

Systematic review: applications and future of gastric electrical stimulation

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SUMMARY

Background

Over the past 20 years, gastric electrical stimulation has received increasing attention among researchers and clinicians.

Aim

To give a systematic review on the effects, mechanisms and applications of gastric electrical stimulation.

Methods

Medline was used to identify the articles to be included in this review. Key words used for the search included gastric electrical stimulation, gastric pacing, electrical stimulation, stomach, gastrointestinal motility, central nervous system, gastroparesis, nausea and vomiting; obesity and weight loss. Combinational uses of these keywords were made to identify relevant articles. Most of the articles included in this review ranged from 1985 to 2006.

Results

Based on the general search, the review was structured as follows: (i) peripheral and central effects and mechanisms of gastric electrical stimulation; (ii) clinical applications of gastric electrical stimulation for gastroparesis and obesity and (iii) future development of gastric electrical stimulation.

Conclusions

Great progress has been made during the past decades. Gastric electrical stimulation has been shown to be effective in normalizing gastric dysrhythmia, accelerating gastric emptying and improving nausea and vomiting. Implantable device has been made available for treating gastroparesis as well as obesity. However, development of a new device and controlled clinical studies are required to further prove clinical efficacy of gastric electrical stimulation.

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INTRODUCTION

Gastrointestinal (GI) electrical stimulation or pacing was advocated as a possible treatment for gastric motor dysfunction as early as in 1963. Bilgutay *et al.* reported the use of intraluminal electrical stimulation via the tip of a nasogastric tube to induce peristalsis and shorten the recovery period from ileus after laparotomy.¹ They stimulated the stomachs of both dogs and humans using electrical stimuli consisting of pulse bursts and observed augmented gastric contractions fluoroscopically and increased gastric emptying but did not record either electrical or mechanical activity. Subsequent randomized-controlled studies, however, failed to confirm any significant effect of this type of GI stimulation on the duration of post-operative ileus.²⁻⁴ In the late 1960s and early 1970s, experiments, primarily in the canine model, began to elucidate the nature of GI myoelectrical activity and its relation to contractile activity.⁵⁻⁹ These results and the development of techniques of myoelectrical recording were critical to further research in GI pacing. Since that time and before 1990s, there have been more reports on the applications of electrical stimulation to affect GI motility both acutely and chronically.¹⁰⁻¹³

During the past decade, a great progress has been made on the effects, mechanisms and clinical applications of gastric electrical stimulation (GES). Numerous reports are available in the literature on electrical stimulation of various organs of the GI tract, such as stomach, small intestine, colon and rectum for the treatment or therapeutic potentials of various conditions, such as gastroparesis, short bowel syndrome, intestinal pseudo-obstruction and faecal incontinence. This study is focused on GES, its peripheral and central effects, mechanisms and clinical applications in gastroparesis as well as obesity; topics on electrical stimulation of other GI organs can be found in previous reviews.¹⁴⁻²⁰

GASTRIC ELECTRICAL STIMULATION: EFFECTS AND MECHANISMS

Methods of gastric electrical stimulation

Gastric electrical stimulation consists of a series of pulses, usually in a rectangular shape with a constant current or a constant voltage. Several stimulation parameters are involved in electrical stimulation, including frequency, pulse width and amplitude (usu-

ally in the order of a few mA without much variation). Various methods of electrical stimulation are derived from the variations of electrical stimuli. These include long-pulse stimulation, short-pulse stimulation and stimulation with trains of pulses instead of repetitive single pulses. Based on the number of stimulation electrodes, GES can be classified into single-channel GES and multi-channel GES.

Long-pulse stimulation

This method is most frequently reported in the literature because it is able to 'pace' or entrain natural slow waves. It is also called electrical pacing or gastric pacing. In this method, the electrical stimulus is composed of repetitive single pulses with a pulse width in the order of milliseconds (10–600 ms), and a stimulation frequency in the vicinity of the physiological frequency of the gastric slow wave (see Figure 1a). However, it should be noted that currently there are

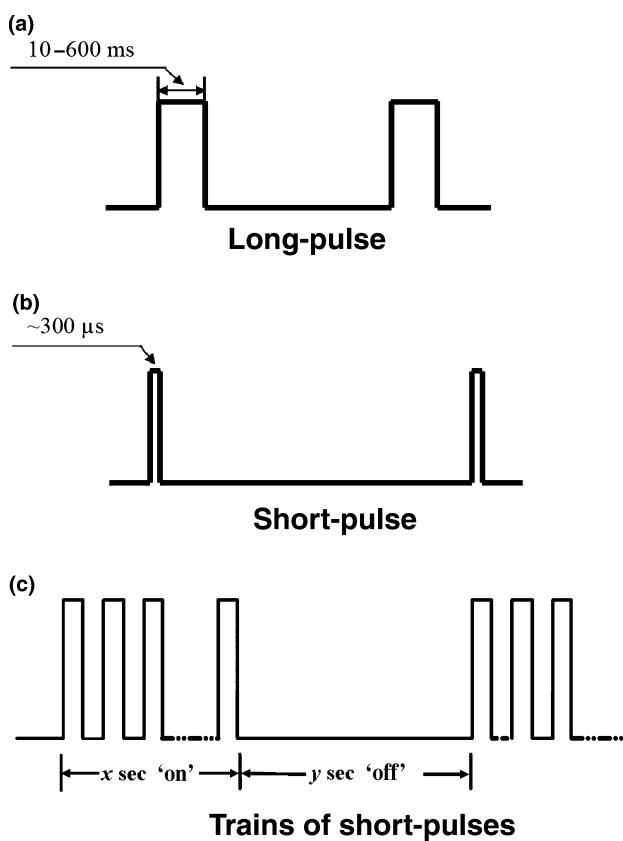


Figure 1. Electrical stimuli used in three different methods of gastric electrical stimulation.

no implantable devices available in the market capable of generating pulses with a width longer than 2 ms.

Short-pulse stimulation

In contrast to long-pulse stimulation, the pulse width in this method is substantially shorter and is in the order of a few hundred microseconds (μ s). The stimulation frequency is usually a few times higher than the physiological frequency of the gastric slow wave (see Figure 1b). Most of the commercially available cardiac pacemakers or nerve stimulators are capable of generating short pulses.

