Glucagon-like peptide-1: a potent regulator of food intake in humans

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Abstract

Background/Aims—Studies in animals suggest a physiological role for glucagon-like peptide-1 ([7–36]-amide (GLP-1) in regulating satiety. The role of GLP-1 in regulating food intake in man has, however, not been investigated.

Subjects—Sixteen healthy male subjects were examined in a double blind placebo controlled fashion.

Methods—The effect of graded intravenous doses (0, 0.375, 0.75, and 1.5 pmol/kg/min) of synthetic human GLP-1 on food intake and feelings of hunger and satiety was tested in healthy volunteers.

Results—Graded GLP-1 infusions resulted in a dose dependent reduction in food intake (maximal inhibition 35%, p<0.001 vs control) and a similar reduction in calorie intake (32%; p<0.001). Fluid ingestion was also reduced by GLP-1 (18% reduction, p<0.01). No overt side effects were produced by GLP-1, but subjects experienced less hunger and early fullness in the period before a meal during GLP-1 infusion at the highest dose (p<0.05).

Conclusions—Intravenous infusions of GLP-1 decrease spontaneous food intake even at physiological plasma concentrations, implying an important role for GLP-1 in the regulation of the early satiety response in humans.

(Gut 1999;44:81–86)

Keywords: glucagon-like peptide-1; satiety; food intake; hunger and fullness score

The physiological mechanisms that produce satiety after food intake have not yet been defined. Several peptides secreted from the gastrointestinal tract during eating have been shown to suppress food intake if given before meals.1-3 During recent years, the role of the preabsorptive release of gut peptides (especially cholecystokinin (CCK), bombesin-like peptides, and glucagon-like peptides) in the production of meal-ending satiety has been extensively investigated in animals.4-11

CCK and bombesin-like peptides have also been studied in humans.12-15 CCK, the first gut peptide proposed to act as a satiety signal,1 has received the major share of interest in human studies to date, with a dozen reports in the literature.

Glucagon-like peptide-1 (GLP-1), a biologically active product of the post-translational processing of the prohormone proglucagon, is released from enteroendocrine L-cells from the distal gut in response to food intake.16-18 Oral glucose is a stimulus for GLP-1 release, whereas intravenously applied glucose has no effect on endogenous GLP-1. Unexpectedly, later experiments in rats showed that GLP-1 reduced food intake in rats if administered intracerebroventriculally, but had no effect when given peripherally.1 Additional experiments with a specific GLP-1 receptor antagonist that acts specifically to block endogenous peptide and thus affects only physiologically active circuits showed that blockade of endogenous GLP-1 caused healthy already satiated animals to eat more; in fact, the animals more than doubled their food intake. The authors suggested therefore that GLP-1 is a physiological satiety factor.2 The effects of GLP-1 on food intake in humans are not known. Therefore the present study was designed to investigate the effects of intravenous infusions of synthetic human GLP-1 on food intake, meal duration, satiety, and feelings of fullness in healthy male subjects.

Materials and methods

SUBJECTS

A randomised double blind four period latin square design was carried out in 16 healthy men aged 23.6 (0.5) years. The weight of all subjects was within the normal range considering their age, sex, and height.

Each subject gave written informed consent for the study. The protocol was approved by the human ethical research committees of the University Hospitals of Basel and Aarau. Before being accepted, participants were required to complete a medical interview, receive a full physical examination, and participate in an initial laboratory screening. None were taking any medication or had a history of food allergies, disturbances of carbohydrate tolerance, or dietary restrictions.

DOSE-RESPONSE CURVE TO GLP-1

Four treatments, separated by at least seven days, were performed in 16 subjects. The treatments were identical in design (fig 1) except for the intravenous infusion (5% glucose as placebo control or one dose of GLP-1); the order of the experiments was randomised. An identical standard meal was presented to the subjects on each occasion. The meal consisted of orange juice as an appetiser (480 kcal/l), ham sandwiches (60 g bread, 10 g butter, 25 g ham; 266 kcal per sandwich), more orange juice and

Abbreviations used in this paper: GLP-1, glucagon-like peptide-1; CCK, cholecystokinin.
The quantity of food eaten and volume of fluid drunk were measured. The time taken to complete the meal was also measured. From these observations, the average rate of food and fluid intake as well as the calorie intake could be calculated. In the periods before and after eating, blood was drawn at regular intervals in ethylenediaminetetraacetic acid tubes containing aprotonin (1000 KIU/ml blood) for glucose and hormone determinations. Adverse effects were assessed by the attending physician through close observation of the participants; in addition, after each experiment and after all tests had been completed, participants were asked whether they had experienced any adverse effects.

