Scientific Research Institute of Neurosciences and Medicine, Novosibirsk, Russia

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

Akopyan A.A., Pupyshev A.B., Dubrovina N.I., Tikhonova M.A.

The motivation and aim of research:

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. Thus, 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.

Experimental groups:

Control (mice were injected with saline instead of MPTP)

MPTP(in saline)

MPTP + solvent(solvent of rapamycin)

MPTP+ Rapamycin (10 mg/kg)

MPTP+Trehalose

MPTP + Rapamycin + Trehalose

Control (B6.Cg-Tg)

B6.Cg-Tg+solvent (solvent of Rapamycin)

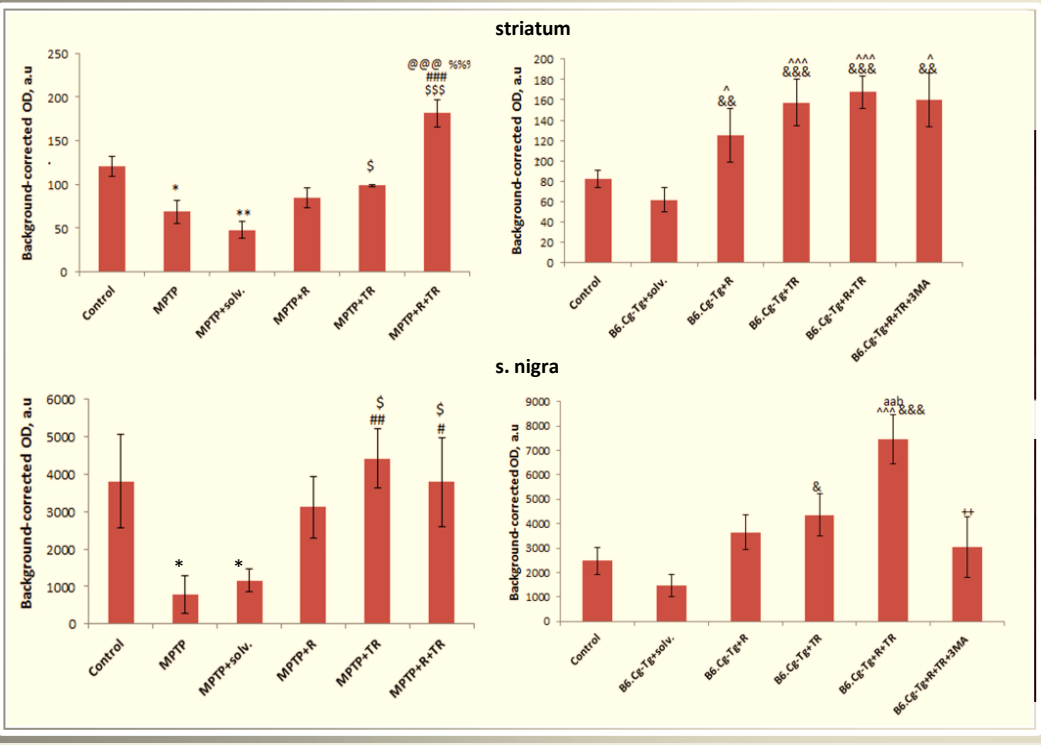
B6.Cg-Tg+Rapamycin

B6.Cg-Tg+Trehalose

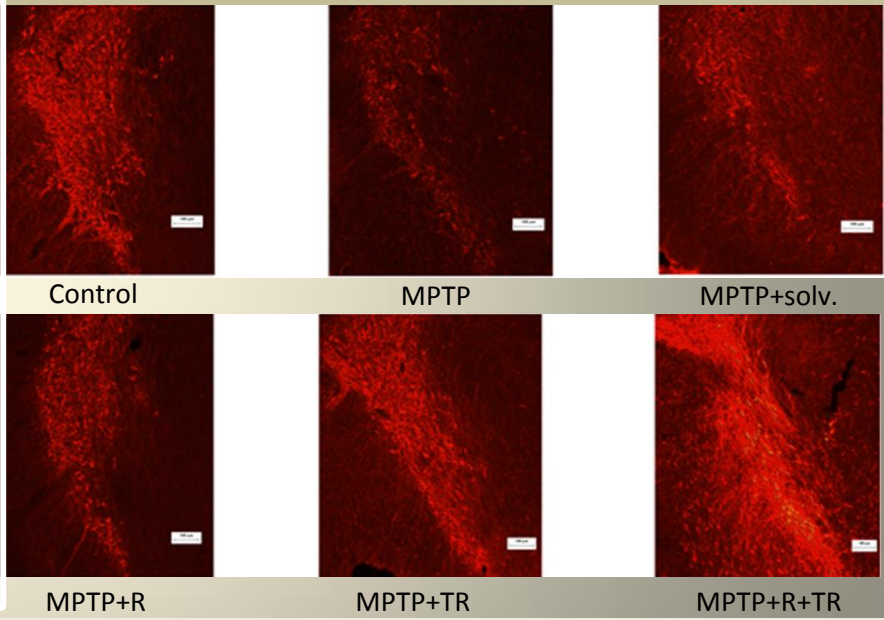
B6.Cg-Tg+Rapamycin+Trehalose

B6.Cg-Tg+Rapamycin+Trehalose+3MA (3-Methyladenine)

The effect of rapamycin, trehalose and their combined use on the expression of TH in the striatum and substantia nigra in a transgenic model (B6.Cg-Tg) and an MPTP-induced model of PD with attenuated neuroinflammation in mice.



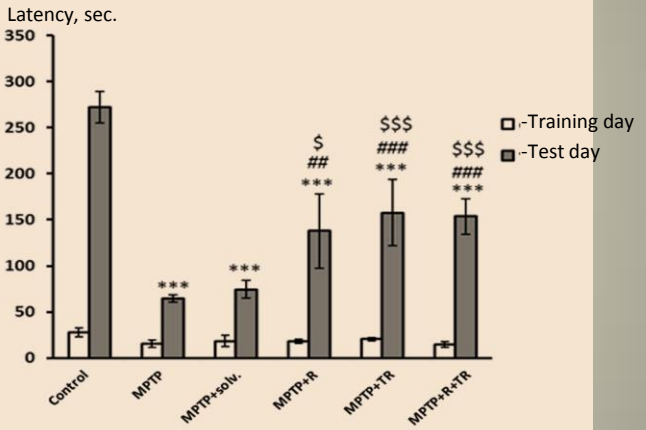
Effect of autophagy inducers on **TH** expression in the substantia nigra



Treatment of MPTP-induced PD model was started 7 days after the last intoxication. N=3-4 in the group. Statistically significant differences: * - p<0.05, ** - p<0.01 compared with the control; # - p<0.05, ## - p<0.01, ### - p<0.001 compared to MPTP; $ - p<0.05, $$$ - p<0.001 compared with MPTP+r-l; @@@ - p<0.001 compared to MPTP+R; %%% - p<0.001 compared to MPTP+TR; ^ - p<0.05, ^^^ - p<0.001 compared with B6.Cg-Tg; & - p<0.05, && - p<0.01, &&& - p<0.001 compared to B6.Cg-Tg + p-l; aa - p<0.01 compared to B6.Cg-Tg +P; b - p<0.05 compared to MPTP+TR; ++ - p<0.01 compared to B6.Cg-Tg +P+TP.

Effect of autophagy inducers (rapamycin and trehalose) on learning and memory in the cognitive test in the MPTP-induced PD model with attenuated neuroinfammation in mice.