Trains of short-pulses

In this method, the stimulus is composed of repetitive trains of short pulses and is derived from the combination of two signals: (i) continuous short pulses with a high frequency (in the order of 5–100 Hz) and (ii) a control signal to turn the pulses on and off, such as x seconds 'on' and y seconds 'off'. The addition of x and y then determines the frequency of the pulse train (Figure 1c). This kind of stimulation has been frequently used in nerve stimulation. Commercially available stimulators are capable of generating trains of pulses with a pulse width of below 2 ms.

Multi-channel GES

With single-channel GES, the stimuli are applied to the proximal stomach only. In a normally functioning stomach the gastric slow wave originates in the proximal stomach, and propagates circumferentially and distally towards the pylorus, with increasing velocity and propagation direction of gastric contractions. It is the distal stomach that plays a crucial role in the emptying of solids. Therefore, stimulation in the distal stomach is most important for emptying of the stomach. However, single-channel GES cannot be applied to the distal stomach as the food would get pushed towards the proximal stomach (retrograde pacing) and not towards the gut. This would result in a delay of emptying rather than in the intended acceleration. Multi-channel GES delivers electrical pulses to multiple locations along the greater curvature of the stomach (the electrical stimuli at each point can be individually customized) through electrodes in the seromuscular layer. It can be used to mimic the natural propagation and characteristics of the slow wave.

Two- to four-channel GES has been proposed in a number of studies.^{21–24}

Peripheral effects of GES

A number of studies have been performed to investigate the effect of GES on the normalization of gastric myoelectrical dysrhythmias or entrainment of gastric slow waves, fundic/antral tone, antral contractions and gastric emptying. The majority of these studies seems to indicate that GES, depending on the parameters employed and stimulation sites, is able to alter gastric functions.

Alterations of gastric slow waves

Only GES with long pulses is capable of altering gastric slow waves. This is due to the fact that the smooth muscle has a long time constant of about 100–300 ms.^{25, 26} In general, GES with short pulses or trains of short pulses has no effects on gastric slow waves.²⁷ In some circumstances, GES with short pulses or trains of short pulses may also be able to alter gastric slow waves if the stimulation frequency is sufficiently high. This is because at the end of each pulse, there is a slow decay in voltage; if the subsequent pulse is sufficiently close to the preceding pulse, the two short pulses may be effectively considered as one pulse and a train of short pulses may be effectively considered as a long pulse.

Entrainment of gastric slow waves or pacing has been reported in a number of studies with GES of long pulses with a pulse width in the order of a few hundred milliseconds.^{26, 28–32} Typically, GES was performed at a frequency slightly higher than the measured intrinsic frequency of gastric slow waves. When entrainment or pacing occurs, the natural slow waves are phase-locked with stimuli. However, it has been reported that the highest frequency that the gastric slow wave can be driven is about 50% higher than its normal frequency.³³

Normalization of gastric dysrhythmia has been reported in both humans and dogs. GES with long pulse/low frequency was reported to normalize vasopressin- or glucagon-induced gastric dysrhythmia and slow wave uncoupling in dogs and dysrhythmia in a rodent model of diabetes.^{33–36} Normalization of dysrhythmia was also reported in patients with gastroparesis and postsurgical patients using the same method of GES.^{37, 38} While the exact mechanisms involved in

the normalization of gastric dysrhythmia with long pulse/low frequency GES are unclear, it is known that it does not involve the vagal or cholinergic pathway.^{32, 36} A recent study reported the entrainment of slow waves in the absence of interstitial cells of Cajal (ICC) in mice, suggesting that pacing can be achieved without ICC.³⁹ Similar findings were also reported in *in vitro* studies in ICC knocked out mice.^{40, 41}

Because of its pacing capability, GES with long pulses is also able to induce tachygastria when delivered at a tachygastral frequency (a frequency higher than the physiological frequency).^{42, 43} GES-induced tachygastria was reported to be associated with antral hypomotility, mediated via the adrenergic pathway.⁴³

Antral contractions

One early canine study showed an increase in gastric motility index with GES of short pulses.⁴⁴ However, this has not been substantiated in any follow-up studies. On the contrary, GES with long pulses delivered at a tachygastria frequency was reported to inhibit antral contractions.⁴³ Accordingly, GES at the tachygastral frequency may be able to delay gastric emptying and may have a therapeutic potential for obesity.

Gastric tone and gastric accommodation

Gastric (both fundic and antral) tone and gastric accommodation have been reported to be altered with various methods of GES. It seems that GES with short pulses may enhance the relaxation of the stomach and thus improve gastric accommodation although the results have not been consistent. Whereas, GES with long pulses reduces gastric tone substantially and consistently and may lead to symptoms of early satiety.

A recent canine study using GES of short pulses or the so-called Enterra Therapy (Medtronic, Minneapolis, MN, USA) (repetitive trains of two short pulses with a pulse frequency of 14 Hz and width of about 300 μ s, it could be considered as trains of short pulses) showed a slight but significant reduction of fundic tone and enhancement of postprandial fundic relaxation accompanied by an improvement in gastric distention-induced symptoms in dogs.⁴⁵ However, more studies are needed to confirm these findings.

Gastric electrical stimulation with long pulses is capable of altering gastric (both fundic and antral) tone substantially in dogs.⁴⁶⁻⁴⁸ With low stimulation energy, GES with long pulses may change the gastric

tone slightly, which may be beneficial to patients with an impaired gastric relaxation. With high stimulation energy, GES could substantially inhibit the gastric tone and result in a substantial distention of the stomach, which may actually lead to an early satiety and be applied for treating obesity rather than gastroparesis. Canine studies have shown that this inhibitory effect of GES on gastric tone is mediated via the nitrergic pathway.^{48, 49}

Gastric emptying

Alteration of gastric emptying with GES of long pulses has been reported in a number of canine as well as clinical studies. It seems that a single channel GES with long pulses has no effects on gastric emptying in healthy dogs but is capable of improving gastric emptying in a canine model of gastroparesis and a rodent model of diabetes.^{29, 34, 50} Whereas, two- or four-channel GES with long pulses is able to improve gastric emptying in both healthy and diseased model of canines,^{21, 22} similar results (improvement in liquid and solid gastric emptying) were also observed with a multi-channel sequential GES of trains of pulses with a pulse width in the order of a few milliseconds.^{23, 24} GES with long pulses showed similar improvement in gastric emptying in patients with gastroparesis.³⁷ The findings on the effects of GES with trains of short pulses or Enterra Therapy on gastric emptying have been controversial.

