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ORIGINAL CONTRIBUTIONS

Gastric Electrical Stimulation Optimized to Inhibit Gastric Motility Reduces Food Intake in Dogs

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Abstract
Aims The aim of this study was to test the hypothesis that that a method of gastric electrical stimulation (GES) optimized to inhibit gastric motility was effective in reducing food intake in dogs.
Methods Female dogs with a gastric cannula and gastric serosal electrodes were studied in three experiments: (1) to determine the best parameters and locations of GES in inhibiting gastric tone, slow waves, and contractions in dogs;(2) to investigate the reproducibility of the inhibitory effects of GES; and (3) to study the effect of the GES method on food intake in dogs.
Results (1) For GES to exert significant effects on gastric motility, a pulse width of ≥2 ms was required, and with other appropriate inhibitory parameters, GES was able to increase gastric volume by 190.4 %, reduce antral contractions by 39.7 %, and decrease the percentage of normal slow waves by 47.6 %. In addition, the inhibitory effect of GES was more potent with the stimulation electrodes placed along the lesser or greater curvature than placed in the middle, and more potent with the electrodes placed in the distal stomach than in the proximal stomach; (2) the inhibitory effects of GES on gastric motility were reproducible; (3) the GES method optimized to inhibit gastric motility produced a 20 % reduction in food intakes in non-obese dogs.
Conclusion GES with appropriate parameters inhibits gastric motility, and the effects are reproducible. The GES method optimized to inhibit gastric motility reduces food intake in healthy dogs and may have a therapeutic potential for treating obesity.

Keywords Gastric electrical stimulation · Obesity · Food intake · Gastric motility

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Introduction

Gastric electrical stimulation (GES) has been investigated for treating obesity. The method of GES used in clinical studies of obesity is called implantable gastric stimulation (IGS). The stimuli in IGS are trains of short pulses with a width of ~0.3 ms that is comparable to electrical nerve stimulation [1]. A number of non-controlled clinical studies of GES with short pulses (~0.3 ms) have shown significant weight loss in obese patients [2–5]. However, some patients did not lose weight, and overall, the weight loss with the existing method of GES (pulse width of <1 ms) was not substantial [6]. In addition, two placebo-controlled multi-center clinical trials both failed to yield clinically significant weight loss [7, 8].

Recent studies indicated that GES with a wider pulse (≥2 ms) produced a significant reduction in gastric ghrelin [9] and activated satiety neurons in ventromedial hypothalamus [10]. One study in rats showed that GES of both the wider pulse (3 ms) and short pulse (0.3 ms) activated gastric

distention-responsive neurons and increased the number of neurons expressing the anorexigenic hormone, oxytocin, in the paraventricular nucleus of the hypothalamus; however, the effects were more potent with GES of wider pulse than with GES of shorter pulses [10]. Given that gastric balloon distention is known to be associated with reduced food intake [11–13] and the observed central neural and hormonal effects are directly associated with satiety, the findings of these studies seem to suggest that GES with wider pulses may be more effective in treating patients with obesity [10].

In addition to hormonal and neuronal mechanisms, gastrointestinal motility is also involved in the regulation of food intake. We hypothesize that inhibition of gastric motility leads to reduced food intake, resulting in weight loss. We further hypothesize that for GES to be effective in reducing food intake and body weight, it should be designed to inhibit gastric motility. Although none of approved anti-obesity drugs were developed to inhibit gastric motility, most of these medications delay gastric emptying [14, 15]. GES with single repetitive long pulses (pulse width of >100 ms) delivered at a frequency higher than the physiological frequency of intrinsic gastric slow waves was reported to inhibit gastric motility and concurrently reduce food intake in dogs [16] and humans [17, 18]. However, technically, it is difficult to build an implantable pulse generator (IPG) that is capable of delivering pulses with a width of a few hundred milliseconds. The alternative is to build a new generation of IPG capable of delivering trains of pulses that exerts inhibitory effects on gastric motility. However, there is a lack of systematic studies in investigating the inhibitory effects of GES using pulse trains with different parameters and stimulation locations.

Accordingly, the aims of the present study were (1) to find a method of GES with pulses trains most effective in inhibiting gastric motility, including gastric tone, slow waves, and contractions; (2) to prove that the inhibitory effects of such a method of GES on gastric motility were reproducible; and (3) to prove that this inhibitory GES method indeed reduced food intake in dogs.

