

Molecular Dynamics Studies of Ionotropic Glutamate Receptors

Stephen Holmes, Alex Hahn, Lisa Gentile and Carol Parish

*Department of Chemistry, Gottwald Center for the Sciences, University of Richmond, Richmond,
VA 23173*

Ionotropic glutamate receptors, iGluRs, are a family of ligand gated channels located in the post-synaptic neural membrane. These receptors serve a major role in the excitation of the neural cells, which is important for all neurotransmissions in the central nervous system. There are three subfamilies of iGluRs: NMDA, AMPA, and kainate receptors. NMDA receptors mediate the slower component of the excitatory post synaptic potential. AMPA receptors mediate fast synaptic transmission in the central nervous system. Kainate receptors have a major role in both excitatory and inhibitory neurotransmission. A conformational change that opens a membrane pore is caused by the binding of the neurotransmitter glutamate to an extracellular binding site on these receptors. This allows cations to flow into the post-synaptic neural cell. Because glutamate functions as a major excitatory neurotransmitter in the central nervous system, the level of activity of iGluRs is strictly controlled. Neurodegenerative diseases such as schizophrenia and Alzheimer's, Parkinson's, and Huntington's diseases have been linked to mis-regulation of glutamate. Long time scale molecular dynamics studies using the highly efficient DESMOND molecular dynamics algorithms were performed on a homology model for the S1S2 domain of the NMDA iGluR receptor. The resulting stable trajectories were subjected to exhaustive analysis. Dynamical results will be presented that shed light on the structure and function of these glutamate receptors.