Privileged crosstalk between TRPV1 channels and mitochondrial calcium shuttling machinery controls nociception.


Abstract:

The nociceptive noxious heat-activated receptor - TRPV1, conducts calcium and sodium, thus producing a depolarizing receptor potential, leading to activation of nociceptive neurons. TRPV1-mediated calcium and sodium influx is negatively modulated by calcium, via calcium-dependent desensitization of TRPV1 channels. A mitochondrial Ca(2+) uniporter - MCU, controls mitochondrial Ca(2+) entry while a sodium/calcium transporter - NCLX shapes calcium and sodium transients by mediating sodium entry into and removing calcium from the mitochondria. The functional interplay between TRPV1, MCU and NCLX, in controlling the cytosolic and mitochondrial calcium and sodium transients and subsequently the nociceptive excitability, is poorly understood. Here, we used cytosolic and mitochondrial fluorescent calcium and sodium imaging together with electrophysiological recordings of TRPV1-induced currents in HEK293T cells and nociceptor-like dissociated rat dorsal root ganglion neurons, while modulating NCLX or MCU expression using specific small interfering RNA (siNCLX). We show that the propagation of the TRPV1-induced cytosolic calcium and sodium fluxes into mitochondria is dependent on coordinated activity of NCLX and MCU. Thus, knocking-down of NCLX triggers down regulation of MCU dependent mitochondrial Ca(2+) uptake. This in turn decreases rate and amplitude of TRPV1-mediated cytosolic calcium, which inhibits capsaicin-induced inward current and neuronal firing. TRPV1-mediated currents were fully rescued by intracellular inclusion of the fast calcium chelator BAPTA. Finally, NCLX controls capsaicin-induced cell death, by supporting massive mitochondrial Ca(2+) shuttling. Altogether, our results suggest that NCLX, by regulating cytosolic and mitochondrial ionic transients, modulates calcium-dependent desensitization of TRPV1 channels, thereby, controlling nociceptive signaling.

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