CM28, A NOVEL PEPTIDE FROM SCORPION VENOM, INHIBITS K_V1.2 AND K_V1.3 WITH HIGH AFFINITY

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Scorpion venoms are rich in ion channel modulator peptides toxins. A novel short peptide (Cm28), consists of 27 amino acids with 2820 Da molecular weight, was isolated from the venom of scorpion *Centruroides margaritatus*. Cm28 inhibited voltage-gated potassium channels Kv1.2 and Kv1.3 with K_d value of 0.96 and 1.3 nM, respectively. There was no significant shift in the conductance-voltage (G-V) relationship for both channels in the presence of toxin. Toxin binding kinetics showed that the on- and off-rates are consistent with a pseudo-first order reaction, on-rate increases with toxin concentration whereas off-rate remains constant. Based on these we conclude that Cm28 is not a gating modifier, rather a pore blocker.

During selectivity profiling against 5 other subtypes of Kv channels (Kv1.1, Kv1.5, Kv11.1, KCa1.1, KCa3.1), 2 subtypes of Nav channels (Nav1.5 and Nav1.4) and the proton channel hHv1, Cm28 did not affect the activity of any channel at a concentration of 150nM except ~27% blockage of Kv1.1 current. In biological functional assay, Cm28 strongly inhibited the expression of the activation markers interleukin-2 receptor a and CD40 ligand in anti-CD3-activated $CD4^+$ T_{EM} lymphocytes. Sequence analysis identified that Cm28 has less than 40% similarity with other known α-KTx from scorpions and lacks the typical functional dyad (lysine-tyrosine) required to block Kv channels. However, its unique amino acid sequence contains the three disulfide-bond trait of the well-characterized scorpion α-KTx which adopts the cysteine-stabilized α/β scaffold. Results suggest that the novel Cm28 peptide could be a new subfamily of α-KTx toxins.