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Therapeutic Potential of Gastric Electrical Stimulation for Obesity and Its Possible Mechanisms

A Preliminary Canine Study

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Our aim was to investigate the effects of gastric electrical stimulation on food intake, weight, gastric myoelectrical, and parasympathetic activity. Dogs were implanted with serosal electrodes and a subcutaneous stimulator. The stimulator was turned on and off alternately every month for 4 months. Food intake, weight, gastric myoelectrical activity, and electrocardiograms were recorded. Daily food intake and weight were significantly decreased during the months with stimulation. Stimulation did not show any acute effect on gastric myoelectrical activity; however, it chronically and significantly impaired gastric myoelectrical activity in the fed state, but not in the fasting state. The parasympathetic activity in the fasting state assessed from the spectral analysis of heart rate variability was markedly decreased with stimulation both acutely and chronically. In conclusion, chronic gastric electrical stimulation results in a reduction in food intake, weight loss, a reduction in parasympathetic activity, and chronic inhibition of gastric myoelectrical activity. These data suggest that gastric electrical stimulation is a potential therapy for the treatment of obesity and its inhibitory effect on food intake and weight may involve both muscles and the vagal afferent pathway.

KEY WORDS: gastric electrical stimulation; gastric myoelectrical activity; heart rate variability; obesity.

The prevalence of obesity around the world is rising to epidemic proportions at an alarming rate. Obesity is one of the most prevalent public health problems in the United States. Morbid obesity, or clinically severe obesity (BM $\geq$ 40 or $>$100 lb over normal weight), affects more than 15 million Americans and causes an estimated 300,000 deaths per year. The treatment of obesity and its primary comorbidities costs the US healthcare system more than $99 billion each year (1–4). Moreover, obesity is associated with an increased prevalence of socioeconomic hardship due to a higher rate of disability, early retirement, and widespread discrimination (5).

The conventional treatments of obesity can be classified into three categories: basic treatment, pharmacotherapy, and surgical treatment. Typically, an obese patient first undergoes basic treatment. Acceptable weight loss is usually achieved with basic treatment. However, maintaining weight loss seems to be more difficult than losing weight, particularly for patients who were treated with calorie restriction (6). A number of FDA-approved drugs are currently available for the medical treatment of obesity. These include sibutramine, diethylpropion, mazindol, phentermine, phenylpropanolamine, and orlistat (7, 8). 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 comorbidities. While surgical treatment induces

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satisfactory long-term weight loss, its use is very limited due to substantial risks and complications associated with the surgical procedure (9, 10).

A recent preliminary study indicated the potential of electrical stimulation for obesity (11). The first human study using a gastric stimulator for the treatment of morbid obesity was performed in 1995 and resulted in a substantial weight loss (12).

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. To accomplish its functions effectively, the gut needs to generate not only simple contractions but also coordinated contractions (peristalsis). Coordinated gastric contractions are necessary for the emptying of the stomach, thus, impairment in gastric motility may result in delayed emptying of the stomach.

Gastric motility (contractile activity) is in turn regulated by the myoelectrical activity of the stomach, called slow waves. The gastric slow wave originates in the proximal stomach and propagates distally toward the pylorus. It determines the maximum frequency, propagation velocity, and propagation direction of gastric contractions. The normal frequency of the gastric slow wave is about 3 cycles per minute (cpm) in humans and 5 cpm in dogs. Abnormalities in gastric slow waves lead to gastric motor disorders and have been frequently observed in patients with functional disorders of the gut, such as gastroparesis, functional dyspepsia, anorexia, etc (13–19).

The aims of this study were to investigate the effects of gastric electrical stimulation on food intake and weight loss and its possible mechanisms.

