Gastric relaxation induced by hyperglycemia is mediated by vagal afferent pathways in the rat

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Submitted 11 February 2008; accepted in final form 11 March 2008

Zhou S-Y, Lu Y-X, Owyang C. Gastric relaxation induced by hyperglycemia is mediated by vagal afferent pathways in the rat. Am J Physiol Gastrointest Liver Physiol 294: G1158–G1164, 2008. First published March 20, 2008; doi:10.1152/ajpgi.00067.2008.—Hyperglycemia has a profound effect on gastric motility. However, little is known about the site and mechanism that sense alteration in blood glucose level. The identification of glucose-sensing neurons in the nodose ganglia led us to hypothesize that hyperglycemia acts through vagal afferent pathways to inhibit gastric motility. With the use of a glucose-clamp rat model, we showed that glucose decreased intragastric pressure in a dose-dependent manner. In contrast to intravenous infusion of glucose, intracisternal injection of glucose at 250 and 500 mg/dl had little effect on intragastric pressure. Pretreatment with intragastric nitric oxide (NO)- and peptide VIP-containing fibers were performed with an in vivo rat model.

MATERIALS AND METHODS

Ethical approval. All experiments involving animals were approved by the University Committee on Use and Care of Animals at the University of Michigan.

Materials. The following materials were purchased: N\textsuperscript{6}-nitro-L-arginine methyl ester (L-NAME) and VIP antagonist each partially reduced gastric relaxation induced by hyperglycemia and, in combination, completely abolished gastric responses. In conclusion, hyperglycemia inhibits gastric motility through a capsaicin-sensitive vagal afferent pathway originating from the gastroduodenal mucosa. Hyperglycemia stimulates vagal afferents, which, in turn, activate vagal efferent cholinergic pathways synapsing with intragastric nitric oxide- and VIP-containing neurons to mediate gastric relaxation.

Little is known about the site and mechanism that sense alteration in blood glucose level. The vagovagal reflex plays an important role in the mediation of many digestive functions including gastrointestinal motility (23, 25, 37, 38). The primary vagal afferents transmit sensory information about the physiological status of the gastrointestinal tract, including mechanical and chemical stimulation and energy metabolism. The identification of glucose-sensing neurons in the nodose ganglia (13, 46) led us to hypothesize that hyperglycemia acts through vagal afferent pathways to inhibit gastric motility.

In this study, we examined the hypothesis that hyperglycemia stimulates vagal afferents that act by way of the brainstem to stimulate the vagal efferent cholinergic pathway synapsing with intragastric nitric oxide (NO)- and peptide VIP-containing neurons to mediate gastric relaxation. Pharmacological studies, surgical resection, and chemical ablation of vagal afferent fibers were performed with an in vivo rat model.

HYPERGlyCENaIA HAS A WIDE RANGE of effects on gastrointestinal functions. The inhibitory effect of hyperglycemia on gastric motility is well known. Bulato and Carlson (8) were the first to report that hyperglycemia inhibits hunger contractions in the fasted dog, and, conversely, insulin-induced hypoglycemia produces gastric hypermotility that can be inhibited by intravenous glucose administration. Similarly, in healthy human subjects, glucagon-induced hyperglycemia abolishes hunger contractions, as measured with an intragastric balloon, and, when blood glucose levels return to control levels, gastric contractions are restored (36). Aylett (2) showed that blood glucose elevation slows gastric emptying. Barnett and Owyang (4) used a glucose clamp study to demonstrate that acute hyperglycemia inhibits the occurrence of the gastric interdigestive migrating motor complex in healthy volunteers. During the 3-h hyperglycemic period, gastric contractions were significantly reduced at 140 and 175 mg/dl and were almost completely absent at a blood glucose level of 250 mg/dl. This observation has important clinical implications for patients with diabetic gastroparesis, as it may explain the common observation that stable gastric neuropathies often exhibit wide day-to-day fluctuations in gastric emptying rates and symptoms of nausea and vomiting (12, 14, 16, 17).

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applied to the vagal trunks of the control rats. Hyperglycemia studies as described in the previous section were performed 5 days after surgery in the capsaicin-treated and control rats.

