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Molecular engineering of the TRPC3 pore structure identifies Ca^{2+} permeation through TRPC3 channels as a key determinant of cardiac calcineurin/NFAT signaling

Michaela Lichtenegger[1], Hannes Schleifer[1], Thomas Stockner[2], Christoph Romanin[3], Michael Poteser[1], Klaus Groschner[1*]

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Background

TRPC channels have been identified as key players in cardiac remodeling and as crucial upstream components of NFAT signaling. The linkage between non-selective TRPC conductances and calcineurin/NFAT signaling may involve either direct TRC-mediated Ca^{2+} entry or indirect mechanisms involving crosstalk with other cardiac Ca^{2+} transport systems.

Methods

The pore structure of TRPC3 was analyzed by site-directed mutagenesis guided by a molecular modeling approach combined with patch-clamp measurements in the HEK293 expression system. TRPC3-mediated Ca^{2+} entry as well as NFAT translocation was investigated by fluorescence microscopy using Fura-2 and expression of a GFP-NFAT fusion protein in HEK293 as well as in HL1 cells.

Results

Elimination of Ca^{2+} permeation through TRPC3 abrogated its ability to trigger NFAT translocation in both HEK293 cells and in HL-1 atrial myocytes. Wild-type TRPC3 was found capable of initiating NFAT translocation in atrial myocytes by a small, homogenous elevation of cytoplasmic Ca^{2+} that was independent of voltage-gated $Ca_V1.2$ channels. By contrast, a Ca^{2+} impermeant TRPC3 mutant strongly promoted endothelin-induced Ca^{2+} signals in HL1 cells via enhanced activity of $Ca_V1.2$ channels without concomitant NFAT translocation.

Conclusions

Our results demonstrate two strictly separated Ca^{2+} signaling functions of cardiac TRPC3 channels as well as a tight and efficient link between TRPC3-mediated Ca^{2+} permeation and calcineurin/NFAT signaling.

Author details
[1]Institute of Pharmaceutical Sciences – Pharmacology and Toxicology, University of Graz, 8010 Graz, Austria. [2]Institute of Pharmacology, Center for Physiology and Pharmacology, Medical University of Vienna, 1090 Vienna, Austria. [3]Institute of Biophysics, University of Linz, 4040 Linz, Austria.

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* Correspondence: klaus.groschner@uni-graz.at
[1]Institute of Pharmaceutical Sciences – Pharmacology and Toxicology, University of Graz, 8010 Graz, Austria
Full list of author information is available at the end of the article