*J. Physiol.* (1986), **371**, *pp.* 179–189
*With 5 text-figures*
*Printed in Great Britain*



# EFFECTS OF FREQUENCY ON THE WAVE FORM OF PROPAGATED SLOW WAVES IN CANINE GASTRIC ANTRAL MUSCLE

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(*Received 13 November 1984*)

SUMMARY

1. Experiments were performed to test the effects of frequency on the wave form of electrical slow waves in canine antral circular muscle.

2. At frequencies between 3·0 and 5·6 cycles per minute antral slow waves revealed an alternating wave form pattern.

3. At physiological frequencies antral muscle was incapable of consistently propagating mechanically productive slow waves.

4. Two components of the slow wave were identified on the basis of propagation refractory period. At inter-slow-wave intervals of 3–14 s, the amplitude and duration of the plateau phase wave decreased, but the upstroke phase of the slow wave was minimally affected. Intervals of 2·5–4 s resulted in a normal upstroke event but abolished the plateau. At shorter intervals the upstroke phase of the slow wave was greatly reduced or abolished.

5. The absolute propagation refractory period averaged $2{\cdot}8 \pm 0{\cdot}9$ s ($n = 7$) following repolarization of a 'conditioning' slow wave. Slow waves failed to propagate within the absolute propagation refractory period.

6. Acetylcholine decreased the interval required for the plateau phase of the slow wave to recover and permitted conduction of mechanically productive slow waves at or above physiological frequencies.

7. The data presented suggest that gastric motility is modulated by extrinsic and intrinsic factors which regulate slow-wave frequency.

## INTRODUCTION

Slow waves are recognized as the dominant electrical events triggering excitation–contraction coupling in the stomach (Papasova, Nagai & Prosser, 1968; Szurszewski, 1975, 1981). These events normally originate in the proximal stomach at a frequency of 4·5–5·7 cycles per minute (c.p.m.; Daniel & Chapman 1963; Kelly, Code & Elveback, 1969) and propagate toward the pylorus at a velocity of 8–40 mm/s (Carlson, Code & Nelson, 1966; Kelly *et al.* 1969; Sarna & Daniel, 1973). When antral muscle is removed from the gastric syncytium and studied *in vitro* it demonstrates intrinsic pace-maker activity at a much lower frequency (El-Sharkawy, Morgan & Szurszewski, 1978) and aboard propagation velocity is 6–10 mm/s (Bauer, Publicover

& Sanders, 1982; Publicover & Sanders, 1985). Such preparations have been studied widely and it has been generally assumed that the muscle, although intrinsically active at a lower frequency, is capable of propagating the events delivered to it by the proximal stomach. Recently, our laboratory has reported that conduction velocity in the distal stomach is significantly affected by pacing frequency, and this effect occurs predominantly in the long axis of the stomach, parallel to longitudinal fibres (Publicover & Sanders, 1985). This dependence of propagation on pacing frequency occurs in the physiological range of frequencies recorded from the stomach of conscious, healthy dogs (McCoy & Bass, 1963; Carlson *et al.* 1966; Nelsen, Eigenbrodt, Keoshian, Bunker & Johnson, 1967; Kelly *et al.* 1969).

In the present study we tested the effects of frequency on slow-wave shape. This is important because previous studies have shown that the magnitude of the contractile event in the antrum is dependent upon the amplitude and duration of the depolarization achieved during the plateau phase of the slow wave (Szurszewski, 1975; Morgan & Szurszewski, 1980; Szurszewski, 1981). If the cells of the antrum are unable to regenerate slow waves at frequencies set by the proximal stomach, then motor performance may be compromised. Inspection of some *in vivo* extracellular records in the literature reveals that at physiological frequencies, the duration (and therefore, possibly the amplitude), as determined by the time between the upstroke excursion and the plateau repolarization deflexion, alternate in length in successive events (Carlson *et al.* 1966). This suggests that the *in vivo* duration, and possibly the amplitude, is not constant from event to event, but may fluctuate.

