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Alpha-synuclein overexpression and inactivation of respiratory chain complex I increase sensitivity of mitochondrial oxidative energy metabolism and neuronal loss: Implications in Parkinson's disease

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Alpha-synuclein is a major component of intra-neuronal inclusions found in Lewy bodies in Parkinson's disease patients. The mitochondria represent a highly promising target for the development of novel therapeutic agents as they are seats of many metabolic processes including oxidative energy metabolism. In the present study we report mechanisms underlying cellular toxicity of alpha-synuclein overexpression under conditions of inactivation of mitochondrial respiratory chain complex I.

A two-step PCR strategy was performed to create alpha-synuclein A53T and A30P expression vectors. To create wild type alpha-synuclein expression vector, a regular PCR was performed using N- and C-terminal human alpha-synuclein primers and subcloned into the p-TARGET, while a self-ligated plasmid of the p-TARGET was used as control vector. Wild type and A53T and A30P alpha-synuclein mutants were transfected to human dopaminergic neuroblastoma SHSY cells. Cellular aggregations of alpha-synuclein, reactive oxygen species (ROS), protein tyrosine nitration, mitochondrial transmembrane potential, and cytochrome c release were determined by immunofluorescence, immunogold electron microscopy and immuno-blotting techniques.

Results show that over expression of both A53T and A30P mutants or the wild-type alpha-synuclein augmented the aggregation of alpha-synuclein and that the aggregates were localized within the mitochondria of overexpressing cells. Over expressing cells show increase in cellular and mitochondrial ROS, nitration of proteins, decreased mitochondrial transmembrane potential and cellular respiration, and release of cytochrome c from the mitochondria. The degree of ROS production, cellular respiration and mitochondrial dysfunctioning was increased in A53T and A30P mutants or the wild-type alpha-synuclein overexpressed cells when complex I was inactivated.

These findings suggest a direct role of mitochondrial respiratory chain complex I in alpha-synuclein toxicity in neuronal cells and suggest possible therapeutic intervention in Parkinson's disease involving prevention of aggregation, translocation of alpha-synuclein into mitochondria and inactivation of complex I.

Biography

Dr. Mordhwaj S. Parihar is a professor in Biochemistry & Molecular Biology at Vikram University, Ujjain, India. He completed his PhD from Vikram University Ujjain, India and postdoctoral studies from Southern Illinois University School of Medicine, Springfield, Illinois, USA. He worked on molecular and biochemical mechanisms of pathogenesis of Alzheimer's and Parkinson's Diseases employing mutations, gene silencing and transcriptional changes. His current interest includes epigenetic and metabolic factors that contribute to various neurodegenerative and other human diseases. He has published more than 55 papers in international journals and serving as an ad hock editorial members member of reputed journals and member international grant review committees.