On the other hand, retrograde GES with long pulses delivered via electrodes placed at the distal antrum was reported to delay gastric emptying in both dogs and humans.⁵¹⁻⁵³ It was further reported that the inhibitory effects of retrograde GES on gastric emptying in healthy volunteers was associated with reduced food intake and reduced gastric accommodation.^{53, 54}

Effects of GES on gastrointestinal organs other than the stomach

In addition to its effects on gastric functions, GES was found to affect other organs along the GI tract. GES with long pulses was reported to increase the pressure of the lower oesophageal sphincter in anaesthetized dogs.⁵⁵ In conscious dogs, this excitatory effect on the lower oesophageal sphincter was noted with GES of long pulses as well as GES with trains of short pulses.⁵⁶ These findings suggest a therapeutic potential of GES for the treatment of gastro-oesophageal reflux

disease. However, further studies are necessary to prove this potential.

Gastric electrical stimulation was reported to have no effects on small intestinal slow wave.³³ However, it is unknown whether GES may exert any effects on small intestinal motility. While none of previous studies has investigated the effect of GES on the colon, effects of GES on the rectum have recently been reported. Rectal tone was reduced with GES of long pulses and the inhibitory effect was found to be mediated via the sympathetic pathway.⁵⁷

Central effects of GES

Most of the previous studies were focused on the peripheral effects of GES; little is known on the central mechanisms of GES. Recently, there have been a few studies investigating the central effects of GES described as follows.

Involvement of vagal afferent pathway

Involvement of the vagal afferent pathway was noted in a recent rodent study by using various methods of GES. GES was found to activate neurones responsive to gastric distention in the nucleus tractus solitarius, suggesting the involvement of the vagal afferent pathway. About 40% of neurones responsive to gastric distention were activated with GES of long pulses or GES with trains of short pulses.⁵⁸ With GES of trains of short pulses, it was further noted that an increase in pulse width or amplitude resulted in activation of more neurones. In another rodent study, vagal afferent fibres were activated when antral contractions were induced with GES.⁵⁹

Central neuronal effects

Using the extracellular recording in the anaesthetized rats, a recent study reported the activation of gastric distention-responsive neurones in the paraventricular nucleus with various methods of GES.⁶⁰ All three methods of GES (short pulse, long pulse and trains of short pulses) were able to activate these neurones. However, in one specific type of neurones (gastric distention-inhibitory neurones), opposite effects were noted between GES with trains of short pulses (with parameters used for treating obesity) and GES of short pulses (with parameters used for treating nausea and vomiting in patients with gastroparesis). These data

suggest possible different central mechanisms with different methods of GES.

Similar central neuronal effects with GES were also noted in the other areas of the brain, such as the hippocampus⁶¹ and ventromedial nucleus of the hypothalamus.⁶²

Central humoral effects

A few recent studies have investigated the possible central humoral mechanisms of GES of trains of short pulses with parameters used for treating obesity and reported a decrease in certain orexigenic peptides and an increase in anorexigenic peptides. After 2 h GES with trains of short pulses, neurones expressing orexin were significantly decreased in the lateral hypothalamic area, whereas neurones expressing oxytocin and cholecystokinin were increased in the paraventricular nucleus and hippocampus, respectively.^{61, 63}

GASTRIC ELECTRICAL STIMULATION: CLINICAL APPLICATIONS

Clinical studies on GES have been limited because of the following reasons: (i) no implantable pulse generators have been designed or developed for GES and (ii) with the current methodologies of GES, an abdominal surgery is required for performing GES.

GES for treatment of gastroparesis

Gastroparesis is one of major GI motility diseases. It is a chronic disorder of diabetic (both type 1 and type 2 diabetes) or idiopathic aetiology (approximately 25–30% of cases are idiopathic). Symptoms of gastroparesis range from early satiety, fullness, bloating, mild nausea and vomiting, to dehydration and nutritional deficiency and poor glycaemic control (in diabetics) in severe cases. While most commonly associated with diabetes, gastroparesis is also found in chronic pseudo-obstruction, connective tissue disorders, Parkinson's disease and psychological pathology. Abnormalities in gastroparesis may include impaired gastric accommodation, visceral hypersensitivity, gastric dysrhythmia, antral hypomotility and delayed gastric emptying.⁶⁴ Currently, medical management for gastroparesis includes hydration, dietary manipulation, nutritional supplementation and pharmacological therapy: prokinetic agents, such as domperidone and metoclopramide; antiemetic agents, such as

granisetron, or ondansetron.⁶⁵⁻⁷⁰ Severe cases may require enteral tube feedings (jejunostomy tube) or total parenteral nutrition (nutrition is fed into the blood stream) to sustain nutritional support.

Two methods of GES have been applied for their therapeutic potentials in gastroparesis: GES with short pulses (or called high frequency/low energy) and GES with long pulses (or called low frequency/high energy). In both these methods, cardiac pacing electrodes are used and implanted laparoscopically or laparotomically on the serosa of the proximal stomach along the greater curvature.

GES with short pulses

This method is also called Enterra Therapy. The stimulus in this method is composed of two short pulses with an interval of 72 ms, width of about 0.3 ms and amplitude of about 5 mA. These two pulses are repeated every 5 s. This GES therapy has received approval from the U.S. Food and Drug Administration (FDA). The FDA approval was given through a 'humanitarian device exemption'. This regulatory category was established in 1996 and only applies to devices intended to benefit <4000 patients.

Clinical studies have shown that the Enterra Therapy decreases upper GI symptoms, reduces hospitalizations, the use of prokinetic agents and medical costs, and improves nutritional status and quality of life in patients with drug-refractory diabetic, idiopathic or postsurgical gastroparesis.⁷¹⁻⁸¹ The most interesting finding in these studies was the dramatic improvement in nausea and vomiting. Depending on study centres, this improvement was noted in 60-75% of patients. In a multicentre study with a controlled phase (1 month) followed with an open-label phase (12 months), a 50% reduction in nausea and vomiting was noted but the reduction in the total symptom score was not significant during the controlled period, whereas a substantial reduction in nausea and vomiting and a significant improvement in overall dyspeptic symptoms were observed in the open-label follow-up period,⁷¹ suggesting a possible placebo effect with GES in patients with gastroparesis. However, similar improvement in dyspeptic signs, especially vomiting, was also reported in controlled canine studies.³⁶

