DEPARTMENT OF PHARMACOLOGY
SEMINAR SERIES

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Jennifer Donegan, Ph.D.
Instructor/Research
Department of Pharmacology
UT Health San Antonio
San Antonio, Texas

Targeting Interneurons to Treat and Understand Schizophrenia

Schizophrenia is a devastating psychiatric disorder characterized by positive symptoms, e.g. delusions and hallucinations, negative symptoms, e.g. reduced social interaction and anhedonia, and cognitive deficits. Increased hippocampal activity has been observed in schizophrenia patients, caused by a deficit in inhibitory GABAergic interneurons. Therefore, we hypothesized that restoring inhibitory function in the vHipp would reverse schizophrenia-like deficits in a rodent model. To test this, we used a mouse embryonic stem cell line to grow enriched populations of parvalbumin (PV)- or somatostatin (SST)-positive interneurons, which were transplanted into the vHipp. Both PV- and SST-positive interneurons attenuate positive symptoms but PV-positive transplants also reduce negative and cognitive symptoms. Because interneurons regulate pyramidal cell activity, we next tested the hypothesis that increasing GABAergic signaling in pyramidal cells would improve schizophrenia-like deficits. Using a lenti virus, we overexpressed the α5 subunit of the $GABA_A$ receptor in pyramidal cells of the vHipp. We found that α5 over-expression improved both positive and cognitive symptoms of the disorder. Finally, to determine which efferent pathways were mediating the therapeutic effects, we used chemogenetics to selectively inactivate pathways from the vHipp to the nucleus accumbens (NAc) or the medial prefrontal cortex (mPFC). We found that the vHipp-NAc pathway regulates positive symptoms, while the vHipp-mPFC pathway regulates negative and cognitive symptoms. Together, these results provide a novel therapeutic target for the treatment of schizophrenia and identify the neural pathways involved.

For more information, please contact the Department of Pharmacology
Ann Miller at 567-4205 (millera5@uthscsa.edu)