

Enhancement of Peptone-Induced Gastric Acid Secretion in Streptozotocin-Induced Diabetic Rats

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ABSTRACT—We compared the acid secretory response to peptone in normal and streptozotocin-induced diabetic rats. Animals were injected with streptozotocin and used after 5 weeks of diabetes with blood glucose levels of >350 mg/dl. Under urethane anesthesia, 2 ml peptone solution (2–8%) was instilled in the stomach through an acute fistula every 30 min. Peptone increased acid secretion in a concentration-dependent manner in normal rats, the maximal response being obtained at 8%. Likewise, the increased acid response was observed in diabetic rats, yet the maximal response observed at 4% was significantly greater than that in normal rats. In both cases, this response was inhibited potently by famotidine as well as YM-022 (a CCK_B antagonist) and partially inhibited by atropine. Peptone increased luminal histamine and plasma gastrin levels in both normal and diabetic rats, and the former response was significantly greater in diabetic animals. The altered acid secretion and histamine output in diabetic rats were reverted by insulin treatment. Pentagastrin- but not histamine-induced acid secretion was also increased in diabetic rats. We conclude that peptone-induced acid secretion is increased in diabetic conditions. This phenomenon is insulin-dependent and associated with an enhanced release of histamine but not with an increased sensitivity of the parietal cells.

Keywords: Diabetic rat, Acid secretion, Peptone, Gastrin, Histamine

In patients with prolonged diabetics, deleterious influences on various functions in the gastrointestinal tract, such as a decrease in acid secretion and motility are observed (1–3). The disturbances in gastric secretion, commonly associated with diabetes mellitus, are in general attributed to autonomic neuropathy (1, 4, 5). Indeed, clinical studies showed that long-standing insulin-dependent diabetic patients reduced gastric acid secretory response to sham-feeding (1). Similar findings were also observed in the streptozotocin (STZ)-induced diabetic rats, an accepted model of insulin-dependent diabetes (4, 5), but the results are controversial (6–8). We recently found that STZ-diabetic animals showed different changes in acid secretion in response to various stimuli: no change to histamine, a decrease to YM-14673 (an analogue of thyrotropin-releasing factor) or vagal electrical stimulation, and an increase to both pentagastrin and carbachol (9). However, little is known about peptone-induced acid secretion in diabetic rats.

It is known that circulating gastrin is an important factor in acid secretory response to meal (10). Intragastric pep-

tone instillation mimics chemical stimulus in the gastric phase of postprandial acid secretion. Previous studies reported that neutralization of gastrin by a specific monoclonal antibody markedly inhibited acid secretion in response to intragastric instillation of peptone in rats (11, 12). Lichtenberger et al. (13, 14) reported that serum gastrin levels were increased in nonfasted diabetic animals, contributing to some of the gastrointestinal alterations seen in diabetic conditions. Thus, it is of interest to study the influence of diabetes on peptone-induced acid secretion, which mimics the gastric phase of postprandial acid secretion.

In the present study, we examined the gastric acid secretory response induced by peptone in normal and STZ-diabetic rats and characterized the alteration of acid secretion in diabetic conditions.

MATERIALS AND METHODS

Animals

Male Sprague-Dawley GS rats (260–280 g; Charles River, Yokohama) were used. The animals were fed standard rat chow and tap water ad libitum. One week after purchase, they were given STZ (70 mg/kg, i.p.) and fed

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normally thereafter. Control animals received an equal volume of saline. All experimental procedures described here were approved by the Experimental Animal Research Committee of the Kyoto Pharmaceutical University.