Possible mechanisms involved in the improvement of nausea and vomiting in patients with gastroparesis are not completely understood. The Enterra Therapy does not alter gastric slow waves^{27, 36} but may reduce

gastric tone and thus improve gastric accommodation as reported in a canine study.⁴⁵ Not much information is available regarding the effect of the Enterra Therapy on visceral hypersensitivity. However, two recent preliminary studies in humans seem to suggest a potential role of the therapy in altering visceral hypersensitivity. In patients with gastroparesis, GES with Enterra parameters was found to increase the perception threshold of the patients to gastric distention.^{82, 83} The findings on the effect of the Enterra Therapy on gastric emptying are conflicting. Some studies reported an improvement in gastric emptying with chronic GES, whereas, others indicated no such improvement.^{71, 72, 74} In our opinion, GES with short pulses does not seem to be able to alter or improve gastric emptying in patients with gastroparesis. The improvement in gastric emptying observed in a previous multicentre study might be attributed to the improvement in nausea and vomiting as well as overall clinical profile instead of the direct causative effect of GES.⁷¹

Central mechanisms, although not well understood, are definitely involved with GES of short pulses or the Enterra Therapy. The parameters used in the therapy are similar to those used in nerve stimulation. As mentioned in the previous section, both canine studies and rodent studies have indicated the involvement of the vagal afferent pathway and the central hypothalamic effects. In a recent preliminary study in seven patients with GES of Enterra Therapy the scan of Fluoro-Deoxy Glucose (fdg) positron emission tomography (PET) revealed at least one-step increase in the colour scale (10%) in bilateral thalamic activity reflecting a substantial upregulation of metabolic activity.⁸³ Future brain imaging studies may elucidate the central mechanisms involved with the Enterra Therapy.

GES with long pulses

Due to unavailability of implantable pulse generators capable of generating long pulses, there has been only one single-centre study applying GES with long pulses to patients with gastroparesis.³⁷ Using a portable stimulator, acute and short-term (1 month) effects of GES with long pulses on gastroparesis were investigated in an open-label single-centre study. It was found that GES with long pulses was capable of normalizing gastric dysrhythmia, improving gastric emptying and reducing gastroparetic symptoms.³⁷ The improvement in gastric slow waves and gastric emptying was supported by the controlled animal

studies,^{29, 33–36} whereas, the improvement in symptoms was not demonstrated in the canine studies.³⁶ It was therefore, unclear whether the improvement in gastroparetic symptoms was attributable to the direct effects of GES or to the overall improvement in clinical profile of the patients.

In summary, GES with short pulses improves the symptoms of nausea and vomiting but may have little effects on gastric motility, whereas GES with long pulses is capable of improving or altering gastric motility but may be less effective in treating the symptoms of nausea and vomiting. Accordingly, the selection of the therapies should be based on the pathogenesis of gastroparesis.

GES for treatment of obesity

Obesity is a growing worldwide epidemic. In the United States, nearly one-third of adults are obese (body mass index, BMI >30%), it is also an increasing health concern among American children as well as adolescents. Morbid obesity or clinically severe obesity (BMI ≥40) affects more than 15 million Americans and causes an estimated 300 000 deaths per year.⁸⁴ Obesity creates major health problems because of its comorbidities, such as type 2 diabetes, cardiovascular diseases, etc. Treatment of obesity and its primary comorbidities costs the US healthcare system more than \$100 billion each year.

While various methods of GES have been under investigation for the treatment of obesity, clinical studies have been confined to the use of GES with trains of short pulses with the following typical parameters: a train on-time of 2 s, off-time of 3 s, a pulse frequency of 40 Hz (within the train), width of about 0.3 ms and amplitude of 5–10 mA.^{85, 86} The clinical therapy is called implantable gastric stimulation (IGS, Medtronic, Minneapolis, MN, USA).

IGS has also been proposed to increase the feeling of satiety with subsequent reduced food intake and weight loss. It employs an implantable, pacemaker-like device to deliver low-level electrical stimulation to the stomach. The stimulation electrodes are sutured to the outer lining of the stomach wall along the lesser curvature and connected to the device, which is implanted just under the skin on the abdomen. An external programmer is used to remotely communicate with the device. IGS requires an approximately 1-h laparoscopic insertion time using 4–6 trocar sites. It is proposed as an innovative attempt to reduce weight in morbidly

obese individuals, less aggressive than the drastic bariatric surgery.⁸⁷

The first gastric stimulator for the treatment of morbid obesity was implanted by Cigaina in 1995 and the patient lost 80% of her excess weight over the first 21 months of treatment. In the following two separate studies in a total of 36 patients with the IGS therapy, the majority of the patients reported a mean excess weight loss of 30% or 16 kg 9 months after the treatment.^{85, 88} Similar results were reported in a number of other studies.^{89–91} However, it should also be noted that none of these studies was blinded or controlled. Similar to GES for gastroparesis, possible placebo effects on the reported weight loss could not be ruled out.

A number of mechanistic studies suggested various peripheral and central effects of IGS in both humans and animals.⁹² In patients with obesity, acute and chronic IGS was found to increase satiety and reduce appetite,⁹² and alter in the number of plasma hormones related to satiety.⁹³ Canine studies reported a reduction in gastric tone and antral contractions with acute IGS^{94, 95} and an impairment in postprandial gastric slow waves with chronic IGS (1 month continuous GES).⁹⁶ However, the reduction in gastric tone and inhibition in antral contractions with IGS of parameters currently used in clinical obesity studies may not be of clinical significance in resulting in a substantial increase in satiety or impairment in digestive process. Central neuronal and humoral effects of IGS have been reported in rats. As stated earlier, GES of trains of short pulses with the parameters used for treating obesity in clinical studies activates neurones and increases the expression of anorexigenic hormones and reduces the expression of orexigenic hormones in various nuclei of the hypothalamus and hippocampus.^{61, 63}

In summary, GES with trains of short pulses (or IGS) may have a therapeutic potential for obesity. However, it has failed to produce consistent and positive weight loss in obese patients in double-blinded placebo-controlled studies although promising results were obtained in open-label studies. While its effects on the central nervous system are consistent and robust, IGS with parameters currently used in clinical trials for obesity does not seem to result in clinically significant effects on gastric myoelectrical activity, motility or emptying. A more powerful device capable of generating wider pulses may be needed.

PERSPECTIVES OF GES FOR GASTROINTESTINAL MOTILITY DISORDERS

While there have been numerous studies in the literature on GES, clinical applications of GES have been limited and the results have not been satisfactory because of the followings: (i) there has not been an implantable stimulator, which is specially designed and developed for GES and (ii) with the current methodologies of GES, there is a lack of efficacy in tackling the various abnormalities associated with gastric motility disorders. Future research should be focused on the advancement in the methodology of GES and the development of an appropriate implantable device.

