

Antidyskinetic activity of adenosine A_{2A} and 5-HT_{1A/1B} receptor targeting in models of Parkinson's disease: acute and chronic studies

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Recent report demonstrated that mixed serotonin 5-HT_{1A/1B} receptor agonist, eltoprazine, produces a near to full suppression of dyskinetic-like behaviors in animal models of Parkinson's disease (PD). However, eltoprazine resulted in a partial reduction of motility induced by L-dopa, both in rodents and in non-human primates. Moreover, in a recent clinical trial, the partial 5-HT_{1A} agonist sarizotan has been found to be only partially effective. Preclinical and clinical studies showed that adenosine A_{2A} receptor antagonists as preladenant, significantly increase L-dopa efficacy in PD, without exacerbating dyskinetic-like behaviors. On this basis, we hypothesize that combination of eltoprazine with preladenant may produce prevention or suppression of L-dopa-induced dyskinesia, without impairing the efficacy of L-dopa in relieving motor symptoms. Unilateral 6-hydroxydopamine-lesioned rats, L-dopa-naïve or rendered dyskinetic by repeated-L-dopa-treatment, were administered with eltoprazine (0.3 or 0.6 mg/kg) and preladenant (0.3 or 1 mg/kg), alone or in combination with L-dopa (4 or 6 mg/kg), and rotational behavior, as index of motility, and abnormal involuntary movements (AIMs) as index of dyskinesia, were evaluated.

Results show that combined administration of L-dopa (4 mg/kg) plus eltoprazine (0.6 mg/kg) plus preladenant (0.3 mg/kg) significantly prevented or reduced dyskinetic-like behaviors, as revealed by AIMs test without impairing the motor activity, as revealed by similar number of contralateral and ipsilateral rotations. Moreover, acutely, the combined treatment appears to prevent worsening of the motor performance induced in L-dopa-naïve animals by eltoprazine plus L-dopa in the adjusting step test and the initiation time of stepping, two tests with high predictive validity of PD associated motor disability. Analogous results were obtained with the vibrissae-evoked forelimb placing test, which is used to specifically evaluate sensory-motor impairment.

Overall these data suggest that combination of L-dopa (4 mg/kg) with eltoprazine (0.6 mg/kg) and preladenant (0.3 mg/kg) could be a new therapeutic strategy for treating motor symptoms and dyskinesia in PD.