Pacing the canine stomach with electric stimulation

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KELLY, KEITH A. AND RICHARD C. LA FORCE. Pacing the canine stomach with electric stimulation. Am. J. Physiol. 222(3): 588-594. 1972.—Certain aspects of gastric electric activity in six conscious dogs were controlled by electric stimulation from encircling and point gastric electrodes. The natural gastric pacemaker potential (PP) arose in the orad corpus at a mean frequency of 5.0 ± 0.1 cycles/min and was propagated aborad. Rectangular electric pulses given 5 times/min generated PP at the cathode of each type of electrode, except in the fundus, and simultaneously suppressed the natural PP. The PP propagating aborad had the same configuration and time of propagation as the natural PP; that propagating orad had a different configuration but the same time. The frequency of the generated PP could be increased to 8.0 or decreased to 4.2 cycles/min by changing the frequency of the stimulus. When electric stimulation was stopped, the natural PP reappeared after one to four natural periods. Gastric instillation of 500 ml of water at 37 C reduced the mean frequency of the PP from 4.9 to 4.1 cycles/min within 5 min, but did not affect the frequency of response to stimulation at 5.1 pulses/min.

gastric electric activity; gastric smooth muscle; gastric motility; electrophysiology of smooth muscle

RECENT EXPERIMENTS HAVE SHOWN that a gastric pacemaker is present in the orad corpus of the canine stomach near the greater curvature (9, 21). The pacemaker generates a regular, cyclic change in electric potential called the "pacemaker potential" (PP), slow wave, or initial potential (8) at a frequency of about 5 cycles/min (10). The PP is propagated with increasing velocity from its site of origin in the orad corpus to the gastroduodenal junction. It has been proposed that as it sweeps caudally through the gastric wall the PP synchronizes the gastric smooth muscle so that when contractions occur, they will be coordinated and peristaltic instead of disorganized and random (7).

The object of these experiments was to control the canine gastric pacemaker potential in the conscious dog by electric stimulation.

METHODS

Six mongrel dogs weighing between 10 and 14 kg were used. Electric stimulation was performed through two kinds of chronically implanted silver electrodes. The first type consisted of a pair of silver wires 0.25 mm in diameter and about 10 cm in length. Insulated copper leads were soldered to the midpoint of each wire and connected to a radio tube socket mounted with epoxy resin in a stainless steel cannula. The second type consisted of silver point electrodes 1 mm in diameter that projected 2 mm from an acrylic plastic disk similar to disks used previously in this labora-
tory (1). The shafts of the electrodes were insulated, but their tips were exposed. Silver chloride was deposited electrolytically on the tips. The electrodes were soldered to copper wires, and the soldered junctions were then cast within the insulating acrylic disks. Two holes were drilled in each disk and sutures passed through the holes to anchor the disks to the stomach. The insulated copper wires led from the disks to pins in the same radio tube socket to which the first type of electrodes were attached.

All electrodes were implanted at operation using sterile technique in animals anesthetized with sodium pentobarbital. Four dogs (dogs 1, 2, 3, and 4) received both types of electrodes, while only point electrodes were implanted in dogs 5 and 6. The silver wire electrodes were threaded entirely around the stomach so that they completely encircled the viscus parallel to the circular muscle. The wires were placed 1 cm apart with the more caudal ones 3 cm orad to the pylorus, and both rested on the gastric serosal surface. After positioning, the ends of the wires were twisted together, excess wire was trimmed off, and the wires were anchored in place with sutures. Subsequently these electrodes will be referred to herein as encircling electrodes.

Point electrodes were implanted on the anterior serosal surface of the stomach along a longitudinal axis midway between the greater and lesser curve. In dog 1, four of these electrodes were used, the first of which was 1 cm orad to the proximal encircling electrode. The second, third, and fourth electrodes were positioned 1 cm apart, beginning 1 cm aborad to the distal encircling electrode.

Dogs 2, 3, and 4 each had eight point electrodes. Two were positioned 1.5 cm apart in the fundus; three were 6.5, 4, and 2 cm orad to the proximal encircling electrode; one was between the encircling electrodes; and two were 1 and 2 cm aborad to the distal encircling electrode. Dogs 5 and 6 had four point electrodes sewn 2 cm apart, and the most distal was 2 cm aborad to the pylorus.

