Effect of phosphorylation on the structural dynamics and thermal stability of human Dopamine Transporter: a simulation study using Normal Modes, Molecular Dynamics and Markov State Model

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Abstract

The Human Dopamine Transporter (hDAT) plays an essential role in modulating the Influx/Efflux of dopamine, and it is involved in the mechanism of certain neurodegenerative diseases such as Parkinson's disease. Macromolecules adopt many conformations in solution depending on their structure and shape, which determine their dynamics and function. In this context, several studies have reported important meta-states for Dopamine transport: outward-facing open state (OFo), the outward-facing closed state (OFc), the holo-occluded state closed (holo), and the inward-facing open state (IFo). Furthermore, experimental assays have shown that different phosphorylation conditions can affect the rate of dopamine absorption. This work presents a protocol using hybrid simulation methods to study the conformational dynamics and stability of meta-states of hDAT under different phosphorylation states. With this protocol, we explored the conformational space of hDAT, identified the meta-states, and evaluated the free energy differences and the transition probabilities between them in each of the phosphorylation cases. We also presented the conformational changes and correlated them with those described in the literature. The results suggest that the phosphorylation corresponding to NP-333, where (all sites [Ser/Thr](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4380854/) from residue 2 to 62 and residue 254 to 613 are phosphorylated, except residue 333) is the one that would affect dopamine transport the most, corroborating the experimental results. Furthermore, our results showed that just single phosphorylation/dephosphorylation could alter intrinsic protein motions affecting the sampling of one or more meta-states necessary for dopamine transport. In this sense, the modification of phosphorylation influences protein movements and conformational preferences, affecting the stability of meta-states and the transition between them and, therefore, the transport.

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