General procedures

The experiments were performed in normal and 5 week STZ-diabetic rats. Blood was sampled from the tail vein and blood glucose levels were determined by Glucostar-Gucostix (Mies-Sankyo Co., Ltd., Tokyo). STZ-treated animals with blood glucose levels of less than 350 mg/dl under nonfasting conditions were excluded from the study. In some of the diabetic rats, zinc-insulin with a long duration of action (4 units/rat, s.c.) was administered once daily for 4 weeks starting 1 week after STZ treatment. The animals were deprived of food but allowed free access to tap water for 9 h before the experiment, because a prolonged fasting period of over 12 h causes damage in the stomach (4). All studies were carried out using 4–7 rats per group, under anesthetized conditions induced by urethane (1.25 g/kg, i.p.).

Measurement of gastric acid secretion

Under urethane anesthesia (1.25 g/kg, i.p.), the trachea was cannulated to ensure a patent airway, and the body temperature was maintained at $36 \pm 1^\circ\text{C}$ using a heating lamp. Acid secretion was measured in the acute fistula rat, according to a previously published method (15). In brief, the abdomen was incised, both the stomach and duodenum were exposed, and the cardiac portion was ligated without interfering with vagus nerves. An acute fistula (inside diameter, 3 mm) made with a polyethylene tube was inserted into the stomach from a small incision made in the duodenum and held in place by a ligature around the pylorus. At the beginning of each experiment, the stomach was rinsed several times with physiological saline (154 mM NaCl) and filled with 2 ml of saline for 30 min for determination of the basal secretion. Then, the stomach was instilled with various concentrations (2%, 4% and 8%) of peptone solution through the fistula and the solution changed every 30 min. The collected samples were titrated to pH 7.0 against 100 mM NaOH using an autoburette (Comitite-8; Hirayama, Tokyo). The effects of the following drugs were examined on the gastric acid secretion induced by 4% peptone; atropine (3 mg/kg), famotidine (100 mg/kg) and YM-022 [cholecystokinin (CCK)_B/gastrin receptor antagonist, 3 mg/kg] (16) were administered i.p. 30 min before the first instillation of peptone. In some cases, the acid secretory response to histamine and pentagastrin was examined in both normal and diabetic rats. After obtaining the basal acid secretion for 30 min, histamine (4 mg/kg per hour) or pentagastrin (60 $\mu\text{g}/\text{kg}$ per hour) was continuously infused i.v. from the tail vein.

Measurement of plasma gastrin levels

Plasma gastrin levels were measured before and after intragastric instillation of peptone. The stomach was filled with 2 ml of saline through the fistula, and the solution was changed every 30 min. After the basal acid secretion had stabilized, 4% peptone (2 ml) was instilled into the stomach in place of saline. Blood was collected from the descending aorta in the presence of heparin, at 30 min before and 60 min after peptone treatment, centrifuged at 3500 rpm for 15 min at 4°C , and the plasma samples were stored at -80°C until the assay. The concentration of gastrin was determined by RIA.

Measurement of luminal histamine output

Luminal histamine output was measured before and after intragastric instillation of peptone. The stomach was filled with 2 ml of saline through the fistula, and the solution was changed every 30 min. After the basal acid secretion had stabilized, 4% peptone (2 ml) was instilled into the stomach in place of saline, and the collected samples were measured for histamine contents, at 30 min before and 60 min after peptone treatment. The amount of histamine in gastric contents was determined by enzyme immunoassay (Histamine EIA kit; Immunotech, Marseilles, France).

Drugs

The drugs used were urethane (Tokyo Kasei, Tokyo); streptozotocin (STZ), atropine, histamine 2HCl (Nacal Tesque, Kyoto); pentagastrin (Sigma Chemicals, St. Louis, MO, USA); insulin (Novo, Copenhagen, Denmark); and peptone (Difco Lab., Detroit, Michigan, USA). Famotidine and YM-022 were kindly supplied by Yamanouchi Pharmaceutical Co., Ltd. (Tokyo). Famotidine and YM-022 were suspended in saline with a drop of Tween 80 (Wako, Osaka). Other drugs were dissolved in saline. Each drug was prepared immediately before use and administered i.p. in a volume of 0.5 ml per 100 g body weight or infused i.v. in a volume of 1 ml/h.

