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

By else_admin
Created 9/15/2016
By else_admin September 15, 2016


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.

Journal:
Biochimica et biophysica acta

Date Published:
2016 Sep 11

Custom 1:
It is now widely accepted that deciphering the enigma of the brain is the most challenging intellectual endeavor of the 21st century, "The Century of the Brain" - Join our quest and become a friend of ELSC.

**ELSC Friends**

Our Int'l Ph.D. program provides outstanding students with top-notch courses in computational neuroscience.

**Studying at ELSC**

The Jerusalem Brain Sciences Building will provide a state-of-the-art research and teaching facility for the Edmond and Lily Safra Center for Brain Sciences.

**The Building**

Get into our media channel and investigate ELSC's latest videos: seminars, public lectures, courses and video articles.

**ELSC Media Channel**

---

Source URL: http://elsc.huji.ac.il/binshtok/publications/privileged-crosstalk-between-trpv1-channels-and-mitochondrial-calcium-shuttlin