Ca^{2+} phase waves - a fundamental mechanism underlying propagation of gastric slow waves

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Gastrointestinal motility is fundamentally dependent on rhythmic depolarisations termed slow waves, events that open voltage dependent Ca^{2+} channels and cause smooth muscle (SM) contraction. A key feature of slow waves is that they propagate relatively rapidly circumferentially near synchronously squeezing the gut but spread more slowly in an oral-anal direction to appropriately direct gastric contents. Yet key aspects such as how slow waves propagate remain in dispute with two primary hypotheses namely conventional action potential-based propagation contrasted against propagation occurring through phase waves generated by intracellular oscillators interacting as coupled oscillators (Daniel *et al.,* 1994).

Recently, we presented evidence for such an oscillator this being the intracellular ER/SR Ca^{2+} store and that slow waves propagated as phase waves resulting through these stores interacting as coupled oscillators (van Helden & Imtiaz, 2003). We termed these Ca^{2+} phase waves, a mechanism that represents a novel means for intercellular signalling that is very different to the conventional action potential. These studies were performed in single bundle strips from the gastric pylorus of the guinea-pig. In generalising this observation, we have investigated whether Ca^{2+} phase waves also underlie slow wave propagation across large multi-bundle sheets of gastric smooth muscle.

Animals were euthanased by exsanguination during deep isoflurane-induced anaesthesia (5-10% in air), a method approved by the University of Newcastle Animal Care and Ethics Committee. Tissue sheets of circular smooth muscle isolated from the gastric distal antrum dissected free of myenteric interstitial cells of Cajal (ICC-MY) showed robust slow waves and contractions. L-type Ca^{2+} channel blockade using nifedipine inhibited contractions without obvious effects on slow waves or slow wave propagation. Agents that inhibit store refill and/or inositol 1,4,5-trisphosphate receptors (IP3Rs) inhibited slow waves consistent with the view that slow waves are generated by (IP3R)-mediated Ca^{2+} release from intracellular Ca^{2+} stores. Slow waves exhibited much slower apparent conduction velocities ("CVs") across than along muscle bundles, this loosely paralleling electrical connectivity. T-type or other voltage dependent Ca^{2+} channels did not have a role in slow wave generation and/or propagation in this tissue. Importantly, the regenerative component of the slow wave was not essential for slow wave propagation, as pacemaker events that trigger the regenerative slow wave component, when subthreshold exhibited "CVs" that paralleled those of regenerative slow waves. Acetylcholine (ACh), a muscarinic agonist known to induce synthesis of IP3, enhanced synchronicity but at high concentrations decoupled slow waves. The findings support the hypothesis that slow waves propagate as Ca^{2+} phase waves, these arising through pacemaker-related Ca^{2+} stores interacting as coupled oscillators within and across the multibundle gastric tissue.

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van Helden DF, Imtiaz MS. (2003) *Journal of Physiology*, **548:** 271-96.