Based on inspection of such records, the ability of antral muscles to propagate slow waves as a function of frequency was studied. In these experiments we determined (i) the propagation refractory periods for slow waves, and (ii) whether or not each component of the slow wave was dependent on frequency. The experiments were conducted *in vitro*, and intracellular recordings of membrane potential were made so that various slow-wave parameters could be quantified.

## METHODS

Mongrel dogs of either sex were anaesthetized with sodium pentobarbitone 30 mg/kg. After opening the abdomen the entire stomach was removed and placed in a bath of Krebs–bicarbonate solution. A sheet of muscularis from the ventral surface, 7–9 cm proximal to the pyloric junction, was removed from the underlying submucosa.

The muscle was pinned out in a dish and a strip, 3 × 15 mm, was cut parallel to the circular muscle layer. The strip was turned on its side and half of the circular muscle was trimmed away and discarded. The remaining circular muscle strip, which also included the full thickness of the longitudinal muscle, was transferred to a chamber designed for electrophysiological experiments and pinned, serosal side down, to the Sylgard rubber floor. Muscle viability was maintained by a continuous perfusion of the recording chamber with warm, oxygenated Krebs–bicarbonate solution. The solution contained the following solutes (mM): $Na^+$, 137·5; $K^+$, 5·9; $Ca^{2+}$, 2·5; $Mg^{2+}$, 1·2; $Cl^-$, 134; $HCO_3^-$, 15·5; $H_2PO_4^-$, 1·2; dextrose, 11·5. This solution when bubbled with 97 % $O_2$–3 % $CO_2$ had a pH of 7·3–7·4. Temperature was regulated to 37·5 ± 0·5 °C.

A region of the muscle strip, 5 mm in length, was pinned securely to facilitate intracellular impalements of muscle cells. The muscle strip was then cut transversely, part-way across the width of the strip, to create a 'stimulating flap' that was connected to the recording area via a 1 mm commissure of muscle. The end of the stimulating flap was drawn into a glass capillary suction electrode with light suction and secured along its remaining length with dissecting pins.

The suction electrode was connected to the output of a stimulus isolation unit which was driven by a square-wave generator (Grass S88). The circuit to deliver electrical stimuli was completed by a Ag–AgCl electrode placed near the stimulating flap. Stimulus parameters had to be adjusted from preparation to preparation, but generally pulses of 50–100 ms in duration and 5–15 V in amplitude were sufficient to evoke slow waves which propagated through the muscle commissure into the recording region. The arrangement of the preparation was such that cells either in the axis parallel to the circular fibres ($X$ axis) or perpendicular to the circular fibres ($Y$ axis) could be impaled. The conduction velocities of events in these two axes (45 mm/s, $X$ axis; 6·5 mm/s, $Y$ axis; Publicover & Sanders, 1985) were such that events evoked in the stimulating flaps reached cells impaled in the recording sheet with a latency of at least 250 ms. This was sufficient to clearly isolate the stimulus artifact from the recording of the propagated event.

Muscle cells were impaled with micro-electrodes having resistances of 30–40 MΩ when filled with 3 M-KCl. Impalements were accepted based on previously described criteria (Sanders & Bauer, 1982). Membrane potential was amplified by standard high-input impedance electronics (WPI-707) and recorded on magnetic tape (Hewlett-Packard FM tape recorder). Hard copies were made on-line by a polygraph (Gould). Most data were also digitized on-line by a Cromemco System III microcomputer using an analog-to-digital converter (California Data) which sampled output from the electrometer at 500 Hz. Parameters of slow waves such as maximum rate of rise of the upstroke ($dV/dt$), upstroke amplitude (mV), plateau amplitude (mV), slow-wave duration (s), and slow-wave area (volts × seconds) were calculated by the computer using software specifically developed to analyse these events. Hard copies of slow waves, superpositions and processed data were plotted by a digital $X$–$Y$ plotter (Tektronix).

