Origin and propagation of the slow wave in the canine stomach: the outlines of a gastric conduction system

Wim J. E. P. Lammers,1 Luc Ver Donck,2 Betty Stephen,1 Dirk Smets,2 and Jan A. J. Schuurkes3

1Faculty of Medicine and Health Sciences, Department of Physiology, United Arab Emirates University, Al Ain, United Arab Emirates; 2Department of Internal Medicine, Johnson & Johnson Pharmaceutical Research and Development, a Division of Janssen Pharmaceutica, Beerse, Belgium; and 3Movetis, Turnhout, Belgium

Submitted 6 October 2008; accepted in final form 6 April 2009

Lammers WJ, Ver Donck L, Stephen B, Smets D, Schuurkes JA. Origin and propagation of the slow wave in the canine stomach: the outlines of a gastric conduction system. Am J Physiol Gastrointest Liver Physiol 296: G1200–G1210, 2009. First published April 9, 2009; doi:10.1152/ajpgi.90581.2008.—Slow waves are known to originate orally in the stomach and to propagate toward the antrum, but the exact location of the pacemaker and the precise pattern of propagation have not yet been studied. Using assemblies of 240 extracellular electrodes, simultaneous recordings of electrical activity were made on the fundus, corpus, and antrum in open abdominal anesthetized dogs. The signals were analyzed off-line, pathways of slow wave propagation were reconstructed, and slow wave velocities and amplitudes were measured. The gastric pacemaker is located in the upper part of the fundus, along the greater curvature. Extracellularly recorded slow waves in the pacemaker area exhibited large amplitudes (1.8 ± 1.0 mV) and rapid velocities (1.5 ± 0.9 cm/s), whereas propagation in the remainder of the fundus and in the corpus was slow (0.5 ± 0.2 cm/s) with low-amplitude waveforms (0.8 ± 0.5 mV). In the antrum, slow wave propagation was fast (1.5 ± 0.6 cm/s) with large amplitude deflections (2.0 ± 1.3 mV). Two areas were identified where slow waves did not propagate, the first in the oral medial fundus and the second distal in the antrum. Finally, recordings from the entire ventral surface revealed the presence of three to five simultaneously propagating slow waves. High resolution mapping of the origin and propagation of the slow wave in the canine stomach revealed areas of high amplitude and rapid velocity, areas with fractionated low amplitude and low velocity, and areas with no propagation; all these components together constitute the elements of a gastric conduction system.

slow wave; pacemaker; velocity; amplitude; gastric conduction system

The first electrical recordings from the serosal gastric surface have shown the omnipresence of the slow wave cycle (1, 5, 30, 46). Kelly and coworkers (18, 19) used 6–10 extracellular electrodes sutured to the stomach to determine the origin and the pattern of propagation of the gastric slow wave. Similar studies were performed with electrodes oriented in the longitudinal direction along the greater curvature, midway between the greater and the lesser curvature, and oriented in the circular direction (7, 20, 34, 35). All of these studies have expanded on the original concept of a slow wave that seemingly originates from the mid- or the upper corpus, does not activate the fundus, and propagates aborally with gradually increasing velocity and amplitude (42).

Fig. 1. Recording electrode arrays used in this study and their locations on the ventral surface of the canine stomach. A: two types of electrode arrays were used to record slow wave activity at high resolution from particular areas: a rectangular electrode was used on the corpus (location C) and an octagonal array that was positioned on either the fundus or oral corpus (F1, F2), on the corpus/antrum (location C-A), or the antro-duodenal area (location A-D). B: size and electrode distribution of the large electrode array shaped to cover as much as possible the ventral stomach surface. Interelectrode distances: rectangular array: 2 mm; octagonal array: 2.5 mm; large array: 5 mm. These panels are shown as insets in Figs. 2–6 to indicate the position of the electrode array on the stomach.

