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THE MANY FACETS OF ICC IN REGULATING SMOOTH MUSCLE FUNCTION

Kenton M. Sanders

Department of Physiology and Cell Biology, University of Nevada School of Medicine, Reno, NV 89557, USA

Cells referred to as interstitial cells of Cajal (ICC) have been identified in a variety of smooth muscle tissues. The physiological role of ICC in most smooth muscles is not yet understood, but if the functions of ICC are generally similar to the many roles of these cells in gastrointestinal (GI) muscles, ICC have important functions in visceral and vascular physiology and pathophysiology. My group and colleagues within my department have spent the last 2 decades trying to decipher the role of ICC in the GI tract.

ICC within the GI tract are situated at important strategic anatomical locations. Morphologists initially showed that ICC were found in specific locations and were coupled via gap junctions to each other and to smooth muscle cells. This led to the suggestion that ICC were the pacemakers that generate spontaneous electrical rhythmicity in GI organs. ICC were also associated with neurons, and this suggested to Ramon y Cajal (the first investigator to describe ICC) that they may be some type of primitive neuron that links the autonomic nervous system to smooth muscles.

We found that isolated ICC displayed electrical rhythmicity (slow wave activity), whereas isolated smooth muscle cells never display this type of activity. Loss of ICC in animals treated with neutralizing antibodies to Kit proteins or in W/W^{V} mutants with abnormally low Kit activity led to loss of slow wave activity. Since these original experiments many more studies have shown that when specific types of ICC are lost or damaged in GI muscles, pacemaker activity is abolished. These experiments collectively demonstrate the pacemaker function of ICC.

It is well know that slow waves propagate for many cm without decrement in GI organs. The ability to propagate slow waves and entrain the activity of a multitude of spontaneously active cells is another important function of ICC. Smooth muscle cells lack the mechanisms necessary to propagate slow waves. Thus, continuity of ICC within pacemaker areas is critical for important functions such as gastric peristalsis and intestinal segmentation.

Another population of ICC lies in very close proximity (<20 nm) to the nerve terminals of enteric motor neurons and there are synaptic contacts between nerve varicosities and intramuscular ICC (ICC-IM. Loss of this class of ICC greatly reduces both inhibitory (nitergic) and excitatory (cholinergic) neurotransmission in GI muscles. Thus, ICC (as suggested by Cajal), mediate inputs from motor neurons, and loss of these cells can cause loss of motor coordination and loss of sphincter function in the GI tract.

ICC-IM also appear to be involved in stretch-dependent responses in GI muscles. ICC express cyclo-oxygenase enzymes and stretch-activated ion channels. Stretch of ICC-IM can cause liberation of eicosanoids that drives up the frequency of spontaneous electrical slow waves. Thus, stretch of GI organs can influence the motor behavior of these tissues. (Supported by NIH DK41315)