ABSTRACT

Title: Molecular Basis of Neuroprotection Against Parkinsonism By Identified Ayurvedic Molecules

Parkinson’s disease (PD) is the most common neurodegenerative movement disorder, resulting from the loss of dopaminergic neurons from substantia nigra pars compacta (SNpc) region of the midbrain. Mitochondrial dysfunction is known to be an integral component of PD pathogenesis, and the present study investigated a novel drug on its potential to correct mitochondrial dynamics and the functional recovery of mitochondrial electron transport chain. 1,2,3,4-tetrahydro-6,7-dihydroxy-3-isoquinolinecarboxylic acid (TIQ), an active component from a herb that is used in treating PD in Ayurveda system of medicine, was isolated and its neuroprotective effect was evaluated in neurotoxins-(in vivo and in vitro) and α-synuclein-(in vitro) induced PD models in laboratory animals or in neuronal cell lines. TIQ was found to possess significant monoamine oxidase (MAO)-B inhibitory potential in vivo in mice. TIQ administration, by gavation (200 mg/kg), in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced parkinsonian mice, and by intra-peritonal administration (50 mg/kg) in 1-methyl-4-phenyl pyridinium ion (MPP+) or 6-hydroxydopamine (6-OHDA) lesioned hemiparkinsonian rats significantly attenuated tyrosine hydroxylase positive neuronal loss from SNpc and provided significant improvement in behavioral abnormalities exhibited in 6-OHDA-induced model. MPP+-induced inhibition of mitochondrial electron transport chain NADH-ubiquinone oxidoreductase (complex-I) activity (ex vivo) was reversed by TIQ at nM concentrations. TIQ treatment recovered impaired mitochondrial state-3 respiration, both in isolated mitochondria (in vivo and ex vivo), as well as in human-derived PD cybrids. MPTP-induced overexpression of the mitochondrial fission protein Drp-1, their mitochondrial translocation, and loss in mitochondrial fusion protein Mfn2 were effectively normalized by TIQ treatment in mice, which in turn blocked the mitochondrial fragmentation and cytochrome-c release from mitochondria thereby controlling neuronal apoptosis. Supporting these findings, TIQ (1 µM) treatment could also reduce Drp1 overexpression in PD-cybrids. Above all, TIQ (1 µM) treatment protected SH-SY5Y cell death against α-synuclein-induced toxicity probably by correcting mitochondrial membrane potential loss and curtailing mitochondrial fragmentation. These results suggest the strength of this novel molecule to be a drug contender for Parkinson’s disease.

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