Materials and Methods

Animal Preparation

Sixteen female hound dogs (18 to 23 kg) were used. All the dogs were examined and proven to be healthy with normal serum thyroid hormones and glucose levels. After an overnight fast, each dog was operated under anesthesia that was induced with intravenous Pentothal (sodium thiopental, 11 mg/kg; Abbott Laboratories, North Chicago, IL) and maintained on 2 to 4 % IsoFlo (Abbott Laboratories) in oxygen (1 l/min) carrier gases delivered from a ventilator after endotracheal intubation. As shown in Fig. 1, in eight dogs, four pairs of serosal electrodes (first pair: #1 and #2; second pair: #3 and #4; third pair: #5 and #6; fourth pair: #7 and #8) were implanted along the lesser curvature at an interval of 0.7 cm with the most distal electrode (#8) 2 cm from the pylorus, and two pairs of electrodes (fifth pair: #11 and #12; sixth: #13 and #14) were implanted along the greater curvature with the most distal electrode (#14) 4 cm above the pylorus. In the other six dogs, three pairs of electrodes (first pair: #3 and #4; second pair: #7 and #8; third pair: #9 and #10) were implanted along the lesser curvature and another two pairs were along the greater curvature (fourth pair: #11 and #12; fifth pair: #13 and #14) with the most distal electrode (#14) 4 cm above the pylorus (Fig. 1). In the remaining two dogs, three pairs were implanted in the mid body (first pair: #15 and #16; second pair: #17 and #18; third pair: #19 and #20) (Fig. 1). The electrodes were temporary pacing wires (Medtronic Inc., Minneapolis, MN). A gastric cannula (inner diameter, 1 cm) was implanted on the anterior side of the stomach, 10 cm above the pylorus in all dogs (Fig. 1). All studies were performed after the animals fully recovered from surgery. The experimental protocols were approved by the Institutional Animal Care and Use Committee at VA Medical Center, Oklahoma City, OK.

Experimental Protocol

The study was composed of three separate experiments. GES was performed via the implanted electrodes on the stomach using an adjustable stimulator (World Precision Instruments, Sarasota, FL).

The first experiment was to determine parameters and locations effective for GES to inhibit gastric tone, slow waves, and contractions in 16 dogs. In the first part of the experiment, gastric tone and slow waves were measured at baseline and during GES of various parameters ranged 0.21–4.0 ms for

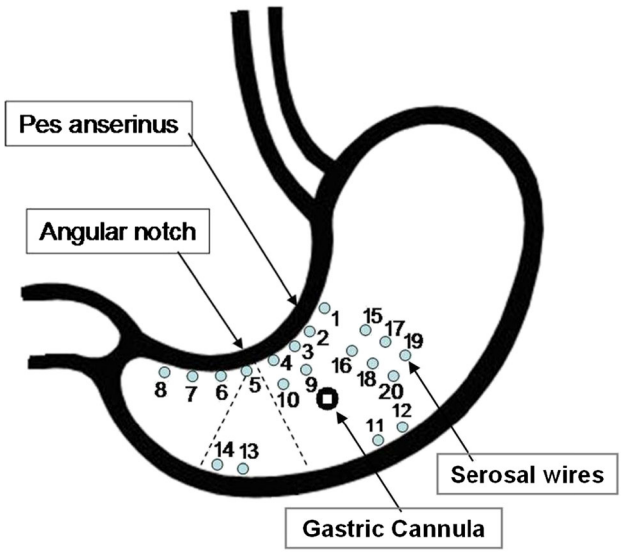

Fig. 1 Locations of electrodes and cannula in the stomach

pulse width, 10–40 Hz for frequency and 5–10 mA for amplitude. The recordings were made after an overnight fast for 20 min at baseline and a series of 10-min periods with GES of different parameter sets. The two consecutive GES periods were separated with a period of 10 min or more in order for gastric tone to recover to the baseline level.

In the second part of the experiment, antral contractions were measured after a solid meal, including a 20-min baseline and a series of 10-min periods with GES (selected parameters and locations which showed inhibitory effects on gastric tone). The two consecutive GES periods were separated with a period of 5 min or more in order for the gastric contraction to recover to the baseline.

The second experiment was designed to study the reproducibility of GES on gastric tone and antral contractions in eight of the 16 dogs. Gastric tone and antral contractions were measured at three different time points (week 2, week 6, and week 10 after surgery) with GES performed at the optimal location and with the optimal parameters (2 ms, 40 Hz, 2 s on and 3 s off, derived from experiment 1). The protocol included a 20-min baseline and a series of 10-min periods with GES of different pulse amplitude (6–8 mA).