MATERIALS AND METHODS

Animals

Five healthy female dogs (15–25 kg) were used in this study. After an overnight fast, each dog was operated on under anesthesia. Anesthesia was initiated with Pentothal (sodium thiopental 5 mg/kg, intravenous, Abbott Laboratories, North Chicago, Illinois, USA). After endotracheal incubation, anesthesia was maintained for the operation with IsoFlo (isoflurane 1.5%, inhalation anesthesia, Abbott) in oxygen–nitrous oxide (1:1) carrier gases delivered from a ventilator. The dog was monitored by observing tongue color, pulse rate, corneal reflexes, etc. A lead with a pair of bipolar stimulating electrodes at the distal end with an interval of about 0.3 cm was implanted into the serosal layer along the lesser curvature at two thirds proximal and one third distal to the stomach and connected to a stimulator (IGS2000, Transneuronix, Inc., Mt Arlington, New Jersey, USA) implanted into a subcutaneous pocket. In addition, three pairs of bipolar electrodes (A&E Medical, Farmingdale, New Jersey, USA) were sutured on the serosa along the greater curvature at an interval of 4 cm, the most distal pair of which was 2 cm above the pylorus. The distance between the two electrodes in each pair was 0.5 cm. Teflon-insulated wires were brought out through the abdominal wall subcutaneously and placed under a sterilized dressing until needed for studies. These electrodes were used to record gastric myoelectrical activity and its responses to gastric electrical stimulation. At the completion of the surgery, the animal was first transferred to an intensive care cage for a few hours and then to the regular cage after a complete recovery from anesthesia. The study was approved by the Institutional Animal Care and Use Committee of the University of Texas Medical Branch at Galveston, Texas, USA.

Experimental Design

After a complete recovery from surgery (about 2 weeks), the dog was given unlimited amounts of regular dog food (Laboratory Canine Diet 5006, PMI Nutrition International). The gross energy per gram of the food is 4.33 kcal. The study protocol was as follows: first month: the stimulator was off; second month: the stimulator was on; third month: the stimulator off; fourth month: the stimulator on; fifth month: the stimulator off. The stimulation parameters used were similar to those used in the preliminary human study (12): pulse frequency: 40 Hz, pulse width: 0.3 msec, the pulses were on for a period of 2 sec and off for a period of 3 sec, the amplitude of the pulse was 6 mA (see Figure 1). During the study period, the amount of food intake was recorded on a daily basis and the dog was weighed weekly. Gastric myoelectrical activity and electrocardiogram were recorded once a week, each recording lasting 2 hr in the fasting state and 1 hr after the meal (regular dog food).

Recording and Analysis of Gastric Myoelectrical Activity

A multichannel recorder (Acknowledge III, EOG 100A, Biopac Systems, Inc. Santa Barbara, California, USA) was used to record gastric myoelectrical activity via the three pairs of serosal electrodes. All recordings were displayed on a computer monitor (Figure 2a) and saved on the hard disk by an IBM-compatible 486 PC. The high cutoff frequency of the amplifier was 35 Hz with an initial sampling frequency of 100 Hz. For the spectral analysis of gastric slow waves, the signals were further filtered using a digital lowpass filter with a cutoff frequency of 1 Hz and down-sampled at 2 Hz to avoid violation of the Nyquist theory. Custom-made computer software developed and validated in our laboratory (20) was applied to derive the following parameters: frequency, power (amplitude) and percentage of regular 4–6 cpm gastric slow waves.

Slow-Wave Frequency and Power. The frequency at which the power spectrum of the electromyographic recording had a peak power was defined as the slow-wave frequency (dominant frequency). The power at the dominant frequency in the power spectrum was defined as the slow-wave power (Figure 2b). An overall spectral analysis method was applied to compute these two parameters (20). The postprandial slow-wave power increase was considered as the difference between the power of the fed state and the fasting state.

