Metabotropic glutamate receptor 3 activation modulates thalamic inputs to the nucleus accumbens and rescues schizophrenia-like physiological and behavioral deficits

Shalini Dogra,1 and P. Jeffrey Conn1

1Vanderbilt Univ

Accumulating evidence suggests that some symptoms of schizophrenia are associated with dysregulated excitatory neurotransmission in the central nervous system (CNS), and recent clinical trials have revealed beneficial effects of nucleus accumbens (NAc) deep brain stimulation in schizophrenia patients. One exciting target that regulates the excitatory transmission in the CNS is metabotropic glutamate receptor 3 (mGlu3) and polymorphisms in GRM3 (the gene encoding the mGlu3 receptor) are associated with an increased likelihood of schizophrenia diagnosis. But the mechanisms by which GRM3 modulates brain circuits involved in schizophrenia are not clear. Interestingly, using newly developed highly selective negative allosteric modulators of mGlu3 receptor, we provide an evidence that mGlu3 receptor activation induces robust depression of excitatory neurotransmission in the NAc. Therefore, we propose a hypothesis that mGlu3 receptor activation can ameliorate schizophrenia-like glutamatergic abnormalities and behavioral deficits, in part, through actions on specific glutamatergic inputs within the NAc. To test this hypothesis, we performed a series of electrophysiological and behavioral studies using a combination of genetically modified mice, optogenetic approaches, and novel pharmacological tools in male and female c57BL6j mice treated with saline or phencyclidine (PCP, 10 mg/kg; s.c., 7 day treatment followed by 7-day washout). Using ex vivo whole-cell patch-clamp electrophysiology, we showed that treatment with PCP enhanced the frequency of excitatory postsynaptic currents onto D1 medium spiny neurons (MSNs), but not onto D2 MSNs in the NAc shell indicating increased glutamatergic signaling in the PCP-treated mice. Interestingly, these effects of PCP were normalized by bath application of mGlu2/3 receptor agonist, LY379268 (100 nM). To evaluate the specific glutamatergic projections affected by PCP, we injected adeno-associated virus expressing Channelrhodopsin (ChR2) into medial thalamus (mThal), or basolateral amygdala, or ventral hippocampus. Our slice optogenetics experiments revealed that PCP treatment specifically enhanced transmission from thalamic inputs to the D1 MSNs of the NAc (Thal-D1 NAc shell). Excitingly, treatment with LY379268 blocked the PCP-induced changes in excitatory transmission at Thal-D1 NAc shell synapse and the effects of LY379268 were blocked by mGlu3 receptor specific negative allosteric modulator (VU650786; 30 mg/kg; i.p.). These studies suggest that activation of mGlu3 receptors can rescue PCP-induced abnormalities in the glutamatergic signaling the NAC of mice modeling schizophrenia-like pathophysiology. We also found that activation of mGlu3 receptors or chemogenetic silencing of Thal-NAc projections rescued the sociability deficits (a behavior relevant for negative symptoms of schizophrenia) in PCP-treated mice. Collectively, these data provide a novel insight into potential mechanisms by which activation of mGlu3 receptors can rescue schizophrenia-like pathophysiology and suggest that targeting these receptors could provide a viable approach for developing new therapeutics for treating schizophrenia.