The third experiment was designed to test the hypothesis that the GES method inhibitory to gastric motility reduces food intake. It was performed in eight of the dogs. GES was performed using the optimal parameters and location derived from exp 1. This experiment lasted 3 weeks, including 1 week for acclimation, 1 week with GES, and 1 week with sham-GES (GES and sham-GES in a randomized order). The animals were first acclimated to 2-h daily feeding in their regular cages. GES or sham-GES was performed only during the 2-h feeding time in the animal housing cage by connecting the chronically implanted electrodes wires in the animal with the external stimulator. To ensure that the animal could walk and move freely in the cage, a special wiring system was established in the cage to bring the connecting wires (enclosed in a cable) from the top-middle of the cage down to the exited electrode wires in the back of the animal. This experimental setup allowed the animals to be tested physiologically without disturbances. During the 2-h feeding/stimulation period, the animals were given 650 g of food (more than any animal could consume). The amount of food intake during the 2-h period with GES or sham-GES was recorded daily for 1 week.

Assessment of Gastric Tone

Gastric tone was measured by the assessment of gastric volume under a constant pressure using a barostat device (G & J Electronics, Ontario, Canada) [19]. A barostat balloon was inserted into the proximal stomach via the cannula, and gastric volume was measured under a constant operating pressure that was 2 mmHg above the minimal distending, individualized for each animal. A high volume represented a lower gastric tone and vice versa.

Measurement and Analysis of Antral Contractions

Antral contractions were measured using a water-perfused manometric system (Synectics Medical, Stockholm, Sweden) by placing a manometric catheter in the distal stomach via the gastric cannula. There were four side holes at an interval of 1 cm in the distal end of the catheter. Four-channel recordings of antral contractions were made. The contractile strength of the distal stomach was calculated by a parameter, called the motility index, defined as the total number of contractions times the average amplitude of the contractions within each recording period. The data presented in this study was obtained from channel 3, which showed the highest quality of the recording [20].

Recording and Analysis of Gastric Slow Waves

Gastric slow waves were measured via the most distal pair of electrodes chronically placed on the serosa of the antrum using a Biopac system (Biopac System, Inc. Santa Barbara, CA) in conjunction with gastric tone in exp 1. The low and high cutoff frequencies of the amplifier were 0.05 and 35 Hz, respectively. For the analysis of gastric slow waves, the signal was further lowpass-filtered with a cutoff frequency of 1 Hz and down-sampled at 2 Hz. Previously validated computerized spectral analyses were performed to compute the percentage of normal gastric slow waves from the recordings, defined as the percentage of time during which regular 4–6 cpm slow waves were presented over a specific analyzed period [21].

Statistical Analysis

The results are expressed as mean±SD. Analysis of variance (ANOVA) was used to compare the data among three or more different periods and the Student's *t* test was used to assess the effect of GES in comparison of the baseline or sham-GES. p values<0.05 were considered statistically significant.

Results

Optimization of GES Parameters Based on Gastric Tone

Effects of Pulse Width GES with fixed parameters of pulse frequency, amplitude, and train on/off time (40 Hz, 5–8 mA, 2 s on and 3 s off) increased gastric volume at a pulse width of 2 ms (168.8±65.1 ml vs. 97.9±27.6 ml, $p=0.018$) and 4 ms (193.1±102.2 ml vs. 85.0±36.6 ml, $p=0.032$) in comparison with the corresponding baseline recording. However, GES

showed no effects on gastric volume with a pulse width of 0.21 ms (p=0.77), 0.45 ms (p=0.46), or 1 ms (p=0.85) (Fig. 2).

Effects of Pulse Frequency GES with fixed parameters of 2 ms, 5–8 mA, 2 s on, and 3 s off significantly increased gastric volume at 40 Hz (204.3±101.5 ml vs. 94.5±31.2 ml at baseline, p=0.042) but not at 10 Hz (p=0.78) or 20 Hz (p=0.11) (Fig. 2).

Effects of Pulse Amplitude GES (with fixed parameters of 2 ms, 40 Hz, 2 s on, and 3 s off) increased gastric volume at pulse amplitude of 5 mA (139.6±62.3 ml vs. 82.3±24.8 ml, p=0.02) and 6 mA (193.1±102.2 ml vs. 85.0±36.6 ml, p=0.042) in comparison with the baseline but not at 3 mA (0.86) or 4 mA (p=0.46) (Fig. 2).