Address for reprint requests and other correspondence: W. J. E. P. Lammers, Dept. of Physiology, Faculty of Medicine and Health Sciences, P.O.Box 17666, Al Ain, United Arab Emirates (e-mail: wlammers@smoothmap.org).
with a similar recording technique (28). In the current study, several electrode arrays were used to perform detailed reconstruction of the normal propagation of the slow wave in several areas of the canine stomach ranging from the oral fundus to the distal antrum.

METHODS

Eighteen overnight fasted dogs (beagles, 10.9 ± 2.1 kg; 14 females, 4 males) were used in this study. Anesthesia was induced with scopolamine (0.015 mg/kg), fentanyl (0.070 mg/kg), and succinylcholine (1 mg/kg) and maintained throughout the duration of the experiments (3–4 h) with etomidate (1.5 mg·kg⁻¹·h⁻¹) and fentanyl (0.025 mg·kg⁻¹·h⁻¹). The animals were ventilated through a tracheal tube, and the left femoral artery was cannulated to record systemic blood pressure. Vital signs such as heart rate and blood pressure were monitored continuously as previously described (25). Housing, care, type of anesthesia, and experimental procedures were approved by the institutional ethics committee.

Following a median laparotomy, the abdominal walls were slightly retracted, and one of three available electrode arrays was carefully positioned on the ventral surface of the stomach. The electrode tips were flush with the recording surface of the assembly, and there were no protruding sharp edges that might otherwise have adversely affected the underlying tissue. A probe to monitor temperature in the experimental area was positioned alongside the stomach, and a heat lamp maintained the area at body temperature. After positioning the electrode assembly, the stomach was allowed to stabilize for 10 min before recordings were performed. At the end of the experiment, the animals were killed (pentobarbital sodium, 200 mg/kg iv).

Three different electrode arrays (Fig. 1), each containing 240 recording electrodes, were used: 1) a rectangular array (46 × 18 mm; interelectrode distance 2.0 mm), 2) an octagonal array (40 × 38 mm; interelectrode distance 2.5 mm), and 3) a large, slightly curved, array

---

**Fig. 2.** A: location of the rectangular electrode array on the canine corpus (C in Fig. 1). B: 24 electrograms recorded in the longitudinal direction. The red bars indicate the local timings of the first slow wave (in s) at each electrode location and, in the second slow wave, the blue brackets plot the amplitude of the waveforms. C: activation times for each individual electrode (time [t] = 0 ms at the electrode in top left). Isochrones were drawn manually around areas activated in steps of 1 s. The drawing of the grid was expanded horizontally to accommodate the digits. The column with circled digits represents the electrodes corresponding to the electrograms shown in B. D: slow wave propagation map in which the individual activation times have been left out and replaced by colored isochrones with additional symbols indicating timing (in s) and direction of propagation. The row with white circles indicates the electrogram recordings shown in B. E: display of direction and magnitude of local conduction velocities. F: mean velocity and amplitude (+SD) as calculated from values averaged along rows (indicated by the dashed rectangles in E) perpendicular to the red dotted line. Note that the no. of velocity bars is one less than the amplitude bars as the velocities are calculated across neighboring electrode sites (25), whereas amplitudes are measured at each site.
Table 1. Conduction velocity, amplitude, and frequency in four gastric regions

<table>
<thead>
<tr>
<th>Area</th>
<th>Pacemaker</th>
<th>Fundus</th>
<th>Corpus</th>
<th>Antrum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Velocity, cm/s</td>
<td>1.52 ± 0.91†</td>
<td>0.39 ± 0.21</td>
<td>0.49 ± 0.14</td>
<td>1.48 ± 0.57†</td>
</tr>
<tr>
<td>Amplitude, mV</td>
<td>1.76 ± 1.04†</td>
<td>0.69 ± 0.44</td>
<td>0.90 ± 0.52</td>
<td>2.02 ± 1.27†</td>
</tr>
<tr>
<td>Frequency, cycle/min</td>
<td>5.4 ± 0.9</td>
<td>4.9 ± 0.7</td>
<td>5.2 ± 0.4</td>
<td>5.0 ± 0.7</td>
</tr>
<tr>
<td>No. of maps/dogs</td>
<td>7/5</td>
<td>5/4</td>
<td>6/6</td>
<td>14/14</td>
</tr>
</tbody>
</table>

All values are means ± SD. *P < 0.001 (ANOVA). †P < 0.05, pacemaker area or antrum compared with fundus or corpus (Tukey).

