Gastric inhibitory polypeptide does not inhibit gastric emptying in humans

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PATIENTS AND METHODS

Study protocol. The study protocol was approved before the study by the ethics committee of the Ruhr-University of Bochum on January 29, 2002 (registration number 1835). Written informed consent was obtained from all participants.

Patients. Fifteen healthy male volunteers participated in the study. The age was 23.9 ± 3.3 yr, the body mass index was 23.7 ± 2.3 kg/m², and the waist-to-hip ratio was 0.96 ± 0.04. Mean Hb A₁c was 0.94 mmol/l (normal: 0.94–1.0%). The fasting glycemia was 4.42 ± 0.15 mmol/l, the total cholesterol concentration was 5.5 ± 0.1% (normal range: 4.8–6.0%), total cholesterol concentrations were 4.42 ± 0.17 mmol/l (normal: <5.2 mmol/l), triglyceride concentrations were 1.17 ± 0.40 mmol/l (normal: <2.3 mmol/l), and fasting glucose concentrations were 5.36 ± 0.94 mmol/l (normal fasting range: <6.0 mmol/l). One subject presented with a plasma glucose concentration of 7.7 mmol/l.

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glucose concentration of 6.1 mmol/l, but on a second occasion glucose values were in the normal range (5.1 mmol/l). All other subjects showed normal fasting glucose concentrations. None of the patients had a history of gastrointestinal disorders, had previously undergone abdominal surgery, or was taking any medication with a known modulating effect on gastrointestinal motility. One patient was a current smoker; the other subjects were nonsmokers.

From all participants, blood was drawn in the fasting state for measurements of standard hematological and clinical chemistry parameters. Subjects with anemia (hemoglobin < 12 g/dl), an elevation in liver enzymes (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, γ-glutamyltransferase) to higher activities than double the respective normal value, or elevated creatinine concentrations (>1.5 mg/dl) were excluded.

Study design. All participants were studied on three occasions. At a screening visit, blood was drawn in the fasting state for laboratory parameters, and a clinical examination was performed. If subjects met the inclusion criteria, they were recruited for the following tests. On separate occasions, gastric emptying was determined over 360 min during the intravenous administration of GIP (2 pmol/kg^-1 min^-1) or placebo (0.9% NaCl with 1% human serum albumin) from −30 to 360 min. The tests were carried out in random order. At least 1 wk had to pass between the tests to avoid carryover effects.

Peptides. Synthetic GIP was purchased from PolyPeptide Laboratories (Wolfenbüttel, Germany) and processed for infusion as described (19).

Experimental procedures. The tests were performed in the morning after an overnight fast with subjects in a supine position throughout the experiments, with the upper body lifted by 30°. Two forearms veins were punctured with a Tellon cannula (Moskito 123, 18 gauge; Vygon, Aachen, Germany) and kept patent using 0.9% NaCl (for blood sampling and for GIP/placebo administration, respectively).

After basal blood samples had been drawn (−45 and −30 min), the experiments were started with the infusion of GIP or placebo at −30 min. After 0 min, a standard test meal (one egg, two slices of white bread, 5 g of magarine, 150 ml of water; 250 kcal) containing 100 mg of [13C]sodium octanoate (100 mg, Euriso-top, Saint-Aubin, France) was mixed into scrambled eggs to contain EDTA and aprotinin (Trasylol; 20,000 kallikrein inhibitor units/ml) and a 10% glucose solution because at these time points the contribution of endogenous GIP secretion was negligible. Integrated incremental areas under the curve for GIP plasma concentrations were calculated according to the trapezoidal rule. For the calculation of endogenous GIP secretion after meal ingestion during GIP infusion, integrated incremental plasma concentrations between 0 and 240 min were calculated over the GIP concentrations from 240 to 360 min, because at these time points steady-state plasma levels were reached.

