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Contributions of the membrane dipole potential to the function of voltage-gated cation channels and modulation by small molecule potentiators

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ABSTRACT

The membrane dipole potential (Ψ_d) constitutes one of three electrical potentials generated by cell membranes. Ψ_d arises from the unfavorable parallel alignment of phospholipid and water dipoles, and varies in magnitude both longitudinally and laterally across the bilayer according to membrane composition and phospholipid packing density. In this work, we propose that dynamic counter-balancing between Ψ_d and the transmembrane potential ($\Delta\Psi_m$) governs the conformational state transitions of voltage-gated ion channels. Ψ_d consists of 1) static outer, and dynamic inner leaflet components ($\Psi_{d(extra)}$ and $\Psi_{d(intra)}$, respectively); and 2) a transmembrane component ($\Delta\Psi_{d(inner–outer)}$), ariing from differences in intra- and extracellular leaflet composition. $\Psi_{d(intra)}$, which transitions between high and low energy states ($\Psi_{d(intra,\ high)}$ and $\Psi_{d(intra,\ low)}$) as a function of channel conformation, is transduced by the pore domain. $\Delta\Psi_{d(inner–outer)}$ is transduced by the voltage-sensing (VS) domain in summation with $\Delta\Psi_m$. Potentiation of voltage-gated ion channels is of interest for the treatment of cardiac, neuronal, and other disorders arising from inherited/acquired ion channel dysfunction. Potentiators are widely believed to alter the rates and voltage-dependencies of channel gating transitions by binding to pockets in the membrane-facing and other regions of ion channel targets. Here, we propose that potentiators alter $\Psi_{d(intra)}$ and/or $\Psi_{d(extra)}$, thereby increasing or decreasing the energy barriers governing channel gating transitions. We used quantum mechanical and molecular dynamics (MD) simulations to predict the overall Ψ_d-modulating effects of a series of published hERG activators partitioned into model DOPC bilayers. Our findings suggest a strong correlation between the magnitude of Ψ_d-lowering and positive hERG potentiation across the series.

ABBREVIATIONS

Molecular dynamics (MD), quantum mechanics (QM), hERG (human Ether-a-go-go-Related Gene), voltage-sensing domain (VS)

KEYWORDS

Voltage-gated ion channel modulation; membrane dipole potential; hERG activators; ion channel activators; molecular dynamics;