Gastroduodenal mucosal application of capsaicin. To determine whether the glucose-sensitiveafferent nerve endings originate from the gastroduodenal mucosa, we examined the effects of the mucosal application of capsaicin in the stomach and duodenum (25). Rats were anesthetized with pentobarbital sodium (50 mg/kg ip). After laparotomy, the stomach and duodenum were isolated and temporarily ligated at both ends. Capsaicin (2 ml) (6 mg/ml dissolved in 10% Tween, 80% in olive oil) was applied topically to the gastroduodenal mucosa for 30 min. A saline application was used in control rats. Hyperglycemia studies were performed 7 days after local capsaicin application. Rats were checked for normal eye wiping movement, which is an indication that local mucosal treatment of capsaicin has no systemic effect (41).

Effects of 5-HT3 receptor antagonist and PCPA treatments. Our previous studies indicated that luminal glucose stimulates the vagal afferent pathway through the release of intestinal 5-HT, which acts as a paracrine substance to mediate vagal signal transduction by way of the 5-HT3 receptor (24, 47). To rule out involvement of the 5-HT3 pathway in the mediation of the gastric motility response to hyperglycemia, we measured the effect of the 5-HT3 receptor antagonist on gastric motility. Gastric motility studies in response to hyperglycemia (250 mg/dl) were performed 15 min after intravenous infusion of granisetron (0.5 mg/kg). To further exclude any role for endogenous 5-HT in the mediation of gastric motility responses to hyperglycemia, we examined the effects of PCPA, a 5-HT synthesis inhibitor. PCPA inhibits tryptophan hydroxylase, the enzyme acting at the rate-limiting step of 5-HT synthesis. Depletion of 5-HT stores in the brain, intestinal tissue, and blood occurs after PCPA treatment (20, 42, 47). PCPA (500 mg/kg) suspended in 2 ml gum arabic solution was administered intraperitoneally on two consecutive days. Controls received only gum arabic. Studies of the gastric motility response to hyperglycemia (250 mg/dl) were conducted as described in the previous section.

Antagonist studies. To determine the role of nicotinic receptors in the mediation of gastric relaxation induced by hyperglycemia, hexamethonium (20 mg/kg bolus) was injected and continuously infused at a rate of 10 mg/kg h−1 for 20 min before the administration of glucose, as previously described (37). To determine the role of NO and VIP, L-NAME (10 mg/kg) and a VIP antagonist (30 nmol/kg) were injected 10 min before the infusion of glucose. These specific doses of L-NAME and the VIP antagonist have been shown to abolish rapid and prolonged relaxation, respectively, in response to vagal stimulation in vivo (37, 47).

Effect of central hyperglycemia on gastric motility. To rule out the possibility that hyperglycemia may act at a central site to induce gastric relaxation, we examined the effect of intracerebral injection of glucose on gastric motility. We adapted the method from a previous study by Adelson et al. (1). Briefly, the rats were anesthetized, and the head of each rat was fixed in a stereotactic holder. A midline incision was made along the back of the head and neck, and the underlying muscles were separated and retracted. The atlanto-occipital membrane was carefully exposed. A small incision was made in the membrane with a 25-gauge needle. A PE 10 polyethylene tube (BD Diagnostics) filled with saline was inserted through the incision into the cisterna magna. The cannula was secured with a drop of cyanoacrylate glue, and the incision was closed.

Gastric motility studies were performed as described in the previous section. After a 30-min recording, 100 μl of glucose (250 or 500 mg/dl) dissolved in 1,000 μl saline was administered with a Hamilton syringe into the cisterna magna over 30 s, followed by a 5-μl saline flush. Intragastric pressure was monitored for 20 min after each injection.

Analysis of data. Results were expressed as means ± SE. Statistical analysis was performed using one-way ANOVA, followed by the
Kruskal-Wallis test (a multiple comparisons procedure) or the Student's t-test, depending on the particular study design. Significance was accepted at the level of $P < 0.05$.

RESULTS

Glucose clamp studies. After an overnight fast, the basal blood glucose level was 90 ± 7 mg/dl ($n = 10$). The intragastric pressure was set at 5–10 cm H$_2$O with balloon distension, and this level remained stable for at least 60 min before the infusion of glucose. Intravenous infusion of dextrose (20%) produced a dose-dependent inhibition of gastric motility (Fig. 1). At blood glucose concentrations of 150, 200, 250, 300, and 350 g/dl, intragastric pressure decreased by $-0.76 \pm 0.34$, $-1.85 \pm 0.38$, $-1.91 \pm 0.28$, $-2.31 \pm 0.23$, and $-2.59 \pm 0.38$ cm H$_2$O, respectively. As shown in Fig. 2, increasing blood glucose levels reduced stomach muscle tone and progressively inhibited phasic gastric activities. Decreasing blood glucose levels from 300 to 150 mg/dl partially restored phasic gastric activities. Subsequent studies were performed with hyperglycemia maintained at 250–300 mg/dl.

