S 4-2

MECHANISM OF SLOW WAVE PROPAGATION IN GASTROINTESTINAL MUSCLES

Kenton M. Sanders

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

Smooth muscle cells generate force and work throughout most of the GI tract, and coordination of many cells is required for normal digestive functions. There are several types of controls systems superimposed upon the functions of smooth muscle cells that are required to generate the complex contractile patterns of GI motility. The first level of organization is the intrinsic electrical rhythmicity (slow waves) of GI muscles. Slow waves are generated within specialized pacemaker regions that are populated by interstitial cells of Cajal (ICC). ICC are the active pacemakers, and these cells express specialized intracellular mechanisms to generate slow waves. ICC are electrically coupled to each other forming a network within the pacemaker areas. ICC are also electrically coupled to smooth muscle cells, but slow waves conduct to the smooth muscle cells and are not actively regenerated within the smooth muscle syncytium. After the initiation of slow waves, these events actively propagate (i.e. are regenerated cell-to-cell without decrement) within the ICC network. This function provides coordination of activity within the ICC network. The rate of propagation (mm to cm per sec) is consistent with a voltage-dependent mechanism that 'entrains' the spontaneous activity of ICC and causes the ICC network to function as a single unit. There are 2 major mechanisms proposed for active propagation of slow waves: i) activation of voltage-dependent Ca^{2+} channels, entry of Ca^{2+} into a restricted volume of subcellular 'pacemaker units' and Ca^{2+} induced Ca^{2+} release from IP_3 receptor-operated stores, and ii) voltage-dependent synthesis of IP_3 or 'sensitization' of IP_3 receptors. My lecture will discuss the pros and cons of these concepts based on current data. At present we favor the concept that propagation depends upon voltage-dependent entry of Ca^{2+} via dihydropyridine-resistant Ca^{2+} channels. Several observations support this concept, while there has never been an experimental demonstration of voltage-dependent IP_3 production or non-Ca^{2+}-dependent, voltage-dependent 'sensitization' of IP_3 receptors in ICC. The frequency of slow waves, propagation velocity of slow waves, and rate-of-rise of the initial upstroke of slow waves are highly dependent upon the extracellular concentration of Ca^{2+}, demonstrating that the Ca^{2+} gradient (i.e. the driving force for Ca^{2+} entry) is critical for propagation. Blockade of dihydropyridine-resistant Ca^{2+} channels slows the propagation velocity and reduces the upstroke velocity in a concentration-dependent manner. High enough concentrations of Ca^{2+} channel blockers inhibit slow wave propagation. Cyclopiazonic acid (CPA), a SERCA pump inhibitor, unloads IP3-receptor operated Ca^{2+} stores and blocks spontaneous pacemaker activity. In the presence of CPA, however, slow wave upstroke potentials can be initiated by electrical pacing and these events propagate. Thus, voltage-dependent Ca^{2+} entry, independent of Ca^{2+} stores, is sufficient to support slow wave propagation. (Supported by NIH DK41315)

S 4-3

PROPERTIES OF SPONTANEOUS ACTIVITY IN STOMACH SMOOTH MUSCLE

Hikaru Suzuki

Department of Physiology, Nagoya City University Medical School, Nagoya, Japan

Although spontaneous activity of gastrointestinal smooth muscle has been considered myogenic, recent studies indicate that the rhythmic activity is originated from interstitial cells of Cajal (ICC) distributed in smooth muscle tissues. Recording electrical responses from smooth muscle tissues isolated from the guinea-pig stomach antrum indicate rhythmic generation of three types of electrical responses; driving potential recorded from ICC distributed in myenteric layer (ICC-MY), follower potential recorded from longitudinal smooth muscle cell and slow wave recorded from circular smooth muscle cell. In addition, circular muscle bundles isolated from antrum region also produce small irregular potentials (unitary potentials) generated in ICC distributed in circular muscle bundle (ICC-IM) and slow potential which is formed by summation of unitary potentials. Slow wave is composed of two components, the 1st component formed by an electrotonic spread of driving potential and the 2nd component formed by slow potentials. Comparison of the time for appearance of spontaneous activity indicates that the driving potential appears first, followed by follower potential and slow wave. These properties suggest that driving potential generated in ICC-MY is pacing gastric activity. Experiments were carried out to investigate the properties of rhythmic electrical activity of smooth muscle tissues isolated from the stomach of guinea-pig and mouse, by recording the activities using intracellular microelectrode. Distribution of slow waves in the stomach indicated that the frequency was the highest in corpus region. Immuno-histochamical investigation indicated that antrum region has distribution of both ICC-MY and ICC-IM, while corpus region has distribution of ICC-IM alone. In considering that the activities with highest frequency would be the dominant source of rhythm in stomach, slow potentials generated in corpus may be the pacemaker of gastric activity. Modulation of slow potentials in response to electrical and chemical stimuli suggested that the frequency and amplitude of slow potentials were determined by different factors; the frequency was coupled with mitochondrial activity while the amplitude was related to the amount of Ca released from internal stores.