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Cyclin dependent kinase 5 (Cdk5) inhibitory peptides, (CIP, P5), inhibit specifically the deregulation of Cdk5 involved in AD model mice and prevent the AD phenotypes

The Biology of Neurodegeneration program evolved in our laboratory studying the basic biology of neuronal cytoskeletal protein phosphorylation regulation during development and normal function in the adult. To understand the molecular basis of neurodegeneration our major focus has been to study the regulation of compartment-specific patterns of cytoskeletal protein phosphorylation in neuronal perikarya and axons. We have demonstrated that phosphorylation of the numerous acceptor sites on neuronal intermediate filament proteins (NIFPs) as neurofilaments (NFs) was tightly regulated topographically and generally confined to the axonal compartment. It was recognized that in neurodegenerative disorders such as Alzheimer's disease (AD) and Amyotrophic lateral sclerosis (ALS), the pathology was characterized by an accumulation of aberrantly and hyper-phosphorylated cytoskeletal proteins in cell bodies, suggesting that topographic regulation had been compromised. This led the discovery of neuronal cyclin dependent kinase 5 (Cdk5). Our studies of neurodegeneration in cell culture and model mice with emphasis on specific neuronal protein kinases, (Cdk5), that targets numerous neuronal proteins including cytoskeletal proteins, which when deregulated, may be responsible for the pathology seen in neurodegeneration. In cell systems, neuronal stress leads to deregulated kinases, for example, deregulation of Cdk5, accompanied by abnormal cytoskeletal protein phosphorylation and cell death characteristic of neurodegeneration. Recently we have developed peptides derived from, p35, a neuron specific activator of Cdk5, for deregulated Cdk5 activity which rescue cells *in vitro* from this stress induced pathology and *in vivo*, in AD model mice. We have investigated (1) how cytoskeletal protein phosphorylation is topographically and tightly regulated in neurons? (2) What factors are responsible for this deregulation? and (3) treated mouse models of AD therapeutically with peptide that specifically inhibit deregulated Cdk5.

Biography

Harish C. Pant supervises and manages a research program dedicated to understanding the mechanisms regulating neuronal cytoskeletal phosphorylation in health and disease. For several years our focus has been on the role of the multifunctional neuronal kinase complex Cdk5/p35, in neuronal cytoskeleton phosphorylation, neuronal development, synapogenesis, and survival. Within the past few years, however, we, and other laboratories, have shown that Cdk5 is abnormally hyperactivated as a Cdk5/p25 complex in several neurodegenerative disorders which correlates with their specific brain pathologies. Serendipitously, we identified a small peptide (p5) derived from the cdk5 activator, p35, that specifically inhibited the abnormally activated Cdk5 without affecting the normal endogenous kinase. Accordingly, current and future studies are designed to (1) determine whether this peptide acts therapeutically in rescuing neurodegenerative model mice sharing the hyperactivated Cdk5-induced phenotypes of Alzheimer Disease (AD), Amyotrophic Sclerosis (ALS), Parkinson's disease (PD) and HIV-dementia. (2) if so, what is its mechanism of action in each case? And, ultimately, (3) does it qualify as a possible candidate for human therapy?

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