Dual pulse GES

Available data from both humans and animals seem to indicate that long pulse GES is able to entrain gastric slow waves, normalize gastric dysrhythmia and possibly improve gastric emptying, but has little effects on symptoms of nausea and vomiting. Whereas, short pulse GES is able to improve gastroparetic symptoms of nausea and vomiting, but has little effects on gastric dysrhythmia. In clinical practice, both impaired gastric motility, such as gastric dysrhythmia, and symptoms are manifested in patients with gastroparesis or other gastric motility disorders. Accordingly, it is important that a therapeutic method is able to treat both impaired gastric motility and symptoms.

A novel method of GES, called dual pulse GES, has recently been proposed by combining short pulses and long pulses. In this method, the stimulus of GES is composed of a short pulse (in the order of a few hundred microseconds) followed by a long pulse (in the order of a few hundred milliseconds; see Figure 2). A canine study has shown that dual pulse GES is capable of both normalizing gastric dysrhythmia and improving the symptoms suggestive of nausea and vomiting induced by infusion of vasopressin.⁹⁷ Apparently, the proposed method of dual pulse GES is more attractive

than the conventional method of electrical stimulation in which only short pulses or long pulses but not both are utilized.

Synchronized GES

Conventionally, GES is performed at a fixed frequency delivered at random without consideration of the occurrence of the intrinsic gastric slow waves. While GES performed at the tachygastric frequency has a potent effect on inhibiting gastric contractions, no solid evidence is available in the literature that GES performed at the physiological frequency is capable of enhancing gastric contractions.

A novel method has recently been proposed: synchronized GES.⁹⁸ Synchronized GES requires the implantation of two pairs of electrodes, one for the detection of gastric slow waves and the other for stimulation. In this proposed method, each electrical stimulus was delivered upon the detection of an intrinsic slow wave peak, i.e. GES is performed at the occurrence of cyclic physiological electrical events of the stomach (Figure 3). By synchronizing each electrical stimulus with the intrinsic physiological electrical activity it is hypothesized that it is capable of enhancing gastric contractions. A recent canine study showed that synchronized GES in fasting state significantly increased the amplitude of gastric contractions and improved the impaired postprandial antral motility induced by glucagons.⁹⁸ Apparently, this method can only be applied in patients with normal gastric slow

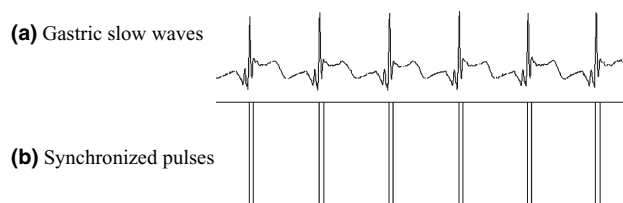


Figure 3. Synchronized gastric electrical stimulation.

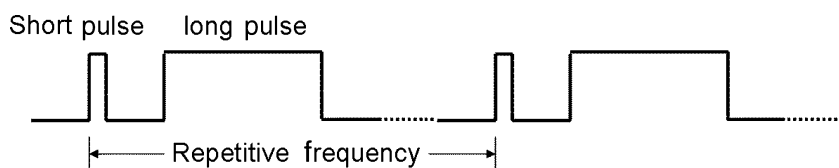


Figure 2. Electrical stimuli in the method of dual pulse gastric electrical stimulation.

waves but antral hypomotility. It would fail if gastric slow waves were dysrhythmic.

DISCUSSION AND CONCLUSIONS

Gastric electrical stimulation can be classified into several categories based on the pattern of the electrical stimuli. While animal studies have shown the effects of GES with various stimulation parameters on gastric slow waves, gastric contractions and gastric emptying, clinical studies are needed to validate these findings. Mechanisms involving GES are largely unknown, especially the central mechanisms involving the vagal and sympathetic pathways and the central nervous system. Both basic studies and clinical studies are needed to further elucidate the mechanisms involved with GES. Clinical studies have been limited up till now. GES with short pulses or the Enterra Therapy seems effective in reducing nausea and vomiting. However, its mechanisms are not known and placebo effects could not be ruled out. Moreover, its effects on gastric motility have been reported controversial. GES as a therapy for obesity is attractive due to the magnitude of the disease and the lack of safe and effective therapies. However, it must be pointed out that none of the published clinical studies on the applications of GES for gastroparesis or obesity has been placebo-controlled. Accordingly, the clinical efficacy of GES has yet to be proven in placebo-controlled clinical studies. In addition, mechanisms involved in the improvement of symptoms of nausea and vomiting resulting from GES or the GES-induced weight loss in obese patients are largely unknown and more mechanistic studies are needed in the future. At the present time, GES has been approved for humanitarian use in treating nausea and vomiting in patients with gastroparesis but has not been approved by FDA for treating obesity. In the application of GES for treating nausea and vomiting,

it seems that better candidates are those with diabetic gastroparesis and those with relatively normal gastric slow waves or motility.

Further research is needed in developing new methodologies of GES so that GES is capable of normalizing the various abnormalities related to gastric motor disorders, such as impaired gastric relaxation, visceral hypersensitivity, gastric dysrhythmia, antral hypomotility and delayed gastric emptying. With the application of GES for treating obesity, higher stimulation energy or an increased stimulation pulse width is necessary so that GES would affect both nerves and smooth muscles (or gastric motor functions).

The major hindrance in the advancement of this field includes the invasive nature of the methodology and the lack of implantable device suitable for GES. Accordingly, a less invasive method of placing stimulation electrodes would be of great significance, such as endoscopic placement of electrodes. The other issue is the development of a suitable implantable stimulator. Current implantable stimulators used for GES were designed for cardiac or nerve stimulation. Cardiac muscles and nerves have a rapid response to electrical stimulation and thus there is no need to use long or wide stimulation pulses. The stomach, however, is composed of smooth muscles, which are slow in response to electrical stimulation, and thus long pulses are needed to alter their functions. Accordingly, a new generation of device capable of altering gastric motility is needed.

