Interaction between antagonists of adenosine A_{2A} receptors and agonists of serotonin 5-$HT_{1A/B}$ receptors: a novel therapeutic strategy for the control of dyskinesia in the therapy of Parkinson's disease

A. Pinna[1,2], G. Costa[2], N. Simola[2], L. Frau[2],E. Tronci[2], M. Carta[2], M. Morelli[1,2]

1.CNR Institute of Neuroscience, Cagliari, Italy; 2. Dept. of Biomedical Sciences, University of Cagliari, Cagliari, Italy

Preclinical and clinical studies showed that adenosine A_{2A} receptor antagonists significantly increase L-DOPA efficacy in PD, without exacerbating dyskinetic-like behaviors. Preladenant, an A_{2A} receptor antagonist under clinical evaluation, has highest affinity and selectivity for the A_{2A} receptor, making it an excellent tool for assessing the role of the A_{2A} receptor in movement disorders. Recently, it has been reported that the mixed serotonin 5-HT1A/B receptor agonist, eltoprazine, produces a near to full suppression of dyskinetic-like behaviors; however, eltoprazine resulted in a partial reduction of the motility effects of L-DOPA, both in rats and in monkeys. Moreover, in a recent clinical trial, the partial 5-HT1A agonist sarizotan has been found to be only partially effective.

On this basis, we hypothesize that combination of eltoprazine with preladenant may produce suppression of L-DOPA-induced dyskinesia, without impairing the efficacy of L-DOPA in relieving motor symptoms. Thus, unilateral 6-hydroxydopamine-lesioned rats, rendered dyskinetic by repeated treatment with L-DOPA (6 mg/kg), were administered with eltoprazine (0.3 or 0.6 mg/kg) and preladenant (0.3 or 1 mg/kg), singularly or in combination together with L-DOPA (4 or 6 mg/kg), and rotational behavior, as index of locomotor activity, and abnormal involuntary movements (AIMs) as index of dyskinesia, were then 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 reduced dyskinetic-like behaviors, as revealed by AIMs test without impairing the motor activity, as revealed by similar number of contralateral and ipsilateral rotations. Overall these data suggest that the use of the 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.