Percentage of Regular 4–6 cpm Slow Waves. The gastric myoelectrical recording was divided into blocks of 1-min each and the power spectrum of each 1-min recording was derived using the autoregressive moving average spectral analysis method (20). The 1-min segment of the recording was defined as normal if its power spectrum had a dominant peak in the frequency range

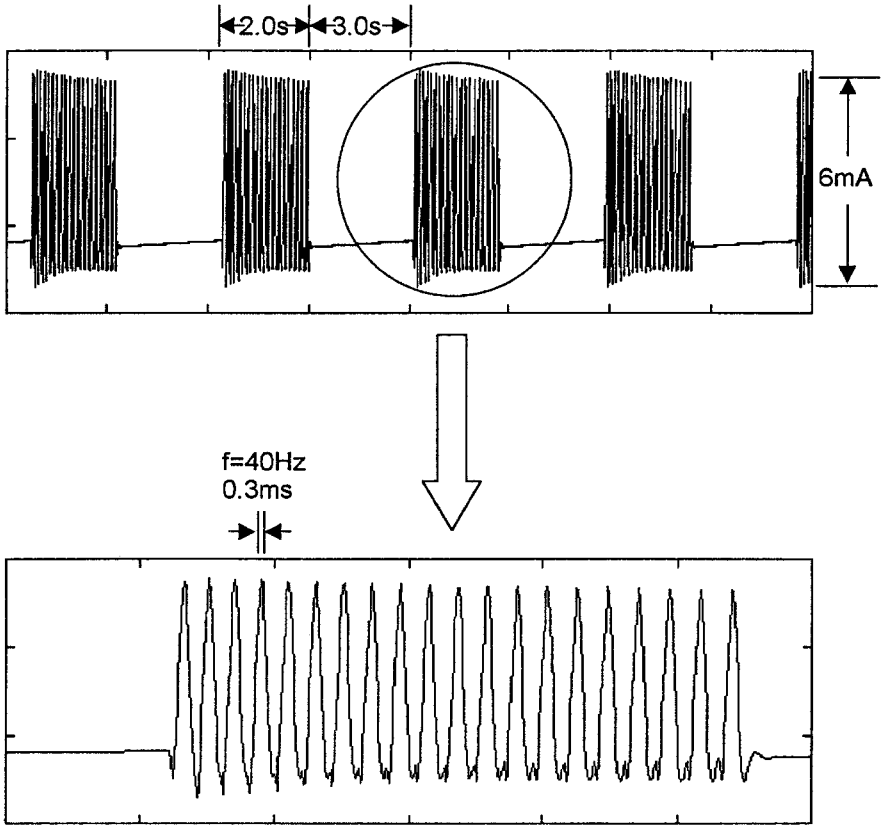

Fig 1. Electrical stimulus. The pulses were on for a period of 2 sec and off for a period of 3 sec, pulse frequency: 40 Hz, pulse width: 0.3 msec, amplitude of the pulse: 6 mA.

of 4–6 cpm (Figure 2c). Otherwise, it was defined as abnormal. The percentage of regular gastric slow waves was determined by the percentage of time during which a dominant spectral peak was noted in the frequency range of 4–6 cpm. The definition of the regular 4–6 cpm frequency range was based on analysis of our previous study in healthy dogs (21).

Recording and Analysis of Parasympathetic Activity

Simultaneously with the recording of gastric myoelectrical activity, the electrocardiogram (ECG) was recorded during the entire experiment from three cutaneous electrodes placed in the intercostal space aborad to the first pair of nipples (two active electrodes) and the right rear leg (one reference electrode) using a special one-channel amplifier with a cutoff frequency of 50 Hz (model 2283 Fti Universal Fetrode Amplifier, UFI, Morro Bay, California, USA). The recorded electrocardiographic signal was sampled at a frequency of 6000 Hz using the analog/digital converter installed on the sound card of the computer. The digitized ECG was further down-sampled to 500 Hz. The heart rate variability signal was derived from the ECG using a special program developed in our laboratory (22) by identifying the R-R peaks, interpolating the R-R intervals so that the time interval between consecutive samples was equal, and finally down-sampling the interpolated R-R interval data to a frequency of 1 Hz.

