

## **Abstract**

Astrocytes exert neuroprotective effects through production of antioxidant molecules and neurotrophic factors. A recent study showed that stimulation of astrocyte serotonin 1A (5-HT<sub>1A</sub>) receptors promotes astrocyte proliferation and upregulation of the antioxidant molecules metallothionein (MT)-1,2, which protect dopaminergic neurons against oxidative stress. Rotigotine, an anti-parkinsonian drug, can bind to dopamine and 5-HT<sub>1A</sub> receptors. In this study, we examined neuroprotective effects of rotigotine in models of Parkinson's disease and involvement of astrocyte 5-HT<sub>1A</sub> receptors in neuroprotective effects of rotigotine against dopaminergic neurodegeneration. Rotigotine increased the number of astrocytes and MT-1,2 expression in cultured astrocytes. Pretreatment with conditioned media from rotigotine-treated astrocytes significantly inhibited 6-hydroxydopamine (6-OHDA)-induced dopaminergic neurotoxicity. These effects were completely blocked by a 5-HT<sub>1A</sub> antagonist or MT-1,2 specific antibody. Subcutaneous administration of rotigotine increased MT-1,2 expression in striatal astrocytes and prevented reduction of dopaminergic neurons in the substantia nigra of a 6-OHDA-lesioned mouse model of Parkinson's disease. These effects were blocked by co-administration with a 5-HT<sub>1A</sub> antagonist. These results suggest that rotigotine exerts neuroprotective effects through upregulation of MT expression in astrocytes by targeting 5-HT<sub>1A</sub> receptors. Our findings provide a possible therapeutic application of rotigotine to prevent dopaminergic neurodegeneration in Parkinson's disease.