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INITIAL ACTIVATION OF ASTROCYTES / DEREGULATION OF CDK5 AXIS IN AD AND ALZHEIMER'S DISEASES

Harish C Pant
NIH / NINDS, Bethesda, Maryland

Astrocytic activation initiating neuroinflammation is closely associated with many neurodegenerative diseases including Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), Multiple Sclerosis (MS). Neuronal insults lead to deregulation and hyperactivation of Cdk5, the major neuronal cell cycle kinase, in the nervous system initiates neuropathology. Using p25Tg AD model mice (CaMPKII P25Tg) we found that initially astrocytes are activated due to higher activity of phospholipase 2A (PLA2) induced by Cdk5 phosphorylation of Cdk5 consensus sequence in PLA2 and affecting phospholipid metabolism. This leads to increase in factors like arachidonic acid and activation of neuroinflammation and neurodegeneration. It is well known that under physiological conditions, the initial interactions among neurons, astrocytes, microglia, and oligodendrocytes are regulated and induce secretion of basal levels of various factors e.g. complement proteins, cytokines and chemokines essential for physiological conditions. The expression of these diverse molecules is tightly regulated since they act as trophic factors essential for nervous system development and function. However, under stress and toxic conditions, additive effects of neuronal chronic stress/insults/toxicity, in addition to ageing leads to overexpression of these factors which leads to neuroinflammation and neurodegeneration. A systematic, time course study of the expression and activation of these factors provided the evidence that activation of astrocytes is the initial step in the deregulation of Alzheimer's disease in AD model system.

panth@ninds.nih.gov