Implantable Gastric Stimulation Inhibits Gastric Motility via Sympathetic Pathway in Dogs

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Background: The aim of this study was to investigate the effect of implantable gastric stimulation (IGS) on gastric antral contractions and the involvement of the sympathetic pathway.

Methods: The study was performed in 5 postprandial sessions in 8 dogs chronically implanted with stimulation electrodes and a gastric cannula: a) IGS via lesser curvature; b) IGS via antrum; c) and d) same as a) and b) but IGS initiated 1 hr before the meal; e) same as a) but with guanethidine.

Results: It was found that: 1) IGS significantly inhibited postprandial antral contractions assessed by manometry, and no significant difference was noted in the effect between the two stimulation sites; 2) IGS initiated 1 hr before the meal was more potent than that initiated 30 minutes after the meal; 3) the inhibitory effect of IGS on postprandial antral motility was completely blocked by guanethidine.

Conclusion: Acute IGS inhibits postprandial antral contractions, and this inhibitory effect is mediated via the sympathetic pathway.

Key words: Gastric electrical stimulation, implantable gastric stimulator, obesity, gastric motility, gastric pacing

Introduction

The prevalence of obesity is reaching an alarming rate worldwide. In the United States alone, there are approximately 300,000 deaths a year caused by obesity and more than \$100 billion is spent each year for the treatment of obesity and its primary co-morbidities.¹⁻⁴ Various treatment options are available

for obesity, such as diet, exercise, drugs, surgery, etc. However, none of the available therapies, including surgery, is completely satisfactory, and there is an urgent need to develop safe and effective methods to treat patients with morbid obesity.⁵

Gastric electrical stimulation (GES) has received increasing attention among researchers and clinicians in recent years, and a number of studies have been performed to investigate the effect of GES on obesity. Cigaina et al⁶ was the first to investigate the potential of GES to induce weight loss in a porcine model in 1992, and the study results showed that GES was safe and effective in inhibiting weight gain and food intake in growing swine. Recently, a number of preliminary clinical studies have shown promising results in treating obesity using the stimulator (IGS).⁷⁻⁹ implantable gastric Accordingly, it is of considerable interest to explore underlying mechanisms involved with the IGS therapy for obesity.

It is known that gastric motility is one of the most critical physiological functions of the human gut. Without coordinated motility, digestion and absorption of dietary nutrients could not take place. To accomplish its functions effectively, the gut needs to generate not just simple contractions but contractions that are coordinated to produce transit of luminal contents (peristalsis). Thus, coordinated gastric contractions are necessary for the emptying of the stomach. Although the contribution of changes in gastric emptying to the pathogenesis of obesity is unclear, there is some evidence suggesting that enhanced gastric emptying may be related to overeating and obesity.¹⁰ Rapid emptying would decrease the negative feedback satiety signal pro-

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duced by the presence of nutrients inside the stomach and may precipitate hunger and shorten the meal interval. Persistently delayed gastric emptying prolongs the presence of food within the stomach, and has been associated with the origin of debilitating upper gastrointestinal symptoms (early satiety, nausea and vomiting, etc.) and less food intake, as frequently seen in patients with functional dyspepsia and gastroparesis.^{11,12} An herbal preparation, which significantly delayed gastric emptying, was reported to be able to reduce the time to perceived gastric fullness and induce significant weight loss over 45 days in overweight patients.¹³ The effect of IGS on gastric antral motility, which is crucial for gastric emptying, has never been reported.

The principal objective of this study was therefore to investigate the effect of gastric electrical stimulation with parameters similar to those used in previous clinical studies on gastric antral contractions. The secondary objective was to investigate whether the sympathetic pathway was involved in this inhibitory effect.

