performed on data from 25 subjects from only two original studies (6, 10), and in one of these studies no significant difference in *ad libitum* energy intake was seen (10).

Well-being was not affected by the GLP-1 infusion in the overall data set including data from 25 subjects. This is in agreement with the findings in the two original studies (6, 10) and with studies from which raw data were not included (7–9). Furthermore, in the original studies, GLP-1 was shown not to affect palatability rating of the *ad libitum* meal (1, 5, 6, 10) or food preferences (5, 7).

GLP-1 has for several years been regarded as a promising agent in the treatment of type II diabetes. GLP-1 is known to

FIG. 3. The linear association between the difference in the mean plasma GLP-1 concentration (pmol/liter) on the 2 test days (day with GLP-1, day with placebo) and the differences in the change in fullness (A), prospective consumption (B), and hunger (C) during the 3- to 5-h postprandial phase (n = 43).

TABLE 3. The effect of GLP-1 infusion on gastric emptying

	0.5 pmol/kg^{-1}·min^{-1} (n = 17)	0.75 pmol/kg^{-1}·min^{-1} (n = 14)
ΔPeak for acetaminophen (% of D_p)	78 (64–91)[a]	30 (15–45)[b]
Incremental AUC for acetaminophen (% of D_p)	70 (60–80)[b]	28 (16–40)[b]
Difference in time to peak ($D_{GLP-1} - D_P$) (min)	34 (−3–70)	49 (2–97)[c]

D_P, Placebo day; D_{GLP-1}, GLP-1 day.
[a] $P < 0.01$, [b] $P < 0.001$ for different from 100%, [c] $P < 0.05$ for difference from 0.

