To systematically evaluate a ubiquitin proteasome system (UPS) impairment mouse model for Parkinson’s disease (PD) research

UPS impairment has been proposed to play an important role in the pathogenesis of PD. Mice with UPS impairment in the nigra have been used for investigating mechanisms underlying dopamine (DA) neuron degeneration and for testing preclinical drugs to treat PD. However, the pathological, biochemical and behavioral features of UPS impairment animal model of PD have not been systematically evaluated.

Animal treatment and proteasome inhibitors application: C57BL/6 mice were microinjected with proteasome inhibitors (lactacystin, PSI or MG-132) into the medial forebrain bundle (mFB), either unilaterally or bilaterally using stereotactic coordination to develop a UPS impairment model of nigral DA neuron degeneration.

Neuropathological examination: Immunohistochemical and immunofluorescent staining and cell counting on brain sections were used to evaluate nigral DA neuron loss, nigral glial activation, α-synuclein intensity and inclusion-like granule in nigral DA neurons; electron microscopy, iron concentration assay and western blot assays were performed on nigral tissue to determine apoptosis, insoluble ubiquitin-conjugates index, intracytoplasmic inclusion and total iron level.

Biochemical assay: High performance liquid chromatography for detection of levels of the striatal DA and its metabolites; Western blot for assaying the nigral-striatal TH level; proteasome activity was determined by cytofluorescent assays.

Motor activity tests: Locomotion, skilled motor activities (vertical pole test, grip strength, suspension test and dowl test)

Conclusions: These pathological, biochemical and behavioral characters in this model, show progressive DA neurodegeneration with increased ubiquitin conjugates and α-synuclein aggregate, mimicking some features of PD at earlier stage. This model may be suitable to investigate the molecular mechanisms of nigral degeneration and to evaluate neuroprotective medications.

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REFERENCES


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FIGURE 2. Reproducible impairment of the nigrostriatal system by other proteasome inhibitors. 1. Loss of nigral DA neurons in the SNc of the PSI-iMFB (A) and MG-132-iMFB (B) mice. 2. Decrease in the level of striatal DA and its metabolites (Lower).