Docking Studies of Ionotropic Glutamate Receptors

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Ionotropic glutamate receptors, or iGluRs, are involved in synaptic transmission and are found in the post synaptic neural membrane[1]. They are a group of ligand-gated ion channels, activated by the main excitatory neurotransmitter glutamate, that are divided into three classes: NMDA, AMPA, and kainite receptors[1]. The binding site for glutamate is made up of the S1 and S2 domains[2]. Over activity or misregulation of iGluR is thought to be linked to stroke, schizophrenia, Alzheimer's, Huntington's, Parkinson's, and dementia[2]. PregaS and PS are two neurosteriods that have the potential to form drugs to fight these diseases. Research shows that PregaS inhibits NMDA receptors while PS partially inhibits AMPA and kainite receptors[3]. This research used theoretical studies for the investigation of iGluR inhibitor binding sites within the S1S2 domains of GluR2 and NR2A along with the NR2B homology model developed in the Parish lab. Structure determination and analysis of binding domains was done computationally by studying the homology, modeling, and docking of the various substrates and domains including glutamate, PregaS and PS. Binding site identification algorithms were used to check for additional existing binding pockets in the S1S2 domain as well as to verify the approach. *Glide* was used to dock the neurosteroids, PregaS and PS, into the iGluRs. The *Glide* docking algorithms were then used to model host-quest interaction, ligand-protein interaction, and drug-target interaction. Differences in binding were measured using a variety of scoring algorithms. This type of analysis can give us a better understanding of the structural behavior of the receptors at an atomic level. Knowledge gained about these binding interactions has the potential to contribute to drug designs for treatment and therapy of neurological diseases

References

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