CHRD 2024: Abstract Submission Form

Presenter Name
Simrat Dhaliwal

Presenter Status
Masters Student

Role in the project
Perform Experiments
Analyze Data
Write Abstract

Research Category
Basic Science

Title
Binding Capacity of Pathogenic Human ELFN1 Variants With mGluR7 In Trans

Background
Approximately 15% of children and adolescents worldwide are affected by neurodevelopmental diseases (NDD). G protein-coupled receptors (GPCRs) are essential in the proper regulation of synaptic transmission; therefore, their pathways act as promising targets for pharmacological intervention with GPCRs already being targeted by 35% of FDA approved pharmaceuticals. Recent studies on GPCR extracellular binding partners highlight the concerningly limited understanding of GPCR synaptic neurobiology, suggesting an explanation for the failure in the successful translation of GPCR pharmaceuticals from bench to bedside. Interestingly, one of these extracellular binding partners is a synaptic adhesion molecule called extracellular leucine-rich repeat and fibronectin type III domain-containing 1 (ELFN1), which can modulate a subset of GPCRs- group 3 metabotropic glutamate receptors (mGluRs). Mutations within the ELFN1 structural domain have been linked to various NDDs including the general etiology of epilepsy, ADHD, and schizophrenia.

Objective
This study aims to determine the trans-synaptic consequence of pathogenic human ELFN1 variants on mGluR7 binding in trans.

Methods
Co-immunoprecipitation experiments were conducted through the co-culturing of HEK293 cells transfected with mGluR7 and a clinically pathogenic ELFN1 variant or wildtype DNA constructs. Binding capacity was analysed via western blotting and densitometry.

Results
In comparison to reference ELFN1, the extracellular hELFN1 variant exhibited over 95% reduction in its binding capacity with mGluR7 (p-value= 0.0006) which suggests the mGluR7-independent mechanism. Intracellular hELFN1 variant did not exhibit a significantly reduced ability to bind mGluR7 (p-value=0.3720) which suggests the mGluR7-dependent mechanism.

Conclusion
Disruption in the mGluR7-ELFN1 complex sheds light on potential therapeutic strategies for patients harboring these variants, especially those patients with the extracellular ELFN1 mutation.

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No

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