Overall power spectral analysis (20) was then applied to the heart rate variability signal and the percentage of power in each frequency subband was calculated. It is well known that the percentage of power in the low-frequency band (0.04–0.15 Hz), Pl, represents mainly sympathetic activity and the percentage of power in the high-frequency band (0.15–0.50 Hz), P2, stands purely for parasympathetic activity. Pl was computed as the ratio between the area under the curve in the frequency range of 0.04–0.15 Hz and the area under the curve in the frequency range of 0.04–0.50 Hz. P2 was assessed as the ratio between the area under the curve in the frequency range of 0.15–0.50 Hz and the area under the curve in the frequency range of 0.04–0.50 Hz.

Statistical Analysis

All data were presented as mean ± SEM. A one-way analysis of variance (ANOVA) was conducted to assess the difference among the data obtained during different times. Paired Student's *t* test was applied to investigate the effect of chronic gastric electrical stimulation on food intake, weight, and the gastric myoelectrical activity between the months with the stimulator on or off. A finding of $P < 0.05$ was considered to be significant.

RESULTS

Effects on Food Intake and Weight

A significant effect of chronic gastric electrical stimulation was observed on food intake. The average daily

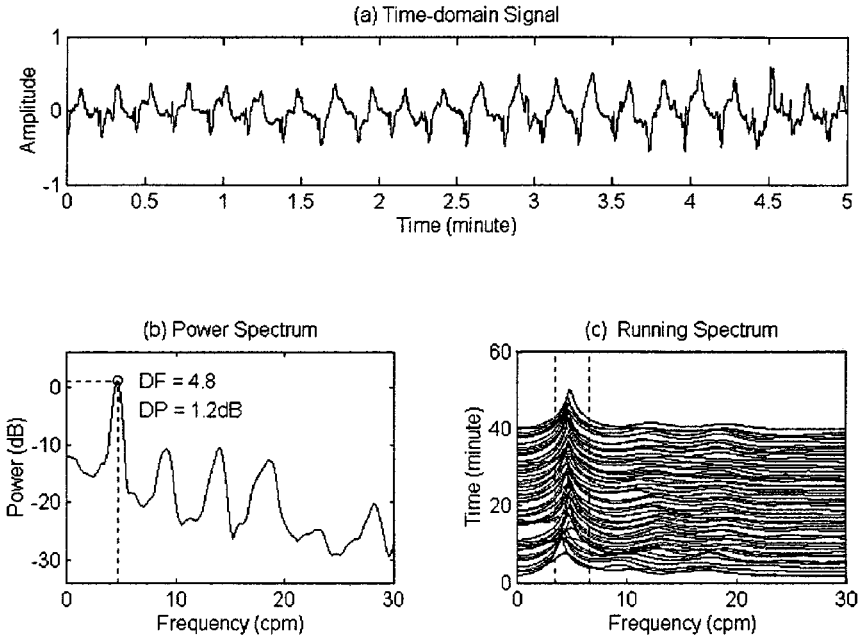

Fig 2. Recording and analysis of gastric myoelectrical activity. (a) Tracing of gastric myoelectrical activity. (b) Power spectrum; the peak values were defined as the frequency and power (amplitude) of the slow wave. (c) Running spectrum: the segment of data was defined as normal if its dominant peak was in the frequency range of 4–6 cpm.

food intake during the 2 months without stimulation was 542.2 ± 34.7 g and was reduced by about 10% to 497.7 ± 43.6 g ($P < 0.04$) during the 2 months with stimulation (Figure 3A). Consistent with the reduction of food intake, chronic gastric electrical stimulation also resulted in a significant weight loss. The average weekly weight was 19.9 ± 2.2 kg during the two months without stimulation and was reduced to 19.1 ± 2.0 kg ($P < 0.04$) during the months with stimulation (Figure 3B).

