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The double-faced role of $P2X_7$ receptors in toxin-induced animal models of Parkinson's disease

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Background

Previous studies indicate a role of $P2X_7$ receptors in processes that lead to neuronal death. The main objective of our study was to examine whether genetic deletion or pharmacological blockade of $P2X_7$ receptors influenced dopaminergic cell death in various models of Parkinson's disease (PD).

Methods

PC12 cells and primary mesencephalic neurons were used in culture, and the striatum and the substantia nigra were prepared from wild-type and $P2X_7$ receptor knockout mice. Rotenone and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) treatments were applied *in vitro* and *in vivo* to reproduce neurochemical hallmarks of PD. Receptor expression, cell survival indicators, and endogenous biogenic amine, amino acid, adenine nucleotide and endocannabinoid contents were analyzed.

Results

mRNA encoding $P2X_7$ and $P2X_4$ receptors was up-regulated after treatment of PC12 cells with MPTP. $P2X_7$ antagonists protected against MPTP- and rotenone-induced toxicity in the LDH assay, but failed to protect after rotenone treatment in the MTT assay in PC12 cells and in primary midbrain culture. *In vivo* MPTP and *in vitro* rotenone pretreatments increased the mRNA expression of $P2X_7$ receptors in the striatum and substantia nigra of wild-type mice. Basal mRNA expression of $P2X_4$ receptors was higher in $P2X_7$ knockout mice and was further up-regulated by MPTP treatment. Genetic deletion or pharmacological inhibition of $P2X_7$ receptors did not change survival rate or depletion of striatal endogenous dopamine (DA) content after *in vivo* MPTP or *in vitro* rotenone treatment. However, depletion of norepinephrine was significant after MPTP treatment only in $P2X_7$ knockout mice. The basal ATP content was higher in the substantia nigra of wild-type mice, but the ADP level was lower. Rotenone treatment elicited a similar reduction in ATP content in the substantia nigra of both genotypes, whereas reduction of ATP was more pronounced after rotenone treatment in striatal slices of $P2X_7$-deficient mice. Although the endogenous amino acid content remained unchanged, the level of the endocannabinoid, 2-arachidonoyl glycerol (2-AG), was elevated by rotenone in the striatum of wild-type mice, an effect that was absent in mice deficient in $P2X_7$ receptors.

Conclusions

We conclude that $P2X_7$ receptor deficiency or inhibition does not support the survival of dopaminergic neurons in *in vivo* or *in vitro* models of PD.

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