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Novel implications of Lingo-1 and its signaling partners in the Dorsolateral Prefrontal Cortex in Schizophrenia

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Background

Myelination and neurite outgrowth both occur during brain development and their disturbance has been previously implicated in the pathophysiology of schizophrenia. Leucine-rich repeat and immunoglobulin domain-containing protein (Lingo-1), is a potent negative regulator of axonal myelination and neurite extension. Since co-factors of Lingo-1 signaling (Nogo receptor (NgR), With No Lysine (K) (WNK1) and Myelin transcription factor 1 (Myt1)) have been previously implicated in the genetics of schizophrenia, we explored for the first time the role of Lingo-1 signaling pathways in this disorder. Lingo-1 protein, together with its co-receptor and cofactor proteins NgR, TNF receptor orphan Y (TROY), p75, WNK1 and Myt1, have never been explored in the pathogenesis of schizophrenia.

Methods

We examined protein levels of Lingo-1, NgR, TROY, p75, WNK1 and Myt1 within the post-mortem dorsolateral prefrontal cortex (DLPFC), a brain region highly disrupted in schizophrenia pathophysiology; from 37 schizophrenia patients versus 37 matched controls from the NSWBrain Bank Network.

Results

Lingo-1 protein expression was found to be significantly increased by 12% (\(p=0.006\)) in the DLPFC of schizophrenia subjects. A significant 19.5% increase in Lingo-1 expression was found in schizophrenia males compared to control males (\(p<0.001\)).

In contrast to Lingo-1, NgR protein expression was significantly decreased by 16% (\(p<0.001\)). Interestingly, neither the third receptor in this trimolecular receptor complex p75, nor its homolog TROY, showed any significant difference in levels of protein expression in schizophrenia subjects compared to controls (\(p=0.146\) and \(p=0.500\) respectively). Analysis of WNK1 revealed no statistically significant difference in expression in the DLPFC between schizophrenia and control subjects (\(p=0.864\)). However a significant 11.5% increase in Myt1 expression was observed in schizophrenia compared to control groups (\(p=0.023\)).

Conclusions

This is the first study to examine the expression profile of Lingo-1 and its signaling partner proteins in schizophrenia, identifying alterations of these pathways in the DLPFC from schizophrenia patients. Further analysis will be required to characterize these interactions at a molecular and cell specific level. However, this innovative finding provides the first foundation for a new avenue in the development of future therapies for schizophrenia.