

Acta Physiologica 2010; Volume 198, Supplement 677

Joint Meeting of the Scandinavian and German Physiological Societies

3/27/2010-3/30/2010

Copenhagen, Denmark

WHO IS THE KEEPER OF THE GATE? - SINGLE-CHANNEL PROPERTIES AFTER RECIPROCAL EXCHANGE OF THE PORE IN THE CATION CHANNELS TRPM2 AND TRPM8

Abstract number: P-TUE-125

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Aims: The closely related cation channels TRPM2 and TRPM8 show strongly contrasting properties in respect of their activation and regulation by Ca^{2+} . In order to elucidate the role of the pore and its adjacent domains for channel gating and Ca^{2+} dependence, chimeras of TRPM2 and TRPM8 were created in which the S5-pore-S6 regions were reciprocally exchanged. **Methods:** Functional properties of wild-type and chimeric channels were investigated with patch-clamp analysis on transfected HEK293 cells. Whole-cell measurements were complemented by single-channel recording in the inside-out configuration. **Results:** The chimera M2M8P (i.e. TRPM2 with the S5-pore-S6 segment of TRPM8) showed the same activation behaviour and Ca^{2+} dependence as TRPM2; only at strong hyperpolarization, prolonged closures resulted in a reduction of whole-cell currents. Under standard conditions, single-channel kinetics displayed the extremely long openings characteristic for TRPM2. The reciprocal chimera M8M2P could not be activated by cold and required stronger as well as longer stimulation with menthol and icilin than wild-type TRPM8. Thus, the interaction between voltage sensor of TRPM8 and pore was less effective but principally conserved in the chimera. Regulation by Ca^{2+} was identical in M8M2P and TRPM8. Single-channel characteristics (short openings, bursts, voltage-dependence of open probability) were preserved. **Conclusion:** Single-channel properties, Ca^{2+} dependence and responses to chemical activators were little affected by swapping of the S5-pore-S6 segment. The data suggest that an adaptable gate resides in this region, capable to respond to the diversity of stimuli transduced by TRPM2 and TRPM8.

To cite this abstract, please use the following information:

Acta Physiologica 2010; Volume 198, Supplement 677 :P-TUE-125