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REFERENCES

- 1 Bilgutay AM, Wingrove R, Grifen WO, Bonnabeau RC, Lillehei CW. Gastrointestinal pacing: a new concept in the treatment of ileus. *Ann Surg* 1963; **158**: 338–48.
- 2 Quast DC, Beall AC Jr, DeBaakey ME. Clinical evaluation of the gastrointestinal pacer. *Surg Gynecol Obstet* 1965; **120**: 35–7.
- 3 Berger T, Kewenter J, Kock NG. Response to gastrointestinal pacing: antral, duodenal and jejunal motility in control and postoperative patients. *Ann Surg* 1966; **164**: 139–44.
- 4 Moran JM, Nabseth DC. Electrical stimulation of the bowel. *Arch Surg* 1965; **91**: 449–51.
- 5 Hinder RA, Kelly KA. Human gastric pacemaker potential: site of origin, spread, and response to gastric transection and proximal gastric vagotomy. *Am J Surg* 1977; **133**: 29–33.
- 6 Sarna SK, Bowes KL, Daniel EE. Gastric pacemakers. *Gastroenterology* 1976; **70**: 226–31.
- 7 Hermon-Taylor J, Code CF. Localization of the duodenal pacemaker and its role

- in the organization of duodenal myoelectric activity. *Gut* 1971; 12: 40–7.
- 8 Szurszewski JH, Elveback LR, Code CF. Configuration and frequency gradient of electric slow wave over canine small bowel. *Am J Physiol* 1970; 218: 1468–73.
 - 9 Bunker CE, Johnson LP, Nelsen S. Chronic in situ studies of the electrical activity of the small intestine. *Arch Surg* 1967; 95: 259–68.
 - 10 Akwari OE, Kelly KA, Steinbach JH, et al. Electric pacing of intact and transected canine small intestine and its computer model. *Am J Physiol* 1975; 229: 1188–97.
 - 11 Richter HM III, Kelly KA. Effect of transection and pacing on human jejunal pacemaker potentials. *Gastroenterology* 1986; 91: 1380–5.
 - 12 Karistrom L, Kelly KA. Ectopic jejunal pacemakers and gastric emptying after Roux gastroctomy: effect of intestinal pacing. *Surgery* 1989; 106: 867–71.
 - 13 Soper NJ, Sarr MG, Kelly KA. Human duodenal myoelectric activity after operation and with pacing. *Surgery* 1990; 107: 63–8.
 - 14 Kelly KA. Pacing the gut. *Gastroenterology* 1992; 103: 1967–9.
 - 15 Cullen JJ, Kelly KA. The future of intestinal pacing. *Gastroenterol Clin N Am* 1994; 23: 391–402.
 - 16 Lin ZY, Chen JDZ. Advances in gastrointestinal electrical stimulation. *Crit Rev Biomed Eng* 2002; 30: 419–57.
 - 17 Miedema BW, Sarr MG, Kelly KA. Pacing the human stomach. *Surgery* 1992; 111: 143–50.
 - 18 Eagon JC, Soper NJ. Gastrointestinal pacing. *Surg Clin North Am* 1993; 73: 1161–72.
 - 19 Bortolotti M. The 'electrical way' to cure gastroparesis. *Am J Gastroenterol* 2002; 97: 1874–83.
 - 20 Lin Z, Forster J, Sarosiek I, McCallum RW. Treatment of gastroparesis with electrical stimulation. *Dig Dis Sci* 2003; 48: 8837–48.
 - 21 Song GQ, Hou XH, Yang B, Liu JS, Qian W, Chen JDZ. Two-channel gastric electrical stimulation accelerates delayed gastric emptying induced by vasopressin. *Dig Dis Sci* 2005; 50: 662–8.
 - 22 Chen JDZ, Xu X, Zhang J, et al. Efficiency and efficacy of multi-channel gastric electrical stimulation. *Neurogastroenterol Motil* 2005; 17: 878–82.
 - 23 Mintchev MP, Sanminguel CP, Bowes KL. Microprocessor controlled movement of liquid gastric content using sequentila neural electrical stimulation. *Gut* 1998; 43: 607–11.
 - 24 Mintchev MP, Sanminguel CP, Amaris M, Bowes KL. Microprocessor-controlled movement of solid gastric content using sequentila neural electrical stimulation. *Gastroenterology* 2000; 118: 258–63.
 - 25 Bauer AJ, Sanders KM. Passive and active membrane properties of canine gastric antral circular muscles. *Am J Physiol* 1986; 251: C268–73.
 - 26 Hirst GD, Garcia-Londono AP, Edwards FR. Propagation of slow waves in the guinea-pig gastric antrum. *J Physiol* 2006; 571: 165–77.
 - 27 Lin ZY, Forst J, McCallum RW. Effect of high-frequency gastric electrical stimulation on gastric myoelectrical activity in gastroparetic patients. *Neurogastroenterol Motil* 2004; 16: 205–12.
 - 28 Kelly KA, La Force RC. Pacing the canine stomach with electrical stimulation. *Am J Physiol* 1972; 222: 588–94.
 - 29 Eagon JC, Kelly KA. Effect of electrical stimulation on gastric electrical activity, motility and emptying. *Neurogastroenterol Motil* 1995; 7: 39–45.
 - 30 Sarna SK, Daniel EE. Electrical stimulation of gastric electrical control activity. *Am J Physiol* 1973; 225: 125–31.
 - 31 Lin ZY, McCallum RW, Schirmer BD, Chen JDZ. Effects of pacing parameters in the entrainment of gastric slow waves in patients with gastroparesis. *Am J Physiol* 1998; 274: G186–91.
 - 32 Qian L, Lin X, Chen JDZ. Normalization of atropine-induced postprandial dysrhythmias with gastric pacing. *Am J Physiol* 1999; 276: G387–92.
 - 33 Xu X, Brining DL, Chen JDZ. Effects of vasopressin and long pulse–low frequency gastric electrical stimulation on gastric emptying, gastric and intestinal myoelectrical activity and symptoms in dogs. *Neurogastroenterol Motil* 2005; 17: 236–44.
 - 34 Liu J, Qiao X, Micci MA, Pasricha PJ, Chen JD. Improvement of gastric motility with gastric electrical stimulation in STZ-induced diabetic rats. *Digestion* 2004; 70: 159–66.
 - 35 Xu X, Qian L, Chen JD. Anti-dysrhythmic effects of long-pulse gastric electrical stimulation in dogs. *Digestion* 2004; 69: 63–70.
 - 36 Chen JDZ, Qian LW, Ouyang H, Yin JY. Gastric electrical stimulation with short pulses reduces vomiting but not dysrhythmia in dogs. *Gastroenterology* 2003; 124: 401–9.
 - 37 McCallum RW, Chen JDZ, Lin ZY, Schirmer BD, Williams RD, Ross RA. Gastric pacing improves emptying and symptoms in patients with gastroparesis. *Gastroenterology* 1998; 114: 456–61.
 - 38 Hocking MP, Vogel SB, Sninsky CA. Human gastric myoelectrical activity and gastric emptying following gastric surgery and with pacing. *Gastroenterology* 1992; 103: 1811–6.
 - 39 Hou XH, Yin JY, Pasricha PJ, Chen JDZ. In-vivo gastric and intestinal slow waves in W/Wv mouse. *Dig Dis Sci* 2005; 50: 1335–41.
 - 40 Daniel EE, Boddy G, Bong A, Cho WJ. A new model of pacing in the mouse intestine. *Am J Physiol Gastrointest Liver Physiol* 2004; 286: G253–62.
 - 41 Daniel EE, Willis A, Cho WJ, Boddy GL. Comparisons of neural and pacing activities in intestinal segment for W/W++ and W/Wv mice. *Neurogastroenterol Motil* 2005; 17: 355–65.
 - 42 Zhu HB, Ouyang H, Chen JDZ. Pathophysiological roles of ectopic tachygastria induced with retrograde gastric electrical stimulation. *Digestion* 2005; 71: 192–8.
 - 43 Ouyang H, Xing J, Chen JDZ. Tachygastria induced by gastric electrical stimulation is mediated via α - and β -adrenergic pathway and inhibits antral motility in dogs. *Neurogastroenterol Motil* 2005; 17: 846–53.
 - 44 Familoni BO, Abell T, Nemoto D, Voeller G, Johnson B. Efficacy of electrical stimulation at frequencies higher than basal rate in canine stomach. *Dig Dis Sci* 1997; 42: 892–7.
 - 45 Xing JH, Chen JDZ. Gastric electrical stimulation with parameters for gastroparesis enhances gastric accommodation and alleviates distention-induced symptoms in dogs. *Dig Dis Sci* (in press).
 - 46 Xing JH, Brody F, Brodsky J, Larive B, Ponsky J, Soffer E. Gastric electrical stimulation at proximal stomach induces gastric relaxation in dogs. *Neurogastroenterol Motil* 2003; 15: 15–23.
 - 47 Sun Y, Chen JDZ. Gastric electrical stimulation reduces gastric tone energy dependently. *Scand J Gastroenterol* 2005; 40: 154–9.
 - 48 Sun Y, Chen JDZ. Gastric electrical stimulation inhibits postprandial antral tone partially via nitrenergic pathway in conscious dogs. *Am J Physiol Regul Integr Comp Physiol* 2006; 290: R904–8.
 - 49 Xing JH, Chen JDZ. Effects and mechanisms of long-pulse gastric electrical