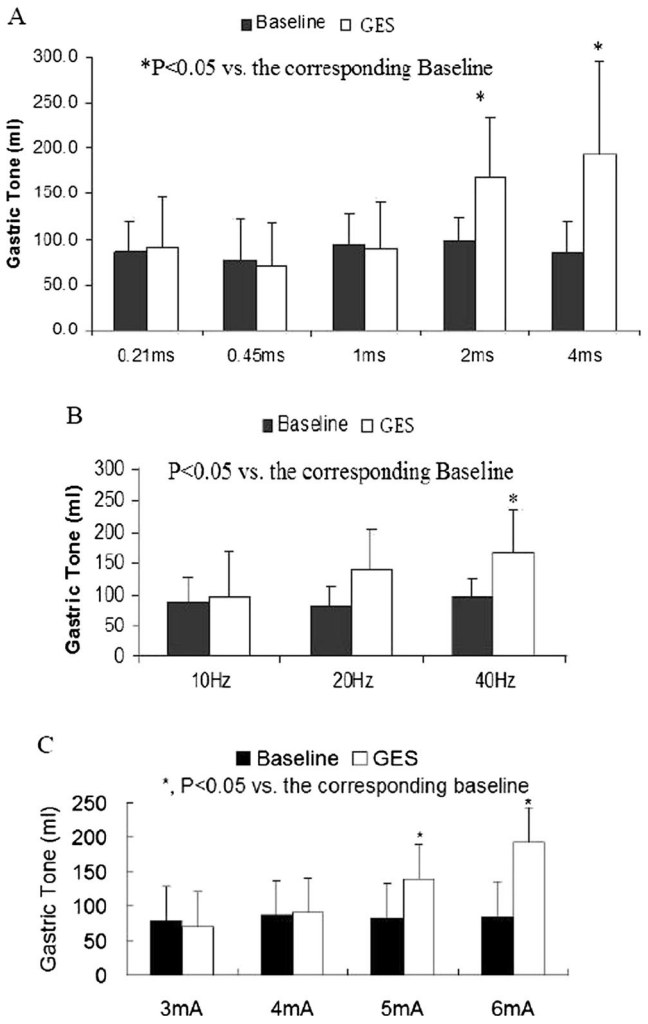

Fig. 2 Effects of GES with various parameters on gastric tone. **a** Pulse widths (0.21, 0.45, 1, 2, and 4 ms). GES with a frequency of 40 Hz, amplitude of 5–8 mA, and a cycle on-time of 2 s and off-time of 3 s was fixed. **b** Frequencies (10, 20, and 40 Hz). GES with pulse width of 2 ms, an amplitude of 5–8 mA, and a cycle on-time of 2 s and off-time of 3 s was fixed. **c** Pulse amplitudes (3, 4, 5, and 6 mA). GES with pulse width of 2 ms, a frequency of 40 Hz, and a cycle on-time of 2 s and off-time of 3 s was fixed

Optimized GES Parameters Based on the above tests, the following set of parameters was considered as most suitable for inhibiting gastric tone (reflected as increased gastric volume): 40 Hz, 2 ms, 2 s on, 3 s off, and 5–8 mA (the exact amplitude might be adjusted individually).

Optimization of GES Locations Based on Gastric Tone

Lesser Curvature, Greater Curvature, and Middle of Body GES with the above optimized parameters delivered at both the lesser and the greater curvatures but at the middle body inhibited gastric tone and antral contractions. A significant increase in gastric volume was observed with GES via the lesser curvature (250.3±35.2 ml vs. 87.4±27.3 ml, p<0.01) and the greater curvature (234.7±77.6 ml vs. 79.4±38.4 ml, p<0.05), but not via the middle gastric body (p=0.46) (Fig. 3). Similarly, inhibition of antral contractions was noted with GES via the lesser curvature (5.8±0.4 vs. 9.2±0.7 motility index (AUC), p<0.01) and the greater curvature (electrodes #11–14) (4.7±0.7 vs. 8.2±0.4 motility index (AUC), p<0.05), but not via the gastric body (8.0±0.6 vs. 8.3±0.5 motility index (AUC), p=0.46) (Fig. 3). GES via the lesser and greater curvatures increased gastric volume by 186.0 and 1 95.6 %, respectively, and reduce antral contractions by 36.9 or 42.6 %, respectively. Although a larger inhibitory effect tendency via lesser curvature was observed, no difference was noted in the inhibitory effect of GES on gastric tone or antral contractions between the lesser curvature and the greater curvature. These data were average values from GES via different pairs of electrodes (electrodes #1–#10 for less curvature, electrodes #11–#14 for greater curvature, and electrodes #15–#20 for gastric body; see Fig. 1).