### Plasma Hormone and Glucose Determinations

Glucose concentrations were measured by the hexokinase method. Plasma concentrations of insulin, CCK, GLP-1, and leptin were measured by a sensitive radioimmunoassay system. For insulin and leptin concentrations, commercially available radioimmunoassay systems were used. Adverse effects were assessed by the attending physician and hormone determinations. Adverse effects were assessed by the attending physician and hormone determinations.

### Statistical Analysis

The amount of food eaten and the amount of fluid drunk, the corresponding energy intake, and the duration of food consumption were measured. The time taken to complete the meal was also measured. From these observations, the average rate of food and fluid intake as well as the calorie intake could be calculated. In the periods before and after eating, blood was drawn at regular intervals in ethylenediaminetetraacetic acid tubes containing aprotonin (1000 KIU/ml blood) for glucose and hormone determinations. Adverse effects were assessed by the attending physician through close observation of the participants; in addition, after each experiment and after all tests had been completed, participants were asked whether they had experienced any adverse effects.

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compared between the four treatments by one way analysis of variance using the general linear model procedure of the SAS software package. In the event of significant differences, analysis of variance was followed by the Newman-Keuls multicomparison test for pairwise comparisons. The same statistical procedure was used to analyse the results of GLP-1 induced changes in plasma hormone concentrations using area under the curve analysis.

Scores for hunger and fullness were compared at the different time points before and after the meal between the different treatments using multiple paired t tests with Bonferroni correction.

Results

EFFECT OF GRATED INFUSION OF GLP-1 ON FOOD INTAKE

Intravenous infusion of graded doses of synthetic human GLP-1 dose-dependently reduced the amount of food eaten and the amount of fluid consumed (p<0.001 and p<0.01 respectively; table 1). The maximal reduction in food consumption with the highest dose of GLP-1 (1.5 pmol/kg/min) amounted to 35% resulting in a decrease in calorie intake of 32% (p<0.001; table 1).

Meal duration during GLP-1 infusions was also dose-dependently decreased compared with that with placebo and reached statistical significance at the highest dose (p<0.05). None of the participants reported any abdominal discomfort or side effects during any infusion of either dose. Furthermore, when questioned at the end of each experiment, none reported any adverse reaction.

EFFECT OF GLP-1 ON EATING BEHAVIOUR

Subjects experienced a reduced degree of hunger and a concomitant feeling of fullness in the period before the meal with increasing doses of GLP-1 infusions. However, the difference reached statistical significance only for the highest dose of GLP-1 with respect to hunger feelings (p<0.05–0.01; fig 2). No statistical differences were observed thereafter in hunger or fullness scores with any treatment after meal intake.

EFFECT OF GLP-1 ON HORMONE LEVELS

Graded doses of exogenous GLP-1 produced dose dependent increases in plasma GLP-1 concentrations (fig 3). The two lower doses produced plasma levels of 3.7 (0.6) and 5.0 (0.6) pmol/l respectively, which can be considered physiological postprandial plasma levels, whereas the highest dose of GLP-1 resulted in supraphysiological plasma concentrations. In the control experiment, glucose levels and insulin concentrations remained stable in the preprandial period. GLP-1 induced a dose dependent short lasting increase in blood glucose and plasma insulin concentrations; the results are depicted as an insulinogenic index in fig 4. Because changes in plasma glucose are invariably associated with changes in plasma insulin, the insulinogenic index, calculated as the quotient insulin/glucose, more appropriately reflects insulin release. Plasma CCK concentrations remained unaltered by any dose.
of GLP-1 in the preprandial period (fig 4). Finally, leptin levels did not change either with any dose of GLP-1 administered or after food intake (fig 5).

