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MEETING ABSTRACT Open Access

New structural determinants of charged local anaesthetic block of voltage-gated sodium channels

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Background

Some blockers of voltage-gated Na^+ and Ca^{2+} channels are assumed to pass through the membrane and then bind to amino acids in the internal vestibule by access from the internal side of the membrane. However, in the heart isoform of the voltage-gated Na^+ channel, in L-type calcium channels and in T-type calcium channels an additional external access pathway (EAP) through the protein has been suggested. Furthermore, in voltage-gated Na^+ channels (Na_V) mutations at a specific site in the middle of the domain IV transmembrane segment 6 (site 1575 in $rNa_V1.4$, 1760 in $rNa_V1.4$) open an EAP for QX-222, a permanently charged, hydrophilic lidocaine analogue. Recently, the first crystal structure of a Na_V was published [1]. In this bacterial channel structure (Na_VAb) the side chain homologous to $rNa_V1.4$ I1575 (I202 in Na_VAb) is in close contact with a pore-loop sidechain, homologous to $rNa_V1.4$ W1531 (W179 in Na_VAb). In contrast, in all currently available structural homology models of Na_V, W1531 is not in contact with I1575. If W1531 were positioned as suggested in the Na_VAb structure then a reduction in the length of the side chain at this site would be predicted to open the EAP. To test this hypothesis we generated the mutations W1531A and W1531G and tested these constructs for block by external QX-222.

Methods

Whole-cell patch clamp measurements were done on TsA 201 cells transiently transfected with plasmids coding the $rNa_V1.4$ α subunit and its mutants, the sodium channel β1 subunit and GFP. Block levels were derived at 2 Hz stimulation frequency from a holding potential of –120 mV.

Results

Mutations W1531A and W1531G were found to be sensitive to extracellular QX-222 (block: 20.6 ± 2% and 17.7 ± 3.5%, respectively).

Conclusions

Our results indicate that position 1531 is an important part of the EAP in $rNa_V1.4$, as predicted from the crystal structure of Na_VAb. Thus the bacterial channel Na_VAb appears to share important structural motifs with eukaryotic sodium channels.

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Reference

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