Distal vs. Proximal GES delivered at the distal stomach was more potent in inhibiting gastric tone and antral contractions than GES via the proximal stomach. A significant increase in gastric volume was observed with GES at the distal stomach (264.6±124.2 ml vs. 88.4±38.3 ml, p<0.05) and the proximal stomach (192.7±122.0 ml vs. 71.6±30.9 ml, p<0.05) (Fig. 3). Similarly, inhibition of antral contractions was noted with GES via both the distal (4.4±0.6 vs. 8.8±0.5 motility index (AUC), p<0.01) and the proximal stomachs (6.4±0.7 vs. 8.8±0.9 motility index (AUC), p<0.05) (Fig. 3). However, the effects were more potent with GES at the distal stomach than at the proximal stomach: GES-induced gastric volume change: 175.8±105.9 ml at distal vs. 121.1±109.5 ml at proximal, p<0.05 and GES-induced motility index reduction: 4.4±0.6 at distal vs. 2.5±0.7 proximal, p<0.05 (Fig. 3),

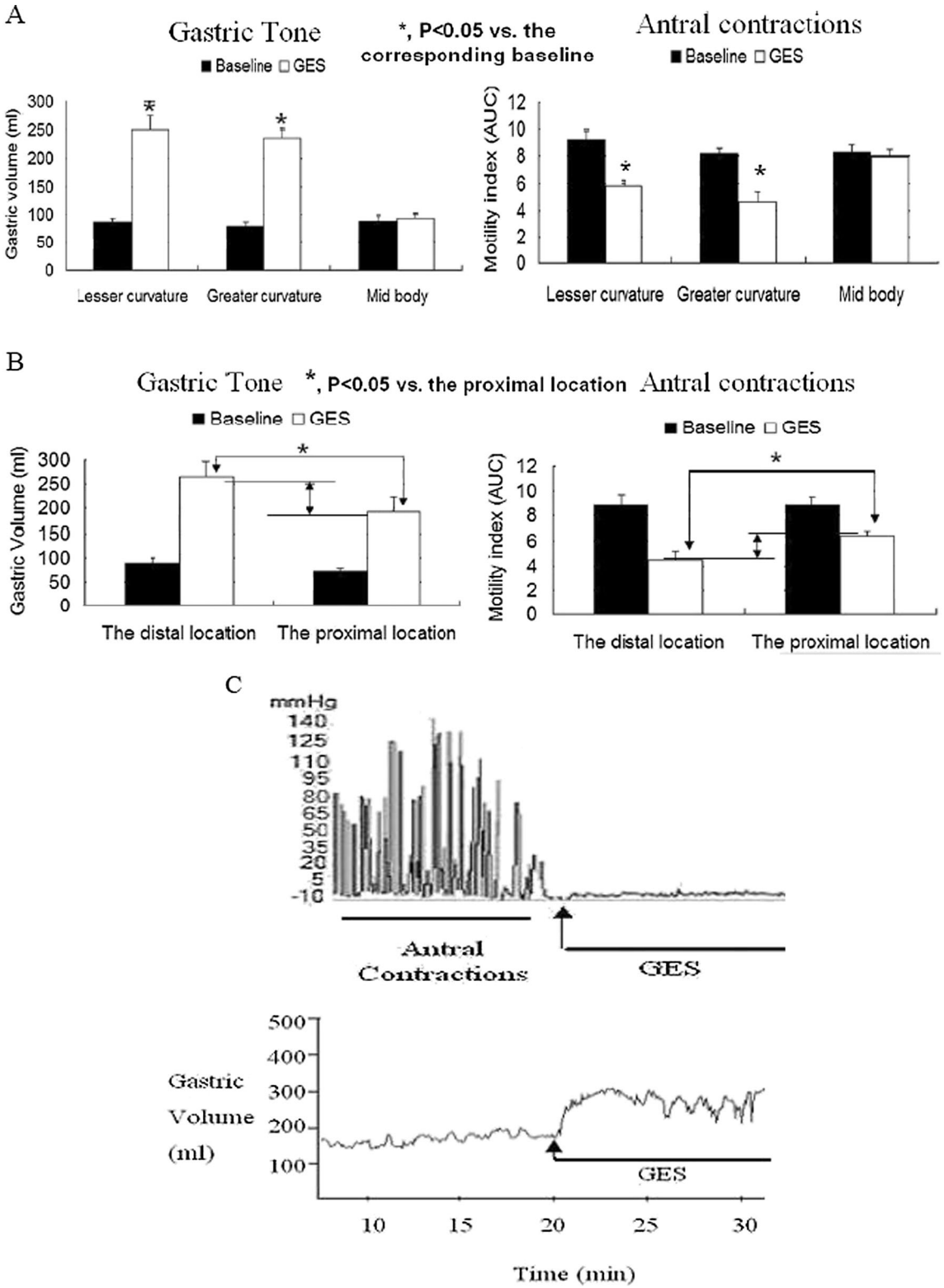

Fig. 3 Effects of GES with different locations on gastric motility. **a** Effects of GES at greater curvature, lesser curvature, and mid body on gastric tone and antral contractions. GES was fixed at a frequency of 40 Hz, pulse width of 2 ms, amplitude of 6–8 mA, and cycle on-time of 2 s and off-time of 3 s. **b** Effects of GES at the distal location and the proximal location on gastric tone and antral contractions. GES was fixed at a frequency of 40 Hz, pulse width of 2 ms, amplitude of 6–8 mA, and cycle on-time of 2 s and off-time of 3 s. **c** Tracings of antral contractions and gastric tone at the baseline and with GES

