ABSTRACT

Voltage-gated sodium (Na⁺) channels initiate and propagate action potentials in excitable cells. Mutations in these channels are responsible for a variety of disorders, including epilepsy and pain syndromes. Therefore, they are the target of a number of drugs used for reducing pain and seizures. In this study, we investigate ion permeation in an open Na⁺Ms channel by performing molecular dynamics simulations and potential of mean force calculations. In simulations, Na⁺ ions are observed to enter the channel from bulk but not from the cytoplasm. Even after loading the channel with extra Na⁺ ions, they are observed to exit only to the bulk side. To understand the energetics of this behavior, we have constructed potential of mean forces for the exit of a Na⁺ ion when the filter is occupied by 1, 2, and 3 Na⁺ ions. In all cases, a substantial energy barrier is found at the intracellular gate, where hydrophobic residues form a narrow neck and prevent passage of a fully hydrated Na⁺ ion. Our results indicate that for conduction of Na⁺ ions either the gate needs to be somewhat more open or the hydration number of Na⁺ should be marginally lower than that predicted by the current force fields.

METHODS: Model Building

Here we choose the 4CBC Na⁺Ms structure [1] for MD simulations as it provides a high-resolution structure, which is slightly more open at the gate compared to the later structures. The 4CBC structure is embedded in a lipid bilayer consisting of 125 POPC molecules and solvated with 9050 water molecules. The system is ionized and neutralized using 34 Na⁺ and 26 Cl⁻ ions to maintain a concentration of 0.15 M. The resulting system contains about 50,000 atoms in a box with dimensions 90 x 90 x 80 Å³.

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