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A small peptide derived from a neuronal cell cycle like kinase activator, P35, is a possible therapeutic candidate to reduce the phenotypes of neurodegenerative disorders like Parkinson's and Alzheimer's diseases

Our previous studies have shown that, neurofilaments, & Tau the major neuronal cytoskeletal proteins are selectively phosphorylated in axons. The phosphorylation activity is tightly regulated under physiological conditions. Under neuropathological conditions, however, phosphorylation is deregulated, occurs abnormally in perikarya and induces pathology resembling that seen in many neurodegenerative diseases (e.g. AD, ALS, PD). We identified cyclin dependent kinase 5 (Cdk5) together with its activator p35, as a major kinase regulating the topographic neuronal cytoskeleton phosphorylation. It is found that Cdk5, when deregulated by neuronal insults (A-beta, glutamate, oxidative stress, mutations and other), is hyperactivated as a stable complex with p25 (a truncated fragment of p35) and induces perikaryal hyperphosphorylated tau, synuclein and NFPs as seen in AD, PD and ALS. At autopsy, AD, PD and ALS brains display hyperactive Cdk5 (Cdk5/p25) and have confirmed that Cdk5/p25 induces neuroinflammation, tau and NF hyperphorylation along with cell death. A p25-overexpressing (P25Tg) AD model mouse displays the typical AD phenotypes. Accordingly, hyperactive Cdk5/p25 has been identified as a possible therapeutic target for neurodegeneration. All the therapeutic approaches inhibiting activities of kinases have been by interfering with ATP binding domains of the kinases that turned out to be non-specific and highly toxic. To modulate the Cdk5 activity instead of using the analogs of ATP we decided to study the effect of different truncated fragments of p35 on the regulation of Cdk5 activity. We identified a 126 amino acid (aa) truncated peptide of p35, (CIP) and smaller peptide p5 (24 aa) bind with Cdk5 with higher affinity than p25 and selectively inhibited Cdk5/p25 hyperactivity in culture, reduced tau, NFP hyperphosphorylation and cell death without toxicity and affecting endogenous Cdk5/p35 activity. The question arise, will CIP and p5 be non-toxic in vivo, in animals as in cell cultures and may prevent the phenotypes of an AD, PD and ALS transgenic mice models? Consistent with the model, we succeeded in showing that pathological and behavioral phenotypes in AD, PD and ALS model mice (over-expressing p25 transgenic) and the 5XFAD double transgenic can be alleviated after co-expression with CIP in p25 Tg and treatment with modified p5 (TFP5). We propose that CIP and TFP5 is novel therapeutic candidate to prevent Alzheimer's disease phenotypes and pathologies.

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 the 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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