Reproducibility of Inhibitory Effects of GES on Gastric Motility

The inhibitory effects of GES on gastric tone and antral contractions were reproducible within a period of 2 months. No significant difference was noted in the effects of GES on gastric tone or antral contractions among three time points (weeks 2, 6, and 10 after the surgical procedure) of the study ($p>0.05$) (Fig. 4): the gastric volume and the antral motility index remained unchanged from week 2 to week 10 with or without GES.

Effect of GES on Gastric Slow Waves

GES with optimized parameters (40 Hz, 2 ms, 2 s on, and 3 s off) and location (distal lesser curvature) was able to interrupt slow waves: the percentage of normal 4–6 cpm slow waves in the antrum was reduced from 91.3±6.2 % at baseline to 47.8± 10.8 % during GES ($p<0.05$) (Fig. 5). Figure 5 represents typical tracings of regular gastric slow waves at baseline and irregular slow waves during GES.

Effects of GES on Food Intake

GES with optimized parameters (40 Hz, 2 ms, 2 s on, and 3 s off) and location (distal lesser curvature) decreased daily food intake from 471.5±138.5 g/day (average value over 1 week) with sham-GES to 377.7±139.4 g/day with GES ($p=0.0055$), a decrease of about 20 % in daily food intake (Fig. 6).

Discussion

In this study, we found that (1) GES only with a pulse width of ≥2 ms was able to inhibit gastric tone, contractions, and slow waves. In addition, the inhibitory effect of GES was more potent when the stimulation was applied along the lesser or greater curvatures than via the middle body and more potent via the distal stomach than via the proximal stomach; (2) the inhibitory effects of GES on gastric motility were reproducible within a tested window of 10 weeks. (3) GES with parameters inhibitory to gastric motility delivered at the distal lesser curvature resulted in a 20 % reduction in food intake.

Although GES has been under intensive investigation for its role in treating obesity [2–5], the implantable devices used in previous clinical studies were adopted from cardiac or nerve stimulation, not specifically developed for GES. Specifically, the commercial stimulators developed for cardiac or nerve stimulation is only capable of generating pulses with the maximum width of <1 ms. For cardiac or nerve stimulation, this pulse width is sufficient because the time constant or the response time of cardiac muscles or nerve is short and there is no need to use longer or wider pulses. For GES, however, the use of an implantable device incapable of generating pulses with a width of >1 ms is problematic because the stomach is composed of smooth muscle cells that have a large time constant [22]. Accordingly, GES with short pulses may not be potent enough to activate smooth muscles and alter their functions.

A review of available clinical findings in patients with obesity and mechanistic studies in animals indeed suggests an inconsistent effect on gastric functions with the clinically tested method of GES with pulse width of <1 ms. Some studies reported that GES with pulse width of <1 ms showed an effect on gastric functions [23, 24], but other studies did not see such an effect [10, 25]. The systematic experiment performed in the current study clearly demonstrated that gastric motility was inhibited only when the pulse width was equal to or wider than 2 ms.

It is known that GES with very long pulses (a pulse width in the order of a few hundred milliseconds, about 1000 times of that used in nerve stimulation) has been reported to be able to pace or entrain the gastric slow wave [26, 27]; however, GES with pulses shorter than 1 ms has never been reported to be able to alter gastric slow waves [28]. Mechanically, GES with very long pulses has been reported to inhibit gastric tone or induce gastric distention [29, 30]. Antral contractions were substantially or even completely abolished with long-pulse GES delivered at a frequency of seven pulses per minute in dogs [21], and retrograde gastric contractions could be induced by reverse pacing [31]; However, the inhibitory effect

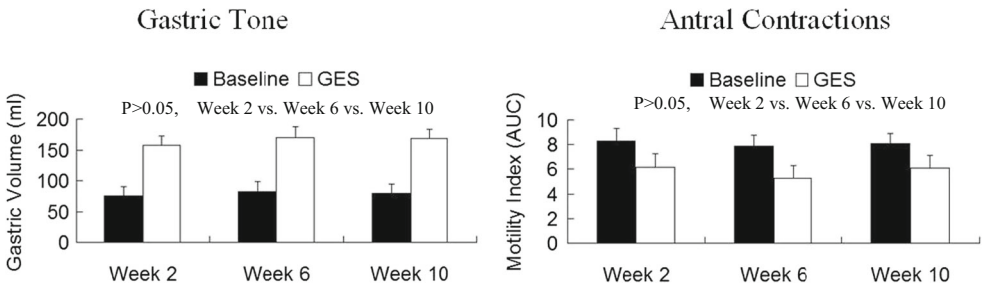

Fig. 4 The inhibitory effects of GES on gastric tone and antral contractions were reproducible within a period of 2 months. No significant difference was noted in the effect of GES on gastric tone or antral contractions among three time points of the study ($p>0.05$). It was also found that the baseline measurements did not change from week 2 to week 10 ($p>0.05$)

