ADENOSINE A2A RECEPTOR BLOCKADE: A PROMISING SYMPTOMATIC AND NEUROPROTECTIVE THERAPY FOR PARKINSON'S DISEASE

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A number of unique features make A_{2A} receptor antagonists leading candidates among non-dopaminergic anti-parkinsonian agents. This class of compounds consistently reverses parkinsonian symptoms in rat and primate models of Parkinson's disease (PD), while the unique distribution of the A_{2A} receptor in a subpopulation of striatal neurons, reduces the liability of these compounds to induce adverse CNS effects. Moreover, when administered in association with a reduced dose of L-DOPA, A_{2A} receptor antagonists produce symptomatic relief comparable to a full L-DOPA dose, without exacerbating dyskinetic movements. Thus, in unilaterally 6-OHDA lesioned rats, blockade of A_{2A} receptors potentiates the contralateral turning response induced by a threshold L-DOPA dose, without eliciting a sensitized response in a chronic regimen. This effect originates from blockade of A_{2A} receptors colocalized with dopamine D_2 receptor in striatopallidal neurons, thus resulting in an enhanced motor response through an action on the so called indirect pathway. Similarly, the low dyskinetic potential displayed by the chronic A_{2A} antagonist plus L-DOPA administration lies on the same mechanism, resulting in a balanced activation of striatal output pathways, at variance with L-DOPA, which elicits intense dyskinesia through an unbalanced iperactivation of the so called direct pathway. Thus, differently from L-DOPA alone, the concurrent A_{2A} receptor blockade doesn't result in the altered expression of striatal markers of neuronal activity, as GAD67, dynorphin and enkephalin mRNAs. Moreover, the investigation of basal ganglia areas downstream the striatum, has revealed that this treatment produces a physiological activation of the substantia nigra reticulata, in contrast to an excessive inhibition observed when a chronic treatment with L-DOPA is given.

A neuroprotective effect of A_{2A} receptor blockade in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) experimental model of PD has been reported as well. Although the mechanism of this effect is not known, an involvement of non-neuronal cells, as glia, can be envisaged. Thus, in mice repeatedly treated with MPTP, the concurrent administration of an A_{2A} antagonist totally prevents the loss of dopaminergic neurons in the substantia nigra pars compacta, while inhibiting both the astroglia and microglia activation induced by the neurotoxin in this area. Therefore, blockade of A_{2A} receptors represents a promising tool in PD therapy, which might have the unique double effect of slowing the neurodegenerative process, while counteracting motor impairment.