Statistics

Data are presented as the means \pm S.E.M. from 4 to 8 rats per group. Statistical analyses were performed using a two-tailed Dunnett's multiple comparison test, and values of $P < 0.05$ were regarded as significant.

RESULTS

Gastric acid secretion induced by peptone

Under urethane anesthetized conditions, normal rats secreted acid at the rate of 5–10 $\mu\text{Eq}/30$ min as the basal secretion when the stomach was instilled with 2 ml of saline. Intragastric instillation of peptone (2 ml of 2%, 4%

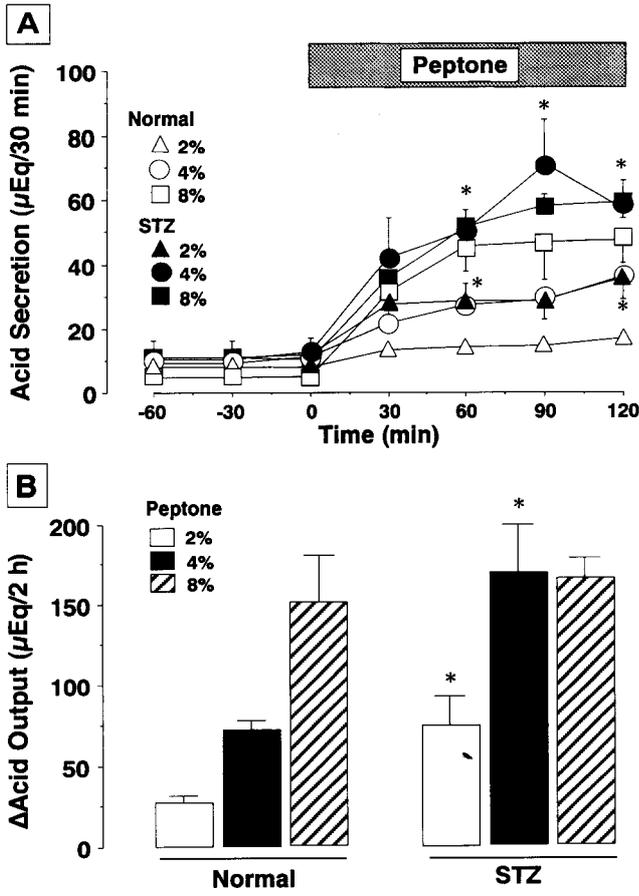


Fig. 1. Gastric acid secretory responses induced by peptone in normal and STZ-diabetic rats under urethane anesthetized conditions. The stomach was instilled with peptone meal (2 ml of 2%, 4% and 8% solution) every 30 min for 2 h, and the recovered samples were titrated with 100 mM NaOH for acid output. A: Data are presented as the means \pm S.E.M. of values determined every 30 min from 4–5 rats per group. B: Values indicate the total net acid output during 2-h peptone treatment and are presented as the means \pm S.E.M. from 4–5 rats. *Significant difference from normal rats, at $P < 0.05$.

and 8% solution) increased the acid secretion in a concentration-dependent manner, and a maximal response was obtained at 8% peptone, the values being $44.1 \pm 4.5 \mu\text{Eq}/30 \text{ min}$ (Fig. 1). Likewise, diabetic rats showed a concentration-dependent increase of acid secretion following peptone-treatment, yet a maximal response was observed at 4% peptone, the values being $71.0 \pm 12.2 \mu\text{Eq}/30 \text{ min}$. The total net acid output induced by 2 and 4% peptone in STZ-diabetic rats was $74.9 \pm 18.2 \mu\text{Eq}/2 \text{ h}$ and $169.6 \pm 30.5 \mu\text{Eq}/2 \text{ h}$, respectively, both of which were significantly greater than those observed in normal rats ($35.3 \pm 1.5 \mu\text{Eq}/2 \text{ h}$ and $72.2 \pm 5.6 \mu\text{Eq}/2 \text{ h}$, respectively, at 2% and 4% peptone). Because the instillation of 8% peptone did not cause any further increase in the acid secretion in STZ-diabetic rats, we performed the subsequent experiments