## RESULTS

### *Spontaneous and evoked events*

Spontaneous oscillations in membrane potential, slow waves, were recorded from all preparations used in this study. Gastric slow waves have been described elsewhere (El-Sharkawy *et al.* 1978) and consist of a rapid upstroke depolarization and a sustained plateau depolarization several seconds in duration (Fig. 1*A*). The spontaneous frequency of these events was in the range 1–2 min *in vitro*.

Slow waves could also be evoked by passing current through the suction electrode attached to the 'stimulating flap'. Evoked events propagated through the commissure, onto the recording sheet and to the impaled cell of the syncytium, with a reproducible latency. Spontaneous and evoked events had essentially identical wave forms (Fig. 1*A* and *B*), as long as the interval between events was sufficiently long.

### *Effects of frequency on shape of slow waves*

The first series of experiments tested the effects of stimulus frequency on the shape of slow waves. In these experiments cells of six muscles from six animals were impaled and trains of stimulus pulses at several frequencies, in the range of 2–7 c.p.m., were passed. The trains of stimuli at each frequency were presented in a randomized sequence. When each preparation was stimulated at low frequencies (less than 3 c.p.m.), all slow waves were of similar shape (Figs. 1*A* and 2*A*). At frequencies of 3·0–4·8 c.p.m. the amplitude and duration of the plateau phase of alternate slow waves were reduced (Fig. 1*C* and *D*). At frequencies of 4·8–5·5 c.p.m. the plateau phase was abolished and the amplitude and $dV/dt$ of upstrokes were reduced (Fig. 1*E* and *F*). In the range of 5·2–5·5 c.p.m. the upstroke consisted of a small transient depolarization of significantly decreased $dV/dt$ (Fig. 1*F*). Above

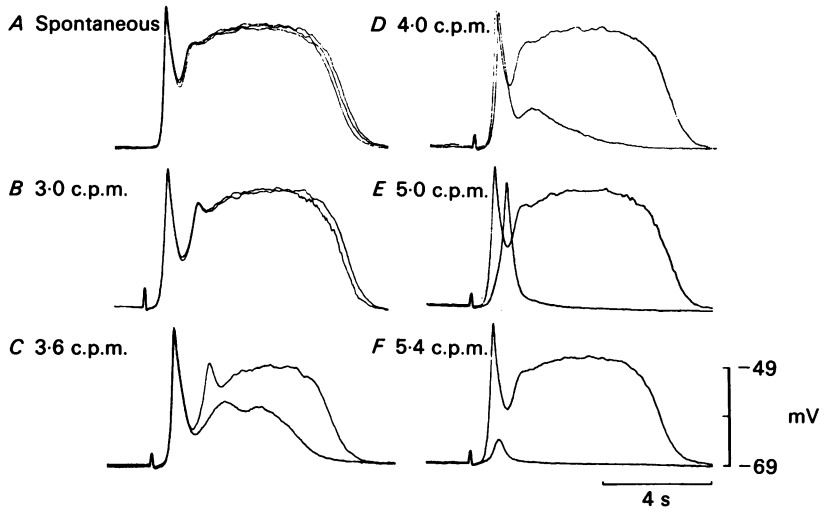


Fig. 1. Dependence of the wave form of slow waves on frequency. *A* shows spontaneous slow waves, which occurred at a frequency of 1–2 c.p.m., and had identical wave forms. At a frequency of 3·0 c.p.m. evoked wave forms were nearly identical to spontaneous events (*B*). At 3·6–4·0 c.p.m. the plateau phase of alternate events (see Fig. 2) was reduced in amplitude and duration (*C* and *D*). The plateaux of alternate events were completely abolished, leaving a large upstroke event at 5·0 c.p.m. (*E*). At 5·4 c.p.m. the large upstroke was abolished, revealing a low-amplitude propagated transient response (*F*).

