SYMPOSIUM REPORT

Electrical events underlying organized myogenic contractions of the guinea pig stomach

G. David S. Hirst and Frank R. Edwards

Division of Neuroscience, John Curtin School of Medical Research, Canberra, ACT, 0200, Australia

The stomach generates a characteristic pattern of coordinated activity whereby rings of contraction regularly start in the corpus and migrate slowly down the stomach to the duodenum. This behaviour persists after isolating the stomach and after blocking nervous activity; hence the response is myogenic, resulting from organized contractions of smooth muscle cells lying in the stomach wall. Each ring of contraction is triggered by a long lasting wave of depolarization, termed a slow wave. Slow waves are now known to be generated by sets of interstitial cells of Cajal (ICC), which intermingle with gastric smooth muscle cells. This article describes some studies which identify the roles played by ICC in the on-going generation of coordinated gastric movements. Intramuscular ICC in the corpus generate slow waves and these provide the dominant pacemaker frequency in the stomach. Corporal slow waves, in turn, activate a network of myenteric ICC, which starts in the antrum and slowly conducts waves of depolarization down the stomach. As these waves pass over bundles of circularly orientated muscle cells, they activate a set of intramuscular ICC which lie in the circular muscle layer: these generate slow waves that rapidly spread radially, so triggering each ring of contraction.

(Received 4 July 2006; accepted 10 July 2006; first published online 27 July 2006)
Corresponding author G. D. S. Hirst: Division of Neuroscience, John Curtin School of Medical Research, Canberra, ACT, 0200, Australia. Email: david.hirst@anu.edu.au

Electrical recordings show that successive descending rings of gastric contraction are triggered by waves of electrical activity which originate in the corpus. The waves occur regularly at 5 waves min^{-1} and in the antrum conduct slowly in an anal direction but more rapidly in a circumferential direction (Szurszewski, 1981; Sanders & Publicover, 1989). Intracellular recordings from different regions of the stomach indicate that all regions, except the fundus (Komori & Suzuki, 1986; Beckett *et al.* 2004; Fig. 1*A*, generate long lasting waves of depolarization, slow waves (Tomita, 1981). The corpus generates slow waves regularly at 5 waves min^{-1} (Hashitani *et al.* 2005; Fig. 1*B* and *Eb*). When the antrum is separated from the corpus, it generates slow waves irregularly with a mean frequency of ∼3 waves min^{-1} (Tsugeno *et al.* 1995; Hirst & Edwards, 2001; Fig. 1*Cb* and *Ec*). Isolated bundles of the antral circular layer generate slow waves erratically at ∼1 wave min^{-1} (Kito *et al.* 2002*b*; Fig. 1*D* and *Ed*). Thus when dissected apart, different regions of the stomach generate slow waves at different frequencies, with corporal slow waves occurring regularly and most frequently. However, in the intact stomach, all regions discharge slow waves regularly at the same frequency as the corpus, indicating that corporal slow waves normally entrain activity throughout the lower stomach.

Involvement of ICC in stomach rhythmicity

The wall of the gastrointestinal tract contains at least two muscle layers: a thin outer longitudinal layer, made up of electrically interconnected smooth muscle cells which are orientated in a longitudinal direction; and an inner thicker circular muscle layer, consisting of electrically interconnected smooth muscle cells which are organized into muscle bundles that run in a circular direction. As slow waves have been recorded from these muscle layers for many years, it was thought that they were generated by smooth muscle cells. Recently it has become clear that slow waves are not generated by smooth muscle cells but are generated by ICC. However, as all ICC are electrically coupled to nearby smooth muscle

This report was presented at *The Journal of Physiology* Symposium on Involvement of interstitial cells of Cajal in the control of smooth muscle excitability, Okayama, Japan, 22 July 2006. It was commissioned by the Editorial Board and reflects the views of the authors.

 DOI: 10.1113/jphysiol.2006.116491

cells, each depolarization that a set of ICC generates will passively depolarize nearby smooth muscle cells: if the depolarization is sufficiently large to activate smooth muscle L-type Ca^{2+} channels (Farrugia, 1999), a contraction will occur. Conversely, if a set of ICC generates a hyperpolarization, nearby smooth muscle cells will be hyperpolarized, making them less likely to contract.

Gastrointestinal ICC selectively bind antibodies to CD117 and the distribution of ICC can be determined immunohistochemically (Sanders, 1996; Komuro *et al.* 1999). In part of the stomach, a myenteric network of ICC lies between the muscle layers (ICC_{MY}; Burns *et al.* 1997). ICC_{MY} appear at the anal end of the corpus at the greater curvature and spread over the antrum and pylorus: their density is highest near the greater curvature and falls towards the lesser curvature (Hirst *et al.* 2002*a*; Mazet & Raynier, 2004). The density of ICC_{MY} also falls as the gastro-duodenal junction is approached (Wang *et al.* 2005). The role of ICC in the generation of slow waves was unequivocally demonstrated in studies on W/W^V mutant mice. The gastrointestinal tract of W/W^V mice shows regional deficits of ICC: their small intestines selectively lack ICC_{MY} and fail to generate slow waves, unlike those of wild-type mice (Ward *et al.* 1994; Huizinga *et al.* 1995). Subsequently, intestinal ICC_{MY} were shown to generate pacemaker potentials (Kito & Suzuki, 2003).