(100 × 80 mm; interelectrode distance 5.0 mm). The rectangular array was used on the corpus (location C), whereas the octagonal array was used on the fundus, the oral corpus (locations F1 or F2), the antrum (location C-A), or on the pyloric region (location A-D). The large array (Fig. 1B) was positioned to cover the entire ventral surface of the stomach. Unipolar electrical recordings were performed with a subcutaneous needle in the back right leg acting as the indifferent pole.

The 240 recording electrodes were connected through shielded wires to 240 AC preamplifiers where the signals were amplified (×4,000), filtered (2–400 Hz), and digitized (1-kHz sampling rate) before being stored on the hard disk of a laptop.

For the off-line analysis, signals were digitally filtered (20-point moving average; low pass filter of ~40 Hz) and displayed on screen in sets of 10–30 electrograms (Fig. 2B). The activation time of a slow wave was determined as the point of maximal negative slope (25) and was marked with a cursor. The peak-to-peak amplitude of each waveform was also measured (Fig. 2B, inset). The activation times of each wave were then displayed on a grid representing the layout of the original recording electrode array (Fig. 2C). All activation times were related to the timing of the first slow wave detected in a map [electrode on top left; time (t) = 0.0 s]. Isochrones were drawn manually around areas activated in steps of 1 s (Fig. 2, C and D). From the local activation times, the direction and the magnitude of the slow wave propagation was calculated and plotted (Fig. 2E) (25). These velocities were then averaged in the direction of propagation (red dashed line) and plotted in a bar chart (Fig. 2F). The amplitudes of the local waveforms were also averaged in the direction of propagation and plotted in a similar manner.

A total of 57 recordings were made, ranging in duration from 2 to 6 min (average recording duration 4.7 min, total recorded time 270 min). After the experiment, all electrograms in a 64-s period were analyzed, and maps were created to determine the quality of the recordings and the major pattern of slow wave propagation. Once the pattern of propagation in a particular recording had been determined, a representative set of 10–24 electrograms was visually inspected while playing back the signals for the duration of the whole recording. If changes in rhythm or in sequence of excitation occurred, additional detailed analysis of such events was performed on all 240 electrograms. In this study, a total of 63 periods (67 min) was analyzed at this high resolution. The frequency of the normal rhythm was determined by measuring the cycle-to-cycle length of each successive slow wave in one representative electrogram.

Fig. 3. Initiation of the slow wave along the greater curvature close to the gastro-esophageal junction (F1 in Fig. 1). A: 16 signals recorded along the path of the slow wave (locations shown in white circles in B). Electrograms 1–9 display high-amplitude bi- or triphasic waveforms, whereas electrograms 10–16 show low-amplitude fractionated waveforms. B: propagation map of the slow wave with initial rapid propagation in the first 2 s (indicated by wider-spaced isochrones) and slower propagation thereafter (crowding of the isochrones). Isochrones are drawn every 0.5 s. The left side of the map, distant from the greater curvature, is not excited at all (block symbol; gray zone). C: local directions of conduction and velocity. The velocities were averaged in rows along the red dotted line and plotted in D demonstrating velocities of ~1.5 cm/s in the area activated in the initial 2 s of propagation and velocities of 0.5 cm/s beyond this area. A similar pattern was seen with the slow wave amplitude.
It is important to note that the extracellular recording technique used in this study only records the extracellular current generated by the depolarization of the slow wave potential and does not record the plateau nor the repolarization phase of the slow wave (4, 5, 17). Furthermore, because the dimension of the electrode tip (0.3 mm diameter) is quite large compared with the size of the cells, the potentials recorded are the sum of the depolarization of hundreds of cells in the recorded region.

Data are presented as means and SDs. Where appropriate, ANOVA was used to evaluate differences for statistical significance.