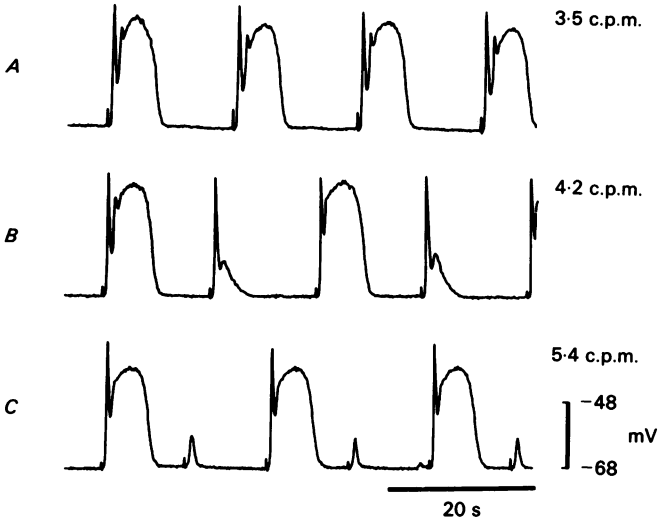


Fig. 2. Three patterns of slow-wave activity. Slow waves were evoked via direct stimulation. At least three different patterns of electrical activity were recorded from the same cell by varying the rate of stimulation. At 3·5 c.p.m. each slow wave was identical, with uncompromised upstroke and plateau phases (*A*). At 4·2 c.p.m. the plateau phase of the slow wave was reduced in amplitude and duration (*B*). At 5·4 c.p.m., the plateau was completely abolished, revealing active propagation of a low-amplitude transient response (*C*). At frequencies above 5·6 c.p.m., the pattern of slow-wave activity became irregular.

5·6 c.p.m., each stimulus did not consistently evoke a slow wave and the alternating sequence of slow waves was abolished.

These experiments revealed that at physiological frequencies (4·5–5·7 c.p.m.; see Kelly *et al.* 1969) the wave form of slow waves was not maintained from event to event. In fact in this range an alternating pattern of slow waves was observed (Fig. 2),

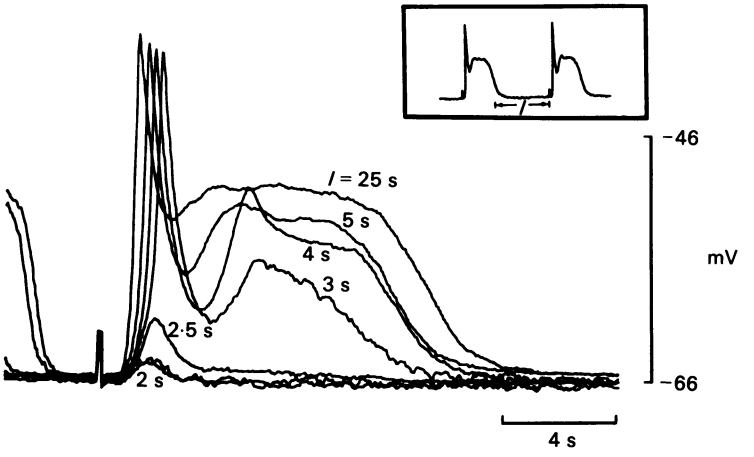


Fig. 3. The effects of interval between slow waves on the wave form. This Figure shows a superposition of seven slow waves evoked at various intervals ($I$) after a conditioning slow wave (see inset for illustration of stimulus protocol). The interval was taken as the time from 90% repolarization to the onset of the next stimulus. At intervals of 2–2·5 s a low-amplitude, active event with a slow upstroke velocity was propagated (intervals labelled above traces). At 3–5 s upstroke amplitude, upstroke velocity, plateau amplitude and plateau duration was compromised. At long intervals ($I$ = 25 s illustrated) evoked slow waves were identical to spontaneous events (see Fig. 1).

