Heterodimerization of two pore domain K⁺ channel TASK1 and TALK2 in HEK293 heterologous expression systems

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Two-pore-domain K⁺ (K2P) channels sense a wide variety of stimuli such as mechanical stress, inhalational anesthetics, and changes in extracellular pH or temperature. The K2P channel activity forms a background K⁺ current and, thereby, contributes to resting membrane potentials. Six subfamilies including fifteen subtypes of K2P channels have been identified. Each K2P channel molecule with two pores consists of a homodimer of each subtype. In addition, a few heterodimers mainly within the same subfamilies have been found recently. In the present study, the possibility of heterodimerization between TASK1 (TWIK-Related Acid-Sensitive K⁺ channel) and TALK2 (TWIK-Related Alkaline pH-Activated K⁺ channel) was examined. These channels belong to separate subfamilies and show extremely different channel properties. Surprisingly, single molecular imaging analyses in this study using a total internal reflection microscope suggested the heterodimerization of TASK1 and TALK2 in a pancreatic cell line, QGP-1. This heterodimer was also detected using a bimolecular fluorescence complementation assay in a HEK293 heterologous expression system. Fluorescence resonance energy transfer analyses showed that the affinity between TASK1 and TALK2 appeared to be close to those of homodimers. Whole-cell patch-clamp recordings revealed that TASK1 currents in HEK293 cells were significantly attenuated by co-expression of a dominant-negative form of TALK2 in comparison with that of wild-type TALK2. The sensitivities of TASK1-TALK2 tandem constructs to extracellular pH and halothane were characterized as a unique hybrid of TASK1 and TALK2. These results suggested that heterodimerization of TASK1 and TALK2 provides cells with the ability to make multiple responses to a variety of physiological and pharmacological stimuli.