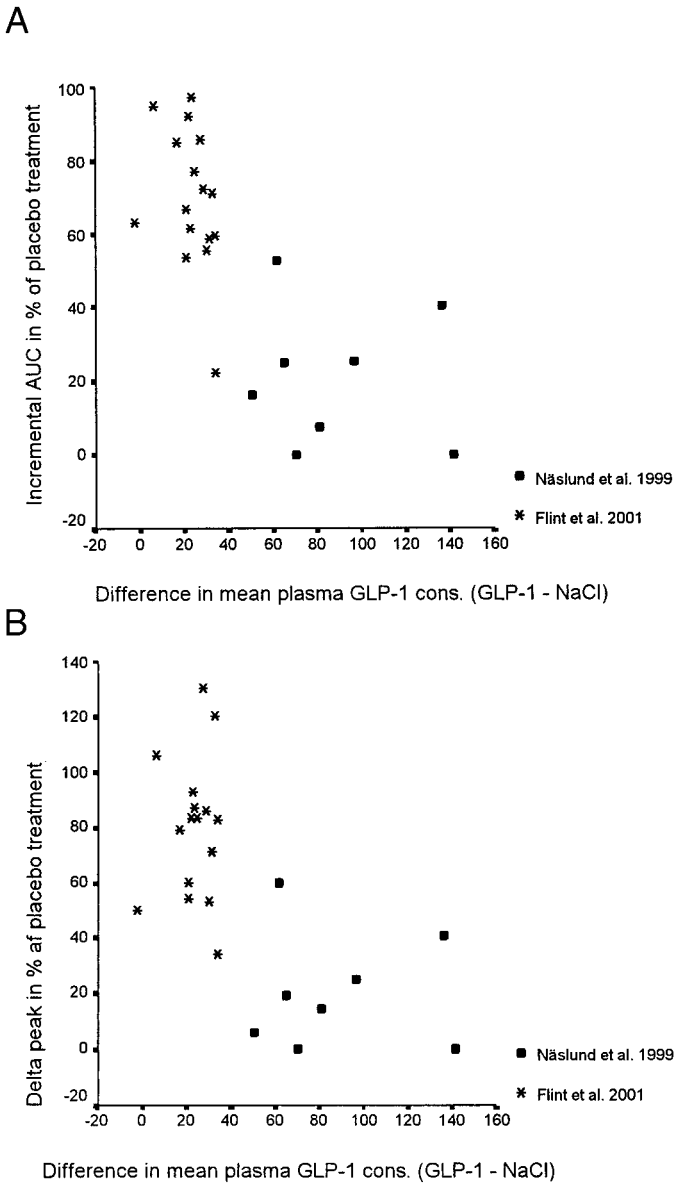


FIG. 4. Scatter plot showing the relationship between the mean plasma GLP-1 concentration (pmol/liter) on the 2 test days (day with GLP-1, day with placebo) and the differences in gastric emptying as estimated incremental AUC for acetaminophen concentration (day with GLP-1 in percentage of day with placebo; A) and by Δpeak for plasma acetaminophen concentration (day with GLP-1 in percentage of day with placebo; B).

be an important incretin hormone stimulating insulin secretion during hyperglycemia and may hereby improve the regulation of plasma glucose in type II diabetics without the risk of hypoglycemia (11, 12, 14, 23). Obesity is the most important cause of type II diabetes, and even a moderate weight reduction is known to improve insulin sensitivity, making weight reduction the primary goal in the treatment of this disease (24). The present meta-analysis confirms that GLP-1 is able to reduce *ad libitum* energy intake and increase satiety both in lean and overweight subjects, without affecting general well-being. Treatment with the GLP-1 agonist, exendin-4, has been shown to decrease food intake, fat deposition, and increase glucose tolerance in Zucker fatty rats (25). Taken together, these findings suggest that GLP-1 or GLP-1 agonists could be extremely valuable in the treatment of type II diabetics and merely obese in humans.

Acknowledgments

Received March 8, 2001. Accepted May 30, 2001.

Address all correspondence and requests for reprints to: Prof. Arne Astrup, Research Department of Human Nutrition, The Royal Veterinary and Agricultural University, Rolighedsvej 30, DK-1958 Frederiksberg C, Denmark. E-mail: ast@kvl.dk.

References

1. **Flint A, Raben A, Astrup A, Holst JJ** 1998 Glucagon-like peptide 1 promotes satiety and suppresses energy intake in humans. J Clin Invest 101:515–520
2. **Holst JJ** 1999 Glucagon-like peptide 1 (GLP-1): an intestinal hormone, signalling nutritional abundance, with an unusual therapeutic potential. Trends Endocrinol Metab 10:229–235
3. **Turton MD, O'Shea D, Gunn I, et al.** 1996 A role for glucagon-like peptide-1 in the central regulation of feeding. Nature 379:69–72
4. **Tang-Christensen M, Larsen PJ, Göke R, et al.** 1996 Central administration of GLP-1-(7–36) amide inhibits food and water intake in rats. Am J Physiol 271:R848–R856
5. **Näslund E, Gutniak M, Skogar S, Rössner S, Hellström PM** 1998 Glucagon-like peptide 1 increases the period of postprandial satiety and slows gastric emptying in obese men. Am J Clin Nutr 68:525–530
6. **Näslund E, Barkeling B, King N, et al.** 1999 Energy intake and appetite are suppressed by glucagon-like peptide-1 (GLP-1) in obese men. Int J Obes Relat Metab Disord 23:304–311
7. **Long SJ, Sutton JA, Amaee WB, et al.** 1999 No effect of glucagon-like peptide-1 on short-term satiety and energy intake in man. Br J Nutr 81:273–279
8. **Gutzwiller JP, Göke B, Drewe J, et al.** 1999 Glucagon-like peptide-1: a potent regulator of food intake in humans. Gut 44:81–86
9. **Gutzwiller JP, Drewe J, Göke B, et al.** 1999 Glucagon-like peptide-1 promotes satiety and reduces food intake in patients with diabetes mellitus type 2. Am J Physiol 276:R1541–R1544
10. **Flint A, Raben A, Ersbøll AK, Holst JJ, Astrup A** 2001 The effect of glucagon-like peptide -1 on appetite, gastric emptying and substrate metabolism. Int J Obes Relat Metab Disord, 25:781–792
11. **Toft-Nielsen M-B, Madsbad S, Holst JJ** 1999 Continuous subcutaneous infusion of glucagon-like peptide 1 lowers plasma glucose and reduces appetite in type 2 diabetic patients. Diabetes Care 22:1137–1143
12. **Nauck MA, Kleine N, Ørskov C, Holst JJ, Willms B, Creutzfeldt W** 1993 Normalization of fasting hyperglycaenmia by exogenous glucagon-like peptide 1 (7–36 amide) in type 2 (non-insulin-dependent) diabetic patients. Diabetologia 36:741–744
13. **Nauck MA, Heimesaat MM, Ørskov C, Holst JJ, Ebert R, Creutzfeldt W** 1993 Preserved incretin activity of glucagon-like peptide 1 [7–36 amide] but not of synthetic human gastric inhibitory polypeptide in patients with type-2 diabetes. J Clin Invest 91:301–307
14. **Nauck MA, Weber I, Bach I, et al.** 1998 Noramlization of fasting glycaemia by intravenous GLP-1 ([7–36 amide] or [7–37] in type 2 diabetic patients. Diabetes Med 15:937–945

