Molecular determinants of toxin selectivity of Kv1.2 and Kv1.3 K^+ channels

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We have identified and characterized two new peptide toxins inhibiting voltage-gated K^+ channels: Css20 from the venom of the scorpion *Centruroides suffusus suffusus* and Tst26 from the venom of the scorpion *Tityus stigmurus*. We showed that these toxins block preferentially the currents of Kv1.2 and Kv1.3 channels of the *Shaker*-family of voltage-gated K^+-channels with high affinity (Css20: K_d = 1.3 nM and 7.2 nM, Tst26: K_d = 1.9 nM and 10.7 nM, for Kv1.2 and Kv1.3, respectively,). These peptides did not affect several other voltage-dependent (mKv1.1, hKv1.4, hKv1.5, hBKCa, hERG along with rKv2.1 for Css20) and calcium-activated (hIKCa1) potassium channels, nor did they inhibit the cardiac sodium channel (hNav1.5). The striking differences in the rates of toxin association and dissociation for Kv1.2 and Kv1.3 indicate dissimilar modes of interaction with these channels in spite of the similar affinities. Tst26 also interfered with the inactivation gating of the Kv1.3 channel: toxin binding destabilized the inactivated state, most likely as a consequence of locking a potassium ion in the selectivity filter of the channel.

Css20 is composed of 38 and Tst26 is composed of 37 amino acid residues and tightly folded through three disulfide bridges, similar to other K^+-channel blocking peptides purified from scorpion venoms. Both contain the "essential dyad" for K^+-channel recognition comprised of a lysine at position 28 (K28) and an aromatic residue (here tyrosine) at position 37 (Y37) for Css20. These residues in corresponding positions are K27 and Y36 for Tst26. Based on the primary structures; the systematic nomenclatures proposed for these peptides are α-KTx2.13 for Css20 and α-KTx4.6 for Tst26.

Sequence comparisons, and computer models of toxin docking to the channels allowed us to isolate key determinants of Kv1.2 or Kv1.3 selectivity. For instance, disrupting Kv1.2-specific interactions of Css20 (Q11 and K33 of the toxin with E355 in different subunits of the channel), could increase Kv1.3 selectivity. Such an approach, successful for other scorpion toxins, would allow targeting appropriate cells and physiological/pathophysiological functions, e.g. specific inhibition of the proliferation of human effector memory T cells. Further studies are required to explore this scenario, which can be guided by the analysis presented in this study.

Keywords:

Centruroides suffusus suffusus, *Tityus stigmurus*, K^+ -channel, T lymphocytes, molecular modeling, scorpion toxin