Discussion
In animals, expression of GLP-1 receptors has been found in the hypothalamus, brainstem, and periventricular area, but not in the cortex. Furthermore, GLP-1 receptors have been found in the endocrine pancreas, adipose tissue, and stomach. Moreover, nerves containing GLP-1 have been identified in the brain. As GLP-1 receptors have been shown to be present at sites at which administration of exogenous GLP-1 appears to cause satiety, experiments are now required to determine if the satiety effect of GLP-1 is physiological, and, if so, whether it is a major satiety factor. Recent animal data have provided experimental evidence that GLP-1 can function as a mediator of food induced satiety in rats and mice provided that it is administered directly into the brain. Injection of GLP-1 into the cerebral ventricles of fasted rats inhibited feeding, and this effect was blocked by the GLP-1 receptor antagonist exendin.thermore, administration of exendin alone doubled food intake in satiated rats. These findings prompted the authors to suggest that GLP-1 is a potent physiological regulator of satiety. These initial observations were confirmed by Scrocchi and co-workers in normal mice; along this line of investigation, the authors postulated that GLP-1 is a physiological regulator of blood glucose and satiety. To ascertain the physiological importance of the peptide as a regulator of feeding behaviour, they generated mice with a targeted disruption of the GLP-1 receptor gene (GLP-1R). These GLP-1R−/− mice developed normally but exhibited increased levels of blood glucose following an oral glucose challenge together with attenuated levels of circulating insulin. However, no evidence for abnormal feeding behaviour was observed in GLP-1R−/− mice, so the biological importance of GLP-1 as a neuropeptide remains controversial.

Based on this information, the purpose of this study was to examine the effect of intravenous administration of graded doses of synthetic human GLP-1 on eating behaviour and satiety in healthy male subjects in order to assess a possible physiological role for the peptide in the regulation of food intake. We were especially interested to test whether intravenous administration of the peptide was able to induce satiety effects. This idea was derived from previous studies showing that several peptides normally secreted from the gastrointestinal tract during eating are able to suppress food intake if given before meals. The results of the present study clearly show that a short term satiety effect can be induced by peripherally infused GLP-1; the results lend further support to the hypothesis that GLP-1 is an endogenous signal involved in the control of food intake in man. The lack of specific GLP-1 receptor antagonists that could be given to humans prevents us for the moment from deciding whether the effects produced by the exogenous administration of GLP-1 (as used in this study) are true physiological effects. However, we have clearly shown that GLP-1
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Glucose-dependent insulinotropic peptide (GLP-1) stimulates adipose tissue to secrete leptin proposed that the postprandial increase in plasma leptin concentrations did not change even during a pharmacological GLP-1 infusion (fig 5), confirming the results of Shalev et al.\(^1\)

The latter finding indicates that food intake suppression induced by GLP-1 is not mediated by leptin. Somatostatin, which has also been proposed to act as a satiety signal, was not measured here, but a previous study has evaluated the effect of intravenous GLP-1 infusion on plasma somatostatin concentration in healthy volunteers and did not show any alteration.\(^10\) GLP-1 is associated with gastric emptying in humans\(^11\)\(^\rightarrow\)\(^12\); it is therefore possible that intravenous administration of GLP-1 activates neural circuits that may cause sensations of fullness by delaying gastric emptying. Additional experiments would be required to test whether changes in gastric function play a role in the suppression of food intake after GLP-1 infusion.

Finally, a non-specific action of GLP-1 can be excluded because no overt side effects were observed in this study. It is noteworthy that GLP-1 reduced food intake to a larger extent than other gut peptides under similar experimental conditions: the maximal reduction in the amount of food eaten was 35% with the highest dose of GLP-1 compared with a maximal effect of gastrin releasing peptide at a high pharmacological dose of 19%\(^11\).\(^\rightarrow\)\(^13\) or a maximal dose of CCK (causing side effects in some volunteers) of 13%.\(^8\) A recent study has shown that therapeutic plasma levels of GLP-1 in healthy volunteers were achieved after a single buccal tablet.\(^14\) Although the bioavailability of buccal GLP-1 was low, the study indicates a potential therapeutic route of administration for GLP-1. Further studies are required to assess whether GLP-1 could provide a new therapeutic approach to the reduction of food intake in patients with non-insulin dependent diabetes mellitus who are overweight and patients with obesity.

In conclusion, we have shown that graded doses of human GLP-1 that produce plasma GLP-1 concentrations within the physiological range reduce intake of food in non-obese healthy male subjects. The mechanism of action requires clarification. Further investigation is needed to define the physiological role of GLP-1 in the control of human food intake and also to assess its therapeutic potential in reducing food consumption.

This work was supported by a grant from the Swiss National Science Foundation (grant No 3200–40604.94/1).

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Gut 1999 44: 81-86
doi: 10.1136/gut.44.1.81

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