RESULTS

Figure 2 presents the major characteristics of slow wave propagation in the canine corpus. The waveforms had a relatively low amplitude (0.88 ± 0.43 mV) and often showed multiple small deflections similar to fractionated electrograms in the heart (Fig. 2B, inset) (10). The pattern of propagation in the corpus (Fig. 2D) was uniform, slightly curved toward the lesser curvature, and had a constant propagation velocity of ~0.5 cm/s. Similar results were seen in five other dogs (Table 1).

Figures 3–5 present the pattern of propagation of the slow wave in the canine fundus. At the most oral location (F1 as indicated in Fig. 1), slow wave propagation was limited to the area adjacent to the greater curvature. Initial waveforms in that area showed high amplitude (>1 mV; Fig. 3A), and the velocity map displayed rapid propagation of ~1.6 cm/s (Fig. 3, C and D). After the slow wave had propagated for ~2 s, velocity decreased to 0.5 cm/s and amplitude to 0.8 mV.

The oral part of the fundus is only partially exited by the slow wave that originates from the greater curvature. In Fig. 3, the distance travelled by the slow wave from the greater curvature in the fundus, before being blocked, was ~20 mm. This distance could vary from one slow wave to another, as shown in Fig. 4. In that recording, spontaneous variations occurred ranging from 10 to 22 mm (Fig. 4, slow waves A and B). The width of this excited area was measured in five dogs and varied between 15 and 30 mm (average 22 ± 5 mm). In the distal fundus (location F2; Fig. 5), no areas of inexcitability were detected (four dogs). The pattern of propagation in the distal fundus was uniform, with low amplitude signals (0.65 mV), fractionated waveforms (Fig. 5A), and a constant low velocity of 0.35 cm/s.

Unlike the pattern of propagation in the canine corpus, the antrum showed high-amplitude signals (3.1 mV; Fig. 6A) and high velocity (1.6 cm/s; Fig. 6D). Similar patterns and amplitudes were observed in 14 dogs (Table 1).
The slow wave did not propagate across the pylorus but was blocked at the antro-duodenal junction (Fig. 7). An area where no propagation occurred was always found between the region activated by the stomach pacemaker and the region activated by the duodenal pacemaker. The length of this unexcited region was 9.7 ± 4.6 mm (n = 5 dogs). Additionally, spikes could be seen in most dogs at 5–11 locations in the distal antrum (~10% of the total area activated in the antrum). The spike patch shown in Fig. 7C was one of the largest seen in this study.

In four dogs, the large electrode array (Fig. 1B) was used to record from the entire ventral surface of the stomach. As shown in Fig. 8A, slow waves were regularly initiated at a frequency of 5.5 cycle/min from a site located near the esophageal junction on the fundus (Fig. 8B). Propagation of the slow wave occurred uniformly along the length of the stomach and took ~40–50 s to reach the distal stomach. Occasionally, a slow wave was blocked that momentarily decreased the frequency in the distal stomach (Fig. 8A).

Because of the time required for the slow wave to reach the distal antrum, new slow waves were already being generated while previous slow waves were still propagating in the aboral direction. As indicated by the vertical line in Fig. 8A, there were four separate slow waves propagating simultaneously along the stomach at that moment in time (Fig. 8C, waves a, b, c, and d). In the accompanying animation,1 it can be seen that the number of simultaneously propagating slow waves fluctuated between three and five.

The velocity and the amplitude of the slow wave, as it propagated from the oral fundus to the distal antrum, was measured as shown in Figs. 2, 3, 5, and 6. This was done for a total of 32 maps, recorded from locations F1, F2, C, and C-A (Fig. 9). For the majority of the stomach, the amplitude and velocity of the slow wave was constant at ~0.9 mV and 0.5

---

1 An animation of slow wave propagation (Fig. 8) is available at www.smoothmap.org or at www.youtube.com, search “stomach slow wave propagations.”
In the pacemaker area, located in the oral fundus, and in the antrum, slow wave velocity was significantly higher (1.52 ± 0.91 and 1.48 ± 0.57 cm/s, respectively; \( P < 0.001 \), Table 1) as was the amplitude of the waveforms (1.76 ± 1.04 and 2.02 ± 1.27 cm/s, respectively; \( P < 0.001 \); Table 1). The frequency of the slow waves was similar in the different regions of the stomach (\( P = 0.832 \); Table 1).

