A modified small peptide derived from the Cdk5 activator p35, crosses blood brain barrier and rescues phenotypes of Alzheimer Disease (AD) model mice; A novel preclinical approach for AD

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Cyclin-dependent kinase 5 (Cdk5), unlike its other cyclin-dependent family members is unique as it is activated by only neuron-specific proteins p35 (35 KDa) and p39 (39 KDa). The activity of Cdk5/p35 is tightly regulated during nervous system development, however, under neuronal stress, p35 gets cleaved by calpain into p25 and p10 fragments. Truncated p25 forms a more stable Cdk5/p25 complex which has higher activit, longer half-life that hyperphosphorylates cytoskeletal proteins (tau and neurofilament) and inducing cell death. Hyperphosphorylation of tau and neurofilament proteins leads to the formation of the neurofibrillary tangles (NFT) which are one of the hall marks of Alzheimer’s disease (AD). It has also been reported that AD brains have higher levels of p25 and Cdk5 activity, suggesting that the Cdk5/p25 complex may be an ideal therapeutic target for AD. The current therapeutic approach lacks specificity as it is based on the compounds resembling roscovitine (a kinase inhibitor) which competes with ATP binding site on Cdk5 and other kinases and therefore, not only inhibits Cdk5/p25 activity but also Cdk5/p35 activity as well as other kinases. In order to search for a specific inhibitor our approach is based on the crystal structure of Cdk5/p25, resulted in several small truncated molecules of p25 that inhibited Cdk5 hyperactivation in vitro. After screening a large number of peptides, the smallest truncated fragments of p25, a 24 amino acid residue (called P5) inhibited Cdk5/p25 activity more effectively than other larger forms. In addition in situ P5 specifically inhibited Cdk5/p25 deregulated activity but not regulated Cdk5/P35, which is essential for nervous system function and survival. Encouraged by these studies, we modified P5 and studied its effect in AD model mice. It is found that P5 – modified peptide crosses the blood brain barrier (BBB) and rescues the AD pathology in the AD model mice. The rescue effect is also seen in various behavior-tests for spatial memory loss and motor deficit indicating that this modified P5 peptide could be a good therapeutic candidate for AD.

Biography

Pant received his M.A. and Ph.D. 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. Dr. Pant 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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