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BASIC RESEARCH

Influence of gastric inhibitory polypeptide on pentagastrin-stimulated gastric acid secretion in patients with type 2 diabetes and healthy controls

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Abstract

AIM: Gastric inhibitory polypeptide is secreted from intestinal K-cells in response to nutrient ingestion and acts as an incretin hormone in human physiology. While animal experiments suggested a role for GIP as an inhibitor of gastric secretion, the GIP effects on gastric acid output in humans are still controversial.

METHODS: Pentagastrin was administered at an infusion rate of 1 μg . kg^{-1} . h^{-1} over 300 min in 8 patients with type 2 diabetes (2 female, 6 male, 54 ± 10 years, BMI 30.5 ± 2.2 kg/m^2; no history of autonomic neuropathy) and 8 healthy subjects (2/6, 46 ± 6 years., 28.9 ± 5.3 kg/m^2). A hyperglycaemic clamp (140 mg/dl) was performed over 240 min. Placebo, GIP at a physiological dose (1 pmol . kg^{-1} . min^{-1}), and GIP at a pharmacological dose (4 pmol . kg^{-1} . min^{-1}) were administered over 60 min each. Boluses of placebo, 20 pmol GIP/kg, and 80 pmol GIP/kg were injected intravenously at the beginning of each infusion period, respectively. Gastric volume, acid and chloride output were analysed in 15-min intervals. Capillary and venous blood samples were drawn for the determination of glucose and total GIP. Statistics were carried out by repeated-measures ANOVA and one-way ANOVA.

RESULTS: Plasma glucose concentrations during the hyperglycaemic clamp experiments were not different between patients with type 2 diabetes and controls. Steady-state GIP plasma levels were 61 ± 8 and 79 ± 12 pmol/l during the low-dose and 327 ± 35 and 327 ± 17 pmol/l during the high-dose infusion of GIP, in healthy control subjects and in patients with type 2 diabetes, respectively ($P = 0.23$ and p 0.99). Pentagastrin markedly increased gastric acid and chloride secretion ($P < 0.001$). There were no significant differences in the rates of gastric acid or chloride output between the experimental periods with placebo or any dose of GIP. The temporal patterns of gastric acid and chloride secretion were similar in patients with type 2 diabetes and healthy controls ($P = 0.86$ and $P = 0.61$, respectively).

CONCLUSION: Pentagastrin-stimulated gastric acid secretion is similar in patients with type 2 diabetes and healthy controls. GIP administration does not influence gastric acid secretion at physiological or pharmacological plasma levels. Therefore, GIP appears to act as an incretin rather than as an enterogastrone in human physiology.

Key words: Gastric inhibitory polypeptide; Gastric acid secretion; Type 2 diabetes; Hyperglycemic clamp; Pentagastrin-stimulated acid secretion

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INTRODUCTION

Gastric inhibitory polypeptide (GIP) is secreted from intestinal K-cells in response to nutrient ingestion and acts to augment insulin secretion from pancreatic beta-cells[1-4]. Together with glucagon-like peptide 1 (GLP-1) it confers approximately 60 % of total postprandial insulin secretion, thus acting as an incretin hormone[5, 6]. Since the insulinotropic effect of GIP appears to be dependent on the prevailing plasma glucose concentrations[7], the term "glucose-

dependent insulinotropic polypeptide" was coined later to denominate the peptide in accordance with its major physiological role[8]. In addition, GIP administration augments glucagon secretion under certain circumstances[7, 9]. While there is little doubt regarding GIP effects on endocrine pancreatic secretion, the case is different for its role in the regulation of gastrointestinal functions. In fact, original studies in canine gastric preparations pointed to an inhibition of gastric acid secretion by GIP[10, 11] and subsequent *in vivo* experiments demonstrated an increase in gastric acid output following antibody blockade of endogenous GIP in dogs, suggesting a physiological importance of GIP in the stomach[12]. These inhibitory effects of GIP on gastric acid secretion were ascribed to the local antral release of somatostain[13].

In humans, a significant inhibition of gastric acid output was only reported during the administration of highly supraphysiological doses of GIP[14, 15], whereas no effects were observed at physiological GIP plasma levels[15, 16].

