# Pentagastrin-Induced Gastric Acid Secretion in the Diabetic Rats: Role of Insulin

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## Abstract

**Streptozotocin-induced diabetic rats have excessively pentagastrin-simulated acid output in which insulin seems to attenuate rather than further stimulate acid output. The aim of this study was to determine the insulin impact on pentagastrin-stimulated acid output of diabetic and non-diabetic rats to resolve whether an attenuated effect does exist. Diabetic rats were induced by the streptozotocin i.v. injection four days before acid study. Some streptozotocin-treated rats additionally received daily insulin (2.4 IU/kg) injection. Using an autotitrator, acid output was measured every five minutes by the titration of gastric perfusate. Basal output was collected for 45 min before the 90-min pentagastrin infusion (0.89 μg/kg/min). Plasma gastric inhibitory polypeptide (GIP) levels were measured. Both doses (0.067and 0.133 IU/kg/min) of insulin infusion resulted in stimulated acid output in normal rats. The subsequent insulin infusion (0.133 IU/kg/min) for non-diabetic rats undergoing pentagastrin-treatment suppressed their stimulated acid output almost down to the basal level. Pentagastrin-stimulation led to the excessively increased acid output of diabetic rats throughout the whole infusion period ($P < 0.01$). Correction of hyperglycemia with insulin for diabetic rats normalized the stimulated acid output. Measured basal and stimulated plasma GIP levels of those diabetic rats during acid stimulation remained higher, regardless of insulin treatment ($P < 0.05$). Our results suggest that insulin has the ability to attenuate pentagastrin-stimulated acid output in rats, whereas GIP is not involved in this attenuation. This effect appears to be responsible for the excessive acid output of diabetic rats undergoing pentagastrin stimulation.**

**Key Words: diabetes, gastric acid, gastric inhibitory polypeptide, insulin, pentagastrin**

## Introduction

Gastric acid secretion is usually diminished among the diabetic patients with autonomic neuropathy (4). In contrast, uncontrolled insulin-dependent diabetic children or adolescents are at risk of developing peptic ulcer diseases, while the pathogenesis is not clearly addressed (3). Among the animal model, streptozotocin (STZ)-induced diabetic rats exhibit various acid outputs depending upon the different periods of housing after induction (30). In addition, the stimulated gastric acid outputs of these animals show divergent responses after treatment with various secretagogues (31, 32). For example, reduced acid output is resulted from vagal stimulation, and acid output remains unchanged to histamine, whereas pentagastrin/carbachol enhances acid output. Similarly, our previous studies obtained excessive acid outputs after pentagastrin-stimulation in diabetic Wistar and Sprague-Dawley (SD) rats receiving STZ induction (7, 21). It is interesting to know why diabetic rats have pentagastrin-enhanced acid output.

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Received: May 19, 2004; Revised: June 8, 2004; Accepted: June 10, 2004.

Tashima *et al* (31, 32) suggest that this acid augmentation is probably the enhanced mucosal histamine release. In their study, insulin correction partially restored augmented pentagastrin-stimulated acid output. Hence, they also suggested that this change was insulin-dependent, rather than due to non-specific effect of STZ (32). It appears that insulin would inhibit pentagastrin-stimulated acid output. Actually, insulin is a potent acid stimulant since a test based on insulin administration has been used to assess the completeness of vagotomy (13). Therefore, it would be interesting to examine whether insulin has a further synergistic effect on pentagastrin-stimulated acid output. Compared to pentagastrin-stimulation alone, a study on healthy subjects finds additional 20% of peak acid output when insulin and pentagastrin are administered together (27). On the other hand, gastric inhibitory polypeptide (GIP) is a product of K cells to enhance insulin secretion behaving as one of the incretins during orally-induced hyperglycemia, hence GIP is essential in the homeostasis for the control of blood glucose level (11, 14, 23). GIP also functions an inhibitor of histamine-/pentagastrin-stimulated acid output according to its initial nomenclature (14, 24). Using rat gastric acid measurement model, the purpose of the present study is to identify the insulin and GIP effects on the pentagastrin-stimulated acid output, particularly after diabetic induction.

