A CHEMICAL CHAPERONE, SODIUM 4-PHENYL BUTYRIC ACID, ATTENUATES THE PATHOGENIC POTENCY IN HUMAN A-SYNUCLEIN A30P+A53T TRANSGENIC MICE

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Aggregation and cytotoxicity of misfolded α-synuclein are postulated to be crucial in the disease processes of Parkinson's disease (PD) and other synucleinopathies. Mutations in the α-synuclein gene in some pedigrees of familial PD have been reported. The mutant α-synuclein has been reported to form fibrillar aggregates resulting in biochemical abnormalities that are responsible for the onset of familial PD. Thus, any agent that effectively prevents the development of misfolded and aggregated α-synuclein would be a disease modifying therapeutic candidate. We examined the efficacy of sodium 4-phenylbutyric acid (PBA), one of the chemical chaperons, in transgenic (Tg) mice overexpressing human α-synuclein containing a double mutation (A30P+A53T). To evaluate the therapeutic efficacy, bradykinesia and motor coordination were assessed using a pole test and a rotarod treadmill task, respectively.

After PBA treatment, these motor deteriorations gradually improved. In immunohistochemical examinations, both a loss of tyrosine hydroxylase-positive neurons and an increase of phosphorylated α-synuclein in the substantia nigra were inhibited, resulting in no depletion of the striatal dopamine content. These data suggest that PBA might be one of the therapeutic reagents for neurodegenerative disorders.