While GIP is the major mediator of the incretin effect in healthy subjects[1, 5], the incretin activity of GIP is almost absent in patients with type 2 diabetes[17-19]. It is yet unclear, whether this is due to a general impairment in beta-cell function in type 2 diabetes or whether the reduced insulinotropic effect of GIP reflects a specific defect, for example of the GIP receptor, in patients with type 2 diabetes[20, 21]. In the latter case, one would expect a loss of GIP action not only with respect to insulin secretion, but also regarding other physiological actions like the inhibition of gastric acid secretion. Therefore, in the present study, the effects of GIP on pentagastrin-stimulated gastric acid secretion at both physiological and supraphysiological plasma levels were investigated in patients with type 2 diabetes and healthy controls. The effects of GIP on insulin secretion have been reported in a separate communication[22].

MATERIALS AND METHODS

Study protocol

The study protocol was approved by the ethics committee of the medical faculty of the Ruhr-University, Bochum on 01-24-2002. Written informed consent was obtained from all participants.

Study design

At a screening visit a clinical examination was performed and laboratory parameters were screened. If the subjects met the inclusion criteria (see below), they were recruited for the following procedure: Pentagastrin-stimulated gastric acid secretion was assessed over 300 min. A hyperglycemic clamp aiming at a steady capillary plasma glucose concentration of 140 mg/dL (7.8 mmol/L) was performed over 240 min. Placebo (1 % human serum albumin in 0.9 % NaCl), GIP at a low infusion rate (1.0 pmol/(kg · min)), and GIP at a high infusion rate (4.0 pmol/(kg · min)) were administered consecutively, each over 60 min. Boluses of placebo, GIP at a low dose (20 pmol/kg) and GIP at a high dose (80 pmol/kg) were administered intravenously at the beginning of each infusion period (at 0, 60, and 120 min, respectively).

In order to exclude a time-dependent order effect on gastric secretion, five of the control subjects were studied on an additional occasion with the administration of placebo only (1 % human serum albumin in 0.9 %NaCl from 0 to 180 min) instead of GIP. Boluses of placebo were administered at 0, 60, and 120 min.

Table 1 Characteristics of the participants (mean±SE)

Parameter (unit)	Healthy controls	Patients with type 2 diabetes	Significance (*P*-value)
Sex (female/male)	2/6	2/6	1.0
Age (years)	46±6	54±10	0.07
Body mass index (kg/m^2)	28.9±5.3	30.5±2.2	0.43
Waist-to-hip ratio (cm/cm)	0.97±0.08	1.00±0.05	0.40
Blood pressure			
Systolic (mmHg)	118±13	138±21	0.044
Diastolic (mmHg)	79±10	92±10	0.026
HbA_{1c} (%)[1]	6.0±0.5	8.3±2.2	0.013
Diabetes duration (years)	-	9 ± 4	-
Total-cholesterol (mg/dL)	223±52	210±35	0.57
HDL-cholesterol (mg/dL)	49±22	34±14	0.15
LDL-cholesterol (mg/dL)	145±37	164±31	0.32
Triglycerides (mg/dL)	161±110	167±92	0.90
Creatinine (mg/dL)	0.86±0.13	1.05±0.29	0.12

Statistics: ANOVA or χ^2 test. [1]Normal range: < 6.5

Subjects/patients

Eight patients with type 2 diabetes and eight healthy control subjects without a family history of diabetes were studied. Patient/subject characteristics are presented in Table 1.

Subjects with anemia (hemoglobin < 11 g/dl), elevation in liver enzymes more than double the respective upper normal limits, or with elevated creatinine concentrations (> 1.3 mg/dl) were excluded. Among the patients with type 2 diabetes, 2 were treated with metformin, whereas the other 6 were on a dietary regimen. All antidiabetic treatment was withdrawn at least 48 hours prior to the experiments. None of the participants had a history of gastrointestinal disease or was taking any kind of medication with a known influence on gastric secretion. In addition, none of the patients had a history or any clinical signs of autonomic or sensory neuropathy. No abnormalities in the responsiveness of both the patellar and Achilles tendon reflexes, as assessed using a reflex hammer, were found. The results of a vibration perception threshold performed at both medial malleoli were within the normal limits

Peptides

Synthetic GIP was purchased from PolyPeptide Laboratories GmbH, Wolfenbüttel,
Germany, and processed for infusion as described[18]. Pentagastrin was purchased from Cambridge Laboratories, UK, Lot-No. 1TT.

