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Structural Insights into Sk Channels: Unveiling Key Determinants for Selective Blocker Development

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Small-conductance calcium-activated potassium (SK/KCa2) channels selectively conduct K+ ions and are activated by Ca2+ via calmodulin molecules. The three known isoforms (SK1-3) are mainly found in the central nervous system. They play a crucial role in regulating neuronal excitability and are potential targets for treating disorders such as schizophrenia, depression and Alzheimer's disease. Although blockers like apamin and UCL-1684 exist, their use is limited due to poor selectivity towards SK subtypes and a narrow therapeutic window. Developing new non-peptidic blockers with both high affinity and selectivity is essential. Our goal is to gain a deeper understanding of how SK channels interact with known blockers by exploring their 3D structures. Using AlphaFold2 models, we identified a unique S3S4 loop conformation in SK1-3, with a conserved phenylalanine near the channel exit, potentially crucial for blocker interactions. Combining in vitro patch clamp and binding assays, we show that replacing this phenylalanine with an alanine in SK2 and SK3 channels disrupts interactions with apamin and UCL-1684. A combination of docking and molecular modelling reveals confident poses for these blockers and provides coherent explanations for previous experiments. The results obtained in this study may be useful in the research and development of new pharmacophores.