## Materials and Methods

*Animals*

Adult SD male rats, 3-4 months old, weighing 350-450 g were obtained from the Animal Room of National Yang-Ming University. They were housed under the controlled conditions of light, humidity and temperature, and fed with standard laboratory food and water *ad libitum*. The animals used were followed in accordance with the guidelines for the animal use of National Yang-Ming University.

*Diabetic Induction*

Diabetes was induced via i.v. injection of tail vein with a freshly prepared STZ (64 mg/kg, Sigma, St. Louis, USA) solution. STZ was dissolved in saline/0.01M citrate buffer and the pH value was adjusted to 4.5 (5). The onset of diabetes was confirmed on the 2nd day by the appearance of polyuria and evident glycosuria (Combur Test® U, Boehringer Mannheim, Germany). Meanwhile, the control rats received i.v. injection of buffered vehicle only. On the 2nd day of STZ administration, another group of STZ-treated rats additionally received daily morning intraperitoneal insulin (Sigma, St. Louis, USA) injection in the dose of 2.4 IU/kg (5). Acid output study was conducted on the 4th day of diabetic induction, regardless of daily insulin treatment.

*Measurement of Basal and Stimulated Gastric Acid Outputs*

Rats were fasted overnight before the anesthesia using pentobarbital (30 mg/kg, TCI, Tokyo, Japan). A cannula was inserted into the trachea to maintain airflow, while a PE-160 (OD: 1.57 mm, ID: 1.14 mm, Clay Adams, Parsippany, NJ, USA) tubing was inserted into esophagus and ligated at the cervical level. A PE-320 (OD: 3 .5 mm, ID: 2.69 mm, Clay Adams) cannula was introduced into stomach through an incision in the duodenum and was ligated at 0.5 cm from pylorus. The right jugular vein and left femoral vein were catheterized respectively with silastic tubing connection (PE-50, OD: 0.965 mm, ID: 0.58 mm, Clay Adams). The stomach was firstly flushed using 10 ml saline at room temperature through the esophageal cannula and then flushed again with saline (0.4 ml/min) *via* a peristaltic pump (Gilson, minipuls-2, France) at least one hour until stabilization. Acid output was measured every 5 min by the titration (Autotitrator VIT 90, Radiometer Corp., Copenhagen, Denmark) of flushed perfusion with 0.01 N NaOH to pH 7.0 (7). Basal acid outputs were collected during the first 45-min period (0-45th min) and then the stimulated acid outputs using continually infused pentagastrin (0.89 μg/kg/min, Sigma) *via* the femoral vein with a peristaltic pump (Gilson) for another 90-min period (45th-135th min) were collected. Finally, perfusates were collected for additional 45-min period (135th-180th min) at the end of pentagastrin infusion. During the acid study, blood samples were intermittently collected *via* the right jugular vein.

*Study Groups*

*1. Direct insulin effect on the acid output*

After the basal acid collection, non-diabetic male rats without vehicle treatment received 30-min (45th-75th min) insulin infusion in the doses of 0.067 (n=5) and 0.133 IU/kg/min (n=5), respectively. Pentagastrin was not infused for these rats.

*2. Simultaneous pentagastrin and insulin effect on the acid output*

At 30 min (75th min) after the onset of pentagastrin stimulation, a separate group of non-diabetic male rats (n=6) simultaneously received insulin infusion (0.133 IU/kg/min) for additional