Experimental procedures

The tests were performed in the morning after an overnight fast. Two forearm veins were punctured with a teflon cannula, and kept patent using 0.9 % NaCl (for blood sampling and for glucose and peptide administrations, respectively). Both ear lobes were made hyperemic using Finalgon® (Nonivamid 4 mg/g, Nicoboxil 25 mg/g). A

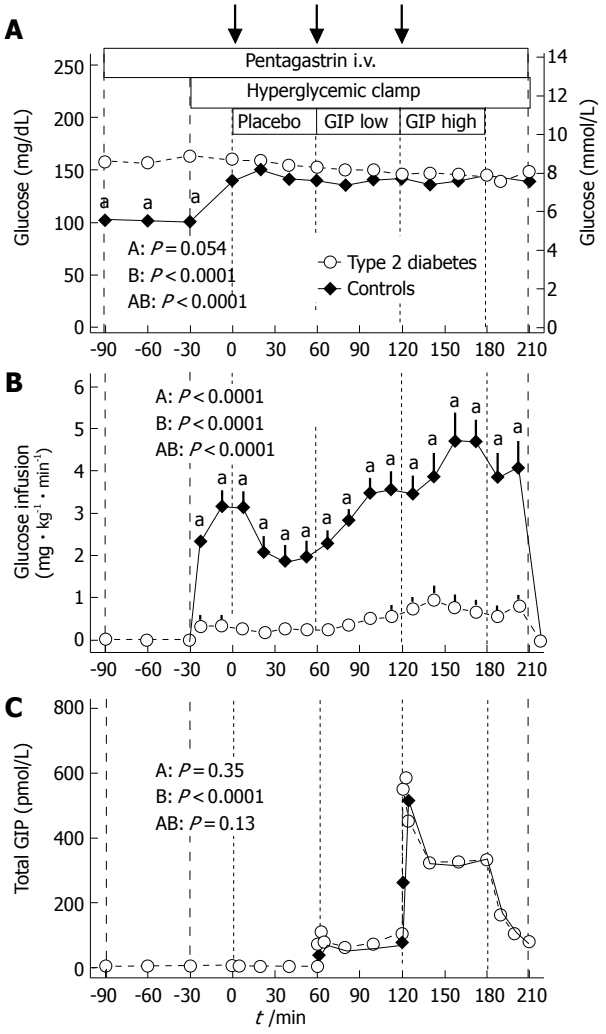

Figure 1 Plasma concentrations of glucose (**A**), glucose infusion rates (**B**) and plasma concentrations of total GIP (C) during hyperglycemic clamp experiments with the intravenous infusion of pentagastrin (1 μg . kg^{-1} . h^{-1}; -90 to 210 min), placebo (0 - 60 min), GIP at a low dose (1 pmol . kg^{-1} . min^{-1}; 60-120 min), and GIP at a high dose (4 pmol . kg^{-1} . min^{-1}; 120 -180 min) in eight patients with type 2 diabetes (open circles) and eight healthy controls (filled diamonds). Arrows indicate bolus administrations of placebo, 20 pmol GIP/kg and 80 pmol GIP/kg, respectively. Data are presented as means ± SEM; *P*-values were calculated using repeated measures ANOVA and one-way ANOVA and denote **A:** differences between the groups, **B:** differences over time and AB: differences due to the interaction of group and time. $^{a}P < 0.05$ patients with type 2 diabetes at individual time points.

nasogastric tube (Total length: 144 cm, diameter 6 mm, Sherwood Medical, Gosport, UK) was positioned for removing gastric acid by intermittent suction at 15 min intervals (HICO Gastrovac, Hirtz & Co., Germany). Basal gastric acid output was assessed over 15 min following a 30 min equilibration period. From -90 to 210 min, pentagastrin was administered intravenously at an infusion rate of 1 μg · kg body $weight^{-1}$ · h^{-1}. All participants remained in a semi-recumbent position, turned to their left side throughout the experiments.

