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Protective and restorative roles of a P5(TP5/TFP5) peptide derived from Cdk5 neuron specific activator protein p35

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Cdk5 is a multifunctional protein kinase important in neuronal development, physiological function, and survival. Its activity is tightly regulated under physiological conditions. However, upon neuronal insults Cdk5 is deregulated, hyperactivated and produces a number of neurodegenerative diseases and may be in part responsible for the hallmark pathology of amyloid plaques and neurofibrillary tangles (NFTs) in AD, hyperphosphorylation of Prx2, an antioxidant enzyme, dysregulation oxidative phosphorylation, essential for mitochondrial dysfunction in PD and aberrant hyper photophosphorylation of neurofilaments in ALS. The etiology of neurodegenerative diseases including Alzheimer's Disease is very complex and arises as a result of kinase dysfunction and other accumulated insults to many cellular, environmental and interacting metabolic pathways during aging. It has been proposed that deregulated and hyperactive Cdk5 results from the overexpression of p25, (a truncated fragment of p35, the normal Cdk5 regulator). p25 has a higher affinity for Cdk5 compared to p35 which when complexes to Cdk5, causes hyperactivation and deregulation, neurofilament and Tau hyperphosphorylation, tangles (NFTs) formation, neuroinflammation, and neuronal death. Thus Cdk5/p25 becomes a pathological target. The objective of our studies has been to inhibit selectively pathological Cdk5/p25 but not Cdk5/p35, the physiological target (Cdk5/p35) *in situ* / *in vivo*. During the course of our studies, we found a small 24 amino acid peptide (p5) derived from p35, Cdk5 activator selectively inhibited the deregulated, Cdk5/p25 but not physiological (Cdk5/p35) activity. Intraperitoneal (i.p.) injections of p5- modified peptide (TFP5), penetrated the blood-brain barrier and significantly rescued AD- pathology in 5XFAD model mice. As a proof of concept, it is essential to demonstrate the peptide's efficacy in a mouse model expressing high levels of p25, such as the inducible CamK-inducible CK-p25Tg, AD model mouse that overexpresses p25 in CamKII positive neurons. Using TFP5 treatment, we show that peptide i.p. injections in these mice decrease Cdk5 hyperactivity, tau, neurofilament-M/H hyperphosphorylation, and restore synaptic function (LTP) and behavior (i.e., spatial working memory, motor defects). It is noteworthy that TFP5 does not inhibit endogenous Cdk5/p35 activity, or other Cdks *in vivo* suggesting it might have no toxic side effects and may serve as an excellent therapeutic candidate for neurodegenerative disorders expressing abnormally high brain levels of p25 and hyperactive Cdk5. We have demonstrated that the peptide, injected into an AD model mouse overexpressing p25 (P25Tg) and 5XFAD, specifically targets the hyperactive kinase, reduces or eliminates familial and sporadic AD phenotypes and restores normal behavior. We suggest that the peptide may serve as a potential therapeutic candidate for neurodegenerative diseases. We believe as the editor of Molecular biology of cell stated; "This is a major advancement basic science, should be considered for clinical applications".

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