15. **Astrup A, Ryan L, Grunwald GK, et al.** 2000 The role of dietary fat in body fatness: evidence from a preliminary meta-analysis of *ad libitum* low-fat dietary intervention studies. Br J Nutr 83:S25–S32
16. **Naslund E, Bogefors J, Gryback P, Jacobsson H, Hellstrom PM** 2000 Gastric emptying: comparison of scintigraphic, polyethylene glycol dilution, and paracetamol tracer assessment technique. Scand J Gastroenterol 35:375–379
17. **Maddern G, Miners J, Collins PJ, Jamieson GG** 1985 Liquid gastric emptying assessed by direct and indirect tecniques:radionucleotide labelled liquid emptying compared with a simple paracetamol marker method. Aust NZ J Surg 55:203–206
18. **Näslund E, Grybäck P, Backman L, et al.** 1998 Distal small bowel hormones: correlation with fasting antroduodenal motility and gastric emptying. Dig Dis Sci 43: 945–952
19. **Ranganath LR, Beety JM, Morgan LM, Wright JW, Howland R, Marks V** 1996 Attenuated GLP-1 secretion in obesity: cause or consequence? Gut 38:916–19
20. **Ranganath L, Norris F, Morgan L, Wright J, Marks V** 1999 Inhibition of carbohydrate-mediated glucagon-like peptide-1 (7–36)amide secretion by circulating non-estrified fatty acids. Clin Sci 96:335–342
21. **Verdich C, Toubro S, Buemann B, Madsen JL, Holst JJ, Astrup A** 2001 The role of postprandial releases of insulin and incretin hormones in meal-induced satiety—effect of obesity and weight reduction. Int J Obes Relat Metab Disord, in press
22. **Nauck MA, Niedereichholz U, Ettler R, et al.** 1997 Glucagon-like peptide 1 inhibition of gastric emptying outweighs its insulinotropic effects in healthy humans. Am J Physiol 273:E981–E988
23. **Nauck MA, Holst JJ, Willms B** 1997 Glucagon-like peptide 1 and its potential in the treatment of non-insulin-dependent diabetes mellitus. Horm Metab Res 29:411–416
24. **Bosello O, Armellini F, Zamboni M, Fitchet M** 1997 The benefits of modest weight loss in type II diabetes. Int J Obes Relat Metab Disord 21:S10–S13
25. **Szayna M, Doyle ME, Betkey JA, et al.** 2000 Exendin-4 decelerates food intake, weight gain, and fat deposition in Zucker rats. Endocrinology 141:1936–1941