Effects of hexamethonium and vagotomy. Administration of hexamethonium ($10 \text{ mg/kg}$) reduced basal intragastric pressure by 25 ± 3%; intragastric pressure returned to basal level within 30 min. Hexamethonium markedly reduced the inhibitory action of hyperglycemia maintained at 250 mg/dl ($P < 0.05$) (Fig. 3). This observation indicates that hyperglycemia acts at a presynaptic site of the cholinergic pathway.

Immediately after truncal vagotomy, basal intragastric pressure was reduced by 26 ± 4%. The intragastric pressure returned to basal level within 30 min, and the glucose infusion experiment was started. Similar to hexamethonium, truncal vagotomy markedly inhibited the gastric response to hyperglycemia at 250 mg/dl ($P < 0.05$) (Fig. 3). This suggests that the vagal pathway is the primary site of action of glucose to inhibit gastric motility.

Effect of perivagal and gastroduodenal mucosal applications of capsaicin. Perivagal application of capsaicin markedly reduced gastric relaxation in response to hyperglycemia (250 mg/dl) ($P < 0.05$) (Fig. 3). Similar to perivagal application of capsaicin, gastroduodenal application of capsaicin also significantly reduced the gastric responses to hyperglycemia ($P < 0.05$) (Fig. 3). In separate studies, we showed that neither perivagal nor gastroduodenal mucosal applications of capsaicin affected gastric responses to electrical vagal stimulation ($n = 6$) (10 V, 5 Hz, 2 ms for 30 s) (data not shown), indicating that administration of capsaicin does not affect efferent vagal transmission.

Effect of hyperglycemia on gastric contraction induced by electrical vaginal stimulation and intravenous administration of carbachol. Electrical vaginal stimulation (10 V, 1.25, 2.5, or 5 Hz; 2 ms for 30 s) induced a frequency-dependent increase in gastric pressure. This contraction was completely abolished by atropine (100 µg·kg$^{-1}$·h$^{-1}$). Electrical stimulation (10 V, 5 Hz, 2 ms for 30 s) of the peripheral cut end of the vagus nerve produced an increase in intragastric pressure (3.32 ± 0.33 cm H$_2$O) ($n = 4$). Infusion of d-glucose to achieve a blood level of 250 mg/dl failed to affect the gastric contraction induced by vagal stimulation (3.26 ± 0.39 cm H$_2$O) ($n = 4$, $P > 0.05$).

To determine whether hyperglycemia affects the muscle response to cholinergic stimulation, we showed that carbachol ($10^{-5}$ M, 0.1 ml iv) produced an increase in intragastric pressure (6.97 ± 0.91 cm H$_2$O) ($n = 4$) in the presence of hexamethonium (10 mg/kg iv). Infusion of glucose to induce hyperglycemia (250 mg/dl) failed to inhibit the contractile response induced by carbachol (6.62 ± 1.36 cm H$_2$O) ($n = 4$, $P > 0.05$).

Effects of 5-HT$_3$ receptor antagonist and PCPA treatments. Intravenous infusion of granisetron (0.5 g/kg) had no effect on intragastric pressure. Fifteen minutes after the administration

[Diagram: Hyperglycemia induced gastric relaxation. A representative tracing shows a decrease in IGP induced by acute hyperglycemia secondary to intravenous infusion of 20% dextrose in a rat. The dextrose infusion produced inhibition of gastric tone and phasic activities. When blood glucose levels were decreased, gastric tone and phasic activities partially recovered.

[Diagram: Effects of vagotomy (VAG), intravenous administration of hexamethonium (HEX), and perivagal (PVcap) or gastroduodenal application (GDcap) of capsaicin on hyperglycemia-induced gastric relaxation. Each procedure significantly reduced hyperglycemia-induced gastric relaxation; $n = 6$ for each group. *$P < 0.05$ compared with control on the basis of a t-test.]
of granisetron, intravenous infusion of 20% dextrose to achieve a blood glucose level of 250 mg/dl produced gastric relaxation similar to that observed under control conditions without granisetron (2.90 ± 0.41 vs. 3.21 ± 0.65 cm H₂O, n = 4, P > 0.05).

