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Interaction Of Kv1.3-specific Inhibitory Peptides with Asymmetric Heterotetrameric Kv1 Channels

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The Kv1.3 voltage-gated K+ channels are primarily expressed in immune cells and the CNS. Kv1.3 subunits can associate with other Kv1.1 to Kv1.6 subunits to form functional heterotetrameric channels. The potent and selective inhibitors of homotetrameric Kv1.3 are native or modified toxins. However, their activity against asymmetric heteromeric channels is usually overlooked. To study the pharmacology of Kv1.3 heterotetramers systematically, we expressed the tandemly linked dimers Kv1.3-Kv1.x and confirmed their expression and well-constrained stoichiometry using fluorescence-detection size-exclusion chromatography. Electrophysiology demonstrated that heterotetrameric channels of Kv1.3 showed mixed inactivation kinetics and their affinity for tetraethylammonium (TEA) obeyed the expected dependency on the ratio of TEA-sensitive or insensitive Kv1 subunits, confirming the assembly of the channels from Kv1.3-Kv1.x dimers. The Kd values of Vm24, Shk-186, and HsTX1[R14A] for Kv1.3-Kv1.x heterotetramers vary between 0.06−10, 0.01−7.8, and 0.8−8.7 nM, respectively. Vm24 has a high affinity (Kd = 64 pM) for Kv1.3-Kv1.2, while Shk-186 and HsTx1[R14A] have a high affinity (Kd of 9.4 pM and 830 pM, respectively) for Kv1.3-Kv1.1. These significant differences in potency for heterotetramers may reflect unique interactions between the toxin and the asymmetric channels.