A hyperglycemic clamp test aiming at a steady capillary plasma glucose concentration of 7.8 mmol/l (140 mg/dl) was started by injecting 40 % glucose as a bolus at -30 min and maintained by infusing glucose (20 % in water, weight/vol.) until 210 min, as appropriate, based on glucose determinations performed every 5 min and until 210 min. At 0 min, an intravenous infusion of placebo (1 % human serum albumin in 0.9 % NaCl) was started and maintained until 60 min. At 60 min, an intravenous infusion of GIP was started with an infusion rate of 1.0 pmol · kg^{-1} · min^{-1}. At 120 min, the GIP infusion rate was increased to 4.0 pmol · kg^{-1} · min^{-1} and maintained until 180 min. At 0 min an intravenous bolus of placebo was administered. GIP was injected as a bolus at 60 min (20 pmol/kg) and at 120 min (80 pmol/kg). Venous blood samples were drawn frequently, as seen in Figure 1.

Blood specimen

Venous blood was drawn into chilled tubes containing EDTA and aprotinin (Trasylol®; 20 000 KIU/ml, 200 μl per 10 ml blood; Bayer AG, Leverkusen, Germany) and kept on ice. After centrifugation at 4 ℃, plasma for hormone analyses was kept frozen at -28 ℃. Capillary blood samples collected from the ear lobe (approximately 100 μl) were stored in NaF (Microvette CB 300; Sarstedt, Nümbrecht, Germany) for the immediate measurement of glucose.

Laboratory determinations

Glucose was measured with a Glucose Analyser 2 (Beckman Instruments, Munich, Germany). GIP immunoreactivity was determined as described[18] using a C-terminal assay involving antiserum R65, which reacts fully with intact GIP (1-42) and the truncated metabolite (3-42), but not with so-called 8-Ku GIP, of which the chemical nature and molecular relation to GIP is uncertain. The assay has a detection limit of less than 2 pmol/l and an intra-assay variation of approximately 6 %. Human GIP (Peninsula Laboratories, Europe, Ltd.) was used as standard, and radiolabeled GIP was obtained from Amersham Pharmacia Biotech Ltd. (Aylesbury, UK).

Gastric volume output was measured in 15-min fractions to the nearest 0.5 ml. Acidity was determined by titration to pH 7.0 using phenol red as an indicator dye. Chloride concentration was measured by a Corning EEL 920 chloride meter (CIBA Corning Diagnostics, Fernwald, Germany).

Statistical analysis

Results are reported as mean ± SEM. Statistical calculations were carried out using repeated-measures analysis of variance (RM-ANOVA), using Statistica Version 5.0 (Statsoft Europe, Hamburg, Germany). This analysis provides p-values for differences between groups (A), differences over time (B), and for the interaction of groups with time (AB). If a significant interaction of treatment and time was documented ($P < 0.05$), values at single time points were compared by one-way ANOVA. A *P*-value < 0.05 was taken to indicate significant differences.

RESULTS

Fasting plasma glucose concentrations were significantly higher in patients with type 2 diabetes compared to control subjects ($P < 0.001$; Figure 1). During the hyperglycemic clamp period, similar glucose levels were obtained in both groups. As expected, glucose infusion rates required to