- stimulation on canine gastric tone and accommodation. *Neurogastroenterol Motil* 2006; 18: 136–43.
- 50 Bellahsene BE, Lind CD, Schirmer BD, Uptdike OL, McCallum RW. Acceleration of gastric emptying with electrical stimulation in a canine model of gastroparesis. *Am J Physiol* 1992; 262: G826–34.
- 51 Eagon JC, Kelly KA. Gastric pacing reverses canine peristalsis, slows emptying, and strengthens contractions. *Am J Surg* 1993; 163: 628.
- 52 Xu XH, Zhu HB, Chen JDZ. Pyloric electrical stimulation for obesity: reduced food intake and possible mechanisms. *Gastroenterology* 2005; 128: 43–50.
- 53 Yao SK, Ke MY, Wang ZF, *et al.* Retrograde gastric electrical stimulation reduces food intake and delays gastric emptying in humans: a therapeutic potential for obesity? *Dig Dis Sci* 2005; 50: 1569–75.
- 54 Yao SK, Ke MY, Wang ZF, Xu DB, Zhang YL, Chen JDZ. Visceral sensitivity to gastric stimulation and its correlation with alterations in gastric emptying and accommodation in humans. *Obes Surg* 2005; 15: 247–53.
- 55 Xing J, Felsner J, Brody F, Soffer E. Gastric electrical stimulation significantly increases canine lower esophageal sphincter pressure. *Dig Dis Sci* 2005; 8: 1481–7.
- 56 Xing J, Lei Y, Chen JDZ. Gastric electrical stimulation (GES) with parameters for morbid obesity elevates lower esophageal sphincter (LES) pressure in conscious dogs. *Obes Surg* 2005; 15: 1321–7.
- 57 Liu S, Wang LJ, Chen JDZ. Cross-talk along gastrointestinal tract during electrical stimulation: effects and mechanisms of gastric/colon stimulation on rectal tone in dogs. *Am J Physiol Gastrointest Liver Physiol* 2005; 288: G1195–8.
- 58 Qin C, Sun Y, Chen JDZ, Foreman R. Gastric electrical stimulation modulates neuronal activity in nucleus tractus solitarius in rats. *Auton Neurosci* 2005; 119: 1–8.
- 59 Peles S, Petersen J, Aviv R, *et al.* Enhancement of antral contractions and vagal afferent signaling with synchronized electrical stimulation. *Am J Physiol Gastrointest Liver Physiol* 2003; 285: G577–85.
- 60 Tang M, Zhang J, Chen JDZ. Central mechanisms of gastric electrical stimulation involving neurons in paraventricular nucleus of hypothalamus in rats. *Obes Surg* 2006; 16: 344–52.
- 61 Xu L, Tang M, Chen JDZ. Effect of gastric electrical stimulation on gastric distention responsive neurons and expression of nNOS in rodent hippocampus. *Gastroenterology* 2005; 128: A624.
- 62 Sun XR, Tang M, Zhang J, Chen JDZ. Excitatory effects of gastric electrical stimulation on gastric distension responsive neurons in ventromedial hypothalamus (VMH) in rats. *Neurosci Res* 2006; 55: 451–7.
- 63 Tang M, Zhang J, Xu L, Chen JDZ. Implantable gastric stimulation alters expression of orexin- and oxytocin-containing neurons in hypothalamus in rats. *Obes Surg* 2006; 16: 762–9.
- 64 Soykan I, Sivri B, Sarosiek I, Kiernan B, McCallum RW. Demography, clinical characteristics, psychological and abuse profiles, treatment, and long-term follow-up of patients with gastroparesis. *Dig Dis Sci* 1998; 43: 2398–404.
- 65 McCallum RW. Clinical pharmacology forum: motility agents and the gastrointestinal tract. *Am J Med Sci* 1996; 312: 19–26.
- 66 Abell TL, Bernstein VK, Cutts T, *et al.* Treatment of gastroparesis: a multidisciplinary clinical review. *Neurogastroenterol Motil* 2006; 18: 263–83.
- 67 Rayner CK, Horowitz M. New management approaches for gastroparesis. *Nat Clin Pract Gastroenterol Hepatol* 2005; 2: 454–62.
- 68 Tack J. Gastric motor and sensory function. *Curr Opin Gastroenterol* 2005; 21: 665–72.
- 69 Hasler WL. Nausea, gastroparesis, and aerophagia. *J Clin Gastroenterol* 2005; 39: S223–9.
- 70 Parkman HP, Hasler WL, Fisher RS. American Gastroenterological Association technical review on the diagnosis and treatment of gastroparesis. *Gastroenterology* 2004; 127: 1592–622.
- 71 Abell T, McCallum R, Hocking M, *et al.* Gastric electrical stimulation for medically refractory gastroparesis. *Gastroenterology* 2003; 125: 421–8.
- 72 Forster J, Sarosiek I, Delcore R, Lin Z, Raju GS, McCallum RW. Gastric pacing is a new surgical treatment for gastroparesis. *Am J Surg* 2001; 182: 676–81.
- 73 Abell TL, Van Cutsem E, Abrahamsson H, *et al.* Gastric electrical stimulation in intractable symptomatic gastroparesis. *Digestion* 2002; 66: 204–12.
- 74 Forster J, Sarosiek I, Lin Z, *et al.* Further experience with gastric stimulation to treat drug refractory gastroparesis. *Am J Surg* 2003; 186: 690–5.
- 75 Luo J, Al-Juburi A, Rashed H, *et al.* Gastric electrical stimulation is associated with improvement in pancreatic exocrine function in humans. *Pancreas* 2004; 29: e41–4.
- 76 Lin Z, Forster J, Sarosiek I, McCallum RW. Treatment of diabetic gastroparesis by high-frequency gastric electrical stimulation. *Diabetes Care* 2004; 27: 1071–6.
- 77 Oubre B, Luo J, Al-Juburi A, Voeller G, Familoni B, Abell TL. Pilot study on gastric electrical stimulation on surgery-associated gastroparesis: long-term outcome. *South Med J* 2005; 98: 693–7.
- 78 Cutts TF, Luo J, Starkebaum W, Rashed H, Abell TL. Is gastric electrical stimulation superior to standard pharmacologic therapy in improving GI symptoms, healthcare resources, and long-term health care benefits? *Neurogastroenterol Motil* 2005; 17: 35–43.
- 79 Lin Z, McElhinney C, Sarosiek I, Forster J, McCallum R. Chronic gastric electrical stimulation for gastroparesis reduces the use of prokinetic and/or antiemetic medications and the need for hospitalizations. *Dig Dis Sci* 2005; 50: 1328–34.
- 80 Familoni BO, Abell TL, Voeller G, Salem A, Gaber O. Electrical stimulation at a frequency higher than basal rate in human stomach. *Dig Dis Sci* 1997; 42: 885–91.
- 81 Lin Z, Sarosiek I, Forster J, McCallum RW. Symptom response, long-term outcomes and adverse events beyond 3 years of high-frequency gastric electrical stimulation for gastroparesis. *Neurogastroenterol Motil* 2006; 18: 18–27.
- 82 Tack J, Coulie B, Van Cutsem E, Ryden J, Janssens J. The influence of gastric electrical stimulation on proximal gastric motor and sensory function in severe idiopathic gastroparesis. *Gastroenterology* 1999; 116: A1090.
- 83 McCallum RW, Dusing RW, McMillin C, *et al.* Fluro-Dexy Glucose (fdg) positron emission tomography (PET) in gastroparetic patients before and during gastric electrical stimulation (GES). *Gastroenterology* 2005; 128: A622.
- 84 Klein S. Clinical perspectives in gastroenterology. *Obesity* 2000; 3: 232–6.
- 85 Cigaina V. Gastric pacing as therapy for morbid obesity: preliminary results. *Obes Surg* 2002; 12: 12S–6S.