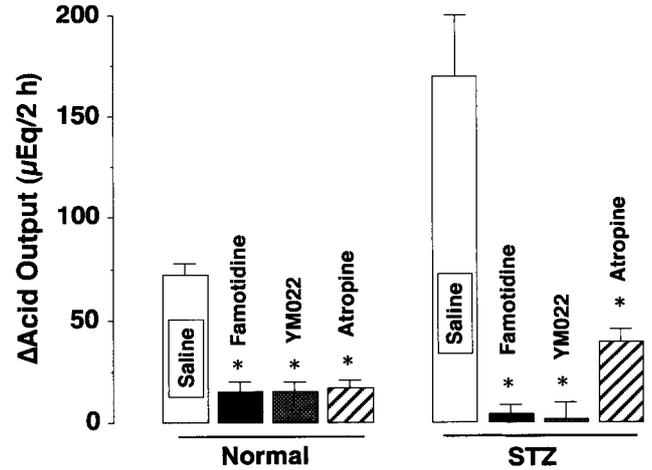


Fig. 2. Effects of various drugs on peptone-induced gastric acid secretion in normal and STZ-diabetic rats under urethane anesthetized conditions. The stomach was instilled with peptone meal (2 ml of 4% solution) every 30 min for 2 h, and the recovered samples were titrated with 100 mM NaOH for acid output. Famotidine (100 mg/kg), YM-022 (3 mg/kg) or atropine (3 mg/kg) was administered i.p. 30 min before the first instillation of peptone. Values indicate the total net acid output during 2-h peptone treatment and are presented as the means \pm S.E.M. from 4–5 rats. *Significant difference from saline, at $P < 0.05$.

using 4% solution of peptone.

Effects of various treatments on peptone-induced acid secretion

Intragastric instillation of 4% peptone caused an increase in acid secretion in normal rats, the total net acid output being $72.2 \pm 5.6 \mu\text{Eq}/2 \text{ h}$. The acid secretion induced by 4% peptone in normal rats was significantly inhibited by prior administration of famotidine (100 mg/kg, i.p.) and atropine (3 mg/kg, i.p.) as well as YM-022 (3 mg/kg, i.p.) (Fig. 2). In STZ-diabetic rats, 4% peptone elicited a significantly greater increase in acid secretion (the total net acid output: $169.6 \pm 30.5 \mu\text{Eq}/2 \text{ h}$) as compared to normal rats, yet this response was similarly blocked by pretreatment with either of the above agents. Especially, the acid response to peptone in STZ-diabetic rats was almost totally attenuated by YM-022 as well as famotidine, the inhibition being 98.8% and 97.6%, respectively.

On the other hand, the enhanced acid secretory response to peptone in STZ-diabetic rats was significantly suppressed by daily injection of insulin for 4 weeks starting one week after the administration of STZ (Fig. 3). In these rats, the acid secretion was increased in response to 4% peptone from $11.4 \pm 0.4 \mu\text{Eq}/30 \text{ min}$ to a plateau level of $27.2 \pm 3.0 \mu\text{Eq}/30 \text{ min}$, the total net acid output being $72.5 \pm 17.1 \mu\text{Eq}/2 \text{ h}$, which was significantly lower than that ($169.6 \pm 30.5 \mu\text{Eq}/2 \text{ h}$) observed in diabetic animals