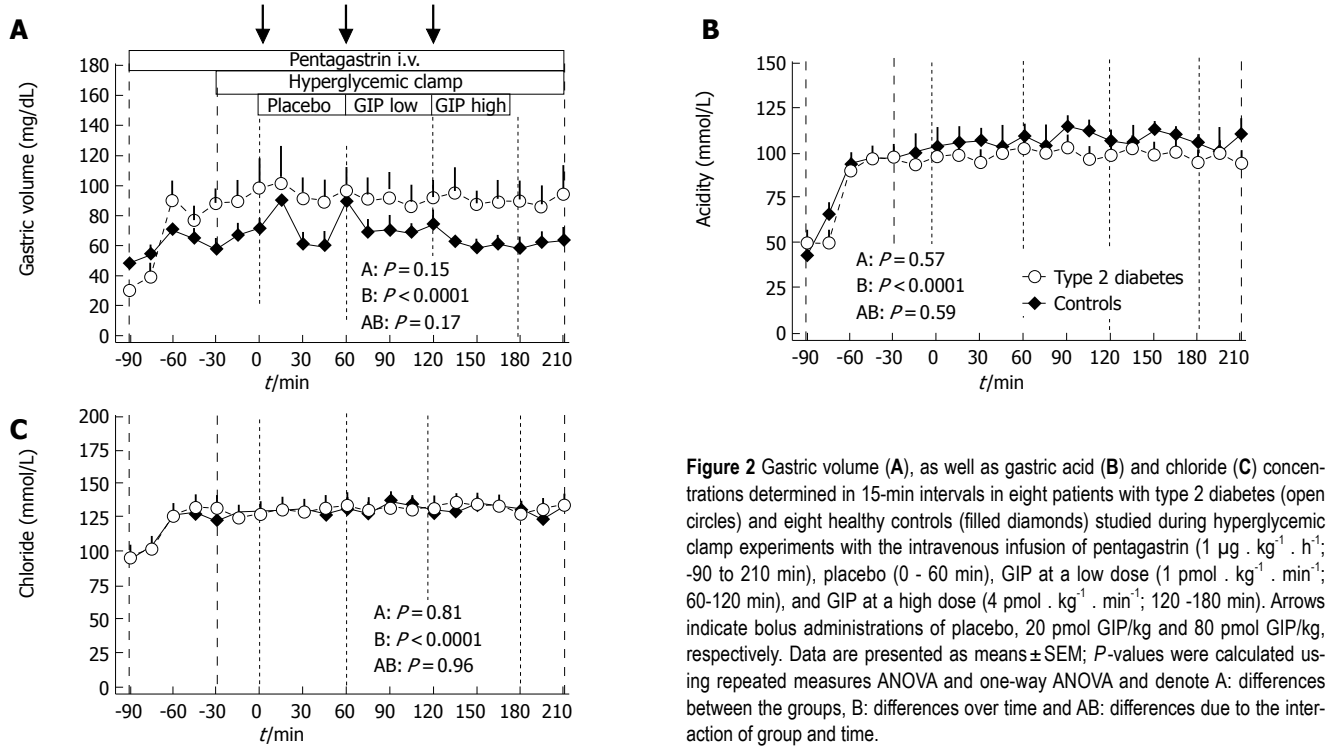

Figure 2 Gastric volume (**A**), as well as gastric acid (**B**) and chloride (**C**) concentrations determined in 15-min intervals in eight patients with type 2 diabetes (open circles) and eight healthy controls (filled diamonds) studied during hyperglycemic clamp experiments with the intravenous infusion of pentagastrin (1 μg . kg^{-1} . h^{-1}; -90 to 210 min), placebo (0 - 60 min), GIP at a low dose (1 pmol . kg^{-1} . min^{-1}; 60-120 min), and GIP at a high dose (4 pmol . kg^{-1} . min^{-1}; 120 -180 min). Arrows indicate bolus administrations of placebo, 20 pmol GIP/kg and 80 pmol GIP/kg, respectively. Data are presented as means ± SEM; *P*-values were calculated using repeated measures ANOVA and one-way ANOVA and denote A: differences between the groups, B: differences over time and AB: differences due to the interaction of group and time.