- 86 McCallum RW, Sarosiek I, Lin Z, Moncure M, the USA Study Group. Preliminary results of gastric electrical stimulation on weight loss and gastric emptying in morbidly obese patients: a randomized double-blinded trial. *Neurogastroenterol Motil* 2002; 14: 440.
- 87 Shikora S. Implantable gastric stimulation – the surgical procedure: combining safety with simplicity. *Obes Surg* 2004; 14: S9–13.
- 88 D'Argent J. Gastric electrical stimulation as therapy of morbid obesity: preliminary results from the French study. *Obes Surg* 2002; 12: 21S–5S.
- 89 De Luca M, Segato G, Busetto L, *et al.* Progress in implantable gastric stimulation: summary of results of the European multi-center study. *Obes Surg* 2004; 14: S33–9.
- 90 Cigaina V. Long-term follow-up of gastric stimulation for obesity: the Metre 8-year experience. *Obes Surg* 2004; 14: S14–22.
- 91 Shikora S. 'What are the Yanks doing?' the US experience with implantable gastric stimulation (IGS) for the treatment of obesity – update on the ongoing clinical trials. *Obes Surg* 2004; 14: S40–8.
- 92 Chen JDZ. Mechanisms of an implantable gastric stimulator for obesity. *Obes Surg* 2004; 14: S28–32.
- 93 Cigaina V, Hirschberg AL. Gastric pacing for morbid obesity: plasma levels of gastrointestinal peptides and leptin. *Obes Res* 2003; 11: 1456–62.
- 94 Lei Y, Xing J, Chen JDZ. Effects and mechanisms of implantable gastric stimulation on proximal gastric distention in conscious dogs. *Obes Surg* 2005; 15: 528–33.
- 95 Zhu HB, Chen JDZ. Implantable gastric stimulation inhibits gastric motility via sympathetic pathway in dogs. *Obes Surg* 2005; 15: 95–100.
- 96 Ouyang H, Yin JY, Chen JDZ. Inhibitory effects of chronic gastric electrical stimulation on food intake and weight and their possible mechanisms. *Dig Dis Sci* 2003; 48: 698–705.
- 97 Liu JS, Qiao X, Chen JDZ. Therapeutic potentials of a novel method of dual-pulse gastric electrical stimulation for gastric dysrhythmia and symptoms of nausea and vomiting. *Am J Surg* 2006; 191: 255–61.
- 98 Zhu HB, Sallam H, Chen JDZ. Synchronized gastric electrical stimulation enhances gastric motility in dogs. *Neurogastroenterol Motil* 2005; 17: 628.