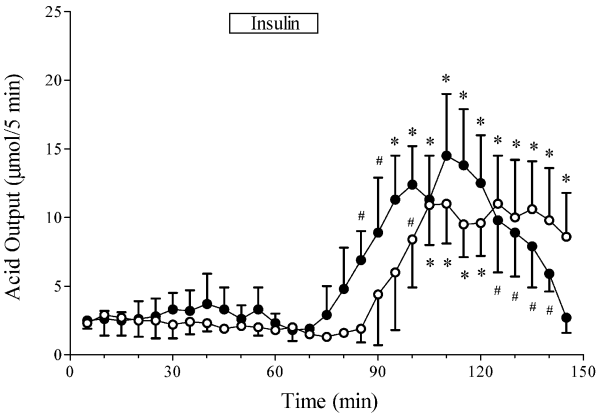


Fig. 1. Insulin effect on the gastric acid output of non-diabetic rats. After the basal acid collection, these rats received two doses (○: 0.067 IU/kg/min; ●: 0.133 IU/kg/ min) of insulin infusion at 45th-75th min of acid study. Stimulated acid outputs were gradually obtained up to the peak about 15 μmol/5 min (#: *vs*. basal acid, $P < 0.05$; *: *vs*. basal acid, $P < 0.01$). Vertical bars are mean±SEM.

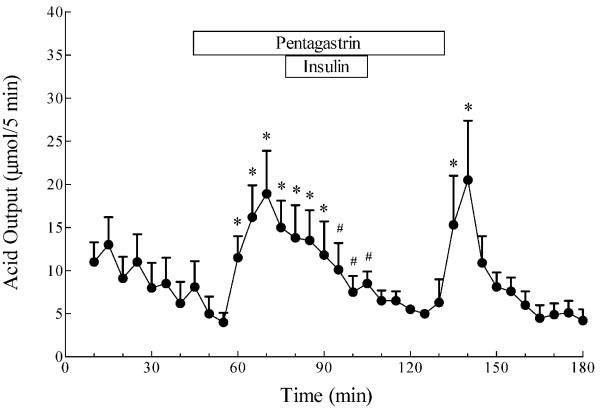


Fig. 2. Dual effects of pentagastrin and subsequent insulin infusions on the gastric acid output of non-diabetic rats. After the basal acid collection, these rats first received pentagastrin infusion (0.89 μg/kg/min) at 45th-135th min of acid study. Then the insulin infusion (0.133 IU/kg/min) was delivered between 75th-105th min. Diminished acid output was observed after the simultaneous insulin treatment. This inhibited acid output was almost restored at 135th min of acid study (#: *vs*. basal acid, $P < 0.05$; *: *vs*. basal acid, $P < 0.01$). Vertical bars are mean±SEM.

30 min (75th-105th min) while pentagastrin stimulation remained maintained in this period.

*3. Pentagastrin-stimulated acid output for vehicle-treated or diabetic rats*

Both STZ induced diabetic (n=8) and vehicle treated non-diabetic control (n=7) rats received usual basal and pentagastrin-stimulated acid output study, respectively.

*4. Pentagastrin-stimulated acid output for diabetic rats received insulin treatment*

After an overnight fasting, another group of diabetic rats (n=8) that had previously received daily insulin treatment were concomitantly infused with insulin (0.133 IU/kg/min) during the whole pentagastrin-stimulated period (45th-135th min). However, these rats did not receive the daily morning insulin treatment on day of the acid study.

*Plasma Glucose and GIP Measurements*

Plasma glucose level was measured using a glucose analyzer (23-A, Yellowsprings Inst. Co., Ohio, USA). The plasma GIP level was measured using our homemade radioimmunoassay kits (6, 8). Its sensitivity was 20 pg per tube, the intra- and inter-assay precisions were 5.1% and 8.3%, respectively.

*Statistics*

All values were expressed as mean±SEM. The areas under the time-concentration curve representing cumulative acid output in these rats were computed. Numerical data were analyzed using either Student's *t*-test or one-way analysis of variance (ANOVA) with Dunnett's post test. A *P*-value less than 0.05 was considered significant.

## Results

During the 30-min insulin infusion for non-diabetic rats, both doses of insulin treatment gradually stimulated acid outputs up to the ranges of 10-15 μmol/5 min. The stimulated peaks were obvious at 105th min and 110th min, respectively (Fig. 1). Basal acid outputs of non-diabetic rats usually ranged between 5-10 μmol/5 min. Initial pentagastrin infusion quickly resulted in markedly increased acid outputs ranging between 15-20 μmol/5 min. However, the subsequent insulin infusion significantly suppressed their already stimulated acid outputs almost down to the basal levels ($P < 0.01$). When the insulin infusion was held, the pentagastrin-stimulated effect on acid output gradually resumed to its original level (Fig. 2). Fig. 3 illustrates the serial changes of plasma glucose levels during the whole collecting period obtained from vehicle-treated controls, STZ-treated diabetic rats and STZ plus daily insulin-treated rats, respectively. STZ treatment indeed led to hyperglycemia, whereas the simultaneous pentagastrin plus insulin infusion gradually corrected plasma glucose levels of those diabetic inducted

