CHRD 2024: Abstract Submission Form

Presenter Name
Kaden Baskerville

Presenter Status
Masters Student

Role in the project
Design
Perform Experiments
Analyze Data
Write Abstract

Research Category
Basic Science

Title
Alternative splicing-dependent interaction between presynaptic neurexin-1β and postsynaptic mGluR5

Background
The molecular mechanisms underlying autism spectrum disorder are still poorly understood. Mutations in certain genes are very well associated with the disorder (ie. NRXN) which could be altering molecular pathways; however, we still don't know how these proteins are supposed to interact "typically". The G protein-coupled receptor (GPCR) superfamily is particularly important in the field of pharmacology as they are the target of approximately 1 in 3 FDA approved drugs. Here we present evidence of a novel trans-cellular interaction between the GPCR know as mGluR5, and the autism-relevant synaptic adhesion molecule neurexin-1 (NRXN1).

Objective
Validate and characterize the trans-synaptic interaction between neurexin-1 and mGluR5. Investigate alterations in accepted pharmacology of mGluR5 via neurexin-1β in trans.

Methods
Potential binding partners were identified via literature analysis of published IP: mGluR5 mass spectrometry data. Verification of the synaptic adhesion molecule neurexin-1 was done via co-immunoprecipitation experiments between mGluR5 and neurexin-1. Similar co-immunoprecipitation experiments were then completed with mGluR5 and a physiologically relevant neurexin-1 isoform, its splice variants, and its ectodomain.

Results
Published mass spectrometry data revealed that neurexin-1 binds with mGluR5. Subsequent co-immunoprecipitation experiments demonstrated that not only does neurexin-1 trans-cellularly bind mGluR5, but the physiologically critical neurexin-1β (AS4-) preferentially binds mGluR5 as compared to neurexin-1β (AS4+). Furthermore, the ectodomain of neurexin-1β (AS4-) was sufficient to bind mGluR5, demonstrating that this interaction occurs extracellularly in trans.

Conclusion
This research demonstrates a novel mGluR-adhesion molecule interaction, the nature of which is rare in the literature due to their recent discovery. Experiments are currently underway to determine if mGluR5 is modulated by neurexin-1β. Interestingly, both mGluR5 and neurexin-1β mutations are strongly associated with autism spectrum disorder, opening up the possibility that disruption of modulation could be linked to the disorder's etiology. A disruption that could potentially be targeted pharmaceutically.

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No

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