The animals were allowed 2 weeks to recover from the operation and then were investigated during 3–6 months. They were fasted for 18–24 hr before each recording session, were fully conscious during all experiments, and were conditioned to stand or rest comfortably in Pavlov slings. Adjacent pairs of electrodes were used for stimulation. The stimulator delivered rectangular pulses of current. The rectangular shape of the stimulus was confirmed by displaying the pulse on an oscilloscope. The amplitude of the stimuli employed ranged between 1 and 8 ma, the duration between 0.1 and 2 sec, and the frequency between 2 and 12 pulses/min. The pulse was usually well tolerated by the animals,
although, on occasion, when electrodes near the diaphragm or heart were being used for stimulation, the animals found the stimulus discomforting and became restless.

Myoelectric activity was recorded concurrently with stimulation. Point electrodes not being used for stimulation were connected through an alternating-current amplifier with a time constant of 1 sec to a Brush Mark V rectilinear pen recorder. The recordings were monopolar, with the indifferent electrode placed subcutaneously on each recording occasion in the anterior abdominal wall near the stomach. The electric apparatus was capable of recording frequencies up to 100 cycles/sec.

The recording amplifiers and the stimulator were electrically isolated from each other. Nonetheless, enough leakage current flowed within the dog at the time of stimulation to saturate the amplifiers. However, within milliseconds after terminating the stimulating pulse, the amplifiers recovered their full sensitivity.

After daily sessions of stimulation over several weeks, polarization sometimes developed at the electrodes so that it became more and more difficult to deliver a pulse of sufficient amplitude to generate PPs. A few days of rest were then allowed, after which the animals could again be stimula-

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>Before stimulation†</th>
<th>With stimulation‡</th>
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<tbody>
<tr>
<td></td>
<td>Mean Frequency of PP, cycles/min*</td>
<td>Maximum obtained</td>
</tr>
<tr>
<td>1</td>
<td>5.0 (n = 7)</td>
<td>7.2 (n = 7)</td>
</tr>
<tr>
<td>2</td>
<td>4.9 (n = 10)</td>
<td>7.3 ± 0.4</td>
</tr>
<tr>
<td>3</td>
<td>4.7</td>
<td>8.4 ± 0.4</td>
</tr>
<tr>
<td>4</td>
<td>4.9</td>
<td>9.1 ± 0.4 (n = 7)</td>
</tr>
<tr>
<td>5</td>
<td>5.2</td>
<td>7.2 (n = 3)</td>
</tr>
<tr>
<td>6</td>
<td>5.0</td>
<td>8.8 ± 0.3</td>
</tr>
<tr>
<td>Overall</td>
<td>5.0</td>
<td>8.0</td>
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* Values are means of 6 different days (n = 6) and SE of means = 0.1 or less, except where given. † Daily values were means over 5 consecutive min. ‡ PP consistently entrained by every stimulus when tested for 2 min or longer.

lulated successfully. Over a period of months, however, polarization became so extensive that threshold stimuli, that is, stimuli with a strength of 1 ma or greater, could not be delivered even though the maximal gain of the stimulator was used. At this time, experiments on the dog had to be terminated.

The recordings were analyzed by noting the occurrence, configuration, and rhythm of the PP at the site of each electrode. The frequency of the PP was determined by counting the number of cycles occurring during a 5-min period and expressing the result as the mean frequency in cycles per minute. The durations of 10 consecutive cycles of the PP were measured, and means and standard errors were determined. The time required for propagation of a PP from one electrode to the next adjacent electrode was noted on six sequential occasions for each pair of electrodes, and the mean time was computed.

Spontaneous gastric dysrhythmias were found on occasion in the fasting dog, and when they occurred, electric stimulation was commenced to determine if generation of a regular rhythm of PPs could be accomplished.

In addition, the response of four dogs on 3 separate days to the gastric instillation via an oral gastric tube of 500 ml of water at 37°C was noted both with and without electric stimulation at 5.1 pulses/min. The frequency of the PP was determined over a 5-min interval before and 1–6 min after instillation of the gastric instillate on each occasion.

RESULTS

All dogs recovered from the operation and were healthy throughout the study. They ate well, did not vomit, and maintained their weight.

Fasting control pattern. The pattern of gastric electric activity in the fasting dogs was similar to that described by others (10). The natural gastric PP was detected by all point electrodes in the corpus and antrum but not by those in the fundus. The initial portion of a typical cycle of the PP was usually triphasic and the second portion, isopotential (Fig. 1). The configuration of the waveform of the PP differed slightly between dogs and between recording sites,
but was characteristic for each dog at each electrode site and varied little from day to day. The frequency of the PP was the same wherever it was detected, and the mean frequency was 5.0 cycles/min (Table 1). The PP arose in the orad corpus and was propagated aborad to the pylorus.

