LS-2-P-2146 Three-Dimensional Ultrastructural Analysis of Neuronal Cells in Brain and Pharmacological Effects of Bromocriptine on Motor Behaviors of hLRRK2 (G2019S) Transgenic Mice

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Leucine-rich repeat kinase 2 (LRRK2) mutations are the most common genetic causes of late-onset, autosomal dominant Parkinson’s disease (PD).1-2 Recently, our group has produced transgenic mice by the insertion of human LRRK2 mutant (G2019S) gene in mouse, showing motor impairments similar with PD.3 In this study, we first investigated the three-dimensional ultrastructural alteration of subcellular organelles in neuronal cell of LRRK2 transgenic mouse using high voltage electron microscope and electron tomography. Most of the mitochondria in neuronal cells were swollen and the mitochondrial membrane and cristae were severely disrupted in the striatum and substantia nigra of transgenic mice. Redundant loops of myelin sheath were shown in both striatum and substantia nigra region of LRRK2 mice (Figures 1 and 2). After we confirmed the structural deterioration of subcellular organelles of neuronal cells, we further investigated pharmacological effects of bromocriptine, a dopamine D2 receptor agonist, on the motor behavior of transgenic mice. LRRK2 (G2019S) transgenic mice (9~20 months old) have motor deficiency in rota-rod test, and also the mice showed impairments in total moving distance, rearing frequency and moving duration in open field test. Treatment with bromocriptine (10mg/kg, for 7days) to LRRK2 (G2019S) transgenic mice had a positive effect on the retention time on rota-rod when compared with control group. In addition, transgenic mice showed increased moving distance, frequency rearing and moving duration that were comparable to control group. These results indicate that administration with bromocriptine can decreased motor deficiency in transgenic mice. These data suggest that LRRK2 (G2019S) transgenic mice model is of value in the screening of drugs against a dopamine D2 receptor agonist for neurodegenerative disease like PD. In future studies, we will analyze whether the bromocriptine treatment can also recover ultrastructural integrity of neuronal cells in striatum and substantia nigra of LRRK2 (G2019S) transgenic mice.

References

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Fig. 1: Ultrastructural alterations of mitochondria and myelin sheath in neuron. Most of the mitochondria (m) in neuronal cell were swollen and the mitochondrial membrane and cristae were severely disrupted in LRRK2 transgenic mice. ds, dendritic spines; m, mitochondria; my, myelin sheath; ps, presynaptic axon.

Fig. 2: Three-Dimensional reconstructions of the mitochondria in substantia nigra from wild-type and LRRK2 (G2019S) TG mouse, with section thickness ranging from 300 to 500 nm. The tilt series containing 121 images were recorded using HVEM, over a tilt range from -60° to 60°, with an interval of 1°.