Role of intracellular Ca^{2+} stores and L-type Ca^{2+} channels in vasospasm

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Many lymphatic and blood vessels display spontaneous constriction-dilation cycle known as vasomotion. Cyclical Ca^{2+} release from inositol 1,4,5-trisphosphate (IP3) operated intracellular Ca^{2+} stores and influx of Ca^{2+} through L-Ca^{2+} channels have been shown to underlie lymphatic vasomotion1. Various neurotransmitters and paracrine or hormonal substances modulate the frequency of vasomotion. Excessive stimulation can result in pathological sustained constriction of the smooth muscle, a phenomena known as vasospasm1. Previously we have shown that L-Ca^{2+} channels form a long-range coupling link between oscillatory Ca^{2+} stores and are essential for synchronization of store Ca^{2+} release2,3. Endothelin 1, a modulator of vasomotion, has been shown to cause vasospasm at high concentrations1. Based on experimental observations we present a theoretical model, which indicates that excessive stimulation of the lymphatic smooth muscle leads to partial inactivation of L-Ca^{2+} channels, and thus leads to loss of synchrony between oscillatory store Ca^{2+} release. Ca^{2+} oscillations now become asynchronous in the absence of this long-range link, this resulting in a sustained asynchronous constriction. The results of this study indicate that during vasospasm: 1) partial inactivation of L-Ca^{2+} channels occurs due to excessive cytosolic Ca^{2+} concentration; 2) this inactivation reduces long-range coupling by L-Ca^{2+} channels leading to asynchrony between Ca^{2+} stores; 3) a sustained influx of Ca^{2+} through L-Ca^{2+} channels is maintained during vasospasm; 4) The high level of stimulation of stores causes these to cycle at high frequencies, which now does not allow full refilling, this in turn causing a sustained influx of Ca^{2+} through store operated Ca^{2+} channels; and 5) the net result is a sustained vasospasm. While this model of vasospasm is derived from studies on lymphatic smooth muscle, it also applies to blood vessels, which parallel lymphatics in exhibiting voltage-dependent Ca^{2+} store-mediated vasomotion.

(1) Zhao, J. & van Helden, D.F. ET-1-associated vasomotion and vasospasm in lymphatic vessels of the guinea-pig mesentery. Brit. J. Pharmacol. 140, 1399-1413 (2003).
(2) Imtiaz, M., Zhao, J., and van Helden D.F. A theoretical study of Ca^{2+} oscillations and pacemaker potentials underlying vasomotion in guinea-pig lymphatic smooth muscle. in Proceedings of the Australian Physiological and Pharmacological Society (2002).
(3) Zhao, J., Imtiaz, M., and van Helden, D.F. Ca^{2+} oscillations and pacemaker potentials underlying vasomotion of guinea-pig lymphatic smooth muscle. in Proceedings of the Australian Physiological and Pharmacological Society (2002).