**Electric stimulation during fasting.** The passage of a rectangular pulse of current 5 times per minute with a duration of 0.5 sec and an amplitude of 4-8 ma through both types of stimulating electrodes generated PPs, but not action potentials (spike potentials), in all areas of the stomach except the fundus. When stimulation was commenced, the natural PP was often recorded for an initial brief period at a frequency slightly different from that of the stimulus. Then, coupling took place between the stimulus and the excitable tissues in the gastric wall so that the frequency of the recorded PP corresponded exactly to the frequency of the stimulus, and the phase lag between the onset of the stimulus and the appearance of the generated PP at electrodes aborad to the site of stimulation was constant (Figs. 1, 2, and 3). Simultaneous suppression of the natural PP took place when coupling occurred, since PPs corresponding to the frequency of the natural pacemaker were no longer recorded (Fig. 1).

Pacesetter potentials were generated both when action potentials (spikes) were occurring spontaneously with the natural PP and when they were not present. If action potentials were present before stimulation, they also appeared with the generated PP. If action potentials were not present before stimulation, they usually were not found with the generated PP (Figs. 1 and 2).

The generated PP detected by electrodes aborad to the site of stimulation had the same configuration as the natural PP (Figs. 1 and 2), but that detected by electrodes placed orad to the site of stimulation often had a larger amplitude of negative deflection of the triphasic complex (Fig. 2).

The generated PP was propagated from sites of electric stimulation both orad through the corpus and aborad to the gastroduodenal junction, but it was not propagated into the gastric fundus. The time required for propagation of the generated PP between any two electrodes was the same whether the PP was propagating orad or aborad (Table 2). The phase lag between the onset of the stimulus at the cathode and the appearance of the generated PP at electrodes aborad to the site of stimulation was unaltered when the duration of the stimulus was increased from 0.5 to 2.0 sec, and the frequency and amplitude of the stimulus were kept constant (Fig. 3). Also, when the more orad electrode of a pair of stimulating electrodes was used as the cathode, the generated PP appeared sooner after onset of the stimulus at a recording electrode aborad to the site of stimulation than when the more orad of the pair of stimulating electrodes was used as the cathode (Fig. 4). These findings indicate that the onset of the stimulus at the cathode was the electric event that generated the PP.

The frequency of the generated PP could be increased to a mean of 8.0 or decreased to a mean of 4.2 cycles/min by changing the frequency of the stimulus (Table 1). Simultaneous suppression of the natural PP occurred. Outside these limits the PP from the natural pacemaker reappeared, and stimulation no longer consistently generated a PP. Increasing the frequency of the stimulus to about twice the frequency of the natural pacemaker, however, generated PPs with every other stimulus and again suppressed the natural PP (Fig. 5).

**TABLE 2. Effect of electric stimulation of stomach on propagation of canine gastric pacesetter potential**

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>Mean Seconds for PP Propagation*</th>
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<tr>
<td></td>
<td>Between adjacent orad electrodest</td>
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<tr>
<td></td>
<td>Before stimulation</td>
</tr>
<tr>
<td>1</td>
<td>5.9</td>
</tr>
<tr>
<td>2</td>
<td>4.8</td>
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<tr>
<td>3</td>
<td>4.6</td>
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<tr>
<td>4</td>
<td>2.8</td>
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* Of 10 consecutive cycles; se of means = 0.1 or less. † To site of stimulation. ‡ Using pulses with amplitude 4 ma, duration 0.5 sec, and frequency between 5.0 and 5.5 pulses/min.

**FIG. 3. Phase lag between onset of stimulus and appearance of generated PP was unaltered when duration of stimulus was increased from 0.5 to 2 sec, and frequency and amplitude of stimulus were kept constant at 5 pulses/min and 5 ma.**
at electrodes 5–8 cm orad to the pylorus (frequency, 5 pulses/min; amplitude, 4–8 ma; duration, 0.5 sec) and the stimulus then stopped, the first natural gastric PP appeared between one and four natural periods after the last generated PP was detected at electrodes distal to the site of stimulation. After two natural cycles had reappeared, the same electric stimulus was resumed for five more cycles, stopped, and again the interval for reappearance of the natural PP was within the same range. Ten replications of this sequence showed that the natural PP always reappeared after one and before four natural periods had elapsed (Fig. 7). The period of the natural PP shortened progressively

FIG. 6. Every other stimulus at 3.3 pulses/min, 0.5 sec, and 4 ma generated a PP and suppressed natural PP. A compensatory pause occurred after generated PP, and natural pacesetter potential was again detected at its natural period.