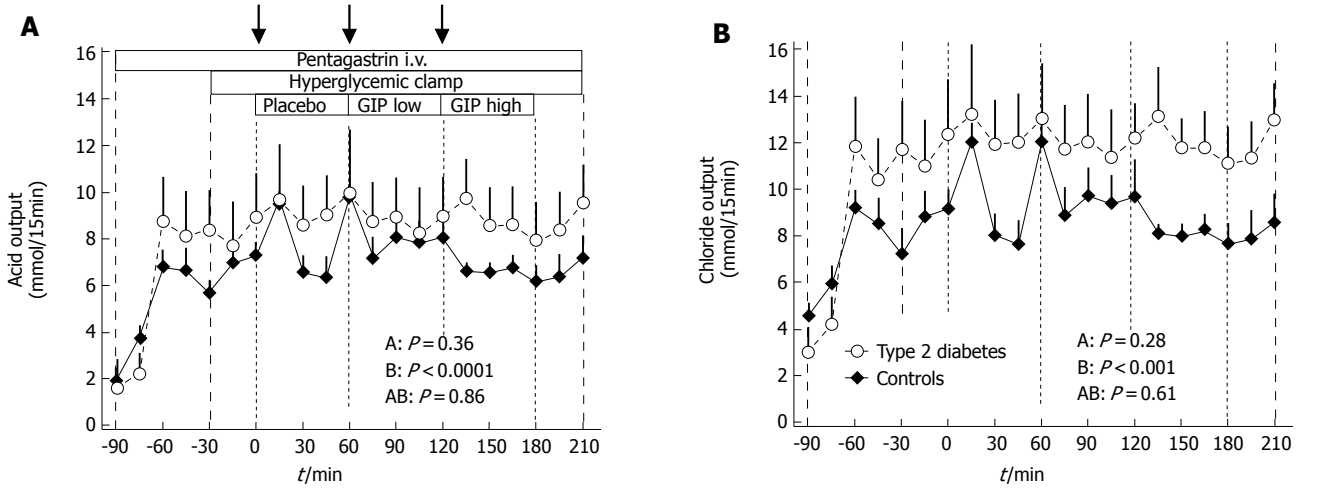

Figure 3 Gastric acid (**A**), and chloride (**B**) secretion rates per 15 min in eight patients with type 2 diabetes (open circles) and eight healthy controls (filled diamonds) studied during hyperglycemic clamp experiments with the intravenous infusion of pentagastrin (1 μg . kg^{-1} . h^{-1}; -90 to 210 min), placebo (0 - 60 min), GIP at a low dose (1 pmol . kg^{-1} . min^{-1}; 60-120 min), and GIP at a high dose (4 pmol . kg^{-1} . min^{-1}; 120 -180 min). Arrows indicate bolus administrations of placebo, 20 pmol GIP/kg and 80 pmol GIP/kg, respectively. Data are presented as means ± SEM; p-values were calculated using repeated measures ANOVA and one-way ANOVA and denote **A:** differences between the groups, **B:** differences over time and AB: differences due to the interaction of group and time.

maintain the hyperglycaemic clamp conditions were much higher in the controls than in the patients with type 2 diabetes ($P < 0.0001$).

GIP plasma levels increased to steady-state levels of 61 ± 8 and 79 ± 12 pmol/l during the low-dose and 327 ± 35 and 327 ± 17 pmol/l during the high-dose infusion of GIP, in healthy control subjects and in patients with type 2 diabetes, respectively ($P = 0.23$ and $P = 0.99$).

Basal gastric acid output was 1.9 ± 0.4 mmol/15 min and 1.6 ± 0.4 mmol/15 min (in healthy controls and in patients with type 2 diabetes, respectively; $P = 0.56$). The secretion of both gastric acid and chloride was markedly increased during the administration of pentagastrin ($P < 0.001$; Figures 2 and 3). In contrast, intravenous glucose administration had no effects on gastric acid or chloride output (Figure 2 and 3; Table 2). There were no differences in the rates of gastric acid or chloride output between the experimental periods with the administration of placebo, the low GIP dose, and the high GIP dose (Figure 3; Table 2). The lack of GIP effect on gastric secretion was confirmed in the five control experiments with the administration of placebo only and with GIP ($P = 0.87$ for acid output and $P = 0.59$ for chloride output, respectively; details not shown). The temporal pattern of

Table 2 Gastric acid and chloride secretion in patients with type 2 diabetes and healthy controls (mean±SE)

Experimental period: Time (min):	Basal (-90)	Pentagastrin (-45 to -30)	Hyperglycemia (-15 to 0)	Placebo (45 to 60)	GIP low 105 to 120)	GIP high (165 to 180)	Significance (*P* -value)
Healthy controls							
H^+ -secretion [mmol/15 min]	1.9±0.4	6.2±0.9	7.2±0.7	8.1±1.1	7.9±1.0	6.5±0.5	< 0.001
Cl^- -secretion [mmol/15 min]	1.9±0.4	7.9±1.0	9.0±0.8	9.9±1.3	9.6±1.2	8.0±0.7	< 0.001
Patients with type 2 diabetes							
H^+ -secretion [mmol/15 min]	1.6±0.4	8.3±1.7	8.3±1.7	9.5±1.8	8.6±1.7	8.2±1.6	< 0.01
Cl^- -secretion [mmol/15 min]	1.6±0.4	11.1±1.4	11.7±2.1	12.5±2.1	11.8±1.7	11.4±1.5	< 0.001

Statistics: ANOVA

gastric acid and chloride secretion was similar in patients with type 2 diabetes and healthy controls ($P = 0.86$ and $P = 0.61$, respectively; Figure 3).

