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

Jessica L. Andrews  
University of Wollongong, ja393@uowmail.edu.au

Ryan Sullivan  
University of Wollongong, rps759@uowmail.edu.au

Kelly Newell  
University of Wollongong, knewell@uow.edu.au

Xu-Feng Huang  
University of Wollongong, xhuang@uow.edu.au

Francesca Fernandez-Enright  
University of Wollongong, fernande@uow.edu.au

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Abstract

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Authors: *J. L. ANDREWS*1,2, R. P. SULLIVAN3, K. A. NEWELL1,2, X.-F. HUANG1,2, F. FERNANDEZ-ENRIGHT1,2,4; 1Illawarra Hlth. and Med. Res. Inst., University of Wollongong, Australia; 2Ctr. for Translational Neurosci., Schizophrenia Res. Inst., Sydney, Australia; 3ARC Ctr. of Excellence for Electromaterials Sci., Intelligent Polymer Res. Institute/AIIM Fac., Innovation Campus, University of Wollongong, Australia; 4Sch. of Psychology, Fac. of Social Sci., University of Wollongong, Australia

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.