A second set of ICC have an intramuscular location, ICC_{IM}. In all regions of the stomach, ICC_{IM} are scattered amongst the smooth muscle cells of the circular layer. Similarly ICC_{IM} intermingle with longitudinal smooth muscle cells in the fundus and corpus (Burns *et al.* 1997) but are infrequent in the longitudinal layer of the antrum (Cousins *et al.* 2003). ICC_{IM} play a key role in both the generation of gastric slow waves and in the pathway between enteric nerve terminals and smooth muscle cells. The stomachs of W/W^V mice, unlike their small intestines, contain ICC_{MY} but lack ICC_{IM} (Sanders, 1996). Antral preparations from W/W^V mice generate incomplete slow waves (Dickens *et al.* 2001): gastric preparations from W/W^V mice also fail to respond to excitatory cholinergic or inhibitory nitrergic nerve stimulation unlike those from wild types (Hirst & Ward, 2003).

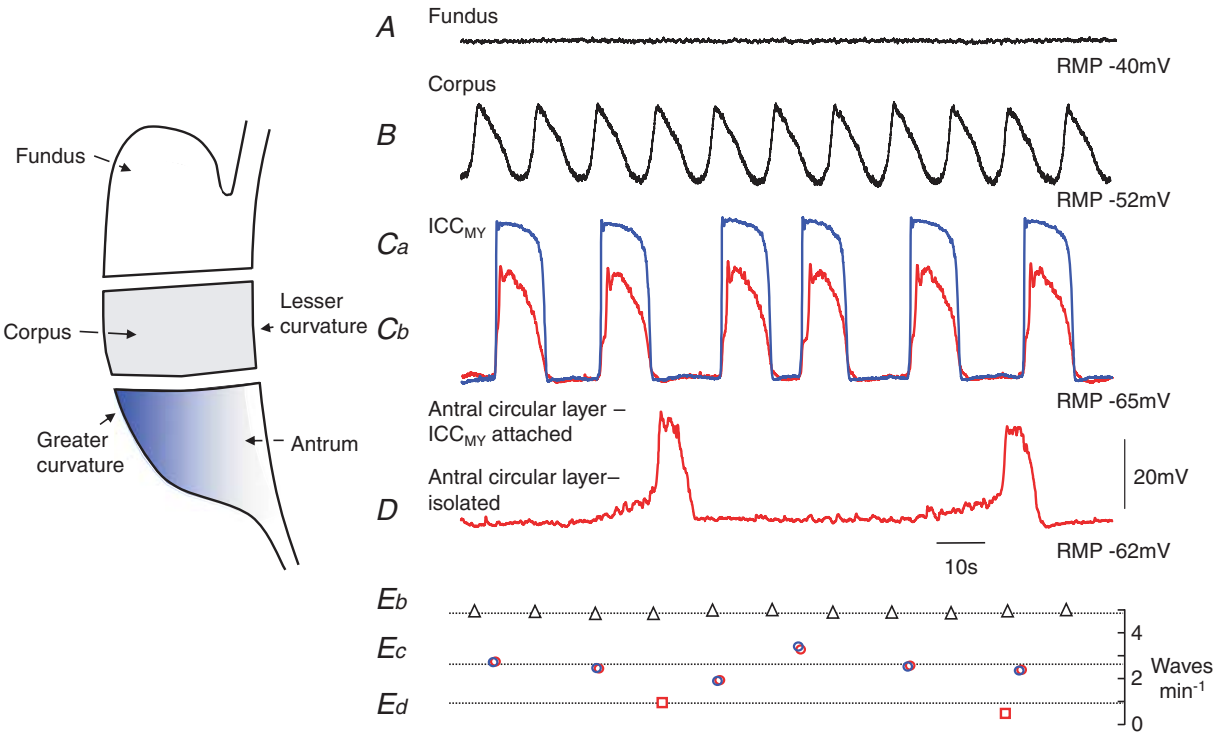

Figure 1. Electrical activity recorded from isolated regions of the guinea pig stomach
The upper trace (*A*) shows a recording from the circular muscle layer of the isolated fundus: although an ongoing discharge of membrane noise occurred, rhythmical activity was not detected. Trace *B* shows slow waves recorded from the circular muscle layer of the isolated corpus: slow waves occurred regularly at 5 waves min^{-1} (*Eb*). The next set of superimposed traces show simultaneous recordings from an ICC_{MY} (*Ca*; blue trace) and a nearby smooth muscle cell in the circular layer (*Cb*; red trace: modified from Hirst & Edwards, 2001): pacemaker potentials and slow waves occurred synchronously and their rate of occurrence fluctuated around 3 waves min^{-1} (*Ec*). Trace *D* shows spontaneous electrical activity recorded from an isolated bundle of antral circular muscle: regenerative potentials occur at about 1 wave min^{-1} (*Ed*). The time and voltage calibration bars apply to all traces.