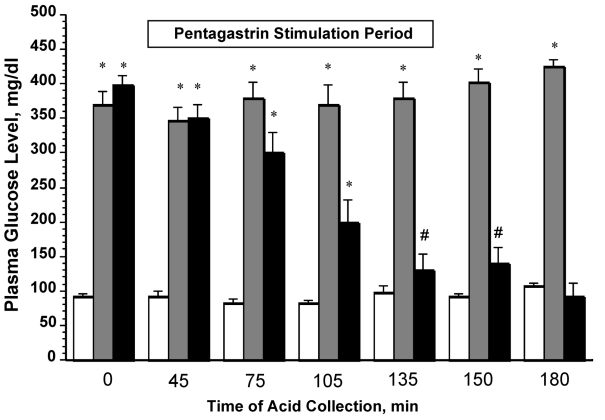


Fig. 3. The monitored blood glucose levels of vehicle treated (□), streptozotocin inducted diabetic (▩) and diabetic plus daily insulin treated rats (■), respectively. In the lest group, insulin and pentagastrin infusions were started simultaneously (45th-135th min). Gradually diminished blood glucose levels were found in these rats following insulin infusion (#: *vs*. vehicle treated rats, $P < 0.05$; *: *vs*. vehicle treated rats, $P < 0.01$). Vertical bars are mean±SEM.

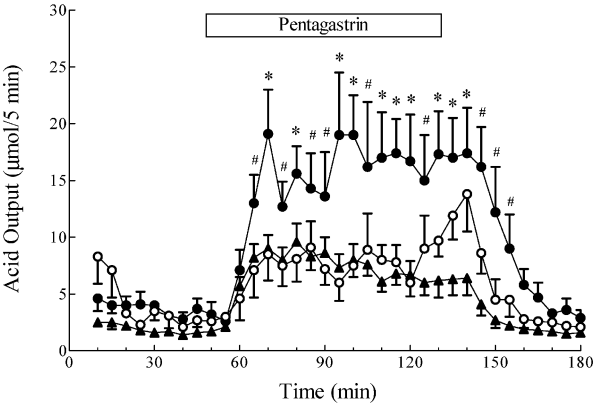


Fig. 4. Pentagastrin effects on the gastric acid outputs of vehicle treated (○), diabetic (●) and diabetic plus daily insulin treated rats (▲), respectively. Insulin infusion (45th-135th min) was only delivered for those diabetic plus daily insulin treated rats (▲). Markedly elevated acid output after pentagastrin stimulation was observed in diabetic rats, compared with the vehicle treated rats (#: *vs*. vehicle treated rats, $P < 0.05$; *: *vs*. vehicle treated rats, $P < 0.01$). Concomitant insulin infusion for the diabetic and insulin treated rats exhibited similar acid output ability of vehicle treated rats during the pentagastrin stimulatory period. Vertical bars are mean±SEM.

rats. The restored glucose levels never returned to their hyperglycemic state, even at the end of study.

Compared to vehicle-treated rats, pentagastrin-stimulation led to excessive acid outputs in the diabetic rats almost throughout the whole infusion period. The simultaneous pentagastrin and insulin infusion elicited acid outputs of the rats receiving daily insulin treatment were not different from those of the vehicle-treated rats during their stimulated period (Fig. 4). In order to illustrate their relationship, we divided cumulative acid outputs of stimulated periods into 45th-75th min, 75th-105th min and 105th-135th min, respectively (Fig. 5). Diabetic rats displayed the excessive pentagastrin-stimulated acid outputs throughout the whole stimulation period ($P < 0.01$). Correction of hyperglycemia for the insulin-treated rats restored the enhanced acid output. The basal plasma GIP levels were higher in diabetic rats, regardless of insulin treatment. Throughout the whole pentagastrin- or pentagastrin plus insulin-stimulation period, most plasma GIP levels remained higher compared to controls, regardless of previous insulin treatment (Fig. 6).