PCPA (500 mg/kg) was injected intraperitoneally into 6 rats on two consecutive days, and 4 rats were pretreated with vehicle (gum arabic) solution. Hyperglycemia (250 mg/dl) induced by glucose infusion stimulated a similar degree of gastric relaxation in both PCPA- and vehicle-treated rats (3.18 ± 0.45 vs. 2.94 ± 0.54 cm H₂O, n = 6, P > 0.05).

**Effects of L-NAME and VIP antagonist.** To determine whether NO and VIP play a role in mediating gastric relaxation induced by hyperglycemia, we examined the effects of L-NAME and a potent VIP antagonist. NO and VIP have been shown to mediate vagally induced gastric relaxation (28). Administration of L-NAME (10 mg/kg), which abolished the rapid transient relaxation induced by electrical vagal stimulation (28), reduced the gastric relaxation induced by hyperglycemia (250 mg/dl) by 76 ± 9% (P < 0.05) (Fig. 4). Intravenous administration of the VIP antagonist (30 nmol/kg) also decreased gastric relaxation in response to hyperglycemia (250 mg/dl) by 53 ± 12% (P < 0.05) (Fig. 4). A combination of L-NAME and the VIP antagonist completely abolished the gastric relaxation stimulated by hyperglycemia (250 mg/dl) (Fig. 4).

**Effect of intracisternal injection of glucose.** In contrast to intravenous infusion of glucose, intracisternal injection of glucose at 250 or 500 mg/dl did not significantly affect intragastric pressure. A tracing from one gastric pressure recording is shown in Fig. 5. Blood glucose remained euglycemic after intracisternal injection of glucose.

**DISCUSSION**

This study showed that hyperglycemia reduced gastric motility in a dose-dependent manner. This effect was abolished by perivagal or gastroduodenal mucosal application of capsaicin. Furthermore, we provided evidence that hyperglycemia stimulated vagal afferent pathways, which, in turn, activated vagal efferent cholinergic pathways synapsing with intragastric NO and VIP neurons to mediate gastric relaxation. This is the first demonstration that hyperglycemia inhibits gastric motility by activating the vagal afferent pathways innervating the gastroduodenal mucosa.

The infusion of concentrated dextrose as performed in the present study caused an elevation in blood insulin levels. It has been shown that insulin injection activated neurons in the enteric plexus in the stomach. The action is vagally mediated since vagotomy abolished the c-Fos expression in the stomach in response to insulin-induced hypoglycemia (45). Although it is conceivable that hyperinsulinism, secondary to hyperglycemia, is responsible for the inhibition of gastric motility, it is unlikely because previous work indicates a stimulatory role for insulin on gastrointestinal tract motility. Prasad and Sarna (29) reported that administration of insulin to fasted dogs results in premature migrating myoelectric complex phase III activity. Other investigators observed disruption of the migrating myoelectric complex and development of intestinal hyperactivity characteristic of a fed-like pattern during insulin infusion (7).

Althoough the presence of glucose-sensing neurons in the hypothalamus was first reported in 1953 (27), little is known about the site and mechanism that sense alteration in blood glucose level and modulate gastric motility. In general, the glucose-sensing neurons located in the brain are involved in the control of neuroendocrine function, nutrient metabolism, and energy homeostasis (21). These central nervous system neurons are unlikely to play a major role in mediating digestive functions in response to changes in circulating glucose under physiological conditions because the glucose level in the cerebrospinal fluid ranges between 10 and 30% of blood glucose levels, and, hence, these neurons are too insensitive to detect physiological changes in blood glucose concentrations (34). In this study, we further demonstrated that intracisternal injection of glucose into the cisterna magna failed to affect gastric motility, thus ruling out a central site of action of glucose to inhibit gastric motility.

