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CLEAVAGE OF NEUREGULIN 1 AND BACE1 EXPRESSION IN FRONTAL CORTEX OF SCHIZOPHRENIA PATIENTS

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Introduction: Neuregulin1 (Nrg1) is a candidate gene linked to schizophrenia. Cleavage of Nrg1 full-length (Nrg1-FL) precursor protein by BACE1 mediates activation of erbB receptors and triggers a cascade of downstream signalling events that lead to activation of GABA, NMDA, and nicotinic receptors. Studies with BACE1 knock out mouse models have demonstrated impaired Nrg1-/ErbB signalling leads to SZ-like phenotypes that can be rescued by antipsychotics.
Objectives: We analysed frontal cortex brain tissue of schizophrenia (SZ) and healthy control (HC) subjects for expression of BACE1, Nrg1-FL and Nrg1 cleaved fragment.
Aim: To explore the possible mis-cleavage of Nrg1 by BACE1 in SZ as this may disrupt some neuronal circuits in the brain and trigger schizophrenia.
Methods: Samples from Brodmann area 6 region (40 SZ and 20 HC) were homogenized with TRIzol and proteins were analysed by western blotting. Also samples were analysed for RNA integrity and 18 SZ and 20 HC with high RIN were selected for qRT-PCR study.
Results: About 50% decrease in Nrg1 C-terminal fragment (CTF) was observed in the SZ group compared to the HC group ($p < 0.001$). A strong correlation between Nrg-FL and BACE1 was observed ($r = 0.82$, $P < 0.001$). Results of qRT-PCR showed a significant increase in the expression of BACE1-432 splice variant in SZ compared to HC ($P = 0.005$). A strong inverse correlation was found between BACE1 activity and 432/501 BACE1 splice variants expression.
Conclusion: Our results suggest that altered expression of BACE1 and decreased cleavage of Nrg1 are associated with SZ.

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