Methods

Animal Preparation

Eight healthy female hound dogs (15-22 kg) were involved in this study. After an overnight fast, anesthesia was induced in each dog with Pentothal (sodium thiopental 11 mg/kg intravenous; Abbott Laboratories, North Chicago, IL, USA) and maintained on 2% to 4% IsoFlo (Abbott Laboratories, North Chicago, IL, USA) in Oxygen (1L/min) carrier gases delivered from a ventilator after endotracheal intubation. A cannula was placed on the anterior side of the stomach, 6 cm above the pylorus. The gastric cannula was exteriorized through the abdominal wall and provided direct access to the gastric lumen for the assessment of gastric contractions. One pair of 28-gauge stainless steel cardiac pacing wires (A&E Medical, Farmingdale, NJ, USA) was implanted on the serosal surface along the greater curvature 10 cm above the pylorus. Another pair was implanted at the lesser curvature 3 cm below the gastroesophageal junction. The two electrodes in the pair were 1 cm apart. The electrode wires were tunneled through the anterior abdominal wall subcutaneously along the right side of the trunk, and placed outside the skin around the right hypochondrium for attachment to the recording equipment. After surgery, the dog was transferred to a recovery cage. All studies were initiated when the dogs had completely recovered, usually 2 weeks after surgery. The protocol was approved by the animal committee of the Veterans Affairs Hospital, Oklahoma City, OK.

Experimental Protocol

The study consisted of five randomized sessions on separate days with an interval of at least 2 days. Session 1 was composed of three 30-min postprandial periods (baseline, stimulation and recovery). Dogs were fed with a can of solid meal (413 calories) immediately before the session. Stimulus was composed of trains of short pulses and the parameters were similar to those used in the previous clinical studies:^{7,9} train on time of 2s and off time of 3s, pulse frequency of 40 Hz, width of 0.6ms and amplitude of 10 mA. The stimulation was delivered via the electrodes in the antrum. Session 2 was the same as session 1, except that stimulation location was at the lesser curvature. Session 3 was the same as session 1, except that the stimulation was initiated 1 hour before the meal. Session 4 was identical to session 2, except that the stimulation was initiated 1 hour before the meal. Session 5 was same as session 1, except that guanethidine (3 mg/kg) was injected intravenously 20 minutes before the initialization of stimulation. Gastric contractions were measured during the entire period using a manometric system.

Measurement and Analysis of Antral Motility

Antral contractile activity was recorded from four pressure sensors of 1 cm apart attached to the manometric catheter by using a PC polygraf HR system (Synectics Medical, Stockholm, Sweden) and a microcapillary infusion system (Synectics, Stockholm, Sweden). All recordings were displayed on a computer monitor. A parameter, called the Area Under the Curve (AUC), was used to represent the contractile strength of the distal stomach. It was defined as the area under each of the contractions and was calculated by Polygram Function Testing Software (Medtronic, version 2.03, Synectics Medical, Stockholm, Sweden). The data presented in this study were obtained from channel 3, which was of the highest quality of the recording.

Statistical Analysis

Data were expressed as mean \pm SE. One way analysis of variance (ANOVA) and the student's *t*-test were used to compare the differences among three or more parameters and between two parameters, respectively. *P* values <0.05 were considered statistically significant.

Results

Inhibitory Effects of IGS on Antral Motility

IGS inhibited gastric antral contractions (Figure 1). In session 1: the motility index was 20.4 ± 3.0 at baseline and decreased to 11.7 ± 1.5 (*P*=0.01 vs baseline) during stimulation at the antrum. In session 2: the motility index was 10.6 ± 0.6 at baseline and decreased to 8.2 ± 0.7 (*P*<0.01 vs baseline) during stimulation at the lesser curvature. The motility index was 3.5 ± 0.4 (*P*<0.01 vs baseline) during stimulation at the antrum initiated 1 hour before the meal and 5.0 ± 0.5 (*P*<0.01 vs baseline) during stimulation at the lesser curvature initiated 1 hour before the meal and 5.0 ± 0.5 (*P*<0.01 vs baseline) during stimulation at the lesser curvature initiated 1 hour before the meal and 5.0 ± 0.5 (*P*<0.01 vs baseline) during stimulation at the lesser curvature initiated 1 hour before meal.