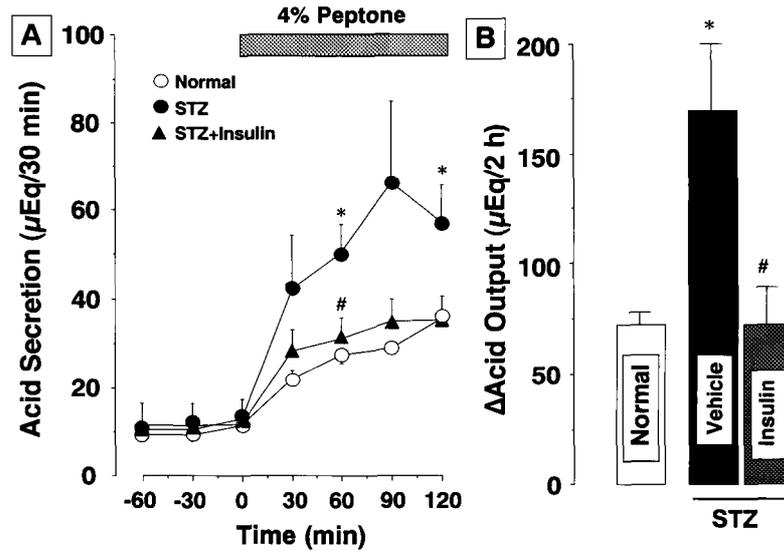


Fig. 3. Effect of insulin treatment on the altered acid secretory response to peptone in STZ-diabetic rats under urethane anesthetized conditions. Insulin (4 unit/rat) was administered s.c. once daily for 4 weeks, starting one week after STZ treatment. The stomach was instilled with peptone meal (2 ml of 4% solution) every 30 min for 2 h, and the recovered samples were titrated with 100 mM NaOH for acid output. A: Data are presented as the means \pm S.E.M. of values determined every 30 min from 4–6 rats per group. B: Values indicate the total net acid output during 2-h peptone treatment and are presented as the means \pm S.E.M. from 4–6 rats. Significant difference at $P < 0.05$: *from normal, #from STZ-diabetic rats.

without insulin treatment.

Plasma gastrin levels following peptone treatment

Under urethane anesthetized conditions, basal plasma gastrin concentrations in normal rats were 102.2 ± 14.9 pg/ml. Intra-gastric instillation of peptone (4%) caused a significant increase of plasma gastrin levels, the values reaching 243.3 ± 25.4 pg/ml, about 2.4 times the basal values (Fig. 4). The plasma gastrin levels in STZ-diabetic rats remained in similar ranges under both basal and peptone-stimulated conditions as those observed in normal rats, and the values were increased from 104.3 ± 12.3 pg/ml to 258.9 ± 28.5 pg/ml following intra-gastric instillation of 4% peptone. Likewise, the insulin treatment did not have any effect on the plasma gastrin levels in STZ-diabetic rats; the values increased from 110.3 ± 21.0 pg/ml to 237.1 ± 15.8 pg/ml following intra-gastric instillation of peptone at 4%.

Luminal histamine release following peptone treatment

Intra-gastric instillation of peptone (4%) markedly increased the luminal release of histamine from 1.2 ± 0.3 pmol to 183.8 ± 5.3 pmol in normal rats, within 60 min following the treatment (Fig. 5). A marked increase in the luminal release of histamine was similarly observed in STZ-diabetic rat stomachs following peptone, and the values obtained at 60-min post treatment were 233.2 ± 6.9 pmol, which was significantly higher than those in normal rats.

