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DISSERTATION

The effects of acid-sensing ion channel ASIC3 and stomatin-like proteins on mechanosensation and nociception

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von

Rabih Moshourab

aus Libanon

Gutachter: 1. Prof. Dr. phil. G. Lewin
2. Prof. Dr. H. Handwerker
3. Prof. Dr. med. M. Schmelz

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Abstract

Transformation of mechanical energy into electrical signals in mechanosensory neurons is essential for mechanosensation and nociception. This transformation occurs via sensory transduction channels that are activated by external force. Recent genetic and electrophysiological studies in *Caenorhabditis elegans* have directly shown that the degenerin/epithelial sodium channel (DEG/ENaC) ion channel subunits, MEC-4 and MEC-10, and the accessory ion channel subunits MEC-2 and MEC-6 form a sensory transduction ion channel within a mechanotransduction complex that also includes intra- and extracellular proteins. In mammals DEG/ENaC ion channel subunits are also proposed to function as mechanotransducers. Consistent with a function in mechanosensation, the mammalian acid-sensing ion channel subunit ASIC3 belongs to the DEG/ENaC family of ion channels; it is highly expressed in mechanosensory neurons including their peripheral structures; and it has been shown to be required for normal mechanosensation in mice. MEC-2 protein, which contains a stomatin-like domain in its central region, interacts and modulates MEC-4 ion channel activity. Mammalian stomatin-like proteins, like stomatin and stomatin-like protein (SLP3), might have similar roles. Here we show that ASIC3 coimmunoprecipitates with stomatin and SLP3 in a heterologous system. We asked whether the physical interaction between ASIC3 and stomatin proteins has any effects on mechanotransduction in mechanosensory neurons innervating skin. To look for a functional interaction between ASIC3 and stomatin in mechanosensory neurons single fiber analysis of mechanosensitivity in *ASIC3*/*stomatin* double mutant mice in the *in vitro* skin nerve preparation were used. The loss of ASIC3 function specifically increases mechanosensitivity in rapidly adapting mechanoreceptors (RAM) and reduces the sensitivity of nociceptors, including A-mechanonociceptors (AM) and C-fibers. In comparison, the additional loss of stomatin does not alter the increased mechanosensitivity in RAM; however, it slightly decreases the speed of response (mechanical latency). In addition, AM and C-fibers in *ASIC3*/*stomatin* double mutants show reduced mechanosensitivity that is not significantly different from the alterations due to loss of ASIC3 alone. However, polymodal nociceptors (C-MH) in *ASIC3*/*stomatin* double mutants show significant decrease in mechanosensitivity to suprathreshold stimuli compared to C-MH in *ASIC3* single mutants. Therefore, the loss of stomatin produced additional alteration in mechanoreceptor function already altered by loss of ASIC3. The data suggest that ASIC3 is required for normal mechanoreceptor function and that a weak functional interaction exists between ASIC3 and stomatin.

Index

List of Figures

List of Tables

Erklärung

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Publication list

1. Dubreuil AS, Boukhaddaoui H, Desmadryl G, Martinez-Salgado C, Moshourab R, Lewin GR, Carroll P, Valmier J, Scamps F (2004) Role of T-type calcium current in identified D-hair mechanoreceptor neurons studied in vitro. J Neurosci 24:8480-8484.

2. Lewin GR, Moshourab R (2004) Mechanosensation and pain. J Neurobiol 61:30-44.

3. Wetzel C, Hu J, Riethmacher D, Benckendorff A, Harder L, Eilers A, Moshourab R, Kozlenkov A, Labuz D, Caspani O, Erdmann B, Machelska H, Heppenstall PA, Lewin GR (2006) A stomatin-domain protein essential for touch sensation in the mouse. Nature. 2007 Jan 11;445(7124):206-9 .

Lebenslauf

Mein Lebenslauf wird aus Datenschutzgründen in der elektronischen Version meiner Arbeit nicht mit veröffentlicht.