CHRD 2024: Abstract Submission Form

Presenter Name
Simran Dhaliwal

Presenter Status
Masters Student

Role in the project
Perform Experiments
Analyze Data
Write Abstract

Research Category
Basic Science

Title
Structure-function analysis of ELFN1 in autoregulation and pharmacological modulation of mGluR7

Background
According to the National Longitudinal Survey of Children and Youth, childhood neurodisability affects 1/11 Canadians aged four-to-eleven-years-old. This emphasizes our striking need to understand brain cell communication and the impacts of genetic mutations on these interactions. Previously, we found a group of structural proteins, ELFNs, altered the activity of an important subset of receptors known as metabotropic glutamate receptors (mGluRs), which are essential in regulating excitatory brain signals. Interestingly, recent studies identified human ELFN1 mutants with pathogenic and correlative roles in neurodevelopmental disorders (NDDs) including ADHD and epilepsy.

Objective
This study aims to reveal the consequence of human ELFN1 variation on mGluR-dependent and -independent functions in hopes of identifying new drug targets for youth with NDDs.

Methods
Clinical ELFN1 variants (ELFN1ΔCT, NTΔELFN1) from youth with ELFN1-dependent NDDs were used to determine mGluR-dependent effects through co-immunoprecipitation (co-IP) with mGluR7 in HEK293 cells. Structure-function analyses were performed using ELFN1 constructs lacking critical regions in the extracellular or intracellular side to explore dimerization. Statistical significance was determined using a students t-test or one-way ANOVA at a significance level of 0.05%.

Results
Co-IP of NTΔELFN1 with mGluR7 revealed a 96% reduction in binding capacity (p-value=0.0006), whereas ELFN1ΔCT was unaffected (p-value=0.3720) in comparison to reference ELFN1. We pinpoint the extracellular LRR domain, distinct from mGluR7-interaction sites, is important for dimerization using a panel of extracellularly truncated ELFN1 constructs co-IPed with reference ELFN1. Alternatively, exploration of our panel of intracellularly truncated ELFN1 constructs and reference ELFN1 reveals no impaired dimerization.

Conclusion
GPCRs, including mGluRs, are key players in brain cell communication with 35% of FDA-approved drugs targeting their function. Excitingly, we found extracellular ELFN1 variants disrupt mGluR-interactions and dimerization whereas intracellular interactions seem to effect mGluR-independent functions, highlighting potential pathological mechanisms. Illuminating this can guide development of novel drug strategies for NDD youth harbouring ELFN1 variations.

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