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Presenting Author Category

PhD Student

Research Category

Basic Science

Abstract Title

Novel extracellular interaction of mGluR5 and neurexin-1

Background

The molecular mechanisms underlying autism spectrum disorder are still poorly understood. Genetic variants of certain synaptic adhesion molecules (SAMs) are very well associated with the disorder (i.e., NRXN1), which could be altering molecular pathways at synapses. The prominent G protein-coupled receptor (GPCR) superfamily is the target of ~1 in 3 FDA approved drugs. Several GPCRs have recently been discovered to be modulated by SAMs. Excitingly, this has creating new avenues for the molecular etiology and drug design in various neurological conditions.

Objective

To validate and characterize the trans-synaptic interaction between neurexin-1 and mGluR5, and to investigate alterations in accepted pharmacology of mGluR5 via neurexin-1.

Methods

Potential binding partners were identified via literature analysis of published IP: mGluR5 mass spectrometry data. Co-immunoprecipitation assays tested binding between mGluR5 and neurexin-1's: ectodomain, splice variants, and canonical binding partner (neuroligin-1) in a competitive binding assay. The ONE-GO GPCR biosensors are being utilized to visualize mGluR5 activity upon stimulation with and without the co-presence of neurexin-1 in advanced trans-cellular assays.

Results

Published mass spectrometry data revealed that neurexin-1 binds with mGluR5. The physiologically critical neurexin-1 (SS4-) splice variant demonstrated ~2-fold increase in binding affinity of mGluR5 vs. SS4+. Neurexin-1's ectodomain was sufficient to bind mGluR5 (demonstrating interaction is extracellular). Interestingly, co-presence of neuroligin-1 enhanced the binding affinity of neurexin-1 for mGluR5. Finally, the biosensors have been optimized for mGluR5, and experiments are underway to determine the function of this interaction.

Conclusion

This research demonstrates a novel GPCR-SAM interaction, the nature of which is rare in the literature due to their recent discovery. Interestingly, both mGluR5 and neurexin-1 genetic variants are strongly associated with autism spectrum disorder, opening the possibility that disruption of modulation could be linked to the disorder's etiology: a disruption that could potentially be targeted pharmacologically.

Authors

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