SYNAPTIC PLASTICITY IN PARKINSON’S DISEASE AS REVEALED BY THE STUDY OF TRANS-SYNAPTIC CELL ADHESION MOLECULES

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It is known that Parkinson’s disease (PD) pathophysiology involves loss of dopaminergic striatal projections with subsequent neuronal discharge abnormalities in the entire motor circuit. The classical “basal ganglia-thalamocortical circuitry” model posits that striatal dysfunction in PD leads to imbalances in neuronal firing rates in direct and indirect pathways. However, the predictions made by the model are not fully supported by numerous electrophysiological and metabolic studies. The limits of this model suggest that more complex changes occur at the molecular level in extra-striatal neurons. Cell-adhesion proteins neurexins and neuroligins mediate synaptic maturation, synaptic neurotransmission and neuronal activity. We report preliminary studies in post-mortem human brains that demonstrate extensive neuroligin-1 (NLGN1) expression in pallidal segments of normal brains, but dramatic decreases in NLGN1 levels in pallidal segments of brains from PD patients. Three human brains with PD and age-matched controls were studied. Immunohistochemistry and western blots demonstrated decreased NLGN1 levels in the globus pallidus interna and externa (GPi and GPe) of PD patients compared to control patients. Semi-quantitative reverse transcriptase polymerase chain reaction experiments confirmed decreased NLGN1 expression in the GPi and GPe of PD patients. Thus, we provide evidence for a specific molecular change at extra-striatal synapses that may contribute to alteration of neuronal firing and circuitry in PD.