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STRESS-AXIS REGULATED EXON (STREX) IN THE C TERMINUS OF BK_{Ca} CHANNELS IS RESPONSIBLE FOR THE STRETCH SENSITIVITY

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Identification of a mechanosensing domain is central to the biophysics of stretch-activated (SA) channels. Here, we identify that Stress-axis Regulated Exon (STREX), a particular amino-acid sequence at the C-terminus of the stretch-activated, large-conductance, calcium- and voltage-activated potassium (BK_{Ca}) channels cloned from chick embryonic heart (we designated as SAK_{Ca} channels), is responsible for the stretch sensitivity through the interaction with cytoskeletal complex (elongation factor 1A (EF-1 α)/actin). Deletion of the STREX insert diminished the stretch sensitivity of the channel. Sequence analysis revealed that the $ERA_{672\text{-}674}$ sequence of the STREX is indispensable for channel stretch sensitivity and single amino acid substitution from Ala674 to Thr674 completely eliminated the stretch sensitivity. Co-expression of chick STREX-EGFP and SAK_{Ca} in CHO cells, induced a strong GFP signal in the cell membrane and inhibited the stretch sensitivity significantly, implying that the STREX requires binding partner(s) to contribute to the stretch sensitivity. We found that actin and EF-1 α bind specifically to STREX and the knockdown of EF-1 α by siRNA treatment severely inhibited the stretch sensitivity of SAK_{Ca}. These results suggest that SAK_{Ca} senses membrane tension through an interaction between STREX and cytoskeletal complex such as actin and EF-1 α.

Key Words: K channel, SA channel, SAKCA

S 19-3

PHYSIOLOGY OF SK CHANNELS

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Small conductance Ca-activated K channels (SK channels) are important determinants of neuronal excitability. SK channels are gated solely by intracellular Ca ions and are activated by increased levels of cytosolic Ca such as occur during an action potential. SK channel activity exerts a repolarizing effect that continues past the action potential spike and in many neurons contributes to a prolonged afterhyperpolarization. Structurally, SK channels are tetramers of the alpha, pore-forming subunits, together with four calmodulins (CaM). CaM binds to the intracellular C-terminus of the channel subunits. Ca binding to the N-lobe E-F hands of CaM induces channel gating. Recent studies reveal that the SK channel complex contains several additional, constitutively associated regulatory proteins. Moreover, the molecular composition of the SK channel complex may vary in distinct subcellular compartments, suggesting that the same expressed alpha subunit may serve a variety of roles depending upon subcellular address and macromolecular identity. The distinct coupling of SK channels to different Ca sources in dendrites, where they affect dendritic integration, and in spines where they modulate NMDA receptor function and impact synaptic plasticity supports this concept.