There was no significant difference in the inhibitory effect on antral motility between IGS at the antrum and IGS at the lesser curvature (P=0.065). However, IGS initiated 1 hour before the meal was significantly more potent than that initiated 30 min after the meal. In comparison with the reduction in motility index of 8.7 ± 2.7 and 2.5 ± 0.4 with IGS at the antrum and the lesser curvature, respectively, the corresponding reductions with IGS initiated 1 hour before the meal were 16.9 ± 3.1 (P<0.01) and 5.6 ± 0.6 (P=0.006), respectively.

Involvement of Sympathetic Pathway

Injection of guanethidine completely abolished the inhibitory effect of IGS (Figure 2). In the session with guanethidine, the motility index was 17.5 ± 2.5







B. IGS at lesser curvature inhibited antrum contraction.

Figure 1A and B. Effect of IGS (implantable gastric stimulator) on antral motility expressed as area under the contractile curve (AUC). IGS significantly decreased the AUC at different locations when stimulation started after the meal. GES = gastric electrical stimulation.



Figure 2. Effects of guanethidine on IGS-induced inhibition on antral motility in the guanethidine session. Guanethidine infusion with IGS did not alter the antral motility, compared with the value in guanethidine infusion without IGS and the baseline before guanethidine infusion (P=0.9, ANOVA).

at baseline, 15.4 ± 2.5 after injection of guanethidine, 16.9 ± 2.4 during IGS and 17.9 ± 2.8 during recovery period (*P*=0.9, ANOVA) (Figure 3).

Discussion

In this study, we found that IGS inhibited postprandial antral contractions and this inhibitory effect was completely blocked by guanethidine.

The conventional treatments of obesity can be classified into three categories: basic treatment, pharmacotherapy, and surgical treatment. Typically, basic treatment is tried first in an obese patient. Acceptable weight loss is usually achieved with basic treatment. However, maintaining weight loss seems more difficult than losing weight, particularly for patients who were treated with calorie restriction.¹⁴ Basic treatment seems effective only in the short term. A number of FDA-approved drugs are currently available for the medical treatment of obesity. These include sibutramine, diethylpropion, mazindol, phentermine, phenylpropanolamine, and

orlistat.^{15,16} Similar to the basic treatment, pharmacotherapy is also effective only for short-term use. In addition, adverse effects of these drugs limit their use in patients with various co-morbidities. While surgical treatment induces satisfactory long-term weight loss, morbidity and mortality limit its wide applications.^{5,17}

Gastric electrical stimulation has been under intensive investigation for its therapeutic potential for gastrointestinal motility disorders.¹⁸⁻²⁷ Over the past years, different methods of electrical stimulation have been derived from the variation of stimulation parameters, including long-pulse stimulation, short-pulse stimulation, and stimulation with train of pulses. Most previous studies explored therapeutic potentials of electrical stimulation for treating patients with motility disorders, as electrical stimulation of the gut seems capable of altering motor functions of the stomach or small intestine. In these studies, gastric electrical stimulation was designed and tuned to improve gastric slow-waves,18-20 enhance gastric emptying^{21,22} and relieve symptoms of nausea and vomiting.²³

Recently, the therapeutic potential of gastric elec-



B. Inhibitory effect of IGS on antral motility was abolished by administration of guanethidine.

Figure 3A and B. Manometric tracings showing the effects of IGS on antral motility with or without administration of guanethidine.

trical stimulation for obesity has also been under investigation. Promising preliminary clinical data has been obtained on its efficacy and safety in reducing weight in morbidly obese patients.^{7-9,28,29} Different from the methods of GES used for treating gastric motility disorder, the stimulus in the GES used for treating obesity is composed of trains of short pulses instead of repetitive single long pulses or single short pulses. That is, the stimulus is composed of trains of short pulses, repeated at a certain frequency. The effects of GES with this kind of stimulus on gastric motility have rarely been investigated. One previous study using the same method showed that IGS had no acute effect on gastric myoelectrical activity but exerted a chronic inhibitory effect: the gastric slow wave was impaired in both rhythmicity and amplitude in the fed state after 1 month of continuous IGS.30

