MOLECULAR SIMULATION
OF SODIUM IONS AT THEIR ALLOSTERIC BINDING SITES IN
THE DOPAMINERGIC D₂ RECEPTOR

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Sodium ions have been shown to play an important role in the modulation of agonist and antagonist binding to the well-known D3.32 of various G-protein coupled receptors (GPCRs)¹. The putative sodium binding site is assumed to be in the center of a pyramidal hydrogen-bonding network formed by the residues D2.50, S3.39, N7.45, and S7.46². In an effort to understand the mechanism of the sodium-induced effect on receptor function, we investigated computationally the mobility of sodium ions in the sodium-sensitive D₂ receptor embedded in a membrane bilayer environment under physiological ionic strength conditions. Using long-term unconstrained molecular dynamics simulations for a total of 10 μs, we studied for the first time the pathway of a sodium ion entering the GPCR from the extracellular site along negatively charged residues into the receptor and its electrostatic interaction in the pyramidal hydrogen-bonding network at D2.50. The simulation reveals on one hand the energetics which drives sodium ion’s mobility. On the other hand, the study discloses diverse sodium ion binding sites in between D3.32 and D2.50 which we propose as being part of the sodium-induced effect on ligand binding in the D₂ receptor.

Our finding supports the existence of a sodium ion trapped in the pyramidal hydrogen-bonding network and provides novel implication of a sodium ion as an allosteric modulator for sodium-sensitive GPCRs, an issue highly relevant in drug design.