CHARACTERIZATION OF THE ANTIPARKINSONIAN EFFECTS OF THE NEW ADENOSINE A_{2A} RECEPTOR ANTAGONIST ST1535: ACUTE AND SUBCHRONIC STUDIES IN RATS

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Adenosine A_{2A} receptor antagonists, on the basis of preclinical and initial clinical studies showing that these compounds improve motor deficits, have been proposed as new candidate drugs in the treatment of Parkinson's disease (PD).
Using unilaterally 6-hydroxydopamine (6-OHDA) lesioned rats model of PD, we evaluated effects of the new preferential adenosine A_{2A} receptor antagonist 2-butyl-9-methyl-8-(2H-1,2,3-triazol-2-yl)-9H-purin-6-ylamina (ST1535) on motor behaviour; moreover, changes on striatal mRNA expression were evaluated by *in situ* hybridization technique.
Acute ST1535 (20 mg/kg i.p.) potentiated contralateral turning behaviour induced by a threshold dose of L-3,4-dihydroxyphenylalanine (L-DOPA) (3 mg/kg i.p.), suggesting that ST1535 has the ability of potentiate therapeutic effect of L-DOPA. ST1535 (20 mg/kg i.p.) + L-DOPA (3 mg/kg i.p.), given subchronically (twice a day for 18 days), differently to a full dose of L-DOPA (6 mg/kg i.p.), did not induce sensitization to turning behaviour or abnormal involuntary movements (AIMs), although it induced a similar number of contralateral rotations at the beginning of the treatment, indicating a low dyskinetic potential of the combined drug treatment. Moreover, while subchronic administration of L-DOPA (6 mg/kg i.p.) significantly increased GAD67, dynorphin and enkephalin mRNA levels in the lesioned striatum, subchronic ST1535 (20 mg/kg i.p.) + L-DOPA (3 mg/kg i.p.) did not modify any of these markers. Finally, we have observed that acute administration of ST1535 (20 mg/kg i.p.) was able to reduce jaw tremors in tacrine model of PD tremor in normal rats.
Results obtained in this study showed that ST1535, by potentiating the antiparkinsonian effects of a low dose of L-DOPA, induced motor effects similar to those induced by a full dose of L-DOPA, without exacerbating abnormal motor side effects and producing no long-term modification in neuronal activity during a subchronic treatment. Moreover, blockade of adenosine A_{2A} receptor by ST1535 produced positive antitremorigenic effects.