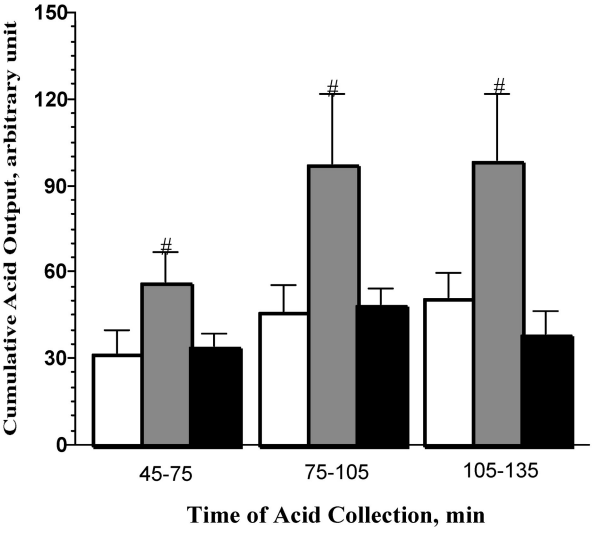


Fig. 5. The cumulative acid outputs in vehicle treated (□), streptozotocin inducted diabetic (▩) and diabetic plus daily insulin treated rats (■), respectively. These cumulative outputs were divided into the collection periods of 45th-75th, 75th-105th and 105th-135th min, respectively. Diabetic rats without insulin treatment had larger cumulative outputs in various stimulated periods, compared with the vehicle treated rats (#: $P < 0.05$). Vertical bars are mean±SEM.

## Discussion

Both pentagastrin and histamine have the ability of directly activating parietal cells to enhance gastric acid output (29). Our study confirmed the pentagastrin-/insulin-stimulated effect on the rat acid output (9). However, we also found that the maximal acid output in non-diabetic rats undergoing pentagastrin-stimulation was significantly reduced when insulin infusion was treated together, while the removal of insulin infusion gradually restored their original acid output ability. Unlike the human

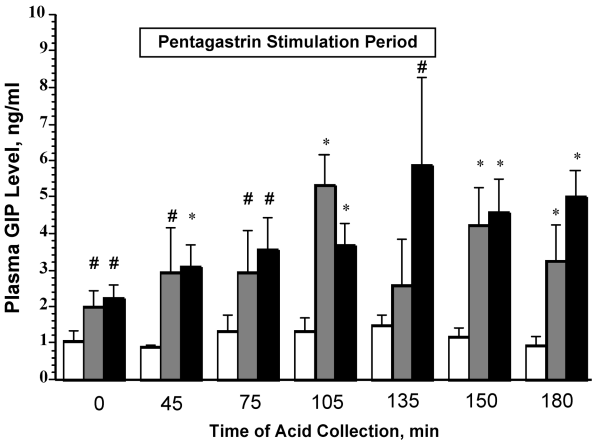


Fig. 6. The monitored plasma gastric inhibitory polypeptide (GIP) levels of vehicle treated (□), diabetic (▨) and diabetic plus daily insulin treated rats (■), respectively. Throughout the whole study period, GIP levels remained higher regardless of insulin treatment (#: *vs*. vehicle treated rats, $P < 0.05$; *: *vs*. vehicle treated rats, $P < 0.01$). Vertical bars are mean±SEM.

study of synergistic effect on the enhancement of additional acid output (27), our study appeared to mean that insulin has an inhibitory rather than synergistic effect on the rat pentagastrin-stimulated acid output. Yet we do not know whether the differences in study models, acid measurements, species and used doses account for the divergent acid output results.