In this study, we found that GES resulted in an inhibition of antral contractions. This finding suggests one of the possible mechanisms involved with IGS for obesity. Gastric motility in patients with obesity has been extensively studied. Although controversial, most of the reported studies seem to conclude that patients with obesity have an abnormally rapid rate of solid gastric emptying. Antral motility plays an important role in the regulation of gastric emptying. Malbert et al^{31} reported that the rate of abomasal outflow depended primarily upon the strength of antral contractions. Motility is one of the most critical physiological functions of the human gut. Without coordinated motility, digestion and absorption of dietary nutrients cannot take place. Coordinated gastric contractions are necessary for the emptying of the stomach. The inhibition in antral contractions observed in this study with IGS is believed to slow down the digestive process and lead to increased satiety, as frequently reported in obesity patients treated with IGS.

We further found that the inhibitory effect of IGS on antral motility was mediated via the sympathetic pathway. Sympathetic activity is a major inhibitory factor on gastrointestinal motility. Guanethidine is an adrenergic blocker for preventing release of nor-epinephrine, and norepinephrine is an agonist at α -and β -adrenergic receptors. Our results showed that the administration of guanethidine did not affect antral motility, but prevented the inhibitory effect of IGS on antral motility, indicating that the inhibitory

effect of IGS on antral motility was mediated via the adrenergic nerve activation.

In addition to the finding of this current study, several previous studies have explored other possible mechanisms involved with the IGS therapy for obesity.³² IGS has been reported to induce gastric distention, reduce gastric accommodation, chronically impair gastric slow-waves in both humans and dogs, activate neurons in the nucleus tractus solitarri and alter plasma levels of gastrointestinal peptides.^{30,33-36}

In conclusion, acute IGS inhibits postprandial antral contractions and this inhibitory effect is mediated via the sympathetic pathway.

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References

- 1. <u>Klein S. Obesity. Clinical Perspectives in</u> <u>Gastroenterology 2000; 3: 232-6.</u>
- Martin LF, Hunter SM, Lauve RM et al. Severe obesity: expensive to society, frustrating to treat, but important to confront. South Med J 1995; 88: 895-902.
- Colditz GA. Economic costs of obesity. Am J Clin Nutr.1992; 55(Suppl 2): 503S-507S.
- Wolf AM, Colditz GA. Current estimates of the economic cost of obesity in the United States. <u>Obes Res</u> <u>1998; 6: 97-106.</u>
- 5. Gastrointestinal surgery for severe obesity. National Institutes of Health Concensus Development Conference Draft Statement. <u>Obes Surg 2001; 1: 257-</u> 66.
- 6. Cigaina V, Saggioro A, Rigo V et al. Long-term effects of gastric pacing to reduce feed intake in swine. Obes Surg 1996; 6: 250-3.
- D'Argent J. Gastric electrical stimulation as therapy of morbid obesity: preliminary results from the French study. Obes Surg 2002; 12 (Suppl 1): 21S-25S.
- Favretti F, De Luca M, Segato G et al. Treatment of morbid obesity with the transcend implantable gastric stimulator (IGS): a prospective survey. <u>Obes Surg</u> 2004; 14: 666-70.
- 9. Cigaina V. Gastric pacing as therapy for morbid obesity: preliminary results. Obes Surg 2002; 12 (Suppl

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1): 12S-16S.

