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MEETING ABSTRACT Open Access

A conformational change of the domain IV S6 segment of the voltage-gated sodium channel during inactivation

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Background

In voltage-gated Na^+ channels the S6 transmembrane segment of domain IV (DIV-S6) is part of the lining of the inner part of the pore. It is of pivotal importance for inactivation gating. We recently showed that amino acid I1581 of DIV-S6 ($rNa_V1.4$ amino acid numbering) is extraordinarily sensitive to both local and distal mutations suggesting a unique role in coupling of voltage-sensor movements to conformational changes in the pore. To date the only structural information relevant to voltage-gated Na^+ channels can be derived from the recently crystallized bacterial channel Na_VAb. In this structure the amino acid homologous to I1581 faces the lipid phase and is in close spacial relationship to the voltage-sensing apparatus. If this arrangement holds true for the eukaryotic Na^+ channel then site 1581 should not be exposed to bulk solution.

Methods

The following methods were used: site-directed mutagenesis of amino acids in the S6 segment of domain IV of the $rNa_V1.4$ channel; heterologous expression of the constructs in tsA 201 cells and *Xenopus laevis* oocytes; exploration of the kinetic effects of the mutations and gating sensitivity of the amino acid residue in the S6 segment of domain IV of the $rNa_V1.4$ channel by whole-cell patch clamp and two-electrode voltage clamp technique.

Results

We tested the hypothesis by replacing I1581 by a titrable histidine. In wild-type channels changing the pH of the bulk solution from 7.4 to 8.2 had no effect on the voltage-dependence of fast inactivation. However, in I1581H the same change in pH resulted in a 9.51 ± 1.98 mV hyperpolarizing shift ($p < 0.05$) of the voltage-dependence of fast inactivation.

Conclusions

The data suggest that during inactivation site 1581 is at least partially exposed to the bulk solution and not completely embedded in the lipid phase. The DIV-S6 segment may undergo a conformational change during inactivation, most likely a rotational movement, which allows access of external protons to site 1581.

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