

A non-canonical VSD-pore coupling in KCNQ channels

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In voltage-gated ion channels, interactions between the voltage sensor domain (VSD) and the pore couple the VSD activation to the pore opening. However, the VSD-pore coupling mechanism remains largely unclear. The KCNQ1 potassium channel is open when the VSD is activated to either the intermediate state (termed IO) or the fully activated state (AO), with the AO state physiologically more important in the heart. Here, using a small molecular compound, we identified key residues that form intersubunit interactions between the S4-S5 linker and the pore to mediate the AO state VSD-pore coupling, revealing a non-canonical VSD-pore coupling mechanism. We further determined other molecular determinants for the AO state including the gating charge transfer center, c-terminus of the S4 segment, and the PAG motif, all of which are well conserved among voltage-gated ion channels. These results reveal a chain of interactions in bridging VSD activation to pore opening, and this non-canonical VSD-pore coupling mechanism may provide insights into ion channel gating in general.