Title: Monte Carlo Simulation of Mechanism of Proton Transfer in Aquaporin Channel: as an approach for drug design

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Abstract: The regulation of water balance in the brain is crucial. A disruption in this equilibrium causes an increase in brain water content that significantly contributes to the pathophysiology of traumatic brain injury, hydrocephalus, and a variety of neurological disorders. ÓAquaporins are membrane water channels that play critical role in controlling the water contents of cells. Therefore, the generation of Aquaporin structure models is useful for solving mechanistic questions on the channel selectivity and especially for virtual drug design. For achieving to this purpose, in this study, we have used molecular dynamics simulations to solve a biological mystery: how water molecules can pass through a protein pore in a cell membrane as rapidly as they do without ferrying extra protons across with them. Water permeation and electrostatic interactions between water and channel are investigated in the Aqp4, a member of the Aquaporin water channel family, by Charmm software. Aqp4 is constitutively expressed in the brain predominantly in astrocyte cell. In our study, on the regulation and detailed mechanism of action of AQP4 was considered at DMPC membrane. The simulation reveals a delicately choreographed dance of the water molecules, directed by carefully positioned amino acid residues throughout the channel interior. Water molecules passing the channel are forced, by the protein's electrostatic forces, to flip at the center of the channel. Therefore, breaking the alternative donor-acceptor arrangement is necessary for proton translocation. These results are show for improve undressing of water permission in membrane and also we hope to our model simulation be useful for synthesis of functional inhibitor antibiotics drugs for this group of water channel in future.

Key words: Aquaporins, water channel, water permission, molecular dynamics