Generation of slow waves in the corpus

Although electrical activity originates in the corpus, few electrophysiological studies have been carried out on this region of the stomach. The guinea pig corpus lacks ICC_{MY} but contains ICC_{IM}, distributed in the circular and longitudinal layers. The intact corpus and isolated circular bundles of the corpus generate slow waves regularly at 5 waves min^{-1} (Fig. 1*B* and *Eb*). Corporal slow waves have peak amplitudes of ~15 mV, superimposed on a peak negative potential around −50 mV. They have low rates of rise (< 10 mV s^{-1}) (Fig. 2*Ba* and *Bb*) and are abolished by buffering the internal concentration of calcium ions to low levels (Hashitani *et al.* 2005). Given their similarities with other slow waves, it seems most likely that corporal slow waves are generated by corporal ICC_{IM}. Their high rate of occurrence indicates that corporal slow waves are the source of dominant pacemaker activity in the intact stomach.

Generation of slow waves in the antrum

Recordings from identified antral ICC_{MY} indicate that they generate large-amplitude pacemaker potentials superimposed on a peak negative potential of some −65 mV (Dickens *et al.* 1999; Fig. 1*Ca*). Each pacemaker potential consists of two components, a rapidly rising initial component, lasting about 2 s; this is followed by a plateau component that lasts a further 5–10 s (Hirst & Edwards, 2001; Kito *et al.* 2002*a*). In the isolated antrum the discharge of pacemaker potentials occurs irregularly with a mean frequency of 3 waves min^{-1} (Fig. 1*Ec*). Simultaneous recordings from ICC_{MY} and either the circular (Fig. 1*Ca* and *Cb*) or longitudinal layers show that ICC_{MY} trigger attenuated waves of depolarization in each layer as pacemaker current flows through the electrical connections between ICC_{MY} and adjacent layers (Cousins *et al.* 2003; Edwards & Hirst, 2005).

