K_V7 Channels of the Urinary Bladder Smooth Muscle: Functional Roles and Therapeutic Potential

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Overactive bladder (OAB) is a pervasive and debilitating condition for which effective therapeutic modalities are lacking. As potential novel pharmacological targets for lower urinary tract dysfunction, our recent studies have demonstrated voltage-gated K_V7 channels ($K_V7.1$-$K_V7.5$) to be functionally expressed in detrusor smooth muscle (DSM) of the urinary bladder. Nonetheless, the specific roles of individual K_V7 channel subtypes remains poorly understood. Using Western blot, immunocytochemistry, isometric DSM tension recordings, ratiometric fluorescence Ca^{2+} imaging, and patch-clamp electrophysiology, we demonstrated expression and key physiologic roles for the $K_V7.2/K_V7.3$ channels in guinea pig DSM using the novel and selective $K_V7.2/K_V7.3$ channel opener *N*-(2-Chloro-5-pyrimidinyl)-3,4-difluorobenzamide (ICA-069673). We further sought to pharmacologically target $K_V7.4$- and $K_V7.5$-containing channels, which evidence suggests are the prominent subtypes expressed in smooth muscle, to determine their involvement in regulating DSM excitation-contraction coupling. The novel $K_V7.4/K_V7.5$ channel activator *N*-(2,4,6-Trimethylphenyl)-bicyclo[2.2.1]heptane-2-carboxamide (ML213) was shown to enhance K_V7 channel currents in isolated DSM cells, hyperpolarize the DSM cell membrane potential, and attenuate the contractile activity of DSM isolated strips via a Ca^{2+}-dependent mechanism. ML213 exhibited significantly greater potency for inhibition of DSM contractility in comparison to $K_V7.2/K_V7.3$ channel opener ICA-069673. Using *in situ* proximity ligation assay (PLA), it was further revealed $K_V7.4$ and $K_V7.5$ channel α-subunits co-localize to form heteromeric $K_V7.4/K_V7.5$ channel complexes in DSM isolated cells. These studies suggest $K_V7.4/K_V7.5$ channels are functionally expressed in guinea pig DSM, where they critically regulate DSM excitability and contractility. Finally, to ascertain the translational implications of our aforementioned findings from experimental animals, we examined K_V7 channel expression and function in human DSM. K_V7 channel activators and inhibitors were shown to attenuate and potentiate, respectively, human DSM excitability and contractility in normal and OAB samples. Noteworthy, using *in situ* PLA, we confirmed the molecular interaction between $K_V7.4$ and $K_V7.5$ channel α-subunits, suggesting heteromeric $K_V7.4$/KV7.5 channel subtype expression at the cellular level in human DSM cells. These findings are consistent with our findings in guinea pig DSM and provide strong support to suggest $K_V7.4/K_V7.5$ channels are among the key subtypes regulating human DSM function. In conclusion, our combined studies reveal novel insights into the expression, subunit composition, and physiological roles of K_V7 channel in DSM, providing critical information for directing future research efforts concerning the utility of K_V7 channels as therapeutic targets for OAB.