The development of a conditioned passive avoidance reaction was carried out according to the method of single training in an automated installation **"Gemini avoidance system"** (San Diego Instruments). The maximum observation time for the animal was 300 sec. The test was carried out for 3 days.
The effectiveness of learning the conditioned reaction of passive avoidance (the formation of a fear memory trace) was assessed as a significant increase in the latent period of the transition during testing (day 3) compared with the day of training (day 2).



A significant influence of learning factors ($F(1.20)=212.1$, $p<0.001$), pharmacological effects ($F(5.20)=12.6$, $p<0.001$) and interaction of factors ($F(5.20)=13.2$, $p<0.001$) for the latent period. Statistically significant differences: *** - $p<0.001$ compared with intact; ## - $p<0.01$, ### - $p<0.001$ compared to MPTP; $$$ - $p<0.001$ compared to MPTP+ r-l.

Results: In general, under the action of trehalose, and especially in its combination with rapamycin, a significant recovery of nigrostriatal neurons was noted, as assessed by TH expression. A similar result was obtained for microglial activity (marker IBA1). Trehalose and its combination with rapamycin restored suppressed microglial activity to control values (results not shown here). Therapy with autophagy inducers significantly improved the cognitive functions of learning and memory in mice with PD-like pathology. An enhanced therapeutic effect of combined treatment with autophagy inducers on TH expression was revealed, but not in the passive avoidance test.

Conclusion: Thus, in models of PD with reduced neuroinflammation, activation of both pathways of autophagy regulation (mTOR-dependent and mTOR-independent) can restore neuronal viability and cognitive activity in mice.