pH and other determinants of conductance of a voltage gated sodium channel

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Abstract

Through molecular dynamics and free energy simulations in electric fields we examine the factors influencing conductance of bacterial voltage gated sodium channel Na_vMs. The channel utilizes four glutamic acid residues in the selectivity filter (SF). Previously we have shown, through constant pH and free energy calculations of pKa values, that fully deprotonated, singly protonated and doubly protonated states are all feasible at physiological pH, depending on how many ions are bound in the SF[1]. With 173 molecular dynamics simulations of 450 ns or 500 ns and additional free energy simulations, we determine the conductance of these protonation states, and show that the deprotonated state is most conductive, with conductance further decreasing with each additional proton bound. We also determine the dependence of the pKa value of the four glutamic residues for the transition between deprotonated and singly protonated state on voltage, and show that there is a small voltage dependence and that the pKa value is close to the physiological pH. The pKa value and conductance trends are in agreement with experimental work on bacterial Na_v channels which show a decrease in maximal conductance with lowering of pH, with pKa in the physiological range[2]. We examine binding sites for Na^+ in the SF, compare with previous work, and note a dependence on starting structures, in particularly in terms of the width of the selectivity filter. We find that the narrowing of the gate backbone to values lower than the PDB backbone radius reduces the conductance, while increasing the gate radius further does not affect the conductance. Simulations with some amount of negatively charged lipids as opposed to purely neutral lipids increases the conductance, as do simulations at higher voltages.

1. Damjanovic A, Chen AY, Rosenberg RL, Roe DR, Wu X, Brooks BR. Protonation state of the selectivity filter of bacterial voltage-gated sodium channels is modulated by ions. Proteins Struct Funct Bioinforma 2020;88(3):527–539.
2. DeCaen PG, Takahashi Y, Krulwich TA, Ito M, Clapham DE. Ionic selectivity and thermal adaptations within the voltage-gated sodium channel family of alkaliphilic Bacillus. Elife 2014;3:e04387.