However, it should be noted that, in contrast to peripheral hyperglycemia, insulin hypoglycemia on gastrointestinal functions appears to be centrally mediated (45). These investigators showed that hypoglycemia induced by insulin induced neuronal activation in the brain vagal-regulatory nuclei including the paraventricular nucleus of the hypothalamus, locus coeruleus, dorsal motor nucleus of the vagus, and nucleus tractus solitarii (NTS). These, in turn, altered gastrointestinal functions by activating the vagal efferent pathways. This action of hypoglycemia is independent of the vagal afferents (45), as bilateral cervical vagotomy did not influence insulin-induced Fos expression in the brain. Thus it appears that both glucose-
sensitive neurons and glucose sensors are located both centrally and peripherally. Our present studies indicate that peripheral hyperglycemia causes gastric relaxation via its action on vagal afferents. Others show that insulin hypoglycemia exerts its action mainly in the CNS to alter gastric functions. These suggest that central and peripheral glucose-sensitive neurons may have differential sensitivity to hypo- and hyperglycemia.

Recent studies suggest that acute hyperglycemia affects a subpopulation of neurons in the NTS and the dorsal motor nucleus of the vagus (3, 11, 19, 28, 43). These investigators demonstrated a prominent action of glucose to increase vagal afferent excitatory synaptic transmission to NTS neurons. Sakaguchi et al. (31, 32) reported that glucose injection into the dorsal motor nucleus of the vagus of anesthetized rats decreases gastric motility. In addition, Ferreira et al. (11) demonstrated that administration of glucose into the NTS modulates gastric motor and secretory functions. The physiological relevance of these observations is unknown; these investigators did not demonstrate that neurons in the NTS or the dorsal motor nucleus of the vagus are true primary sensors of changes in peripheral glucose levels.

Our study showed that the nicotinic receptor antagonist hexamethonium markedly reduced the inhibitory effect of hyperglycemia on gastric motility, suggesting that hyperglycemia is acting on a presynaptic site along the cholinergic pathway. To further identify the location of action, we examined the effect of bilateral subdiaphragmatic vagotomy. Similar to hexamethonium, vagotomy also markedly reduced the inhibitory action of hyperglycemia, suggesting that hyperglycemia inhibits gastric motility via a vagal pathway. To determine whether hyperglycemia exerts its action via an afferent or an efferent vagal pathway, we examined the effect of perivagal treatment with the sensory neurotoxin capsaicin. Capsaicin has been widely used as a tool to investigate the role of afferent C fibers in many physiological processes (5, 6, 25, 30, 35). Systemic administration of capsaicin affects neurotransmission in all somatic and visceral capsaicin-sensitive fibers. In this study, we applied capsaicin directly to the vagal trunks to avoid any damage to the afferent nerve terminals in the peripheral and central nervous systems, which has been observed with systemic administration of capsaicin. Previous studies have shown that perivagal capsaicin treatment interrupts the vagal afferent pathways that mediate the action of CCK at satiety (35), gastric motility and emptying (30), and pancreatic enzyme secretion (22). Our studies showed that perivagal pre-treatment with capsaicin markedly reduced the gastric response to hyperglycemia, an effect similar to that observed with vagotomy. Similar observations have been made with secretin, which, at physiological doses, inhibits gastric motility by way of a vagal afferent pathway (25).

To further localize the site of action of hyperglycemia on the vagal afferent pathway, we examined the effect of the mucosal application of capsaicin in the gastroduodenal region. This technique has been used to demonstrate chemically the sensory fibers in the duodenal mucosa (41). We showed that, similar to perivagal capsaicin treatment, gastroduodenal application of capsaicin markedly reduced the inhibitory effect of hyperglycemia, indicating that glucose-sensitive afferent fibers originate from the vagal branch in the mucosa of the stomach and duodenum. These observations were further confirmed with the use of an in vitro vagus stomach preparation that completely eliminated any influence of the central nervous system and/or systemic responses (44). We have previously identified subsets of gastric vagal afferents that are glucose responsive (46).

Hyperglycemia reportedly inhibits cholinergic transmission (40), which may contribute to a delay in gastric emptying (9). To rule out this possibility, we showed that hyperglycemia fails to inhibit gastric contraction induced by electrical field stimulation. This suggests that hyperglycemia does not have a direct inhibitory effect on the vagal release of acetylcholine, which is the principal postsynaptic neuronal neurotransmitter mediating muscle contraction induced by electrical vagus stimulation. Hence, it argues against hyperglycemia-induced inhibition of the vagal efferent pathways to mediate gastric relaxation. Moreover, the failure of hyperglycemia to inhibit gastric contraction induced by carbachol indicates that hyperglycemia does not have a direct inhibitory effect on gastric smooth muscle cells.