FIG. 7. Delay after stopping electric stimulation, expressed in elapsed natural PP periods, between last pacesetter potential stimulated electrically and first generated by natural pacemaker, as detected by an antral electrode distal to site of stimulation (10 trials per dog). Mean natural PP periods are of 10 consecutive cycles before stimulation. Standard error for each mean was <0.1.

Slowing the frequency of the stimulus to less than a mean of 4.2 pulses/min resulted in generation of PPs only when the stimulus occurred during the latter portion of the cycles of the natural PP. When the ratio between the period of the stimulus and the period of the natural PP was about 3:2, every other stimulus generated a PP and simultaneously suppressed the natural PP (Fig. 6). After generation of a PP by the stimulus, a compensatory pause occurred so that two natural periods elapsed between the onset of the natural PP preceding and that following a generated PP. The natural PP was then detected again at its natural period (Fig. 6).

When five consecutive cycles of the PP were generated
after the sequence of electric stimulation was stopped and returned to its prestimulation value in 3–6 min.

After electric stimulation was stopped, the PP could be detected by point electrodes that had just been used for stimulation. However, the configuration of the triphasic complex of the PP recorded by these electrodes was usually distorted temporarily (10–30 min), and its amplitude was often smaller than before stimulation.

Spontaneous gastric dysrhythmias were found 3 times in the fasting dog. On these occasions, electrodes in the antrum recorded a rapid, irregular PP with a frequency of 12–16 cycles/min, while electrodes in the corpus recorded simultaneously PPs at 5 cycles/min, the frequency of the usually dominant corporal pacemaker. These rapid, antral rhythms were converted to the slower, regular rhythm of the natural pacemaker by electric stimulation (Fig. 8).

Electric stimulation during gastric instillation of water. Gastric instillation of 500 ml of water at 37°C decreased the mean frequency of the PP from 4.9 to 4.1 cycles/min within 5 min (Table 3). In contrast, when the stomach was being stimulated electrically at a frequency of 5.1 pulses/min, the same instillation produced no change in the frequency of the PP.

**Discussion**

Our report shows that gastric PPs can be generated at the cathode of a pair of stimulating electrodes when a suitable electric pulse is delivered to the gastric wall of a conscious healthy dog.

Bülbüring, Burnstock, and Holman (6), Tamai and Prosser (20) and, more recently, Mills and Taylor (13) and Specht and Bortoff (19) have reported the entrainment of slow waves (PPs) in longitudinal strips of intestinal muscle by electric stimulation in vitro.

In contrast, attempts to generate PP and to control gastrointestinal motility electrically in the intact gut have met with little documented success. Bilgutay et al. (4) stimulated the stomachs of dogs and humans using electric stimuli given at 1-min intervals with a frequency of 50 cycles/sec, a duration of 5 sec, and an amplitude of 7–10 ma. They saw augmented gastric contractions fluoroscopically and described increased gastric emptying. However, no recordings of either electric or mechanical activity were obtained so that it is difficult to interpret their report. Also, others using similar or identical methods of stimulation to those of Bilgutay et al. were unable to alter patterns of postoperative gastrointestinal motility (14, 17) or to stimulate gastrointestinal contractions (3). Kobayashi, Nagai, and Prosser (11) stimulated the intestine of anesthetized cats with shocks of a “variety of durations and amplitudes,” but were unable to produce PP. They do not state the frequencies of the shocks they gave. Atanassova (2) could not generate PPs in the canine gastric wall with direct-current stimuli of 60–120 μA delivered over 60–90 sec, although she did produce action potentials (spike potentials).

In the past, the failure of workers to generate PPs in the intact gut may have been due to the methods of stimulation. Although Bilgutay et al. (4) used bursts of high-frequency electric impulses and Atanassova (2) used direct-current pulses, both delivered these stimuli over periods that were long in comparison to 12 sec, the period of the natural pacemaker. By delivering electric stimuli at a frequency and with a rhythm similar to those of the natural gastric pacemaker, we were consistently able to produce PPs in the present experiments.

