Synchronization of Ca^{2+} oscillations through interaction of intracellular Ca^{2+} stores and L-type Ca^{2+} channels

M.S. Imtiaz, J. Zhao, K. Hosaka and D.F. van Helden, The Neuroscience Group, School of Biomedical Sciences, Faculty of Health and Medical Sciences, The University of Newcastle, NSW 2308, Australia.

Many lymphatic and blood vessels undergo spontaneous constriction-dilation cycle known as vasomotion. It has been shown that cyclical Ca^{2+} release from inositol 1,4,5-trisphosphate (IP_3) operated intracellular Ca^{2+} stores and influx of Ca^{2+} through L-Ca^{2+} channels underlie lymphatic vasomotion (Zhao & van Helden, 2003). Experimental observations show that blocking L-Ca^{2+} channels abolishes synchronous Ca^{2+} oscillations, leaving only asynchronous oscillations. Based on such experimental observations and theoretical studies, we have previously 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+} release (Imtiaz *et al.*, 2002; Zhao *et al.*, 2002). The present study examines this L-Ca^{2+} channel-mediated long-range coupling mechanism.

Synchronization of Ca^{2+} oscillations can occur through diffusion of Ca^{2+} or IP_3 through gap junctions. In the present study we investigate Ca^{2+} store entrainment through voltage dependent L-Ca^{2+} channel-mediated store Ca^{2+} release for a cell pair. Such a coupling mechanism is significantly more effective than the chemical coupling-based class of models, as membrane potential has a coupling effect over distances several orders of magnitude greater than either diffusion of Ca^{2+} or IP_3 through gap junctions (Imtiaz *et al.*, 2002).

We encapsulate experimental observations in a model where; 1) each local oscillator is composed of a cytosolic-store Ca^{2+} excitable system, 2) local Ca^{2+} oscillations are coupled to membrane potential, and, 3) membrane potential exerts a positive feedback on the local Ca^{2+} oscillator through Ca^{2+} influx through L-Ca^{2+} channels. We construct a coupled cell pair according to the schema outlined above.

We study the synchronization properties of the above cell pair system. It is shown that even weak electrical coupling is sufficient to synchronize heterogeneous cell pairs. A comparison is made between electrical and chemical coupling through diffusion of Ca^{2+} or IP_3. It is shown that chemical coupling is not effective when cells are weakly coupled and have different intrinsic frequencies. This is consistent with experimental observations where only asynchronous oscillations are observed during blockade of L-Ca^{2+} channels. The result of this study show that electrical coupling acting through L-Ca^{2+}-mediated modulation of store Ca^{2+} release is able to synchronize oscillations of cells even when cells are weakly coupled (or widely separated) and/or have different intrinsic frequencies of oscillation.

Imtiaz, M., Zhao, J., & van-Helden, D.F. (2002) *Proceedings of the Australian Physiological and Pharmacological Society* http://www.aups.org.au/Meetings/200211/abstracts/1148.html

Zhao, J., Imtiaz, M., and van Helden, D. (2002) *Proceedings of the Australian Physiological and Pharmacological Society* http://www.aups.org.au/Meetings/200211/abstracts/1149.html

Zhao, J. & van Helden, D.F. (2003) *British Journal of Pharmacology* **140**, 1399-1413.