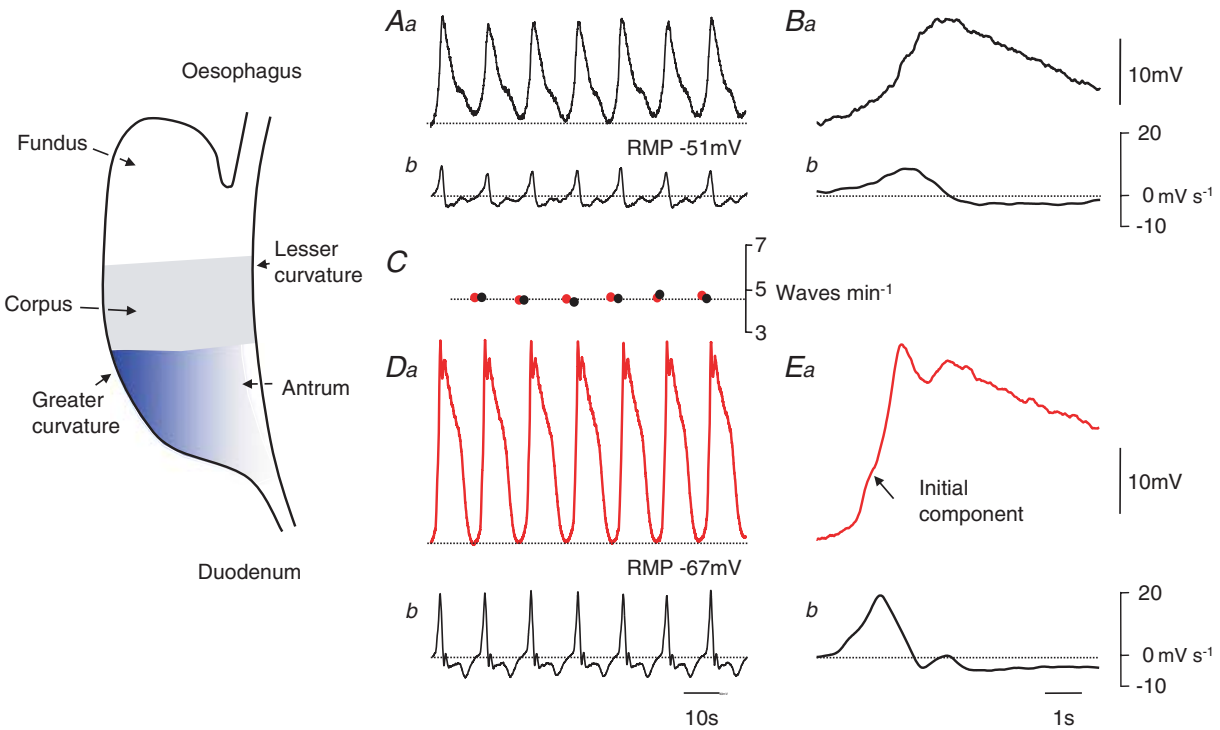

Figure 2. Comparison between corporal and antral slow waves recorded from an attached corpus–antrum preparation
The upper left hand pair of traces shows corporal slow waves recorded near the greater curvature (*Aa*) and their associated d*V*/d*t* (*Ab*). Corporal slow waves had low rates of rise (*Ab*) and occurred regularly at 4.8 waves min^{-1} (*C*). Expanded regions of these traces (*Ba* and *b*) showed that upstroke of the corporal slow wave (*Ba*) lacked an obvious inflection. The lower left hand pair of traces shows antral slow waves, recorded from the same preparation as *Aa*, near the greater curvature (*Da*) and associated d*V*/d*t* (*Db*). Antral slow waves had faster rates of rise (*Db*) and occurred regularly with the same frequency as corporal slow waves (*C*). Expanded regions show that the upstroke of the antral slow wave displayed an initial component (*Ea*). The left hand time calibration bar applies to traces *A* and *D*: the right hand time calibration bar applies to traces *B* and *E*. Figure modified from Hashitani *et al.* (2005).

In the antral circular layer, each passive wave of pacemaker depolarization gives rise to the primary component of the slow wave which triggers a secondary regenerative component (Ohba *et al.* 1975; Suzuki & Hirst, 1999; Figs 1*Cb* and 2*Ea*). The secondary component is generated by ICC_{IM}, being absent in antrums of W/W^V mice which lack ICC_{IM} (Dickens *et al.* 2001). Characteristically the secondary regenerative component is triggered by membrane depolarization and starts about 1 s after the onset of depolarization; it appears to result from the release of calcium ions from inositol 1,4,5-trisphosphate-dependent internal calcium stores and the subsequent activation of chloride-selective channels (Suzuki & Hirst, 1999; Edwards *et al.* 1999; Suzuki *et al.* 2000; Hirst *et al.* 2002*b*). For convenience the secondary component of the slow wave will be referred to as a regenerative potential.

In summary, antral slow waves are generated by two separate sets of ICC, ICC_{MY} and ICC_{IM}.

Anal spread of slow waves in the antrum

In the isolated antrum, pacemaker potentials start at random points within the ICC_{MY} network and conduct away from the point of initiation, orally, anally or circumferentially, at the same speed, ~3 mm s^{-1} (Hennig *et al.* 2004). Thus in isolated preparations, antral slow waves start at varying locations and conduct away from the point of origin. When the ICC_{MY} network is electrically stimulated, pacemaker potentials conduct

