Many parts make a whole: Calcium transients sum for slow waves
Caitlin Sedwick

New JGP study shows how calcium events drive long intestinal slow wave plateaus.

The peristaltic movements that propel food along the digestive tract require coordinated muscle contractions, which are governed by rhythmic electrochemical impulses termed slow waves: periodic membrane depolarization events with a plateau phase lasting ~1 s (1). In stomach and small intestine, slow waves originate in pacemaker cells called interstitial cells of Cajal of the myenteric plexus (ICC-MY; 2). In their paper this month in JGP, Drumm et al. explain how slow waves are generated within ICC-MY (3).

ICC-MY cells are arranged in a fine mesh across the muscle tissue of the small intestine and are connected via gap junctions to smooth muscle cells to convey membrane depolarization to the muscle. Slow wave membrane depolarization in ICC-MY is attributed to the opening of calcium (Ca²⁺)-activated ANO1 chloride channels (4). Thus, slow wave generation ultimately depends on Ca²⁺ influx to the cytoplasmic space, which may occur via activation of voltage-gated plasma membrane calcium channels (5) and/or via Ca²⁺ release from ER intracellular stores (6). However, notes Salah A. Baker, Professor at the University of Nevada School of Medicine (Reno), this poses a conundrum: “[Ca²⁺ transients] occurred in asynchronous fashion and were temporally clustered within the time frame of the slow waves,” explains Baker. “The summation of these Ca²⁺ transients resulted in relatively uniform and prolonged Ca²⁺ responses from slow wave to slow wave.”

Unexpectedly, electrical recordings from muscle cells indicated that muscle cell depolarization preceded the observed Ca²⁺ transients in ICC. Baker suggests this could be because the muscle cells were connected to a dominant pacemaker ICC-MY outside the field of view, or because depolarization was triggered by Ca²⁺ entry mechanisms that could not be resolved by the researchers’ system.

To identify how Ca²⁺ transients are generated, the researchers used pharmacological agents to block different calcium channels in the cell membrane and the ER. Consistent with other studies (5), these experiments showed that transients rely on T-type voltage-gated Ca²⁺ channels in the plasma membrane. The initial influx of Ca²⁺ from those channels was then amplified by activation of Ca²⁺-activated ryanodine receptors on the release Ca²⁺ from intracellular stores. Inositol-1,4,5-triphosphate (IP₃)-stimulated ER Ca²⁺ channels also contributed to Ca²⁺ transients, although ryanodine receptors seemed more prominent. This contrasted with earlier work, which had pointed to a greater role for IP₃ receptors in slow wave generation (6).

These data help explain how ICC-MY generate slow waves, but also raise new questions. For example, Baker and colleagues note that Ca²⁺ transients appear to occur at specialized sites within the cells. They plan to investigate which specific ryanodine receptors and IP₃, Ca²⁺ release channels amplify Ca²⁺ transients at these sites and also whether Ca²⁺ transients are affected by other Ca²⁺ sources, such as mitochondrial stores or sodium/calcium exchange.