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Molecular Modeling of Glycine and Ions Binding to the Glyt1 Transporter

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ABSTRACT

Glycine is a key inhibitory neurotransmitter in the central nervous system. Its synaptic concentration is regulated by glycine transporters (GlyT1,2), which belong to the solute carrier family 6 (SLC6). GlyT1 is predominantly expressed in astrocytes and glutamatergic neurons, whereas GlyT2 is localized to presynaptic glycinergic terminals. Both transporters mediate glycine reuptake coupled with Na^+ and Cl^- ions. The dual role of GlyT1 in modulating inhibitory neurotransmission and excitatory NMDA receptor signaling makes its investigation crucial for understanding the molecular mechanisms of synaptic activity and developing therapies for schizophrenia, neuropathic pain, and other neurological disorders. In this study, we employed molecular dynamics (MD) simulations to examine the coordination of ionic and substrate interactions within GlyT1. The initial protein coordinates were obtained from the outward-open GlyT1 structure (PDB ID: 8WFL). The transporter was embedded in a phosphatidylcholine bilayer and solvated with 150 mM NaCl. Classical MD simulations were performed for 2 μs. To capture rare substrate-binding events and quantify glycine affinity, we also employed enhanced sampling simulations using nonequilibrium MD methods.

Analysis of MD trajectories revealed the sequence of substrate binding and identified key amino acid residues involved in ligand coordination. Free energy calculations derived from enhanced sampling simulations allowed us to estimate glycine affinity under varying scenarios of ion occupancy at binding sites. These findings provide critical insights into the molecular mechanism of GlyT1 and other SLC6 sodium-dependent neurotransmitter transporters. Furthermore, the results can be used to explore potential pharmacological compounds capable of modulating glycinergic and glutamatergic systems functioning.

Keywords: ligand binding, glycine transport, molecular dynamics

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