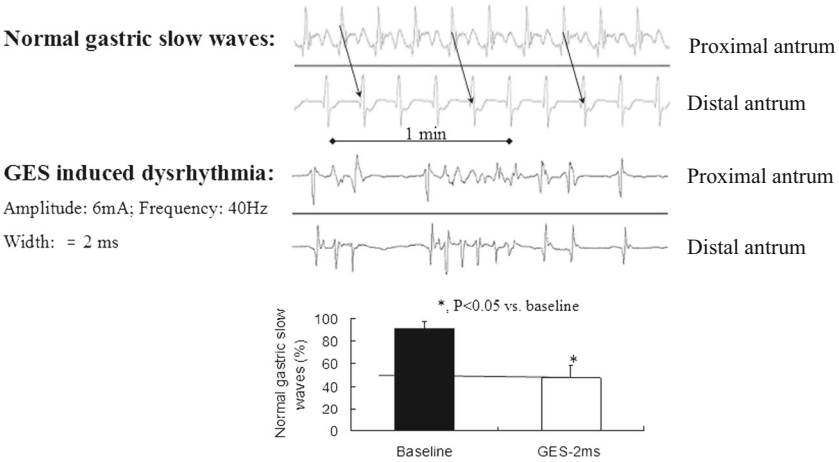

Fig. 5 GES with appropriate parameters impaired gastric slow waves

of GES with a pulse width of 0.3 ms on antral motility was reported to be marginal [20]. Although GES of 0.3 ms has been reported to alter central neuronal and humoral activities (activation of neurons in the satiety center of the brain), these central effects were found to be more potent with GES of wider pulses, such as 3 ms [10]. Clinically, in a few uncontrolled studies, GES of 0.3 ms was reported to induce weight loss in a subgroup of patients, whereas a fair number of patients did not lose weight [7, 32, 33].

More potent gastric motility effects were noted in this study with GES of wider pulses at a frequency of 40 Hz. In dogs, GES of wider pulses (≥2 ms) was able to induce gastric distention (or inhibition of gastric tone) and inhibit antral contractions, while GES of short pulses (~0.3 ms) did not have these effects. In a previous study, electrical stimulation-induced gastric distention was found to be inversely correlated to the amount of food intake, that is, more distention, less food intake [34]. Intragastric balloon was reported to be effective in reducing food intake and leading to a short-term weight loss of up to 6 months [35, 36]. Distention of the stomach may also activate stretch receptors, sending a satiety signal to the brain. The inhibitory effect of GES on gastric tone was previously reported to be mediated via the vagal and nitrergic mechanisms, whereas the GES-induced inhibition on antral contractions was attributed to the induction of tachygastria mediated via the α- and β-adrenergic pathways [21].

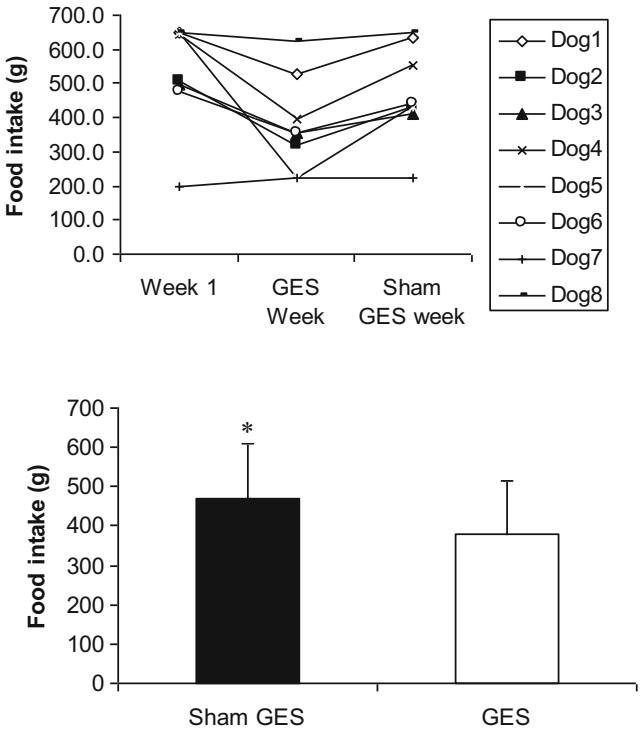

Fig. 6 GES decreased food intake ($p<0.01$)