We also confirmed again that diabetic rats had excessive acid output during the pentagastrin-stimulation period while their basal acid outputs remained unchanged. This enhancement was very similar to our previous studies (7, 21) as well as that of Tashima *et al.* (31), particularly the latter suggested that mucosal histamine release after pentagastrin-stimulation is responsible for the acid output augmentation in diabetic rats, whereas vagal neuropathy diminishes acid output. Diabetic subjects usually manifest an impaired gastric acid secretion in sham feeding test (4, 12). Long-term diabetic rats may have the suppressed outputs in both basal and histamine-stimulation periods (26). All these acid inhibitory events have been the effect of diabetic vagal neuropathy. Our study was conducted on the 4th day of STZ administration. Perhaps the autonomic neuropathy is not exactly induced during this very early period. Only subtle ultrastructural changes such as mitochondrial swelling, variation of axonal diameter, and loss of axoplasmic content occurred within a few days of STZ treatment. These circumstances quickly resolved within weeks. In contrast, several weeks or months are needed for permanent neuronal or axonal degeneration (17). This is probably why Takeuchi *et al.* (30) pointed out that diabetic rats at one-week STZ induction did not change acid output, whereas the suppressed acid output was only measured at the 3-week housing.

Our study conducted on STZ-treated rats indicated again that insulin-plus pentagastrin-stimulation for the early diabetic rats still suppressed the excessively stimulated acid output as well as those obtained among the non-diabetic model. Immediate glucose infusion induced hyperglycemia inhibits pentagastrin-or meal-stimulated acid output (2, 22). This effect has been the hyperglycemic suppression on the activity of cephalic-/vagal-cholinergic nervous systems (15, 20). On the other hand, an early study illustrates that glucose infusion did not alter pentagastrin-stimulated acid output (16). The true coordination between vagal-cholinergic nervous system and blood glucose level in controlling acid output seems to be complex. We are interested in whether physiological insulin and other peptide responses also play a role in this coordination of acid output. According to our study, insulin was likely to diminish rather than further increasing pentagastrin-stimulated acid output in rats at least.

In addition, GIP constitutes one of the members of the glucagon super-family on the basis of its structural homology (1). Infusion of GIP in the pharmacological dose inhibits pentagastrin-stimulated acid output for up to 85%; however, oral glucose loading elicited physiological response to show increased plasma GIP level does not suppress the stimulated acid output (11, 25, 28). Perhaps GIP mainly behaves an insulinotropic activity rather than the acid inhibition (10, 19, 25). Elevated fasting plasma GIP levels exist in the newly diagnosed ketotic insulin-dependent patients before their insulin treatment (18). Thus, hypo-insulinemia and hyperglycemia enable to lead to the elevated plasma GIP level as an attempt to restore the insulin secretion (25). Our result showed that elevated plasma GIP levels in the STZ-treated rats appeared to be comparable to the finding on humen beings. However, we do not know why insulin infusion did not change plasma GIP levels during the whole pentagastrin-stimulation period. Accordingly, our observation suggested that GIP was not involved in the physiological attenuation of stimulated acid output when pentagastrin and insulin were infused together. Perhaps an unknown or undetermined factor was responsible for the insulin attenuation on this kind of stimulated acid output.

Consequently, our observation of insulin attenuation on the pentagastrin-stimulated acid output was logical in explaining why glucose infusion induced hyperglycemia inhibits pentagastrin- or meal-stimulated acid output (2, 22). For example,

physiological response of insulin release in this event probably attenuated stimulated acid output *via* pentagastrin or meal stimulation. Apart from enhanced mucosal histamine release leading to augmented pentagastrin-simulated acid out in STZ treated rats (31), we suggested that the destruction of pancreatic β-cells to block insulin production in STZ-treated rats also induced the unlimited acid output during the pentagastrin-stimulation period.

In conclusion, STZ-treated rats produce excessively pentagastrin-stimulated acid output, whereas insulin infusion in turn to suppress the excessive acid output. The plasma GIP levels of STZ-treated rats remain unchanged. Perhaps insulin *per se* has the ability of attenuating pentagastrin-stimulated acid output, while GIP does not intervene in this attenuation.

## Acknowledgments

This study was supported by the National Science Council, Republic of China (Grant No. NSC 87-2314-B-075-76).

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