**DISCUSSION**

The major findings in this first high-resolution electrical mapping of the stomach are: 1) the slow wave pacemaker is located along the greater curvature high in the fundic area, 2) the pacemaker area is characterized by high-amplitude potentials (1.8 mV) and high-propagation velocity (1.5 cm/s),
3) propagation through the distal fundus and the corpus is slow (0.4–0.5 cm/s) with fractionated low-amplitude (0.4–0.9 mV) potentials, and 4) propagation in the antrum is fast (1.5 cm/s) with high-amplitude potentials (2.0 mV). Finally, because of the long distance between the pacemaker area and the distal antrum, the overall low propagation velocity, and the frequency of the pacemaker, there are three to five separate slow waves propagating simultaneously along the stomach.

Several of these findings constitute significant expansions of earlier results. For example, the location of the pacemaker, as determined by electrical recordings (18, 20) or surgical incisions (19, 46), has been assumed to be located along the greater curvature. The results in this study support that concept but suggest a more oral location. This refinement was made possible by the high spatial resolution of the recording electrodes (2 mm interelectrode distance in 2 dimensions), which makes it possible to identify the propagation of low-amplitude signals from one location to the next (Fig. 2B, inset).

New is our observation that the signals in the pacemaker area differ from the surrounding area, displaying high-amplitude potentials and rapid velocity. Another refinement is the mode of propagation of the slow wave in the fundus itself. We consistently observed low-amplitude fractionated propagation in the fundus close to the greater curvature. There have been a few studies (2, 36, 43) reporting slow wave signals in the fundus, and we can confirm and expand that this is restricted to the immediate vicinity of the greater curvature, at least in the oral fundus. Careful rereading of several classics reveal early observations of a pacemaker located in the upper part of the stomach. Alvarez and Mahoney (1) noted that regular contractions “develop in ripples which come from the neighborhood of the cardia,” a location that was supported by Bozler (5). More recent studies have shown the existence of interstitial cells of Cajal (ICC)-intramuscular (IM) in the fundus (9, 40). Interestingly, pathology such as diabetes or the lack of ICC may remodel the fundus to exhibit or enhance spontaneous activity (15, 32). We also cannot exclude that pacemaker activity could have been unmasked by the anesthesia used. Some reports have suggested that increasing the functional load by a Billroth II surgery (2) or by hyperpolarizing the fundic muscle (42) might uncover or stimulate the pacemaker activity. Furthermore, the border between the excited and the nonexcited fundus is not
necessarily fixed and may vary from one cycle to the next (Fig. 4). Most importantly, this fundic area of slow propagating wave fronts links the natural pacemaker to the rest of the stomach. Indeed, if a block occurs in this region, this will have an immediate effect on the rhythm in the distal stomach (Fig. 8). (39).

By quantifying the conduction velocity and amplitude with high spatial and temporal resolution, we were able to identify in terms of electrical properties three different areas in the stomach: 1) the fundic pacemaker area, 2) the fundus and the corpus, and 3) the antrum. In addition, contrary to the current prevailing view that the slow wave gradually increases in speed as it propagates toward the antrum (18), we did not find such an increase. Instead, as evidenced by tracings 9–10 in Fig. 3 (fundus) and tracings 8–9 in Fig. 6 (corpus to antrum), the transition in velocity and amplitude from one area to the next occurred abruptly, indicating the existence of a clearly demarcated border of at most a few millimeters wide. Detailed studies have revealed the presence of several types of ICC, amongst others ICC-Auerbach’s plexus (AP) and ICC-IM in...
the stomach (8, 9, 13). The ICC-AP are thought to be responsible for the slow wave propagation in the antrum (12, 13). Recent reports have identified ICC-IM as the dominant ICC responsible for propagation in the corpus (11, 41). This suggests that the differences in slow wave velocity and amplitude seen in different parts of the stomach are due to the fact that the slow wave propagated through different types of ICC. Indeed, Komuro (21) recently commented on the fact that the stomach, in contrast to other gastrointestinal organs, is unique in its spatial distribution of several types of ICCs, a fact that could be reflected in the recorded potentials in this study. It remains to be determined which cell type is responsible for the initiation and propagation of the slow wave in the pacemaker area.