Effects on Gastric Myoelectrical Activity

Acutely, gastric electrical stimulation did not show any effect on any of the analyzed parameters of gastric myoelectrical activity in either the fasting or fed state (Table 1). In the fasting state, the values of these parameters during the 60-min period immediately after the initiation of stimulation were not different from those at baseline before stimulation. Similarly, the parameters of gastric myoelectrical activity during the 60-min postprandial period with

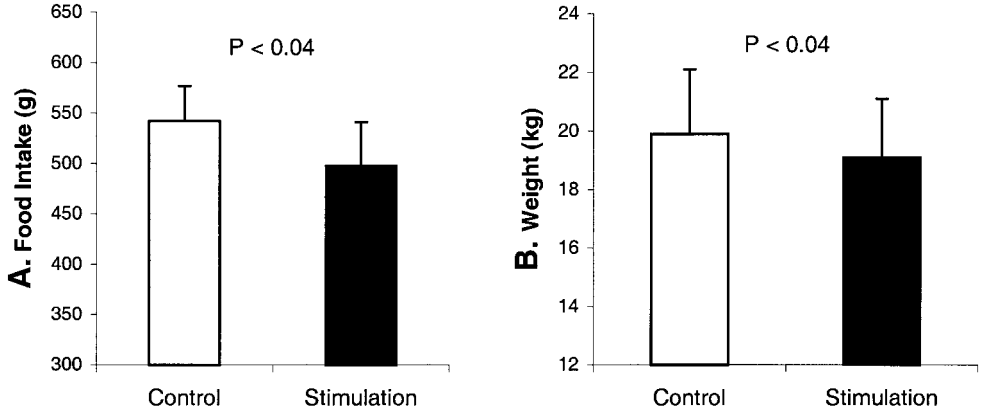

Fig 3. Effects of gastric electrical stimulation on food intake and weight. (A) The daily food intake was significantly decreased during 2 months with stimulation in comparison with the 2 months without stimulation ($P < 0.04$). (B) The average weekly weight was also reduced (stimulation vs control, $P < 0.04$).

TABLE 1. ACUTE EFFECTS OF ELECTRICAL GASTRIC STIMULATION ON GASTRIC MYOELECTRICAL ACTIVITY

Gastric myoelectrical activity	*Baseline*	*Stimulation*	P
Preprandial slow-wave frequency (cpm)	5.29 ± 0.16	5.27 ± 0.22	NS
Preprandial regular 4–6 cpm slow waves (%)	68.8 ± 2.4	71.6 ± 2.8	NS
Postprandial slow-wave frequency (cpm)	4.82 ± 0.17	4.88 ± 0.17	NS
Postprandial regular 4–6 cpm slow waves (%)	82.1 ± 1.1	77.3 ± 3.8	NS
Postprandial slow-wave power increase (dB)	1.05 ± 1.09	1.15 ± 0.61	NS

stimulation were no different from those observed in the preceding study session without stimulation.

Chronically, however, gastric electrical stimulation significantly impaired gastric myoelectrical activity in the fed state, but not in the fasting state (Table 2). Food ingestion resulted in a significant decrease in the frequency of gastric slow waves with (4.87 ± 0.19 cpm vs 5.39 ± 0.15 cpm; $P < 0.01$) or without stimulation (4.73 ± 0.15 cpm vs 5.28 ± 0.25 cpm; $P < 0.05$). Chronic gastric electrical stimulation did not affect gastric slow wave frequency in either the fasting or fed state. However, chronic gastric electrical stimulation resulted in a significant decrease in the percentage of regular 4–6 cpm slow waves at the end of one month of stimulation ($69.6 \pm 5.2\%$) in comparison with that at the end of one month without stimulation ($85.2 \pm 3.4\%$, $P < 0.04$, Figure 4A). In addition, chronic gastric electrical stimulation impaired postprandial response of the gastric slow wave to the meal. The power (amplitude) of gastric slow waves showed a postprandial increase at the end of the one-month period without stimulation but a postprandial decrease at the end of the one-month period with stimulation. The difference in this postprandial response was statistically significant ($P < 0.02$; Figure 4B).