in which every other event had: (i) a decreased upstroke velocity, (ii) a decreased upstroke amplitude, (iii) a decreased plateau amplitude and (iv) a decreased plateau duration. At higher frequencies propagation failed, and if high-frequency stimulation was maintained, propagation was blocked for varying periods resulting in a chaotic pattern of slow waves. Fig. 2 summarizes the patterns of responses to several frequencies of stimulation. These data suggest that there are at least three patterns of slow-wave activity in the gastric antrum: (i) at low frequencies all slow waves have the same wave form; (ii) at physiological frequencies the wave form alternates in amplitude and duration; (iii) at higher frequencies most stimuli fail to elicit propagated events. Because of the dependence of contractions on slow waves in these muscles (Szurszewski, 1981), these electrical patterns should be manifest in antral motility.

*Effects of inter-slow-wave interval on shape of slow wave*

The alternating pattern of slow-wave shape was of interest because it occurs over the range of physiological frequencies recorded from conscious, healthy animals (McCoy & Bass, 1963; Carlson *et al.* 1966; Nelsen *et al.* 1967; Kelly *et al.* 1969). At

a given stimulus frequency the interval between stimuli was constant but the interval between slow waves was not necessarily constant (see Fig. 2*B*). This occurred because slow-wave duration was not constant at stimulus frequencies above 3 c.p.m. We found that the time between repolarization of the plateau and the next stimulus (inter-slow-wave interval) determined the wave form of the next slow wave. The intervals between other reference points on the slow wave, such as upstroke peak or plateau peak, did not correlate as well with the wave form of the next slow wave because of the variability in slow-wave duration. To characterize the effect of inter-slow-wave interval ($I$) on the wave form of slow waves the following stimulus protocol was used: (i) following a prolonged quiescent period, a pulse was generated to evoke a 'conditioning' slow wave; (ii) the time of 90 % repolarization of the plateau was selected as a temporal marker; and (iii) a stimulus pulse was passed to evoke a second slow wave following various intervals (see inset in Fig. 3).

The first series of experiments tested the effect of inter-slow-wave interval on the wave form of the slow wave. Cells were impaled in six preparations and a series of dual stimuli were delivered as described. The inter-slow-wave intervals ($I$) were varied randomly. As inter-slow-wave interval was decreased: (i) the amplitude of the upstroke potential deceased; (ii) the velocity of the upstroke decreased; (iii) the amplitude of the plateau decreased; (iv) the duration of the plateau decreased; and (v) the area under the slow wave decreased. An inter-slow-wave interval of at least 12 s was required for a slow wave to equal the magnitude of the 'conditioning' slow wave. At intervals between approximately 3 and 12 s the plateau area (amplitude and duration) was highly dependent upon the interval. At intervals less than 3 s the plateau phase was abolished and the upstroke velocities were greatly diminished. Following slightly shorter intervals, an active event failed to propagate through the tissue. The mean inter-slow-wave interval at which conduction failed was $2{\cdot}8 \pm 0{\cdot}9$ s ($n = 7$ preparations). Fig. 3 shows a typical example of the effects of inter-slow-wave interval on the wave form of slow waves.

These experiments suggest that the refractory periods for the upstroke and plateau phases of the slow wave differ. To quantify the effects of inter-slow-wave interval on these slow waves phases, the upstroke velocities and areas under the slow waves from the experiments just described were measured.

The upstroke velocity was used as an indicator of the refractory period of the upstroke potential. A typical example of one experiment showing the relationship between upstroke velocity and inter-slow-wave interval is shown in Fig. 4*A*. A sharp increase was observed in $dV/dt$ at intervals of 3–5 s in each of the six experiments. In individual preparations, the rapid increase in $dV/dt$ occurred at a 'threshold' interval. At intervals above this threshold a gradual increase in $dV/dt$ was noted. This increase in upstroke velocity is also apparent in the four large upstroke events shown in Fig. 3 (a different preparation from Fig. 4). Interestingly, at intervals just below the threshold, the value of $dV/dt$ did not fall immediately to 0. In this range a low amplitude, propagated event was observed (see Fig. 1*F*).