The electric stimuli used in these experiments generated PPs at the cathode of both point and circular stimulating electrodes. The calculated density of current at the electrode tips at the site of stimulation in these experiments was enormous, being in the range of 500 ma/cm² at point electrodes and 25 ma/cm² at circular electrodes. However, much of the stimulating current probably was conducted through the surrounding extracellular fluid rather than through the stimulated muscle. At any rate, PPs and action potentials could be recorded from electrodes immediately after they had been used for stimulation, providing evidence that stimulation did not extensively destroy the gastric smooth muscle in the region of the electrodes. Whether the electric stimuli acted on neurons in the gastric wall or directly on the smooth muscle is unknown.

The generated PP that propagated aborad from sites of electric stimulation had the same configuration and required the same time for propagation between electrodes as the natural PP. This suggests that the configuration and the time of propagation of the PP are determined by the characteristics of the gastric wall and the direction and pathway through which the PP is propagated, rather than by the type of stimulus initiating the phenomenon.

The observation that propagation occurs aborad and oral from the site of stimulation is compatible with the concept of an electric syncytium of smooth muscle in the stomach.
gastric wall as proposed by Bozler (5) for other types of visceral smooth muscle. Bidirectional propagation with identical propagation times is also evidence for electric spread of the PP through the gastric wall and against chemical transmission, such as might occur by release of acetylcholine at a synapse between two neurons.

The generation of propagated PPs by electric stimulation does not necessarily mean that gastric contractions or peristalsis ensued. Action potentials always occur with the PP when contractions are present, and action potentials were not generated by the type of stimulus used in these experiments. Our data show that the frequency of the PP in the conscious dog could be increased from 5 to 8.0 cycles/min by increasing the frequency of the electric stimulus. When the duration of the interval between stimuli was shortened to a mean of less than 7.5 sec, however, PPs could no longer be generated consistently. Thus, 7.5 sec was the refractory period to these electric stimuli. Daniel and Irwin (8) also have described a refractory period of about 8 sec, which occurs after the appearance of a PP in the canine antrum and during which a premature PP could not be initiated by an intra-arterial bolus of acetylcholine.

In contrast to our experiments in the conscious dog, the maximal driven frequency achieved by Specht and Bortoff (19) in their in vitro strips of feline intestine was only 12–25% greater than the intrinsic frequency of the strips. The intrinsic frequency of the PP in their duodenal and jejunal strips was 9.7 and 8.7 cycles/min, respectively—about half the frequency detected by others in the intact upper part of the small intestine of the cat (22). Thus, the maximal driven frequency in vitro was even less than the natural frequency in vivo. These differences may be due in part to the fact that Specht and Bortoff (19) conducted their experiments at 30°C. They also found that the velocity of propagation of the PP decreased as the driven frequency increased, whereas the velocity was not altered by changes in the frequency of the driving stimulus in our experiments. The behavior of feline intestinal muscle in vitro differs from that of canine gastric muscle in vivo.

The frequency of the generated PP could be decreased almost 1 cycle/min in these experiments by increasing the interval between electric pulses. Simultaneous suppression of the natural PP occurred. Since the natural PP had a mean period of 12 sec before stimulation, the electric stimuli must have temporarily lengthened the period and slowed the frequency of the natural pacemaker. Frequency pulling between the site of electric stimulation and the site of the natural pacemaker occurred in such a way that the stimuli decreased or pulled down the higher frequency of the natural pacemaker. Otherwise, the natural PP would have appeared at some point between the cycles of the slower, electrically generated PP. However, this frequency pulling had limits. When the interval between electric stimuli was longer than 14 sec, the natural gastric PP reappeared, and its period was then the same as before stimulation.

Nelsen and Becker (15) have proposed that intestinal smooth muscle acts like a matrix of loosely coupled, relaxation oscillators, and Sarna, Daniel, and Kingma (18) have applied this model to the stomach. According to both groups of workers, pacemaking sites oscillate with the most rapid frequency and thereby entrain or couple other areas where intrinsic frequencies are lower. Our data lend some support to such a model. Entrainment of the gastric corpus and antrum followed electric stimulation at a single site in the gastric wall at frequencies the same as, or faster than, the natural pacemaker in these experiments. However, entrainment also occurred at frequencies of stimulation slightly slower than the natural pacemaker. Entrainment at stimulating frequencies slower than the natural frequency has not been predicted by the model, but may still be consistent with it.

The ability to control gastric electric activity, not only during fasting, but also when gastric dyssrhythmias occur and after gastric instillation of water, may prove useful when gastric diseases (12) or gastric operations, such as vagotomy (16), produce disturbances of gastric electric activity.

References


15. Nelsen, T. S., and J. C. Becker. Simulation of the electrical and...


