

Probing Early Inactivation Events in hERG Using the Scorpion Toxin CnErg1

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Inactivation of voltage-gated potassium channels is a critical gating process that modulates ion conduction through conformational changes at the selectivity filter. The human ether-à-go-go-related gene (hERG, Kv11.1) channel exhibits unusually rapid inactivation, yet the structural rearrangement underlying this transition remains incompletely understood. Here, we use the γ -KTx scorpion toxin CnErg1, derived from *Centruroides noxius*, as a molecular probe to capture early conformational changes during hERG inactivation.

CnErg1 binds hERG with nanomolar affinity. Notably, it incompletely blocks wild-type hERG current but fully occludes the inactivation impaired S631A mutant, suggesting a mechanistic coupling between inactivation and toxin binding. Using cryo-electron microscopy, we resolved structures of hERG in complex with CnErg1 in both wild-type and S631A backgrounds. These reveal distinct rearrangements at the selectivity filter, including displacement of the Gly628 carbonyl and vertical movement of the selectivity filter.

Our findings support a model in which CnErg1 stabilises open state in the inactivation pathway, and demonstrate that selectivity filter rearrangements precede inactivation. This work establishes CnErg1 as a state-sensitive probe of hERG gating and provides structural insight into the extracellular conformational dynamics that govern inactivation.