TABLE 2. CHRONIC EFFECTS OF ELECTRICAL GASTRIC STIMULATION ON GASTRIC MYOELECTRICAL ACTIVITY

Gastric myoelectrical activity	*Baseline*	*Stimulation*	P
Preprandial slow-wave frequency (cpm)	5.29 ± 0.25	5.39 ± 0.15	NS
Preprandial regular 4–6 cpm slow waves (%)	69.9 ± 5.3	69.2 ± 3.4	NS
Postprandial slow-wave frequency (cpm)	4.73 ± 0.15*	4.87 ± 0.19†	NS
Postprandial regular 4–6 cpm slow waves (%)	85.2 ± 3.4	69.6 ± 5.2	<0.04
Postprandial slow-wave power increase (dB)	1.09 ± 1.09	-2.20 ± 0.63	<0.02

*$P < 0.05$, vs preprandial slow wave frequency.
†$P < 0.005$, vs preprandial slow wave frequency.

Effects on Parasympathetic Activity

The parasympathetic activity in the fasting state was significantly decreased with gastric electrical stimulation both acutely and chronically. However, no significant effects were noted in the postprandial parasympathetic activity. As shown in Figure 5, in the fasting state, P2 was decreased from 0.86 ± 0.02 at baseline to 0.78 ± 0.03 during the 60-min period immediately after the initiation of stimulation ($P < 0.03$) and was 0.82 ± 0.02 ($P < 0.04$, vs baseline) at the end of one-month stimulation period. In the fed state, P2 was 0.85 ± 0.02 at baseline, 0.84 ± 0.03 with acute stimulation, and 0.80 ± 0.04 at the end of the one-month stimulation period ($P > 0.05$).

Adverse Effects

No adverse effect was observed in the study. No discomfort or sensation was noted when the stimulator was turned on. No dogs vomited when the stimulator was turned on. Similarly, no behavior changes related to nausea were noted. The electrocardiogram (QRS complex) was not found to be affected either acutely or chronically. At the end of the entire study, the animals were killed, and the stomach was removed for visual examination; no dislodgement of electrodes was noted and no damage to the gastric tissues where the electrodes were placed was visually observed.

DISCUSSION

In the present study, we found that gastric electrical stimulation in dogs, reduced food intake, which resulted in weight loss, chronically impaired postprandial gastric myoelectrical activity, and inhibited the parasympathetic activity.

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. For example, Wright et al (23) studied 77 subjects—46 obese and 31 age-, sex-, and race-matched nonobese individuals. The obese subjects showed a more rapid emptying rate than the nonobese subjects. Gastric emptying is believed to play a role in the regulation of food intake and satiety. Several studies have shown that gastric distension acts as a satiety signal to inhibit food intake (24), and rapid gastric emptying is closely related to overeating and obesity (25). Although the significance and cause of this change in gastric emptying remains to be definitively established, several peptides, including cholecystokinin (CCK) and corticotropin-releasing factor (CRF), have been shown to suppress food intake and decrease gastric emptying. The inhibitory effect of peripherally