The area under the slow wave was selected as a parameter to indicate the refractory period of the plateau phase of the slow wave. In each experiment an increase in slow-wave area was noted as inter-slow-wave interval was increased. The increase in the area was more gradual than the increase in $dV/dt$ described above, and always

occurred at longer intervals than the threshold interval for the increase in d$V$/d$t$. In other words, the effects of inter-slow-wave interval on the plateau phase of the slow wave always occurred over longer intervals following the development of the large upstroke event (see Fig. 3). Fig. 4*B* is an example of the relationship between slow-

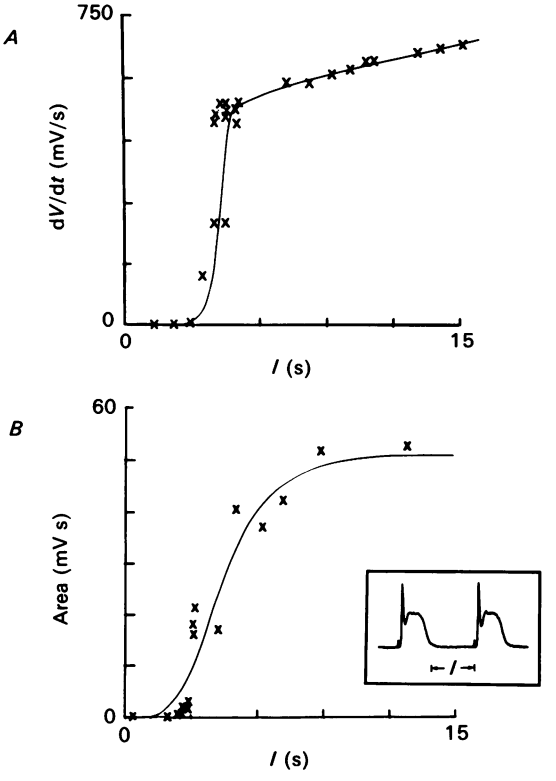


Fig. 4. Inter-slow-wave interval *vs*: *A*, the maximum upstroke velocity and *B*, the area under the slow wave. Upstroke d$V$/d$t$ was measured at the point of maximum velocity and the area under each propagated responses was measured by numerical integration. All data were recorded from a single cell during a continuous impalement. Each measurement ( × ) was plotted as a function of the inter-slow-wave interval (*I*, see inset). *A*, at 4·0 s there was a very sharp increase in upstroke velocity as full sized upstrokes were propagated. Above 4·0 s upstroke velocity showed a further small increase as a function of interval. These data suggest that the propagation refractory period for upstrokes ended at 4·0 s, but input resistance had not returned to resting levels. *B*, at intervals greater than 4 s changes in area occurred as a result of changes in the plateau phase of the slow wave. At intervals between 3 and 4 s only the upstroke remained with a total area only one-third that of a full response. Propagated events below 3 s consisted of small transient responses. Data in this panel were fitted by a Hill function (Hill coefficient, $n = 4$; correlation coefficient, $r = 0{\cdot}96$).

wave area and inter-slow-wave interval. The data in Fig. 4*B* are grouped into three regions describing: (i) intervals too short to elicit full upstroke events; (ii) intervals where only upstrokes occurred, with a mean area approximately $\frac{1}{3}$ of the over-all slow wave; and (iii) intervals where variably sized plateau potentials occurred.