DISCUSSION

The present experiments were undertaken to investigate the influence of GIP on pentagastrin-stimulated gastric acid secretion in patients with type 2 diabetes and in healthy controls. No effects of GIP on gastric acid output were observed at both physiological and pharmacological plasma concentrations.

A role for GIP in the regulation of gastric acid secretion was suggested from initial experiments in dogs[10-13]. Moreover the reduced rates gastric of acid secretion observed after jejuno-ileal shunt operation, when GIP plasma levels are increased, lent support to the concept of GIP as a negative regulator of gastric secretion[23]. In humans however, inhibitory effects of GIP on gastric acid secretion were only described, when supraphysiological GIP doses were used[14, 15], whereas GIP plasma levels that resembled those typically reached following meal ingestion failed to inhibit gastric acid secretion[15, 16]. In the present experiments, no effect of GIP on gastric acid output was observed even at supraphysiological plasma concentrations. The differences between the present and some of the previous studies[14, 15] may be explained by the use of different GIP preparations. In fact, both studies demonstrating inhibitory effects of GIP on gastric acid secretion in humans employed porcine GIP[14, 15], which differs from human GIP in two amino acid positions[24]. Moreover, some earlier peptide preparations contained impurities with cholecystokinin (CCK)-33 and -39, thereby limiting the interpretation of those studies[25]. Therefore, all aspects considered, the role of GIP in the regulation of gastric acid secretion in humans appears negligible.

The present data give rise to reconsider the role of GIP in human physiology. In fact, the peptide was initially considered to act as an enterogastrone[10, 11]. This term was proposed to describe (hormonal) factors from the duodenum that are secreted in response to nutrient ingestion and inhibit upper GI-functions at their typical plasma concentrations[26]. Such effects have been demonstrated for GLP-1 as well as for peptide-YY (PYY)[27-30]. In contrast, GIP does not appear to have any effects on gastric emptying[31] or gastric acid secretion in humans, and therefore does not fulfil the criteria for an enterogastrone. Rather, GIP acts as an incretin hormone, as demonstrated by numerous previous experiments[1, 5, 32]. Of note, a potent augmentation of insulin secretion by GIP was observed in the present experiments as well[22], thereby affirming the activity of the GIP preparations used.

The lack of GIP effect on gastric acid output represents another interesting difference in the biological actions of GIP and the other incretin hormone GLP-1, which is known as a potent inhibitor of gastric secretion[27, 33]. In fact, even though both hormones are secreted almost simultaneously[5, 34] and act in concert to augment glucose-stimulated insulin secretion[5, 32], they do exhibit a number of characteristic differences: Thus, GLP-1 suppresses pancreatic glucagon release[35, 36], whereas GIP has no effect or, at normoglycemic fasting conditions, even stimulates glucagon release[7, 9]. In addition, GLP-1 dose-dependently decelerates gastric emptying, thereby reducing the rise in glycemia following meal ingestion[30, 33, 37, 38]. In contrast, GIP administration has no effect on the velocity of gastric emptying[31]. Taken together, GLP-1 apparently possesses both incretin and enterogastrone activity, whereas GIP mainly acts as incretin hormone.

Another purpose of the present experiments was to compare gastric acid secretion in patients of type 2 diabetes and healthy controls. Since hyperglycemia itself has been shown to inhibit gastric acid output[39], hyperglycaemic clamp conditions were applied to match plasma glucose concentrations in both groups. Under these conditions, no differences occurred in the rates of gastric acid or chloride output. It is important to point out that in the present study only patients without a history or clinical signs of neuropathy were included. In fact, a number of previous studies have demonstrated reduced rates of gastric acid secretion in diabetic patients with overt autonomic neuropathy[40] [41-43]. In contrast, no abnormalities in gastric secretion were reported in patients with diabetes without signs of neuropathy[41, 43]. Therefore, it appears that, unless neuropathy develops, gastric acid secretion is similar in patients with type 2 diabetes and non-diabetic controls, when plasma glucose levels are matched.

In conclusion, gastric inhibitory polypeptide has no effect on gastric acid secretion in patients with type 2 diabetes and healthy controls. Therefore, GIP seems to act as an incretin rather than as an enterogastrone in human physiology.

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