TRPC channel-mediated signaling in cerebellar Purkinje cells: Surprising insights from the analysis of mutant mice

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Cation channels of the TRPC subfamily are widely expressed in the brain. However, their specific roles for brain function are largely unknown. It has been suggested that the mGluR-dependent slow excitatory postsynaptic currents (sEPSCs) require the activation of the TRPC1 subunit (Kim et al., *Nature*, 2003). In order to determine the role of TRPC channels *in vivo*, we studied mGluR-dependent synaptic transmission in mice deficient for different TRPC-subunits (combinations of TRPC1-/-, TRPC4-/- and TRPC6-/-) by using whole-cell recordings and Ca^{2+} imaging in acute cerebellar slices. Surprisingly, we found that repetitive parallel fiber stimulation-evoked sEPSCs persist in these mutant mice, indicating that none of these TRPC channel subunits is needed for sEPSC function. Furthermore, the mGluR1-specific agonist DHPG, was still able to activate robust sEPSC-like inward currents in the absence of TRPC1, TRPC4 and TRPC6. In view of these unexpected results we determined the expression pattern of all TRPC subunits in Purkinje cells. For this purpose we used an approach of quantitative single cell RT-PCR analysis that involves the harvesting of individual neurons from living brain slices (Durand et al., *Pflugers Archiv*, 2006). The single cell RT-PCR analysis demonstrated that, surprisingly, TRPC3 is the by far predominant TRPC subunit expressed in Purkinje cells. TRPC1, TRPC4 and TRPC6 are also present, but much less abundantly found in this cell type. TRPC5 was not detected. As a consequence of these findings we generated a TRPC3-/- mouse. An analysis of cerebellar slice from such mice demonstrated that the sEPSCs, as well as DHPG-evoked inward currents are completely abolished. Remarkably, the mGluR1-mediated calcium release signal seemed entirely unaffected by the deletion of TRPC3, indicating that TRPC3 has no major role in the refilling of intracellular calcium stores. Taken together, our results reveal a decisive role of TRPC3 for mGluR1-evoked slow synaptic potentials and challenge the concept that TRPC channels are of primary importance for the refilling of neuronal calcium stores.