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Basic Science

Abstract Title
Neuroligin-1 interaction and modulation of mGluR2 in trans

Background
G protein-coupled receptor (GPCR) neurobiology advancements have uncovered GPCRs forming trans-synaptic complexes with synaptic adhesion molecules. However, the impact of these interactions on GPCR pharmacology remains largely unexplored. Notably, neuroligin-1 (NLGN1) soluble ectodomain has been found to modulate metabotropic glutamate receptor 2 (mGluR2), hinting at a potential trans-synaptic complex involving two proteins linked to autism spectrum disorder (ASD). Additionally, genetic variants have been identified in the NLGN1 ectodomain of autistic patients, but their effect on mGluR2 binding is unknown.

Objective
We aim to investigate mGluR2 and NLGN1 trans-synaptic complexes, hypothesizing that certain autism-associated NLGN1 variants may affect their interaction.

Methods
Transient transfection of cell populations with empty plasmid or myc-NLGN1 was done, followed by mixing lysates with cells expressing human mGluR2. Immunoprecipitation with myc-antibody and Western blotting with mGluR2-antibody were employed to assess binding efficacy. Expression comparison between autistic-mutant P89L-NLGN1 and WT-NLGN1 was conducted through titration experiments.

Results
Full-length NLGN1 was able to co-immunoprecipitate mGluR2 from another cell population: suggestive of their interaction in trans. We also demonstrate that autism mutant P89L-NLGN1 exhibits >85% reduction of expression levels compared to “wildtype” NLGN1: predominantly in the mature (glycosylated) form. Titration experiments of different levels of NLGN1 DNA determined the condition where NLGN1 and P89L-NLGN1 expression were comparable and determined DNA needed to be provided in a 2:5 ratio to begin functional characterizations. Under these standardized conditions, we will compare the ability of P89L-NLGN1 to bind to mGluR2 in comparison to “wildtype” NLGN1, and their functional consequence on mGluR2 pharmacology using a recently developed transcellular GPCR signalling assay platform.

Conclusion
In conclusion, our study should provide a greater understanding of trans-synaptic interactions between NLGN1 and mGluRs in synaptic neurobiology, and begin to explore the potential of mGluR2 as a pharmacological target for autistic patients harbouring genetic variations in NLGN1.

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