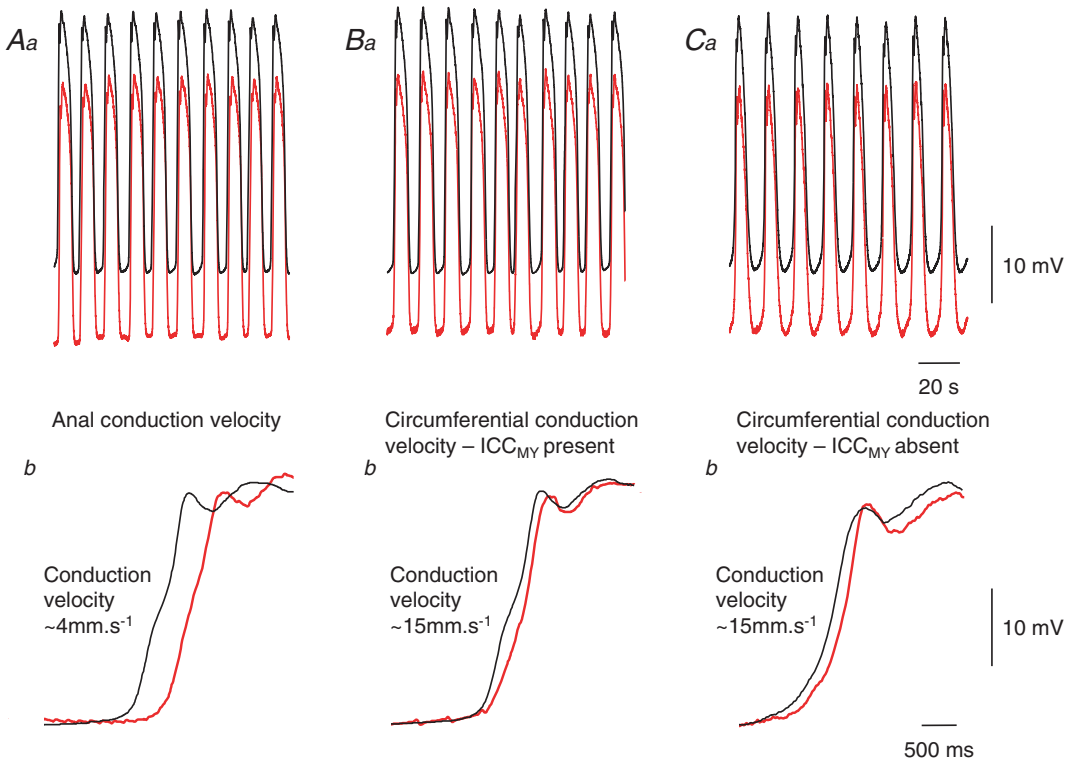

Figure 3. Conduction velocities of slow waves in the anal direction and in the circumferential direction, with ICC_{MY} present and removed
Upper left hand pair of traces (*Aa*) shows slow waves recorded simultaneously from the greater curvature of an antral preparation attached to the corpus. The electrodes were separated by 2 mm with the lower recording (red trace) having a more anal location. Expansions of these traces (*Ab*) show that slow waves were first detected by the electrode nearer the corpus and rising phases were separated by ~500 ms, giving a conduction velocity of ~4 mm s^{-1}. Upper central pair of traces (*Ba*) shows slow waves recorded from antral preparation, attached to the corpus, with intact ICC_{MY} network; electrode separation 2 mm with lower recording (red trace) being circumferentially located. Expansions (*Bb*) show that slow waves were first detected near the greater curvature and rising phases were separated by ~140 ms, giving a conduction velocity of ~15 mm s^{-1}. The upper left hand pair of traces (*Ca*) show simultaneous recordings of slow waves from an antral preparation attached to the corpus in a region from which ICC_{MY} network had been dissected away; electrode separation 2 mm with the lower recording (red trace) circumferentially located. Expansions (*Cb*) show that slow waves were again first detected near the greater curvature and the conduction velocity was again ~15 mm s^{-1}. The upper time calibration bar applies to traces *Aa*, *Ba* and *Ca*: The lower time calibration bar applies to traces *Ab*, *Bb* and *Cb*. Traces modified from Hirst *et al.* (2006).

from the stimulation point with the same conduction velocity anally or circumferentially ($\sim$3 mm s^{-1}, Hirst *et al.* 2006). When the antrum and corpus are left in continuity, antral slow waves invariably start at the corporal end of the antrum at the same frequency as in the corpus (Fig. 2; Hirst *et al.* 2006). Their anal conduction velocity, $\sim$3 mm s^{-1} (Fig. 3*Aa* and *Ab*), is the same as that of pacemaker potentials in the ICC$_{MY}$ network. Why pacemaker potentials should conduct so slowly in the ICC$_{MY}$ network is not understood: it is unlikely to result from poor coupling between neighbouring ICC$_{MY}$ but may reflect the activation properties of the initial component of the pacemaker potential (Goto *et al.* 2004; Edwards & Hirst, 2006).

The way in which corporal slow waves set the frequency of antral pacemaker potentials requires discussion. ICC$_{MY}$ are electrically excitable; electrical stimulation shortly after the end of a pacemaker potential evokes a premature pacemaker potential (Hirst *et al.* 2002*c*), leading to an increased frequency of antral slow waves (Publicover & Sanders, 1986). As ICC$_{MY}$ are electrically coupled to adjacent muscle layers, a depolarization in the circular layer depolarizes the ICC$_{MY}$ network (Cousins *et al.* 2002) and can trigger a premature pacemaker potential. This occurs when antral ICC$_{IM}$ are activated by neurally released acetylcholine (Hirst *et al.* 2002*c*) and will also occur at the corporal–antral interface, where the ICC$_{MY}$ network starts. Corporal slow waves occur more frequently than do pacemaker potentials in the isolated antrum (Fig. 1), hence when corporal slow waves rhythmically depolarize the oral end of the ICC$_{MY}$ network, they will trigger a regular discharge of pacemaker potentials and associated antral slow waves, at the same rate as in the corpus.

Circumferential spread of slow waves in the antrum

When paired recordings of slow waves were made from separated points in the antral circular layer, their circumferential conduction velocity was found to be four to five times faster (Fig. 3*Ba* and *Bb*) than their anal conduction velocity (Fig. 3*Aa* and *Ab*). As pointed out, this does not occur because pacemaker potentials have different