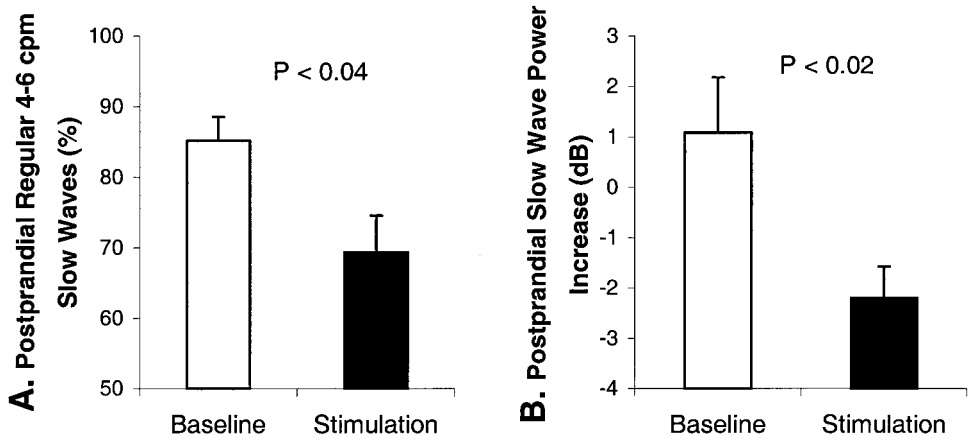

Fig 4. Chronic effects of gastric electrical stimulation on gastric myoelectrical activity. (A) Gastric electrical stimulation resulted in a significant decrease in the percentage of regular 4–6 cpm slow waves in the fed state at the end of the one-month stimulation in comparison with that at the end of one month without stimulation ($P < 0.04$). (B) The power (amplitude) of gastric slow waves showed a postprandial decrease at the end of the one-month stimulation instead of a postprandial increase at the end of one month without stimulation ($P < 0.02$).

administered CCK-8 on the rate of gastric emptying contributes to its ability in inhibiting food intake in various species (26). Peripheral injection of CRF is also known to decrease food intake, as well as the rate of gastric emptying (27). More recently, it was found that *ob/ob* mice (a genetic model of obesity) had a higher rate of gastric emptying when compared to lean mice (28). Urocortin, a 40-amino acid peptide and a member of the CRF family, dose-dependently and potently decreased food intake and body-weight gain, as well as the rate of gastric emptying in *ob/ob* mice.

Gastric emptying is accomplished via gastric peristalsis, ie, coordinated distally propagated gastric contractions. Gastric contractions are regulated by gastric myoelectrical activity. The basic rhythm of gastric myoelectrical activity is called the gastric slow wave. Under normal circumstances, the gastric slow wave propagates distally and determines the frequency and propagation direction of gastric peristalsis. Numerous studies have shown that impaired gastric slow waves are associated with delayed gastric emptying. In this study, we hypothesized that gastric electrical stimulation would impair gastric slow waves and decrease the rate of gastric emptying and thus lead to a reduction in food intake and weight loss. The experiment was therefore designed to investigate the effect of gastric electrical stimulation on food intake, weight loss, and gastric slow waves. Due to technical limitations, the rate of gastric emptying was not assessed.

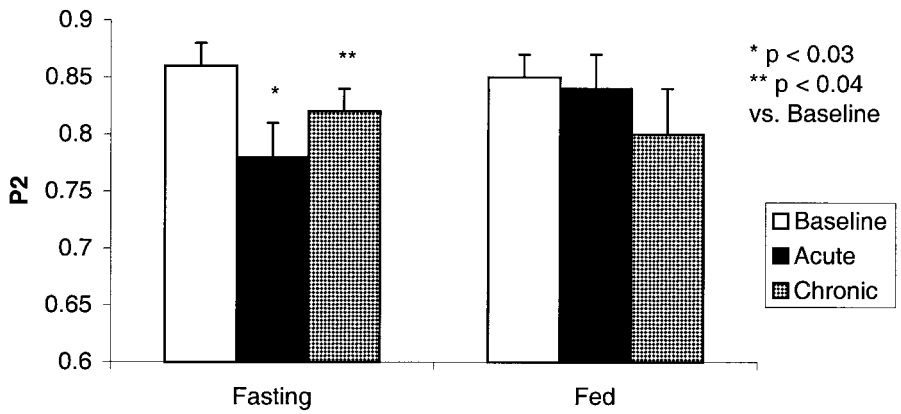

Fig 5. Effect of gastric electrical stimulation on parasympathetic activity. The parasympathetic activity in the fasting state was significantly decreased with gastric electrical stimulation both acutely ($P < 0.03$, before and after the immediate turn-on of the stimulator) and chronically ($P < 0.04$, before and after one month of stimulation). However, no significant effects were noted in the postprandial state.

