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International Conference on

Health Care and Neuroscience

April 08-09, 2019 | Zurich, Switzerland

Neuroprotective and Restorative roles of a small peptide derived from Neuronal cell cycle like kinase (Cdk5) activator protein (p35)

Harish C Pant
National Institutes of Health, USA

Cdk5 is a member of cyclin-dependent kinases. It is unique among cell cycle kinases. It is not activated by cyclins but is regulated exclusively by the brain-specific Cdk5 activator protein of MW p35 kDa and p39 kDa. We have found that a small 24 amino acid truncated peptide derived from p35 implicated in ameliorating various neurodegenerative diseases phenotypes including AD. Cdk5 is a multifunctional protein kinase, essential for nervous system development, function and survival. The heterodimeric, (Cdk5/p35), activity is tightly regulated due to its N-terminus myristoylated head domain anchoring to the membrane, localized to plasma membrane and membranous structures. Now emerging evidence suggest that upon neuronal insults, calcium entry activates calpain produces cleaved p25 kDa protein, which has higher affinity for Cdk5 induces its deregulation and hyperactivation of Cdk5 (Cdk5/p25). Hyperactivity (Cdk5/p25) induces accumulation of hyperphosphorylated cytoskeletal proteins including tau and neurofilament. The aggregation of these neuronal proteins in neuronal cell bodies are highly toxic and are the early stages of neurofibrillary tangles, plaques, Lewy bodies inclusions. These aggregated proteins and peptides are the hallmarks of AD, PD and ALS pathologies. We have proposed Cdk5/p35 is a physiological and Cdk5/p25 is the pathological target. We have discovered p5 a truncated 24 amino acid peptide derived from p35 selectively inhibits the deregulated and hyperactive active (Cdk5/p25) kinase, produced due to neuronal insults, induces pathology but not the Cdk5/p35, essential for nervous system development, function and survival. Recently our laboratory has provided sufficient information that a modified truncated 24-amino acid peptide (TFP5), derived from the Cdk5 activator p35/p25, penetrates and crosses blood-brain barrier upon intraperitoneal injection (i.p), inhibits abnormal Cdk5 hyperactivity, and prevents, AD pathology in 5XFAD and p25Tg AD model mice. In addition, TFP5 treatment also rescues MPTP, a mitochondrial toxin induced Parkinson's disease model mice. The present talk will provide the molecular and cellular mechanisms of the selectivity of these Tp5/TFP5 peptides two forms of the kinases, Cdk5/p35 and Cdk5/p25. We propose Tp5/TFP5 can act as a therapeutic reagent for neurological diseases.

e: panth@ninds.nih.gov

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