*Effect of stimulus intensity on propagation refractory period*

To test the dependence of the propagation refractory period on the stimulus intensity the stimulus frequency was set at a level that would produce an alternating pattern of 'slow-wave failure' – 'slow wave', and the applied current was increased and decreased from the level at which no event was elicited to a level 10 times the

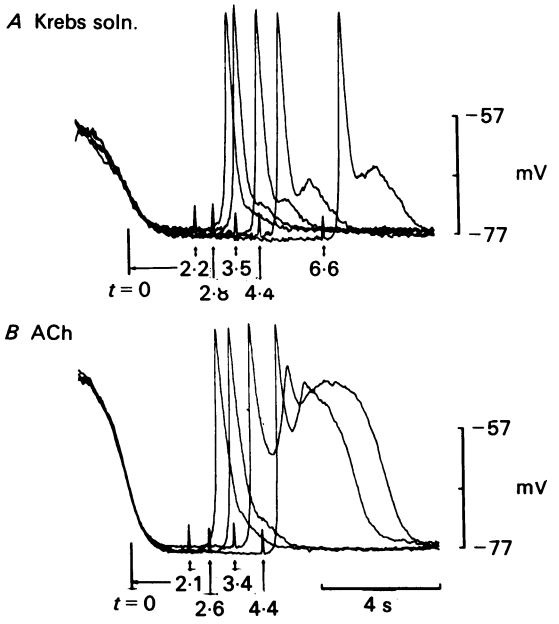


Fig. 5. Effects of ACh on the relationship between slow-wave shape and inter-slow-wave interval. The effects of various intervals on slow-wave shape were studied in Krebs solution. *A* shows the superposition of five slow waves at intervals ranging from 2·2 to 6·6 s. The ACh ($10^{-6}$ M), was added and the effects of interval on slow-wave shape were re-evaluated. Before ACh an interval of more than 15 s (not shown) was needed to reset the mechanisms responsible for the plateau phase. After ACh the plateau refractory period was greatly reduced and uncompromised slow waves could be stimulated with intervals less than 6 s.

activation voltage. Stimulus intensity had no effect on the slow-wave pattern or wave form, and strong intensity stimuli would not evoke an event if a second stimulus was delivered too soon after a conditioning event.

*Effect of acetylcholine on plateau refractory period*

The fact that the propagation refractory period of the plateau phase of the slow wave was long and that slow waves could not be evoked without compromising the wave form at a frequency of 3–5 per minute is physiologically important, because the pace-maker in the corpus drives the canine stomach at 4·5–5·7 c.p.m. (Daniel & Chapman, 1963; Kelly *et al.* 1969). At this rate a clear alternating pattern occurred in all preparations (see Fig. 2) and the plateau of every other slow wave propagating

through antral muscle was significantly decreased. Since the plateau triggers excitation–contraction coupling (Szurszewski, 1981), it was of interest to ask whether intrinsic mechanisms exist which can decrease the duration of the plateau refractory period so that each slow wave can propagate and be mechanically productive.

Others have shown that during the 'gastric phase' of digestion, central input and gastric distension results in reflex release of acetylcholine (ACh) which enhances the plateau phase of the slow wave and enhances the force of contractions (Cooke, 1975). Since this is the time when antral contractions are recruited to perform work on the gastric contents we reasoned that ACh may also decrease the plateau refractory period.

In these experiments ($n = 6$ preparations) the effect of interval was tested on the plateau potential using the same stimulus protocol as described above. After the effects of slow-wave interval were determined in normal Krebs solution, the muscle was immersed in Krebs containing $10^{-6}$ M-ACh. This increased the amplitude of the plateau potential and the frequency of spontaneous slow waves. After 10 min another series of paired stimuli were delivered to determine the effect of interval on plateau amplitude and duration in the presence of ACh. In the presence of ACh, the interval could be reduced to under 4 s and propagation of plateau phases occurred with integrity. Large amplitude upstrokes remained viable following intervals as short as 2 s. Fig. 5 shows a comparison of the effects of various intervals before and after addition of ACh.

## DISCUSSION

In this study we have quantified the effects of frequency on slow-wave shape in canine gastric antral muscles. We have characterized the refractory periods of the upstroke and plateau phases of the slow wave. The mechanism responsible for the upstroke depolarization resets in the range of 2–5 s after repolarization of the previous slow wave, but up to 12 s are required for the plateau event to fully recover. Neither the upstroke nor the plateau appear to be 'all-or-none' events, in the classical sense, since both phases appeared as graded responses dependent upon the inter-slow-wave interval.

