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The impact of electroporative pulses on voltage-gated ion channels

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High-intensity pulsed electric fields are used increasingly in medicine to achieve a transient increase in cell membrane permeability via electroporation. Most electroporation-based treatments directly or indirectly target muscle and nerve cells. These are excitable cells that can generate and transmit electrical signals called action potentials. Excitability is enabled by specialized membrane proteins, primarily voltage-gated ion channels, which open or close upon changes in the transmembrane voltage (TMV). Since voltage-gated ion channels are sensitive to changes in TMV and since electroporative pulses induce a TMV of several hundreds of mV, far beyond the physiological resting voltage or voltage generated during action potentials, one can speculate that these channels become perturbed by the treatment. Indeed, electrophysiologists have demonstrated that electroporative pulses can decrease the ionic currents mediated by different voltage-gated ion channels during action potentials [1–2]. These studies suggested a possible field-induced conformational change of the ion channels, but the associated molecular mechanisms remained unidentified. To fill this gap, we employed atomistic molecular dynamics simulations, which enabled us to explore the molecular events that take place in different voltage-gated ion channels under electroporation conditions, at spatio-temporal resolution that is not achievable by other methods [3]. Simulations revealed that a strong electric field can induce transport of ions through the channel's voltage-sensor domains (VSDs). Such conducting defects can expand into "complex pores", which become stabilized by lipid head-groups (Fig. 1). Further expansion of these complex pores can lead to severe unfolding of a VSD from the channel. It can be anticipated that such unfolded VSDs become dysfunctional, which agrees with previous electrophysiological measurements showing a decrease in the voltage-dependent ionic currents [2–3]. Simulations also showed that formation of complex pores depends on the VSD's hydration and electrostatic profile: the more hydrated the VSD is, and the more electrostatically favorable for the entry of ions, the more easily it porates. These findings are important for development and optimization of electroporation-based applications that target excitable cells including gene electrotransfer and DNA vaccination into skeletal muscles, cardiac ablation for treatment of arrhythmias, and nonthermal ablation of brain tumors.

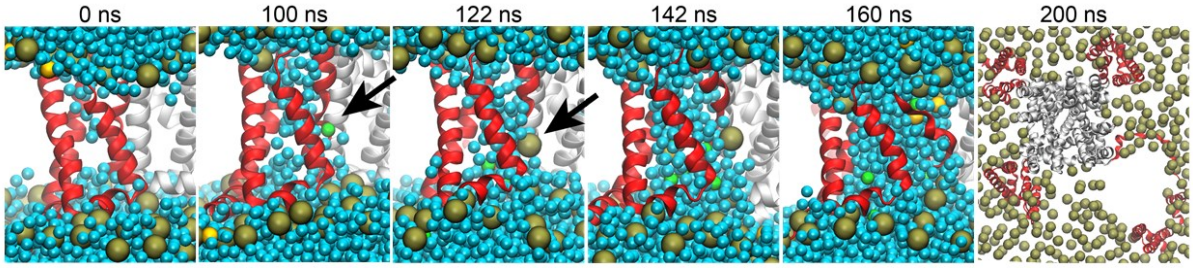

Figure 1. Formation of a complex pore in the voltage sensor domain (VSD) of a sodium voltage-gated ion channel induced by electric field applied at time 0 ns. TMV is about 1.5 V. The last image at 200 ns shows the unfolded VSD when viewing the channel from the extracellular side. The VSD is colored in red, water in cyan, lipid phosphorus atoms in gold, and sodium and chloride ions in yellow and green, respectively. Black arrows mark the first Cl ion within VSD and the first lipid headgroup moving into the pore. Adapted from [3].

References

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