- 10. Duggan JP, Booth DA. Obesity, overeating, and rapid gastric emptying in rats with ventromedial hypothalamic lesions. <u>Science 1986</u>; 231: 609-11.
- 11. Tack J, Caenepeel P, Fischler B et al. Symptoms associated with hypersensitivity to gastric distention in functional dyspepsia. <u>Gastroenterology 2001; 121:</u> 526-35.
- 12. Horowitz M, Su YC, Rayner CK et al. Gastroparesis: prevalence, clinical significance and treatment. <u>Can J</u> Gastroenterol 2001; 15: 805-13.
- Andersen T, Fogh J. Weight loss and delayed gastric emptying following a South American herbal preparation in overweight patients. J Hum Nutr Diet 2001; 14: 243-50.
- 14. AACE/ACE. Position statement on the prevention, diagnosis, and treatment of obesity. <u>Endocrine Pract</u> <u>1998</u>; 4: 297-330.
- 15. Bray GA, Greenway FL. Current and potential drugs for treatment of obesity. Endocr Rev 1999; 20: 805-75.
- Hvizdos KM, Markham A. Orlistat: a review of its use in the management of obesity. <u>Drugs 1999</u>; 58: 743-60.
- 17. Sagar, P.M. Surgical treatment of morbid obesity. <u>Br J</u> Surg 1995; 82: 732-9.
- 18. Lin ZY, McCallum RW, Schirmer BD et al. Effects of pacing parameters on entrainment of gastric waves in patients with gastroparesis. Am J Physiol 1991; 274: G186-G191.
- 19. Qian LW, Lin XM, Chen JDZ. Normalization of atropine-induced postprandial dysrhythmias with gastric pacing. Am J Physiol 1999; 276: G387-G392.
- 20.Xu XH, Qian LW, Chen JDZ. Anti-dysrhythmic effects of long-pulse gastric electrical stimulation in dogs. <u>Digestion 2004; 69: 63-70.</u>
- 21.McCallum RW, Chen JDZ, Lin ZY et al. Gastric pacing improves emptying and symptoms in patients with gastroparesis. <u>Gastroenterology 1998</u>; 114: 456-61.
- 22. Bellahsene BE, Lind CD, Schirmer BD et al. Acceleration of gastric emptying with electrical stimulation in a canine model of gastroparesis. Am J Physiol 1992; 262: G826-G834.
- 23. Abell T, McCallum R, Hocking M et al. Gastric elec-

trical stimulation for medically refractory gastroparesis. <u>Gastroenterology 2003; 125: 421-8.</u>

- 24. Eagon JC, Kelly KA. Effects of gastric pacing on canine gastric motility and emptying. Am J Physiol 1993; 265: G767-G774.
- 25. Forster J, Sarosiek I, Delcore R et al. Gastric pacing is a new surgical treatment for gastroparesis. <u>Am J Surg</u> 2001; 182: 676-81.
- 26. Miedema BW, Sarr MG, Kelly KA. Pacing the human stomach. <u>Surgery 1992; 111: 143-50.</u>
- 27. Sarna SK, Bowes KL, Daniel EE. Gastric pacemaker. Gastroenterology 1976; 70: 226-31.
- Shikora SA. Implantable gastric stimulation for the treatment of severe obesity. <u>Obes Surg 2004</u>; 14: 545-8.
- 29. Cigaina V. Long-term follow-up of gastric stimulation for obesity: the Mestra 8-year experience. Obes Surg 2004; 14 (Suppl 1): S14-S22.
- 30. Ouyang H, Yin JY, Chen JDZ. Inhibitory effects of chronic gastric electrical stimulation on food intake and weight and their possible mechanisms. <u>Dig Dis</u> <u>Sci 2003</u>; 48: 698-705
- Malbert CH, Ruckebusch Y. Gastroduodenal motor activity associated with gastric emptying rate in sheep. J Physiol 1988; 401: 227-39.
- Chen J. Mechanisms of an implantable gastric stimulator for obesity. Obes Surg 2004; 14 (Suppl 1): S28-S32.
- 33.Lin Z, Denton S, Durham S et al. Retrograde gastric electrical stimulation (RGES) impairs gastric myoelectrical activity in patients with mobid obesity. Gastroenterology 2002; 122: A-326 (abst).
- 34. Xing JH, Chen JD. Effects and mechanisms of longpulse gastric electrical stimulation on canine gastric tone and accommodation. <u>Neurogastroenterol Motil</u> 2003; 15: 380 (abst).
- 35.Qin C, Sun Y, Chen JDZ et al. Effects of gastric electric stimulation on neuronal activity in nucleus tractus solitarii (NTS). Gastroenterology 2004; 126: A-10 (abst).
- 36. Cigaina V, Hirschberg AL. Gastric pacing for morbid obesity: plasma levels of gastrointestinal peptides and leptin. <u>Obes Res 2003; 11: 1456-62.</u>

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