EVALUATION OF THE NEUROPROTECTIVE EFFECT OF THE A_{2A} RECEPTOR ANTAGONIST SCH58261 ON THE MPTP MOUSE MODEL OF PARKINSON'S DISEASE

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Neuroinflammation is a major component in the neurodegenerative process associated to Parkinson's disease (PD) as demonstrated by the chronic activation of glial cells, including astocytes, in the SNc and striatum (Str) of PD patients. Adenosine A_{2A} receptor ($A_{2A}R$) antagonists have emerged as a lending non-dopaminergic therapy for targeting PD motor symptoms, as well as for their neuroprotective effect on dopamine (DA) neurons.
In the present study the neuroprotective effect of the $A_{2A}R$ antagonist SCH58261 was investigated in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model of PD. C57Bl/6 mice, 3 months old, were administered with MPTP (20 mg/kg i.p.) or vehicle once daily for four days. The $A_{2A}R$ antagonist SCH58261 (0.5 mg/kg i.p.) was given twice a day throughout the MPTP treatment and until mice were sacrificed 1-3-7 days after MPTP. Tyrosine hydroxylase (TH) immunoreactivity in the SNc showed that MPTP treatment caused a loss of about 40% of TH-positive neurons in SNc. In contrast the SCH58261 plus MPTP treatment totally prevented the MPTP-induced loss of DA neurons, at all the time points analysed. The modulation of astroglia reactivity was examined by a numeric and morphological evaluation of GFAP (glial fibrillary acidic protein) immunopositive cells in the SNc and Str. MPTP treatment caused a significant gliosis, characterized by proliferation and hypertrophy of astrocytes observed after 1, 3, 7 days, in both areas analysed. In the SNc, SCH58261 plus MPTP treatment totally prevented the MPTP-induced astrogliosis at each time point investigated. Moreover, the increase in GFAP-positive cells in this area was significantly correlated to the decrease in TH positive-neurons. In the Str, SCH58261 plus MPTP treatment produced a glial reaction, which was, however, significantly less intense than vehicle plus MPTP-induced gliosis.
The results suggest that $A_{2A}R$ blockade prevented MPTP induced-loss of DA neurons and gliosis in the SNc. The significant correlation between TH and GFAP immunoreactivity suggests that $A_{2A}R$ antagonists might exert a neuroprotective effect on DA neurons through a modulation of astrogliosis. At variance, $A_{2A}R$ blockade was less effective in counteracting MPTP-induced gliosis in the Str, according to the preferential damage exerted by MPTP in this area respect to the SNc. Moreover, lack of neurodegeneration and gliosis reported 1, 3, 7 days after SCH58261 plus MPTP treatment, suggests that $A_{2A}R$ blockade counteracted, rather than delayed, MPTP-induced neuronal damage.