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The N-methyl-D-aspartate receptor ligand binding domain and the interactivity with ion-channel control

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Encephalopathies are a group of brain dysfunctions which leads to cognitive, sensory, and motor impairments. Recent developments in the field have led to the identification of several mutations within the N-methyl-D-aspartate receptor as one of the possible culprits for this group of conditions. However, understanding of the underlying changes to the receptor due to these mutations has been elusive to date. We aimed to determine the effects of one of the first mutations identified within the N-methyl-D-aspartate receptor GluN1 ligand binding domain, Ser688Tyr. This mutation was identified and associated with early onset encephalopathy. We performed molecular docking, randomly seeded molecular dynamics simulations, and binding free energy calculations to determine the behaviour of the 2 main co-agonists: glycine and D-serine and their effects on ion channel function. We determined that the Ser688Tyr mutation leads to instability of both ligands within the ligand binding site due to changes within the ligand binding domain associated with the mutation. Associated binding free energy for both ligands also increased significantly in the mutated receptor. These results reinforce previously observed in vitro electrophysiology data and provides additional information on ligand behaviour. Upcoming studies involve the use of crystallography and neutron scattering to determine the effects of this mutation on ion-channel function. This study provides valuable insight into the consequences of mutations within the N-methyl-D-aspartate receptor GluN1 ligand binding domain.

Level of Expertise

Student

Presenter Gender

Man

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He/Him

Which facility did you use for your research

Australian Centre for Neutron Scattering

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Yes

Do you wish to take part in the Student Poster Slam

Yes

Condition of submission

Yes

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