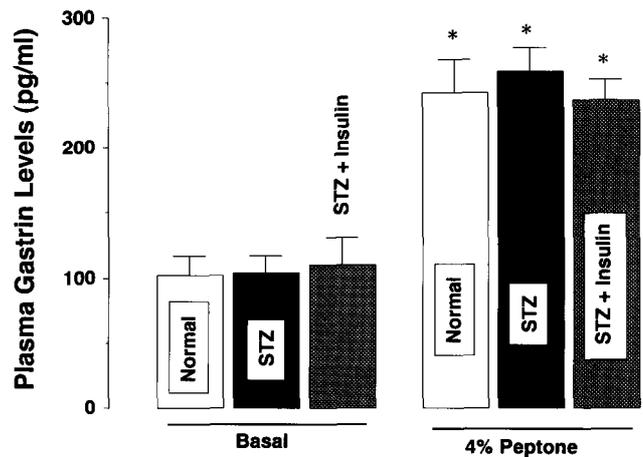


Fig. 4. Plasma gastrin levels before and after intra-gastric instillation of peptone in normal and STZ-diabetic rats under urethane anesthetized conditions. Peptone meal (2 ml of 4% solution) was instilled into the stomach every 30 min, and the blood samples were collected from a descending aorta. Values indicate the plasma gastrin levels at 30 min before and 60 min after the first instillation of peptone and are presented as the means \pm S.E.M. from 4–9 rats. *Significant difference from basal values, at $P < 0.05$.

The enhanced histamine release induced by peptone in diabetic rats was suppressed by daily insulin treatment, and the values (184.9 ± 12.4 pmol) were significantly lower than those observed in diabetic animals without insulin treatment.

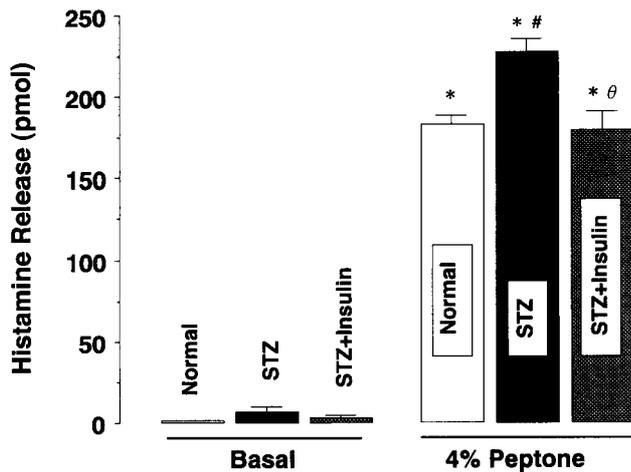


Fig. 5. Luminal release of histamine in response to peptone in normal and STZ-diabetic rats under urethane anesthetized conditions. Insulin (4 units/rat) was administered s.c. once daily for 4 weeks, starting one week after STZ treatment. Peptone meal (2 ml of 4% solution) was instilled into the stomach every 30 min, and the collected gastric contents were measured for histamine output. Values indicate the histamine output for 30 min immediately ($-30-0$ min) before and 60 min ($60-90$ min) after the first instillation of peptone and are presented as the means \pm S.E.M. from 5 rats. Significant difference at $P < 0.05$: *from basal values in each group, #from normal rats, θ from STZ-diabetic rats.

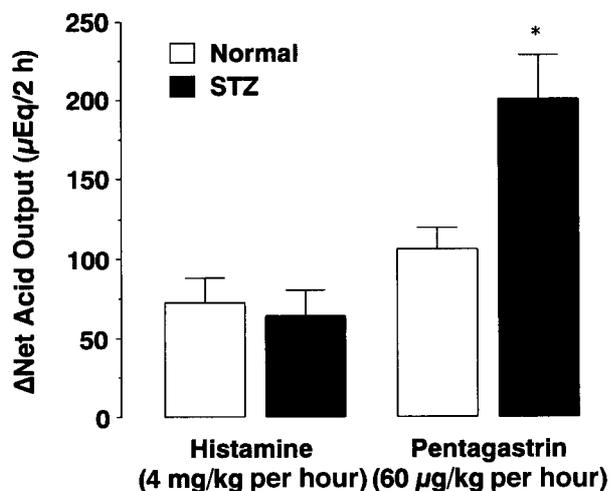


Fig. 6. Gastric acid secretory response to histamine or pentagastrin in normal and diabetic rats under urethane anesthetized conditions. Acid secretion was stimulated by i.v. infusion of histamine (4 mg/kg per hour) or pentagastrin (60 μg/kg per hour) from the tail vein. Values indicate the total net acid output obtained for 2 h after the onset of infusion and are presented as the means \pm S.E.M. from 4–6 rats. *Significant difference from normal rats, at $P < 0.05$.

