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Meeting abstract

Identification of amino acid residues relevant for gating and permeation of the cation channel TRPC3

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Background and methods

Mammalian TRPC3 cation channels are activated through phospholipase type C (PLC)-dependent pathways and play a fundamental role in a variety of physiological functions. So far, only little information is available on structural determinants of channel function, especially domains involved in channel gating and permeation. Therefore, we set out to modify putative permeation-relevant residues of this ion channel by site-directed mutagenesis and analyzed the impact of these mutations on channel functions using a HEK293 expression system and the patch clamp technique.

Results

A triple mutation of the native glutamate or aspartate residues to alanin (E630A, D639A and E644A) within the putative pore region resulted in spontaneous activity and currents with altered (linear) IV-relations, while the principle removal of negative charges at these positions (E to Q and D to N) failed to induce detectable changes in channel function. Single exchange of a negative amino acid in this region (D639A) as well failed to change IV-relations. Surprisingly, double substitution of E by Q near the putative external vestibule (amino acid 615 and 616) eliminated the sensitivity of channels to PLC-mediated activation.

Conclusion

In conclusion, our data suggests an unexpected role of amino acid residues within the outer vestibule of TRPC3 channels in terms of gating and selectivity. These results give rise to a remodelled picture of structure-function relations in TRPC channels.

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