Public Abstract
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Title:Role of T-type calcium channels in lymphatic pacemaking

To actively maintain fluid homeostasis, collecting lymphatic vessels possess lymphatic smooth muscle (LSM) layer that rhythmically contract to pump lymph back to the blood system. As a low-voltage activated calcium channel, T-type calcium channels (with three isoforms Cav3.1, Cav3.2 and Cav3.3) have been suggested a role in pacing of muscle of the heart especially the isoform Cav3.1. Current literature proposed that T-channels determine the pacing of lymphatic contractions, and L-type high-voltage activated calcium channels (L-channels) determine the strength of each contraction. However, previous studies on T-channels in lymphatic contractions relied completely on pharmacological T-channel inhibitors, which have off-target effect on L-channels. To circumvent this limitation, using genetic approaches, I investigated the effect of deleting specific T-channel or L-channel isoform on lymphatic pacing and contraction strength. First, two T-channel isoforms Cav3.1 and Cav3.2, were expressed by mouse LSM as assessed with PCR, immunostaining and electrophysiology. Second, in mouse pressure myograph experiments, treatment with T-channels inhibitors nickel and TTA-A2 mainly inhibited contraction amplitude, suggesting their non-specific effect on L-channels. Third, specific deletion of one L-channel isoform, Cav1.2, from smooth muscle resulted in lymphatic vessels with no rhythmic contractions. In contrast, deletion of either Cav3.1 or Cav3.2 resulted in no significant differences in contractile patterns compared to controls. In Cav3.1 knock-outs (KOs), we then measure dose-response (D-R) relationship to nifedipine, expecting to observe a leftward shift if T-channels contributed as a calcium source. In Cav3.1KOs, frequency tended to be affected at smaller nifedipine concentrations compared to controls, but none of the differences were significant. Likewise, an acetylcholine D-R relationship was also investigated to test if nitric oxide (NO) production by lymphatic endothelium was dependent on T-channel isoform Cav3.1. Without Cav3.1, amplitude tended to be less affected by acetylcholine, suggesting that Cav3.1 could be upstream to endothelial NO release in response to acetylcholine, but the differences were not statistically significant. In conclusion, T-channels were functionally detected in LSM, but selective genetic deletion of either Cav3.1 or Cav3.2 T-channel isoforms did not produce a measurable defect in lymphatic vessel pacemaking. My findings conflicts with the current established view of the role T-channels play in lymphatic pacemaking, a definitive role for T-channels is lymphatic pacemaking remains unknown.