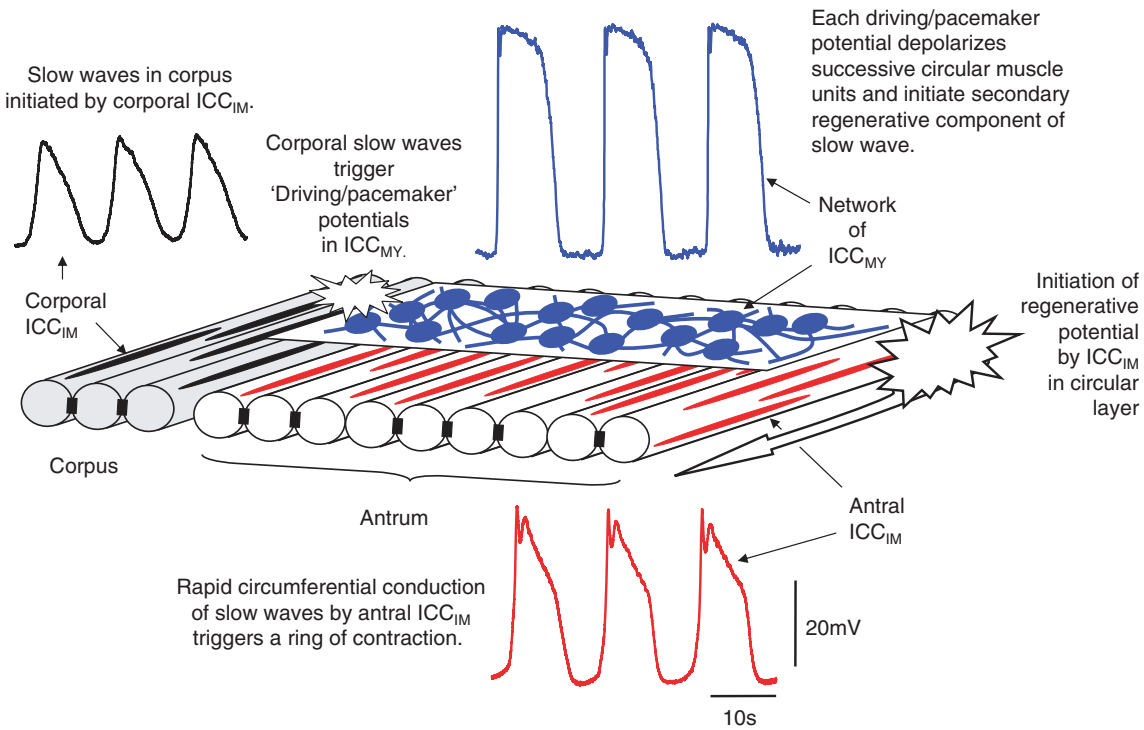

Figure 4. Propagation of slow waves down the guinea pig stomach
ICC$_{IM}$ in the corpus generate a regular discharge of corporal slow waves. At the junction of the corpus and antrum, where ICC$_{MY}$ first appear, each corporal slow wave depolarizes the ICC$_{MY}$ network and triggers a driving/pacemaker potential. Each driving/pacemaker potential propagates anally from the point of initiation through the ICC$_{MY}$ network with a characteristically slow conduction velocity. As driving/pacemaker potentials pass over bundles of circular muscle, the bundles are depolarized, antral ICC$_{IM}$ are activated and the regenerative component of the slow wave is generated. The regenerative potential rapidly conducts circumferentially, depolarizing nearby smooth muscle cells, so triggering a ring of contraction. Electrical connections between adjacent circular muscle bundles are illustrated as closed rectangles: the occasional lack of such connections prevents extensive anal conduction of slow waves within the circular layer. Figure modified from Hirst *et al.* (2006).

anal and circumferential conduction velocities in the ICC_{MY} network. Although antral slow waves are triggered by ICC_{MY}, once initiated, slow waves of normal amplitude are recorded from regions of the antrum which lack ICC_{MY}. In mouse antrum, the density of ICC_{MY} is highest at the greater curvature and falls to undetectable levels at the lesser curvature but slow waves of normal amplitude are recorded throughout, even when ICC_{MY} are absent. However, in the W/W^V mouse, at the lesser curvature, where both ICC_{MY} and ICC_{IM} are absent, slow waves are not detected (Hirst *et al.* 2002*a*). These observations suggest that ICC_{IM} alone sustain the circumferential spread of slow waves. To test this idea further, slow waves were recorded from preparations where all but a narrow band of ICC_{MY} at the greater curvature had been dissected away. Slow waves had similar amplitudes whether ICC_{MY} were present or had been removed (Fig. 3*Ba* and *Ca*); furthermore removing the ICC_{MY} network did not alter the circumferential conduction velocity (Fig. 3*Bb* and *Cb*; Hirst *et al.* 2006). Similarly, isolated bundles of the pyloric circular layer readily conduct regenerative potentials over long lengths with the same conduction velocity as in the antrum (van Helden & Imtiaz, 2003). The simplest explanation is that in the intact stomach pacemaker potentials maximally depolarize the circular layer at the greater curvature, where the density of ICC_{MY} is highest (Hirst *et al.* 2002*a*). Once a band of ICC_{IM} has been excited, they support a circumferentially directed regenerative potential, with the long refractory period of regenerative potentials preventing backfiring (Suzuki & Hirst, 1999). In the antral circular layer, circumferential conduction is aided by the long electrical length constant of the circular bundles but extensive oro-anal conduction does not occur as the bundles are organized into functional units which are electrically isolated from each other (Hirst *et al.* 2006).

