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Novel pharmaceutical interventions to relieve L-DOPA induced dyskinesia in Parkinson's disease

Parkinson's disease (PD) is a neurodegenerative disease caused by the death of dopaminergic neurons in the basal ganglia. The golden standard for the treatment of PD is the dopamine (DA) replacement therapy with L-DOPA. DA acts on DA receptors which belong to the superfamily of G Protein coupled receptors (GPCRs). However chronic treatment with L-DOPA results in super sensitivity of DA receptors and unwanted side effects commonly known as L-DOPA induced dyskinesia. Here we screened different formulations of L-DOPA oral route delivery which could result in a slow, sustained and timely delivery of L-DOPA along with repurposed GPCR receptor antagonists that can up regulate two of the G protein coupled receptor kinases GRK3 and 6 in brain that are down regulated in experimental animal models of PD. Our *in vitro* data in striatal neuronal culture in the presence of DA and GPCR receptor antagonists showed an upregulation of GRK3 and 6 after 24 hours of treatment at lower doses of DA. The behavioral studies in unilateral PD mice with DOPA formulations showed oral delivery of DOPA relieved the akinesia seen in Parkinson's disease and at the same time had less dyskinetic effects as revealed by mouse cylinder test and AIMS respectively. Together our behavioral and signaling data demonstrate that L-DOPA delivered orally in a sustained release form along with the peripheral DOPA decarboxylase inhibitors carbidopa and benserazide could relieve the dyskinetic effects due to L-DOPA therapy in Parkinson's disease.

Biography

Jayakumar Rajadas is the Founding Director of Biomaterials and Advanced Drug Delivery Laboratory at Stanford University. He is also an Adjunct Professor at UCSF School of Pharmacy, University of California. He is currently working on the molecular mechanism of neurodegenerative disorders involved in Alzheimer's and Parkinson's diseases. His research has also been involved in transforming nano science ideas into biomaterials and drug delivery technologies. Before moving to Stanford, he served as the Founding Chair Person of the bio-organic and neurochemistry division at one of India's national laboratories. He is a recipient of several awards including Young Scientist award in Chemistry for the year 1996 from the Government of India. He has also won the Best Scientist award from the Tamil Nadu state Government India in the year 1999. He is co-recipient of nine SPARK transnational awards in Stanford University. He has published over 194 papers with numerous granted/disclosed patents.

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