Altered Homer1b/c Volumes and mGluR1/5-Homer1b/c Colocalization in Parkinson's Disease-Linked LRRK2 G2019S Mice

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Homeostatic plasticity is necessary for maintaining neuronal activity within a set physiological range in response surrounding activity. While it plays a prominent role in learning and memory, evidence defining its relevance in Parkinson's Disease (PD) is lacking. In this study, I probed the mechanisms of homeostatic synaptic scaling within the dorsal medial striatum of LRRK2 G2019S tissue. The LRRK2 G2019S mutation is the most common familial form of PD with a phenotype indistinguishable from idiopathic cases. Through immunostaining, I identified the volumes and colocalization between metabotropic glutamate receptor 1 and 5 (mGluR1/5) and the scaffolding protein Homer1b/c, two interactors that regulate homeostatic synaptic downscaling via ionic glutamatergic hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA receptor) trafficking. I discovered increased mGluR1/5 and Homer1b/c colocalization within the LRRK2 G2019S tissue (Mann-Whitney; ****p<0.0001; WT mean = 30.1591; G2019S mean = 38.4962), suggesting a potential lack of homeostatic synaptic downscaling and an increased probability of long-term depression, which is associated with memory extinction. My data also depicted an increase in Homer1b/c volumes (Mann-Whitney; ****p<0.0001; WT mean = 0.03 µm; G2019S mean = 0.04 µm), potentially reducing space within the postsynaptic density for the AMPA receptor trafficking crucial in synaptic plasticity. Thus, LRRK2 G2019S neuronal slices exhibit a dysregulated relationship between Homer1b/c and mGluR1/5, potentially causing cognitive deficits in both PD tissue models and human patients. With these novel findings, future research should focus on treatments rescuing homeostatic plasticity deficits in order to treat the prominent learning and memory impairments in PD.

Awards Won:

Third Award of $1,000