RESULTS

During the exogenous infusion, GIP plasma concentrations rose to steady-state levels of 159 ± 15 and 34 ± 4 pmol/l for total and intact GIP, respectively (P < 0.0001; Fig. 1). Meal ingestion further increased GIP concentrations to peak levels of 265 ± 20 and 82 ± 9 pmol/l for total and 67 ± 7 and 31 ± 3 pmol/l for intact GIP (during the administration of GIP or
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administration \( (P = 0.22, \ P = 0.13, \text{ and } P = 0.85 \) for glucose, insulin, and C-peptide, respectively; Fig. 3).

Five patients reported mild gastrointestinal side reactions within 24 h after the experiments with GIP infusion. Those were diarrhea in two cases, flatulence in four cases, and abdominal pain in one case. In contrast, no subject reported side reactions after placebo infusion \( (P = 0.014) \).

DISCUSSION

Because GIP is released from endocrine cells in the intestinal mucosa in response to meal ingestion and acts to inhibit gastric acid secretion in animals as well as humans \( (3, 15, 27, 32) \), it was proposed to be an enteroogastrone \( (31, 32) \). On the basis of the original definition, this would also imply inhibitory activities on gastric motility \( (11, 31) \). However, the present data do not support a role for GIP in the regulation of gastric emptying in humans. This was rather unexpected, particularly because the other incretin hormone, GLP-1, potently decelerates emptying of the stomach in healthy subjects as well as in patients with type 2 diabetes \( (16, 23, 30) \).

Given the lack of GIP effect on gastric emptying in the present experiments, the following methodical aspects may be reconsidered. The infusion rate of GIP chosen in the present study raised GIP plasma levels into the supraphysiological range \( (Fig. 1) \). Therefore, inappropriately low dosing of the GIP infusion does not explain the absence of GIP effects. Moreover, the determination of intact, biologically active GIP\-(1-42) with a highly specific immunoassay raised against the NH\(_2\)-terminus of the GIP molecule provided evidence that a considerable proportion \( (\approx 35\%) \) of the total GIP infused was still intact and thus biologically active. The GIP preparation used was from the same charge and manufacturer as in previous studies from our group and has proven its potency to stimulate insulin and glucagon secretion under different experimental conditions \( (17-19) \). Also, the \( [\text{\textsuperscript{13}C}]\)octanoid breath test employed for the determination of gastric emptying has proven

![Figure 1](https://www.ajpendo.org/article/10.220.30.1)  
**Fig. 1.** Plasma concentrations of total gastric inhibitory polypeptide \[GIP-\((1-42)\] plus split products (**A**) and intact GIP\-(1-42) (**B**) during administration of GIP \((2 \text{ pmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}, \bullet)\) or placebo \((\text{human serum albumin}, \bigcirc)\) from \(-30\) to \(360\) min in \(15\) healthy male subjects. At \(0\) min, a mixed meal \((250\ \text{kcal})\) was served (arrows). Data are expressed as means \(\pm\) SE. \(P\) values were calculated using repeated-measures ANOVA and denote differences between experiments (**A**), differences over time (**B**), and differences from interaction of experiment and time (**AB**).

![Figure 2](https://www.ajpendo.org/article/10.220.30.1)  
**Fig. 2.** Time pattern of gastric emptying of a solid meal \((250\ \text{kcal})\) during intravenous administration of GIP \((2 \text{ pmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}, \bullet)\) or placebo \((\text{human serum albumin}, \bigcirc)\) from \(-30\) to \(360\) min in \(15\) healthy male subjects. Gastric emptying was almost complete during the experimental period of \(360\) min, with \(17.5 \pm 2.3\) and \(16.2 \pm 3.8\%\) of the initial content retained in the stomach at the end of the experiments \((\text{for GIP and placebo, respectively; } P = 0.78; \text{Fig. 2})\). There were no differences in the time course of gastric emptying between the experiments \((P = 0.98)\). Gastric half-emptying times were \(120 \pm 9\) min and \(120 \pm 18\) min \((P = 1.0)\), and gastric emptying coefficients were \(2.5 \pm 0.2\) and \(2.6 \pm 0.1\) \((\text{for GIP and placebo, respectively; } P = 0.75)\).