Summary

The slow descending rings of contraction that occur regularly in the intact stomach are triggered by electrical activity generated in successive sets of ICC. The corpus acts as the dominant pacemaker with corporal ICC_{IM} generating a regular high frequency discharge of slow waves (Fig. 4). At the junction between the corpus and the antrum, each corporal slow wave triggers a pacemaker potential in the ICC_{MY} network which conducts slowly down the ICC_{MY} network (Fig. 4). Given that the dominant pacemaker region in the stomach resides in the corpus, it may be misleading to refer to the signals generated by ICC_{MY} as pacemaker potentials. It may be more appropriate to refer to the signals generated by antral ICC_{MY} as 'driving potentials' since their function in the intact stomach is simply to convey excitation in a fixed direction down the wall of the stomach and not to *initiate* spontaneous activity. As each driving/pacemaker potential passes over a circular muscle bundle, ICC_{IM} are depolarized and they initiate the secondary regenerative component of the slow wave. Once initiated, the regenerative potential spreads rapidly in a circumferential direction (Fig. 4), concurrently depolarizing circular smooth muscle cells and causing a ring of contraction to develop. As the driving/pacemaker potential passes over successive anally located bundles, the process repeats, so causing successive bundles of circular muscle to contract. Mechanically this manifests itself as a slowly descending ring of contraction, moving the stomach contents towards the gastro-duodenal junction.

More detailed descriptions of the organization of gastric ICC and their role in neuroeffector transmission appear in the symposium articles by Komuro (2006) and Ward & Sanders (2006), respectively, in this special issue of *The Journal of Physiology*. A detailed description of the generation of gastrointestinal pacemaker potentials appears in the symposium article by Suzuki *et al.* (2006).

References

Beckett EAH, Bayguinov YR, Sanders KM, Ward SM & Hirst GDS (2004). Properties of unitary potentials generated by intramuscular interstitial cells of Cajal in the murine and guinea-pig gastric fundus. *J Physiol* **559**, 259–269.

Burns AJ, Herbert TM, Ward SM & Sanders KM (1997). Interstitial cells of Cajal in the guinea-pig gastrointestinal tract as revealed by c-Kit. *Cell Tissue Res* **290**, 11–20.

Cousins HM, Edwards FR, Hickey H, Hill CE & Hirst GDS (2003). Electrical coupling between the myenteric interstitial cells of Cajal and adjacent muscle layers in the guinea-pig gastric antrum. *J Physiol* **550**, 829–844.

Dickens EJ, Edwards FR & Hirst GDS (2001). Selective knockout of intramuscular interstitial cells reveals their role in the generation of slow waves in mouse stomach. *J Physiol* **531**, 827–833.

Dickens EJ, Hirst GDS & Tomita T (1999). Identification of rhythmically active cells in guinea-pig stomach. *J Physiol* **514**, 515–531.

Edwards FR & Hirst GDS (2005). An electrical description of the generation of slow waves in the antrum of the guinea pig. *J Physiol* **564**, 213–232.

Edwards FR & Hirst GDS (2006). An electrical analysis of slow wave propagation in the guinea pig gastric antrum. *J Physiol* **571**, 179–189.

Edwards FR, Hirst GDS & Suzuki H (1999). Unitary nature of regenerative potentials recorded from circular smooth muscle of guinea-pig antrum. *J Physiol* **519**, 235–250.

Farrugia G (1999). Ionic conductances in gastrointestinal smooth muscles and interstitial cells of Cajal. *Ann Rev Physiol* **61**, 45–84.

Goto K, Matsuoka S & Noma A (2004). Two types of spontaneous depolarizations in the interstitial cells freshly prepared from the murine small intestine. *J Physiol* **559**, 411–422.

Hashitani H, Garcia-Londoño AP, Hirst GDS & Edwards FR (2005). Atypical slow waves generated in gastric corpus provide dominant pacemaker activity in guinea pig stomach. *J Physiol* **569**, 459–465.

Hennig GW, Hirst GDS, Park KJ, Smith CB, Sanders KM, Ward SM & Smith TK (2004). Propagation of pacemaker activity in the guinea-pig antrum. *J Physiol* **556**, 585–599.

Hirst GDS, Beckett EAH, Sanders KM & Ward SM (2002*a*). Regional variation in contribution of myenteric and intramuscular interstitial cells of Cajal to generation of slow waves in mouse gastric antrum. *J Physiol* **540**, 1003–1012.

Hirst GDS, Bramich NJ, Teramoto N, Suzuki H & Edwards FR (2002*b*). Regenerative component of slow waves in the guinea-pig gastric antrum involves a delayed increase in $[Ca^{2+}]_{i\ and}$ Cl^- channels. *J Physiol* **540**, 907–919.

Hirst GDS, Dickens EJ & Edwards FR (2002*c*). Pacemaker shift in the gastric antrum of guinea-pigs produced by excitatory vagal stimulation involves intramuscular interstitial cells. *J Physiol* **541**, 917–928.

Hirst GDS & Edwards FR (2001). Generation of slow waves in the antral region of guinea-pig stomach – a stochastic process. *J Physiol* **535**, 165–180.

