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Effects of pharmacological blockade of Lingo - 1 signaling pathways in a phencyclidine rat model for schizophrenia

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Abstract
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Presentation Abstract
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Presentation Title: Effects of pharmacological blockade of Lingo-1 signaling pathways in a phencyclidine rat model for schizophrenia

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Abstract: Background and Aims: Dysfunctional myelination is one of the strongest hypotheses implicated in schizophrenia pathophysiology. Interestingly, myelination peaks during late adolescence, coinciding with the onset of schizophrenia. Lingo-1, a transmembrane signal-transducing molecule expressed on oligodendrocytes and neurons, is a potent negative regulator of oligodendrocyte differentiation, axonal growth and myelination. Since myelination and neuronal outgrowth disturbances lead to cognitive dysfunction, and considering the involvement of Lingo-1 in these processes, we have investigated the effects of pharmacological inhibition of Lingo-1 as a novel treatment for schizophrenia. Methods: Adolescent male Sprague Dawley rats (4 weeks) were injected subcutaneously with either saline vehicle or PCP (10 mg/kg, Sigma) for a total of 8 days. On the third day, rats (n=12/group) were concurrently treated for 5 days with either saline, olanzapine (Olz) (oral administration by cookie dough 1 mg/kg/day, 3 times/day) or anti-Lingo-1 functional antibody ab23631 (Abcam, UK), (intraventricular injection, with surgery for intracranial cannula implantation performed one week prior). Relative protein expression levels of Lingo-1, and myelination marker myelin basic protein (MBP) were examined within the prefrontal cortex of the treated rats. Results: Lingo-1 levels were significantly increased in PCP treated rats ($p=0.015$) and MBP was significantly reduced in PCP treated rats ($p=0.002$); both were restored to near control levels in anti-Lingo-1/Olz treated rats ($p=0.032$). Restoration of MBP levels was most likely to have been caused by the anti-Lingo-1 treatment, as rats treated with PCP/Olz had similar MBP levels as PCP/Vehicle treated rats in the prefrontal cortex. Conclusions: This is the first study to have shown that Lingo-1 and myelination levels are altered following PCP treatment and that these levels are restored following treatment with a Lingo-1 antagonist. We suggest that Lingo-1 may be a suitable target for the development of new future therapeutic treatments for schizophrenia.