[P22] A new gating site in Human Aquaporin-4: insights from Molecular Dynamics simulations

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Aquaporin-4 (AQP4) is a water channel widely expressed in different organs and tissues. An alteration of its physiological functioning is responsible of several disorders of water regulation and, thus, is considered an attractive target with a promising diagnostic and therapeutic potential. Herein, we show the results from classical Molecular Dynamics (MD) simulations performed on the AQP4 tetramer embedded in a bilayer of lipid molecules with particular focus on the role of spontaneous fluctuations occurring inside the pore. Following the approach by Hashido et al. [1], our analysis on 200 ns trajectory discloses three domains as key elements for water permeation. We describe the gating mechanism associated to the well-known selectivity filter on the extracellular side of the pore and the crucial regulation ensured by the NPA-motifs (asparagine, proline, alanine), which optimizes the transfer of water molecules by directing their movement in a single raw. Importantly, on the cytoplasmic side, we find a putative gate formed by two residues, namely a cysteine belonging to the loop D (C178) and a histidine from loop B (H95). Notably, the spontaneous reorientation of the imidazole ring of H95 acts as a molecular switch enabling H-bond interaction with C178. The occurrence of such local interaction seems to be responsible for the narrowing of the pore and thus of a remarkable decrease in water flux rate [2]. Our findings are in agreement with recent experimental observations and may contribute to understand the molecular events controlling water permeability of AQP4. Herein, the results are discussed in the perspective of establishing a possible starting point to pave the way to the discovery of chemical modulators effective for those pathologies trigged by an altered AQP-dependent water balance.

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[2] D.A; O.N; G. L; G.F.M. submitted.