Acid secretory responses induced by histamine and pentagastrin

The acid secretion was increased in response to i.v. infu-

sion of histamine (4 mg/kg per hour) in normal rats, and the Δ total acid output was $72.7 \pm 14.7 \mu\text{Eq}/2$ h (Fig. 6). STZ-diabetic rats also responded to histamine by an increase in the acid secretion, the Δ total acid output being $63.9 \pm 16.3 \mu\text{Eq}/2$ h, which is not significantly different from that obtained in normal rats. Likewise, pentagastrin increased the acid secretion in both normal and STZ-diabetic rats, yet this response was significantly greater in the latter group; the Δ total acid output was $201.0 \pm 27.9 \mu\text{Eq}/2$ h, about 2 times the levels in normal rats ($106.2 \pm 14.2 \mu\text{Eq}/2$ h).

DISCUSSION

STZ is known to possess diabetogenic properties and cause selective destruction of pancreatic β -cells. In the present study, all STZ-treated animals developed a persistent hyperglycemia, which was observed one week after the administration of STZ. We found in these diabetic rats a marked increase in peptone-induced gastric acid secretion that occurred largely dependent on endogenous gastrin and partly on cholinergic mechanisms. Luminal histamine output and plasma gastrin levels were both markedly elevated by intragastric instillation of peptone, yet the former response was significantly greater in STZ-diabetic animals as compared to normal rats.

The gastric phase in the regulation of acid secretion comprises mainly distension of the stomach and bathing of the gastric mucosa with certain chemicals of food, primarily amino acids and peptides (10). Intragastric peptone instillation mimics chemical stimulus in the gastric phase of postprandial acid secretion, which is accompanied by both elevation of serum gastrin levels and excitation of vagal-cholinergic activity. Indeed, several studies reported that the acid secretion induced by peptone in rats was markedly inhibited by immuno-neutralization of gastrin and CCK_B antagonists as well as vagotomy (11, 12, 17–19). In the present study, we confirmed that peptone-induced acid secretion was inhibited by both YM-022 (a CCK_B /gastrin receptor antagonist) and atropine. It is known that the acid stimulatory action of gastrin is mediated mainly by endogenous histamine released from enterochromaffin-like (ECL) cells (20, 21). Since the peptone-induced acid secretion is potently inhibited by YM-022, it is likely that this response is also mediated by endogenous histamine. Indeed, Lloyd et al. (12) reported that approximately 70% of peptone-stimulated acid secretion was suppressed by an histamine H_2 -receptor antagonist in anesthetized rats. We also observed that the acid secretory response to peptone in both normal and STZ-diabetic rats was potently inhibited by famotidine (a histamine H_2 -receptor antagonist), suggesting that the response is indeed mediated by endogenous histamine.

Of most interest in this study was the finding that the acid secretory response to peptone was significantly enhanced in STZ-diabetic animals as compared to normal rats. Because no difference was found in the histamine-induced acid secretion between normal and diabetic rats, it is unlikely that the enhanced acid response to peptone is due to the increased sensitivity of the parietal cells. Mehta et al. (8) reported a decrease of histamine-stimulated acid secretion in STZ-diabetic rats and suggested that diabetes impairs the acid secretory response of the parietal cells. Others also reported that histamine-induced acid secretion was found to be decreased in alloxan-diabetic rats when compared with their age-matched controls (22). The reasons for the different results in these studies remain unknown, but they may be due to differences in experimental conditions such as species of rats, the dose and the route of histamine administration, and the severity of diabetes.