Propagation in the antrum (Fig. 6) is very similar to that shown in a previous study on antral arrhythmias (28) with large bi- or triphasic signals and rapid velocity. Slow waves always terminated in the distal antrum, and there was a large area of nonpropagation between the antrum and the duodenum (Fig. 7). This is similar to what has been shown in vivo (3) and in vitro in other species (22, 44) and is caused by a regional decrease in ICC-AP (45). Spike activity was regularly seen in the distal antrum with propagation limited to small areas (Fig. 7C; Refs. 23, 24) similar to what has been shown in humans (14).

There is a crucial difference in the propagation pattern in the intact organ and in an excised segment. In the intact stomach, there is only one pacemaker, high up in the stomach along the greater curvature. Propagation from this area is initially radial, propagating both in the longitudinal and in the circumferential direction (arrows 1 and 2 in Fig. 10). This is the same pattern as with slow wave pacemakers in the small intestine (26, recently reviewed in Ref. 16). Further away from the pacemaker, however, the wave front organizes itself toward the aboral and longitudinal direction (arrows 3 in Fig. 10). In other words, in the intact stomach, except for the immediate vicinity of the pacemaker, we have not observed any circumferential propagation. In the excised segment, however, where the connection with the natural pacemaker is disrupted (29, 33), the spontaneous activities of local ICCs will emerge, and propagation from those local pacemakers will occur in all directions, in the longitudinal and the circumferential directions.

There are reports that support the notion of several slow waves simultaneously present in the stomach. Cannon (6) showed the appearance of two peristaltic waves progressing at the same time, and this contraction pattern has been reviewed recently (38). The fact that, on average, four slow waves are simultaneously present on the stomach may cause problems in interpreting the EGG. In the heart, during systole, the electrical propagation spreads over the entire organ, followed by a period of quiescence (diastole). The stomach, however, exhibits multiple propagating slow waves, and there are no periods of "systole" or "diastole." However, judging from the data presented in Fig. 8, most of the waves are located in areas that show slow propagation and low-amplitude signals (fundus and antrum).
corpus), and the cutaneous EGG signal may rely mostly, if not entirely, on the larger current amplitude generated in the antrum.

In summary, this study has identified three distinct areas with distinct electrophysiological properties in the stomach; two of these areas showed slow waves with high amplitude and propagation velocity while the third area, consisting of the fundus and the corpus, showed low slow wave amplitude and propagation velocity. In addition, two areas were found in which slow wave propagation did not occur at all: the first near the esophageal junction in the fundus, close to the lesser curvature, and the second between the distal antrum and the duodenum. Together, these elements constitute a conduction system (Fig. 10) that underlies the basis for the pattern of contraction in the normal stomach (37). This knowledge of the location and the properties of this system is also required for a better understanding of the dysfunctional stomach, be it in the context of gastric arrhythmias, gastroparesis, diabetes, or surgical interventions, especially in those that are now popular in the treatment of esophageal reflex or obesitas. For example, fundoplasty or other surgical procedures may accidentally have repercussions on the function of the natural gastric pacemaker or its connection to the remainder of the stomach, as was stated many years ago (31). A better and more detailed understanding of the gastric conduction system in the human is therefore required to enhance the quality of treatment of these patients.

ACKNOWLEDGMENTS

We acknowledge the expert animal care provided by the staff of the Department of Laboratory Animal Science, in particular Jef Ceulemans, Piet Dierckx, and Leen Roefs. Dr. Brian Hrukpa is acknowledged for advice on style and writing.

REFERENCES