Classically there are two refractory periods which occur in excitable cells: (i) absolute, where no amount of stimulus intensity can elicit a regenerative event; and (ii) relative, where an increase in stimulus intensity can elicit a regenerative event (Erlanger & Gasser, 1938). In the present study we could not distinguish between these, and in fact we measured what should be more accurately referred to as the 'propagation refractory period'. It is unlikely that this refractoriness has a 'relative' phase, because regardless of how much stimulus current is applied, the regenerative current for propagation to occur is still a function of local active currents which, in turn, are a function of the density of activated channels, ionic driving forces, and membrane input impedance. So even if events were evoked at the site of stimulation with pulses of greater intensity, propagation might still be blocked as local currents spread into areas of inactivated channels and increased membrane conductance.

With regard to gastric motility, the most important phase of the slow wave is the plateau (Szurszewski, 1975, 1981). Morgan & Szurszewski (1980) have shown that

excitation–contraction coupling occurs in antral muscle when the level of depolarization exceeds a voltage termed the 'mechanical threshold'. This level falls approximately 30 mV more positive than resting membrane potential, but can be surpassed during slow waves. The relationship between voltage and mechanical force is extremely steep, so maximal forces are generated when the slow waves exceed the mechanical threshold by 5–10 mV. Szurszewski (1981) has also suggested that contractile force is related to the degree of depolarization and the time that membrane potential is sustained above the mechanical threshold. Thus conditions which affect either the amplitude or the duration of slow-wave activity can have a significant effect on the generation of force by gastric antral muscles. In the present study it was observed that the frequency of slow waves can significantly affect both their amplitude and duration, suggesting that gastric motility is highly dependent upon slow wave frequency. The data show that the antral syncytium, in the absence of extrinsic stimuli, cannot propagate events at the frequencies normally recorded *in vivo* (Kelly *et al.* 1969) without a significant compromise in the plateaux of alternating slow waves. The data also show that ACh is capable of increasing the ability of the antral muscle to propagate slow waves at physiological frequencies. At present it is not known how ACh produces this effect; however, one possibility is that ACh reduces the probability that a $K^+$ current remains activated (Sims, Singer & Walsh, 1983).

During the gastric phase of digestion there appears to be at least two mechanisms that act to facilitate propagation of mechanically productive slow waves through the antrum: (i) as just described, ACh, which is released from post-ganglionic parasympathetic nerves, decreased the propagation refractory period of the plateau phase of the slow wave, (ii) Kelly *et al.* (1969) have shown that distension of the canine stomach (which also leads to reflex release of ACh) slows the frequency of slow waves from a fasting rate of about 5 to approximately 3·5 c.p.m. At present it is not known how the gastric pace-maker is modulated during distension, but the data reported here suggest that this may be a significant mechanism of digestion and necessary to enhance the force of antral contractions.

Other myogenic regulatory mechanisms appear to depend upon slow-wave frequency. Recently this laboratory reported that propagation velocity is a function of frequency in the canine antrum (Publicover & Sanders, 1985). This effect occurred over the full range of inter-slow-wave intervals, from the propagation refractory period to the interval between spontaneous events (approximately 2–40 s). In contrast, the effect inter-slow-wave intervals upstroke depolarization occurred over the range of 2–5 s, and the effect on plateau phase occurred over the range of 3–12 s. The differences in the range of inter-slow-wave intervals over which these mechanisms operate suggest that the myogenic mechanisms which regulate the wave form of slow waves are not necessarily the same as those which regulate propagation velocity.

This investigation was supported by Grants AM 32176 and AM 33406 from the National Institutes of Health and AA 05883 from the National Institute on Alcohol Abuse and Alcoholism. Dr Sanders was supported by a Research Career Development Award, AM 01209.

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