As mentioned above, the peptone-induced acid secretion was inhibited by atropine, yet the effect of atropine in STZ-diabetic rats was less potent as compared to YM-022 or famotidine. We have previously reported that STZ-diabetic rats secreted less acid in response to YM-14673 (a TRH analogue) or vagal electrical stimulation, suggesting the impairment of vagal neuronal activity associated with diabetic mellitus (9). These results together suggest that the increased acid secretory response to peptone in diabetic rats is mainly mediated by a gastrin-dependent pathway rather than a vagal-cholinergic mechanism.

As expected, peptone treatment caused an increase of histamine release as well as plasma gastrin levels. Similar to the acid secretory response, the luminal release of histamine following peptone was significantly enhanced in STZ-diabetic rats as compared to normal rats, although no difference was found in plasma gastrin levels between these two groups. These results strongly suggest that the enhanced release of histamine is one of the mechanisms by which diabetic rats showed a greater response to peptone and resulted in significantly higher rates of acid secretion. This contention is compatible with the finding that the acid response to pentagastrin was significantly enhanced in diabetic rats, because this response is known to be, in large part, mediated by endogenous histamine released from ECL cells (20, 21, 23). Certainly, a possibility may also be considered that the increased acid response to peptone is due in part to the increased sensitivity of gastrin receptors in both the parietal cells and ECL cells.

It should be noted in the present study that the difference in peptone-induced histamine output between normal and diabetic rats was much less than the difference in the acid output in these groups. In this study, the histamine output was determined for 30 min from 1 h after the instillation of peptone, although the acid secretion was already in-

creased at 30 min after the peptone treatment. Thus, we might expect a much larger difference in the histamine output between normal and diabetic rats when we measure the histamine output at an earlier time period after instillation of peptone. Alternatively, a small difference of histamine output may result in a large increase of acid secretion when gastrin also acts directly on the parietal cell, together with histamine (24).

Just how peptone-induced histamine release is enhanced in STZ-diabetic rats is not entirely clear. Since alterations in peptone-induced histamine release as well as acid secretion in diabetic rats were significantly reverted by insulin treatment, similar to those in response to pentagastrin (9), it is assumed that these changes are insulin-dependent but not due to the non-specific effect of STZ. Several mechanisms can be considered to explain this phenomenon: an increase of gastrin receptor or histamine forming capacity in ECL cells or their hypertrophic changes (25). Because the increase of histamine release had been similarly observed in response to carbachol in STZ-diabetic rats (9), it is likely that the latter two may be the case, resulting in the increased responsiveness of ECL cells to stimuli, including gastrin. Lichtenberger and Ramswamy (13), however, showed that both antral and serum gastrin concentrations are increased in genetically diabetic mice and that the resultant hypergastrinemia may contribute to some of the gastrointestinal alterations associated with diabetes. Schedl et al. (14) also reported a higher serum gastrin levels in diabetic rats, already at 10 days after STZ treatment. We also observed in a previous study that serum gastrin levels in diabetic rats were significantly higher than those in normal rats under non-fasting conditions (9). If this were the case, it would be possible to speculate that ECL cells are continuously exposed to gastrin, leading to hypertrophic changes with more histamine produced. This possibility is supported by the study of Pinto et al. (26), who showed that genetic diabetic conditions affect the endocrine cell system in the gastrointestinal tract, leading to the increased number of gastrin-immunoreactive cells. Further studies on this point would certainly be needed.

In summary, the present study showed for the first time that diabetic conditions increased gastric acid secretion in response to peptone in rats. This phenomenon is insulin-sensitive and may be associated with an enhanced release of mucosal histamine but not due to an increased sensitivity of the parietal cells. In addition, this study also provides evidence to support the general concept that peptone-induced acid secretion is mediated humorally by gastrin and locally by histamine released from ECL cells. Although it is generally believed that the decrease in acid secretion masks the increased risk of gastric ulceration in diabetic patients, the present study suggests a possibility that the postprandial acid secretion is increased in diabetic patients.

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