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Neuroprotective efficacy of Cdk5 inhibitory peptide TFP5/TP5 in Parkinson's disease and mitochondrial axis

Cdk5 is a proline directed serine/threonine kinase that is increasingly implicated in various nervous system functions, during nervous system development and survival. However, upon deregulation produces many neurodegenerative diseases including PD. Cdk5 is a member of cyclin-dependent kinases. Cdk5 is unique among its family; it is not activated by cyclins but is regulated exclusively by the brain-specific activator p35/p39. Cdk5 is a multifunctional kinase. Emerging evidence suggests that abnormal and hyper Cdk5 activity is implicated in the accumulation of neurofibrillary tangles in AD, synuclein in Lewy bodies in PD, and in inclusions of aberrant phosphorylation of tau and neurofilament proteins the hallmarks of ALS patients. Our recent studies have shown that a modified truncated 24-aa peptide (TFP5/TP5), derived from the Cdk5 activator p35, penetrates the blood-brain barrier after i.p. injections, inhibits abnormal Cdk5 hyperactivity, and significantly rescues AD pathology (up to 70–80%) in 5XFAD and P25Tg AD model mice. In this study, the mutant mice were injected with TFP5 and exhibited behavioral rescue, no toxic side effects, decreased inflammation, amyloid plaques, NFTs, cell death, and extended life by two months has been demonstrated. Neuroprotective and restorative role of TP5/TFP5 has also been demonstrated in other PD model cellular and animal system; human neuroblastoma (SHSY5Y) cell death, c-elegance and amphetamine induced rotational behavior in 5-OHDA rats. These results point out that TFP5/TP5 as a potential therapeutic, toxicity-free neuroprotective drug candidate. These and other studies presented demonstrate TP5/TFP5 exhibit a critical role in mitochondrial function, autophagy induction and neuronal loss in MPTP and other neurotoxic reagents-mediated neuronal toxicity, mitochondrial dysfunction well characterized animal models of PD.

Biography

Harish C Pant received his MA and PhD degrees in Physics from Agra University, Agra, India. His Postdoctoral studies were conducted on the mechanisms of electron and ion transport in model membrane systems at the Department of Biophysics at Michigan State University. He joined the Laboratory of Neurobiology in the NIMH as a Senior Staff Fellow in 1974 with Dr. Ichiji Tasaki where he studied the function of the axonal cytoskeleton in the squid giant axon. In 1979 he moved to the NIAAA extending his studies on the neuronal cytoskeleton and the effects of alcohol on its regulation. He moved to the NINDS, Laboratory of Neurochemistry in 1987 where he is presently Chief of the section on Cytoskeleton Regulation.

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