Luminal stimuli, such as glucose or maltose, induce 5-HT release from mucosal enterochromaffin cells, and this, in turn, activates 5-HT3 receptors on mucosal vagal afferent terminals (47). In this manner, 5-HT acts as a paracrine substance to inhibit gastric motility through a vagal cholinergic pathway. To rule out involvement of the 5-HT3 pathway in the mediation of the gastric motility response to hyperglycemia, we showed that the 5-HT3 antagonist granisetron failed to affect gastric relaxation induced by hyperglycemia. In separate studies, we showed that pharmacological depletion of 5-HT stores with the use of a 5-HT synthesis inhibitor p-chlorophenylalanine, which markedly reduces duodenal mucosal 5-HT levels and abolishes pancreatic secretion induced by luminal administration of glucose (23), also had no effect on gastric relaxation induced by hyperglycemia (250 mg/dl). This suggests that hyperglycemia inhibits gastric motility by way of a 5-HT3-independent pathway.

Vagal stimulation produces two modes of relaxation in the rat stomach, rapid relaxation followed by prolonged relaxation (39). Rapid relaxation is antagonized by a NO inhibitor and prolonged relaxation is blocked by a VIP antagonist (39), which suggests that different neurotransmitters mediate different modes of relaxation. In rats, gastric distension induces a vagovagal reflex that stimulates the NO-containing gastric myenteric plexus (37). On the other hand, secretin-induced gastric relaxation is mediated by a VIP pathway (26). In this study, we showed that L-NAME and the VIP antagonist each partially reduced gastric relaxation induced by hyperglycemia. A combination of the two antagonists completely abolished hyperglycemia-induced gastric relaxation. These observations indicate that activation of vagal afferents by hyperglycemia stimulates vagal efferent cholinergic pathways synapsing with intragastric NO- and VIP-containing neurons to mediate gastric relaxation.

Our finding that acute hyperglycemia inhibits gastric motility differs from that reported by Shi et al. (33), who showed that hyperglycemia failed to inhibit spontaneous or bethanecol-induced gastric contractions in rats, as measured by a strain-gauge force transducer sutured to the antrum. On the other hand, intravenous infusion of glucose inhibited the antral contractions stimulated by insulin-induced hypoglycemia. This inhibitory action of glucose was not affected by sectioning the hepatic branch of the vagus nerve nor by capsaicin treatment.
These differences in findings may be related to the methods used to stimulate and record gastric pressure. We measured gastric pressure with a water-filled balloon inserted into the body of the stomach, whereas Shi et al. (33) measured antral motility using a strain-gauge transducer sutured to the antrum. It is not surprising that the inhibitory effect of glucose on antral contractions induced by hyperglycemia was not sensitive to capsaicin treatment. Since insulin-induced hypoglycemia acts centrally to stimulate gastric contractions, one would not expect this action to be affected by glucose acting on the vagal afferent fibers. In fact, we also observed that hyperglycemia did not affect gastric contractions induced by direct electrical stimulation of the vagus nerve. This further emphasizes the importance of the methods used to stimulate stomach contraction because they will determine the sensitivity of gastric motor function to changes in blood glucose levels.

The demonstration that hyperglycemia inhibits gastric motility has obvious clinical importance. It suggests that hyperglycemia alone, in the absence of underlying neuropathy or myopathy, can alter gastric motor function. This may explain the common clinical observation that diabetic patients with stable motor defects often exhibit wide day-to-day variations in the severity of their symptoms depending on blood glucose control (14). In type I and type II diabetes, there is a strong correlation between delayed gastric emptying of liquids and blood glucose levels >270 mg/dl (16, 17). Similarly, delays in solid emptying occur during periods of hyperglycemia in type I diabetes, which improve during periods of euglycemia (12). This study identifies the site and neural pathways that sense alteration in blood glucose level and modulate gastric motility.

ACKNOWLEDGMENTS

The authors thank Mr. Tin Ming Mok for technical assistance.

GRANTS

This study was supported by the American Diabetes Association Grant 1-06-JF-58 (to S. Zhou) and the National Institute of Diabetes and Digestive and Kidney Diseases Grants P30-DK34933, DK-48419, DK-58913, and DK-061423 (to C. Owang).

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