In addition to the systematic parameter optimization, the major contribution of the present study is the approval of the hypothesis that a GES method inhibitory to gastric motility reduces food intake. As expected, GES with parameters and location optimized to inhibit gastric motility resulted in a substantial and significant reduction in food intake, suggesting a therapeutic potential of appropriate GES for obesity. As stated earlier, similar findings were available in the literature: GES with very long pulses (a few hundred millisecond pulse width) and very low stimulation frequency (a few cycles/min, such as 7–9 cycles/min) also inhibited gastric motility and reduced food intake and body weight in dogs [16]. However, technically, it is almost impossible to develop an implantable pulse generator that meets the requirements of very long pulses and very low frequency due to issue of charge balance. The GES method derived from the present study is however technically feasible. It is similar to existing implantable pulse generators except an increase in pulse width to 2 ms or higher. The issue of electronic charge balance is achievable. The only remaining challenge is the high consumption of battery power. However, technologies are readily available to remotely charge the battery of an implanted pulse generator. In addition, GES could be performed on-demand, such as turned on only during and after meals or turned off at night.

Indeed, individual dogs responded to GES differently. In a previous temporary GES study using intraluminal electrodes

in healthy volunteers, we reported a large variation in response to GES among different subjects [37]. It was found that the gastric responses (such as food intake and gastric emptying) to GES are correlated with visceral sensation to GES; a higher response was noted in subjects who were more sensible to GES. The response of the animals to GES in food intake in this study was similar to the previous findings in humans. These data suggest that future GES therapy may have to be individually optimized. The simplest method would be to set the stimulation strength according to the tolerance of the subject to GES. Technically, this is feasible.

The rationale for the number of dogs used in different settings of electrode placements were as follows: (1) The first eight dogs were used to identify effective locations such as great and lesser curvatures of the stomach; (2) addition of another six dogs gave us more detailed data regarding locations, e.g., lesser vs. greater curvatures and proximal vs. distal. (3) A question raised at that time was whether the location of mid stomach could be a good option as well. Therefore, we included two additional dogs and performed a pilot study and found minimal effects with stimulation via the mid stomach. As we already had found good locations for stimulation with remarkable and sufficient data, we did not include any more dogs regarding the location of the mid stomach. Although it might not sound reasonable scientifically or statistically, it was practicable and cost-effective at that time. In brief, we agree that the additional two dogs for testing the mid stomach location was not statistically sound and more dogs should have been included.

The major limitation of the present study was the lack of weight loss data with the proposed method of GES. It was attributed to (1) the nature of animals used in the study: the healthy and lean dogs are not a good model to study the effect of GES on weight loss and (2) the unavailability of an implantable pulse generator. Obese animal models are needed to investigate the role of GES inhibitory to gastric motility for treating obesity. In diet-induced obese rats, we demonstrated the chronic inhibitory effect of GES with pulse width of 2 ms or higher using external stimulator. Once a new generation of implantable pulse generator capable of delivering pulses with width of 2 ms or higher is made, a chronic study will have to be performed in an obese model of large animals.

A new generation of device that is able to alter gastric motility may also be to treat gastric motility disorders by adequately changing the stimulation location (more proximal) and stimulation frequency to enhance gastric motility. The current device (Enterra; Medtronic, MN) used in clinical applications in patients with gastroparesis is capable of treating nausea and vomiting but has little effect on gastric motility, owing to the narrowness of its pulse width [28, 38–40]. On the other hand, GES with very long pulses and very low frequency has been shown to be able to normalize gastric dysrhythmia [41] and improve gastric emptying in patients with gastroparesis [42]. GES can also result in a significant acceleration of gastric emptying of solids in obese subjects [43]. By appropriately changing other parameters and stimulation locations, GES with 2 ms or higher is also expected to enhance gastric motility.

In summary, GES using pulse trains with wider pulses produces reproducible, substantial, and consistent inhibitory effects on gastric tone and slow waves and antral contractions. GES with parameters inhibitory to gastric motility reduces food intake. These findings suggest that the methodology of GES needs to be revisited and the method of GES inhibitory to gastric motility may have a therapeutic potential for obesity.

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Conflict of Interest None of the authors (Geng-Qing Song, Hongbing Zhu, Yong Lei, Charlene Yuan, Warren Starkebaum, Jieyun Yin, or Jiande DZ Chen) had conflicts of interest.

Informed Consent Statement Informed consent was obtained from all individual participants included in the study.

Statement of Human and Animal Rights All applicable institutional and/or national guidelines for the care and use of animals were followed.

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