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NEUROPROTECTIVE ROLE OF A SMALL PEPTIDE DERIVED FROM NEURONAL CELL CYCLE LIKE KINASE (CDK5) ACTIVATOR (P35)

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Cdk5 is a member of cyclin-dependent kinases. It is unique among Cdk family of kinases; it is not activated by cyclins but is activated exclusively by the brain-specific p35/p25 proteins. It is a multifunctional protein kinase constitutively active in nervous tissues. It is implicated in ameliorating various neurodegenerative diseases phenotypes including AD. Cdk5, (Cdk5/p35), activity is tightly regulated and essential for nervous system development and neuronal functions. Emerging evidence suggests that its deregulation and hyper activation due to neuronal insults produced p25 and accumulation and aggregation of synaptic and cytoskeletal proteins in neuronal cells forming early stages of neurofibrillary tangles, plaques, Lewy bodies inclusions. These aggregated proteins and peptides are the hallmarks of AD, PD and ALS pathologies. On the basis of a large number of studies we have proposed Cdk5/p35 is a physiological and Cdk5/p25 is pathological target. To reduce the pathological phenotypes *in situ* / *in vivo* we discovered p5, a 24-amino acid truncated peptide from Cdk5 activator protein, p35, selectively inhibited the deregulated and hyperactive active Cdk5, (Cdk5/p25), induces pathology, but not Cdk5, (Cdk5/p35), kinase essential for nervous system development, function and survival. Recently it has been provided sufficient information that a modified truncated 24-amino acid peptide (TFP5), derived from the Cdk5 activator p35, penetrates the blood-brain barrier upon intraperitoneal injections (ip), inhibits significantly abnormal Cdk5 hyperactivity, and rescues significantly, AD pathology (up to 70–80%) in 5XFAD, p25Tg AD model. In addition, MPTP induced phenotypes in Parkinson's disease model mice. The present talk will provide the molecular and cellular basis of the selectivity of these two forms of kinases, Cdk5/p35 and Cdk5/p25, physiological and pathological behavior of Cdk5/p35 and Cdk5/p25 kinases. We propose, TFP5 may be able to ameliorate several phenotypes in different neurodegenerative disease.

BIOGRAPHY

Harish C Pant has 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 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. His laboratory is studying the mechanisms of topographic regulation of neuronal cytoskeleton proteins by post-translational modification, including the role of kinase cascades in normal brain and during neurodegeneration.

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