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Therapy of Parkinson's disease-like deficits with rapamycin and trehalose in murine models with attenuated neuroinflammation

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Motivation and Aim: Weakening of the mechanism for cleaning neurons from damaged proteins and organelles is considered as one of the factors inducing neurodegeneration at Parkinson's disease (PD). Being the main catabolic mechanism of a cell, autophagy appears to be promising therapeutic target for PD treatment. In pharmacological modeling of PD, combined damage to nigrostriatal neurons accompanied by acute neuroinflammation leads to behavioral impairment. The inflammation largely subsides in a week after neurointoxication, however, the damage to nigrostriatal neurons persists [1]. On the other hand, the chronic course of PD in humans is not accompanied by severe neuroinflammation [2]. The present study was aimed at the possibilities of PD-like pathology in murine models with attenuated neuroinflammation by activating autophagy along the mTOR-dependent (rapamycin) and mTOR-independent (trehalose) pathways.
Methods and Algorithms: Possible inhibition of neurodegeneration in a pharmacological PD model induced by MPTP (20 mg/kg i.p. daily, 4x) in C57Bl6/J mice and in a transgenic model of early PD stage (five-month-old B6.Cg-Tg(Prnp-SNCA*A53T)23Mkle/J mice) through activation of autophagy by mTOR-dependent (rapamycin; 10 mg/kg i.p. every other day, 7x) and mTOR-independent (trehalose; 2 % solution in drinking water, 2 weeks) pathways was studied. We applied the autophagy-stimulating therapy to the MPTP-induced model of PD in a "postponed" mode (7 days after intoxication) and to a transgenic model at early stage of the disease progression (at the age of 5 months) when neuroinflammatory markers are even decreased in the brain [3]. Using immunohistochemical analysis of the brain cryosections, we evaluated damaged dopaminergic neurons by the expression of tyrosine hydroxylase (TH) and the expression of a marker of autophagy (LC3-II) in the striatum, substantia nigra, frontal cortex, and hippocampus. Recovery of cognitive function was assessed in the passive avoidance test.
Results: A significant reduction (more than two times less) of the autophagosome marker LC3-II indicating the decrease in autophagy activity was observed after 31 days in the substantia nigra in mice of MPTP-treated group vs. controls. Under the influence of the autophagy inducers, the immunofluorescence of the marker significantly augmented after all therapies. Similar pattern was revealed in the transgenic PD model. In the striatum, the decrease in autophagy was less pronounced, as was the activating effect of rapamycin and trehalose in both models. Therapy with autophagy inducers restored the expression of the dopaminergic neuronal marker TH both in the striatum and substantia nigra and significantly improved cognitive function of learning and memory in mice with PD-like pathology. An enhanced therapeutic effect of the combined treatment with the autophagy inducers was revealed on the expression of TH but not in the passive avoidance test.

Conclusion: Thus, in PD models with diminished neuroinflammation, activation of both pathways of autophagy regulation can restore the dopaminergic function of neurons and the cognitive activity in mice.

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