There was no correlation between the total amount of GIP secreted after meal ingestion during the placebo experiments \((\text{AUC}_{\text{GIP} \ 0-360\ \text{min}})\) and the gastric emptying half-times \((r^2 = 0.21, \ P = 0.086 \text{ for total GIP and } P^2 = 0.15, \ P = 0.15 \text{ for intact GIP}; \text{details not shown})\).

After meal ingestion, plasma glucose concentrations increased significantly in both experiments \((P < 0.0001; \text{Fig. 3})\). This was accompanied by a rise in insulin secretion \((P < 0.0001 \text{ for insulin and C-peptide concentrations})\). There were no differences between the experiments with GIP or placebo

placebo, respectively). The total amount of endogenous GIP secreted after the meal was similar during the two experiments \((\text{AUC}_{\text{total GIP} \ 0-240\ \text{min}}: 8938 \pm 1395 \text{ and } 7410 \pm 1040\ \text{pmol} \cdot \text{l}^{-1} \cdot \text{min}, \ P = 0.39; \text{AUC}_{\text{intact GIP} \ 0-240\ \text{min}}: 2178 \pm 289 \text{ and } 1738 \pm 277\ \text{pmol} \cdot \text{l}^{-1} \cdot \text{min}, \ P = 0.28, \text{for GIP and placebo administration, respectively})\).

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Effects. However, in this case one would expect endogenous further raising GIP concentrations did not have additional affected gastric emptying in the placebo experiments and that the meal, it is possible that endogenous GIP had already the infusion of GIP.

Because GIP was also released endogenously in response to the meal, it is possible that endogenous GIP had already affected gastric emptying in the placebo experiments and that further raising GIP concentrations did not have additional effects. However, in this case one would expect endogenous GIP secretion to correlate with the gastric emptying half-times, which was not the case. Also, the total amount of GIP secreted after the test meal was much lower than that reported after the ingestion of larger meals in previous studies (12, 28). Therefore, it appears unlikely that endogenous GIP secretion had a major impact on gastric emptying in the present experiments.

One way to assess the effects of endogenous GIP on gastric emptying in more detail would be to antagonize the peptide by use of receptor antagonists (14, 26). However, because GIP antagonists are not yet available for administration to humans, this question can only be addressed in animal studies.

Interestingly, GIP plasma concentrations were further increased after meal ingestion despite its exogenous administration at relatively high plasma concentrations (Fig. 1). This indicates that the secretion of GIP from K cells is not suppressed by elevated plasma concentrations, as we know it is for other peptide hormones including insulin (8). The absence of such feedback mechanisms may be important for the potential therapeutic use of incretin hormones for the treatment of type 2 diabetes.

In the present study, adding exogenous GIP to endogenously secreted GIP did not affect glycemia as well as insulin secretion. This may also be explained by the fact that peak GIP concentrations after the meal were already close to the upper end of the dose-response curve, as discussed with respect to gastric emptying, but it is more likely that the absence of GIP effects on glycemia and insulin secretion was due to the low peak glucose concentrations (100 and 94 mg/dl with placebo and GIP administration, respectively), at which insulin secretion is almost not influenced by GIP (29).

Our data are in good agreement with previous work from Schirra et al. (24), who studied the interaction of gastric emptying and the endogenous release of GIP and GLP-1. In that study, as in our findings, gastric emptying was not associated with the endogenous secretion of GIP, whereas GLP-1 secretion was identified as a major determinant of gastric emptying (24). These data underline the importance of GLP-1 as a major regulator of gastric motility (23).

Although emptying of the stomach is independent of GIP action, the incretin might be involved in the regulation of distal gut function, particularly in the induction of small bowel motility. Such effects would explain the significantly higher incidence of diarrhea and flatulences after GIP infusion observed in the present experiments. In line with this observation, earlier studies in dogs indicated a stimulation of intestinal motility by GIP (25). It might be of interest to evaluate the effects of GIP on distal gut motility in more detail.

In conclusion, the present data demonstrate no effect of GIP on gastric emptying in normoglycemic human subjects. Therefore, its role as an enterogastrone may be challenged. Given the well-characterized GIP effects on insulin secretion, the term glucose-dependent insulinotropic polypeptide appears to be more appropriate to denote GIP than gastric inhibitory polypeptide.

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