Interestingly, gastric electrical stimulation was found to have an inhibitory chronic effect on gastric slow waves in the postprandial state. It had no acute effect on gastric slow waves in the fasting or fed state, and no chronic effect in the fasting state. Although it is unknown why chronic gastric electrical stimulation inhibited gastric slow waves in the fed state but not in the fasting state, several previous motility studies have shown that in patients with motility disorders, such as delayed gastric emptying, impairment in gastric slow waves usually occurs in the postprandial state (29). It is conceivable that the rate of gastric emptying is associated with the normality of gastric slow waves in the postprandial state instead of the fasting state. The absence of an acute effect of gastric electrical stimulation on gastric slow waves was probably attributed to the low stimulation energy used in this study. In several pervious studies (30–32) in our laboratory, we applied gastric electrical stimulation with a pulse width of several hundred milliseconds (about 1000 times more potent than the current study) and found that gastric slow waves could be completely altered a few minutes after the initiation of electrical stimulation.

The inhibitory effects of chronic gastric electrical stimulation on the gastric slow wave involved a reduction in amplitude and impairment in rhythmicity. All these effects are believed to lead to an impairment of gastric motility. The amplitude of the gastric slow wave is associated with the contractility of the stomach. Physiologically, there is an increase in slow-wave amplitude when the stomach contracts or contracts at a higher amplitude, such as in the postprandial state (33) as well as during the phase III (the period during which the stomach has regular and maximum contractions in the fasting state) of the migrating motor complex (34, 35). Pharmacologically, several studies have shown a concurrent increase in both gastric contractility and slow-wave amplitude with prokinetic agents, such as erythromycin and cisapride, or a concurrent decrease with inhibitory agents, such as octreotide or cholecystokinin (36).

The rhythmicity or percentage of regular 4–6 cpm slow waves is also associated with gastric motility. Excessive gastric dysrhythmia or a reduced percentage of normal slow waves is related to gastric hypomotility and/or delayed gastric emptying (16, 37). In a previous study with simultaneous recordings of gastric emptying and gastric slow waves in patients with suspected gastroparesis, we found that more than 80% of patients with the percentage of normal slow waves below 70% had delayed gastric emptying (38). In this study, the percentage of normal slow waves was substantially reduced when the stimulator was turned on. During the fourth month with the stimulator on, the percentage of normal slow waves was below 70%.

Impairment in gastric slow waves is often associated with dyspeptic symptoms, such as nausea, vomiting, abdominal bloating, and early satiety (13). In this study, however, no vomiting was noted, no symptoms related to nausea were observed, and no behavioral changes were recorded.

The activity of the autonomic nervous system, especially the parasympathetic activity, can be assessed in the frequency domain using spectral analysis of the heart rate variability derived from the electrocardiogram. The spectral analysis of the heart rate variability is regarded as a new probe for the quantitative evalution of autonomic activity because it is noninvasive and easy to perform. The spectral analysis method is a well-established methodology for the noninvasive assessment of parasympathetic activity (39–41). In this current study, a significant decrease in parasympathetic activity in the fasting state was noted both acutely and chronically. However, this change was not observed in the postprandial state. Several previous studies have reported that the ingestion of a meal alters parasympathetic activities (42, 43). The insignificant results of gastric electrical stimulation on the postprandial parasympathetic activity might be attributed to the confounding effect of food ingestion.

Although this is a pilot study, and the experiment was not performed in an obese animal model, our data revealed possible mechanisms involved with gastric electrical stimulation. In previous clinical studies, Cigaina et al (12) used the same technique of gastric electrical stimulation and observed a significant reduction in weight in patients with obesity without any physiological measurements. The data in the current study suggest the reduction in weight with gastric electrical stimulation might be attributed to impairment in gastric slow waves and inhibition of parasympathetic activity.

In summary, chronic gastric electrical stimulation results in a reduction of food intake, weight loss, a reduction in parasympathetic activity, and chronic inhibition of gastric myoelectrical activity. These data suggest that gastric electrical stimulation is a potential therapy for the treatment of obesity, and its inhibitory effect on food intake and weight may involve both muscles and the vagal afferent pathway.

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