Hirst GDS, Garcia-Londoño AP & Edwards FR (2006). Propagation of slow waves in the guinea-pig gastric antrum. *J Physiol* **571**, 165–177.

Hirst GDS & Ward SM (2003). Interstitial cells: involvement in rhythmicity and neural control of gut smooth muscle. *J Physiol* **550**, 337–346.

Huizinga JD, Thuneberg L, Kluppel M, Malysz J, Mikkelsen HB & Bernstein A (1995). W/*kit* gene required for interstitial cells of Cajal and for intestinal pacemaker activity. *Nature* **373**, 347–349.

Kito Y, Fukuta H & Suzuki H (2002*a*). Components of pacemaker potentials recorded from the guinea pig stomach antrum. *Pflugers Arch* **445**, 202–217.

Kito Y, Fukuta H, Yamamoto Y & Suzuki H (2002*b*). Excitation of smooth muscles isolated from the guinea-pig gastric antrum in response to depolarization. *J Physiol* **543**, 155–167.

Kito Y & Suzuki H (2003). Properties of pacemaker potentials recorded from myenteric interstitial cells of Cajal distributed in the mouse small intestine. *J Physiol* **553**, 803–818.

Komori K & Suzuki H (1986). Distribution and properties of excitatory and inhibitory junction potentials in circular muscle of the guinea-pig stomach. *J Physiol* **370**, 339–355.

Komuro T (2006). Structure and organization of interstitial cells of Cajal in the gastrointestinal tract. *J Physiol* **576**, 653–658.

Komuro T, Seki K & Horiguchi K (1999). Ultrastructural characterization of the interstitial cells of Cajal. *Arch Histol Cytol* **62**, 295–316.

Mazet B & Raynier C (2004). Interstitial cells of Cajal in the guinea pig gastric antrum: distribution and regional density. *Cell Tissue Res* **316**, 23–34.

Ohba M, Sakamoto Y & Tomita T (1975). The slow wave in the circular muscle of the guinea-pig stomach. *J Physiol* **253**, 505–516.

Publicover NG & Sanders KM (1986). Effects of frequency on the wave form of propagated slow waves in canine gastric antral muscle. *J Physiol* **371**, 179–189.

Sanders KM (1996). A case for interstitial cells of Cajal as pacemakers and mediators of neurotransmission in the gastrointestinal tract. *Gastroenterology* **111**, 492–515.

Sanders KN & Publicover NG (1989). Electrophysiology of the gastric musculature. In *Handbook of Physiology,* Section 6, *Gastrointestinal System,* Vol. 1, Part 1, pp. 187–216. American Physiological Society, Bethesda, MA.

Suzuki H & Hirst GDS (1999). Regenerative potentials evoked in circular smooth muscle of the antral region of guinea-pig stomach. *J Physiol* **517**, 563–573.

Suzuki H, Takano H, Yamamoto Y, Komuro T, Saito M, Kato K & Mikoshiba K (2000). Properties of gastric smooth muscles obtained from mice which lack inositol trisphosphate receptor. *J Physiol* **525**, 105–111.

Suzuki H, Kito Y, Hashitani H & Nakamura E (2006). Factors modifying the frequency of spontaneous activity in gastric muscle. *J Physiol* **576**, 667–674.

Szurszewski JH (1981). Electrical basis for gastrointestinal motility. In *Physiology of the Gastrointestinal Tract*, ed. Johnson R, pp. 1435–1465. Raven Press, New York.

Tomita T (1981). Electrical activity (spikes and slow waves) in gastrointestinal smooth muscles. In *Smooth Muscle: an Assessment of Current Knowledge*, ed. Bulbring E, Brading A F, Jones AW & Tomita T, pp. 127–156. Edward Arnold, London.

Tsugeno M, Huang S-M, Pang Y-W, Chowdhury JU & Tomita T (1995). Effects of phosphodiesterase inhibitors on spontaneous electrical activity (slow waves) in guinea pig gastric muscle. *J Physiol* **485**, 493–502.

van Helden DF & Imtiaz MS (2003). Ca^{2+} phase waves: a basis for cellular pacemaking and long-range synchronicity in the guinea-pig gastric pylorus. *J Physiol* **548**, 271–296.

Wang X-Y, Lammers WJEP, Bercik P & Huizinga JD (2005). Lack of pyloric interstitial cells of Cajal explains distinct peristaltic motor patterns in stomach and small intestine. *Am J Physiol* **289**, G539–G549.

Ward SM & Sanders KM (2006). Involvement of intramuscular ICC in neuroeffector transmission in the gastrointestinal tract. *J Physiol*

Ward SM, Burns AJ, Torihashi S & Sanders KM (1994). Mutation of the proto-oncogene c-kit blocks development of interstitial cells and electrical rhythmicity in murine intestine. *J Physiol* **480**, 91–97.

Acknowledgements

This project was supported by a grant from the Australian NH and MRC.