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Brain Insulin Resistance in Alzheimer's disease: Targeting Phosphoinositide 3-Kinase (Pi3k)/Akt/Gsk-3β Pathway

Ansab Akhtar1, Sangeeta Pilkhwal Sah1
1Panjab University, India

ICV-STZ was used for the model of sporadic Alzheimer's disease being established. Adult male Wistar rats (48) weighing 200-300 g bred in Central Animal House facility of Panjab University were used. Animals were randomly divided into 8 groups comprising 6 animals in each group as follows: Protocol lasted for 21 days, sacrificing animals on 22nd day followed by isolation of serum and dissection of cortex and hippocampus, preserving the same for further analysis. Behavioral studies like Morris water maze was done for assessing spatial memory, novel object recognition for associative memory and actophotometer was performed for locomotor activity. Biochemical estimations for antioxidant activity or oxidative stress such as reduced glutathione estimation, superoxide dismutase assay, catalase assay, glutathione peroxidase assay, myeloperoxidase assay, glutathione S-transferase assay, lipid peroxidation assay, and protein carbonylation assay were performed in the homogenates of cortex and hippocampus of the brain which are the specific regions for memory, learning and cognition. For nitrosative stress, nitrite estimation was done.

Insulin tolerance in the brain is an significant trait of Alzheimer's disease (AD). This phenomenon will drive many of AD's neural and cognitive disorders by itself. Brain insulin resistance in individuals with or without a history of diabetes is an early and typical characteristic of AD, closely associated with cognitive decline. Brain insulin resistance in AD is a neuronal phenomenon that indicates a reduced insulin response at all levels of the signaling pathway for the insulin receptor – IRS-1–PI3K – Akt. Nevertheless, the first important drop in insulin sensitivity occurs below the receptor, starting with IRS-1.

Amyloid-β-triggered microglial release of proinflammatory cytokines, which inhibits insulin signaling by encouraging serine phosphorylation of IRS-1, appears to be the most immediate cause of brain insulin resistance in AD. It is possible that the rate of increase in brain insulin resistance associated with age will be that. Although there are no established methods to detect it in vivo, brain insulin resistance in persons with peripheral insulin resistance is more likely As such resistance can promote insulin resistance in the brain. Therefore, prediabetic individuals will make lifestyle improvements to reduce peripheral insulin resistance (e.g. loss of excess weight, daily physical exercise, and a Mediterranean diet) to prevent progression not only to T2D, but also to clinical stages of AD.

When clinical phases of this condition occur, improvements in lifestyle are unlikely to normalize reactivity to brain insulin. Nonetheless, this could be done by two GLP-1 analogues approved for T2D by the US FDA, namely exenatide and liraglutide. These drugs display promise at the moderate cognitive impairment stage of AD in restoring natural brain insulin sensitivity but not in AD dementia. Clinical studies of these successful drugs are now being performed on cases of moderate cognitive

Insulin also plays a part in proteostasis, affecting amyloid β peptide clearance, and tau phosphorylation, which are hallmarks of Alzheimer's disease. Insulin also modulates vascular function through vasoreactivity effects, lipid metabolism, and inflammation effects. The insulin dysregulation may lead to neurodegeneration through these multiple pathways.

Since most tumors are genetically complex, mutations / alterations in genes other than PI3 K are likely to predispose a tumor to being responsive or even more likely to be resistant to PI3K-targeted therapy. An apparent resistance source is a mutation or amplification of a part of a downstream pathway.

Just as p110α mutations or PTEN loss can make Her2 positive tumors resistant to trastuzumab, tumors with amplifications or mutations in various downstream kinases are likely to obstruct the action of targeted inhibitors against their upstream components. Therefore it is necessary to select patients likely to respond to PI3K-targeted cancer therapy and to identify patients who are not responding.

Insulin is a peptide secreted by the pancreas and plays an essential part in regulating the absorption of glucose in peripheral tissues. Although insulin's function in the periphery is well recognized, less is known about its multifactorial function within the brain. However, data emerging from human and animal research suggests that insulin affects cerebral bioenergetics, enhances synaptic viability and dendritic spine development, and increases neurotransmitter turnover, such as dopamine.

Perhaps the most frequently activated signaling pathway in human cancer is the phosphoinositide 3-kinase (PI3 K) pathway, a crucial signal transduction mechanism that connects oncogenes and multiple receptor groups to many essential cellular functions. So this route poses both an opportunity for cancer treatment and a challenge. Even as inhibitors targeting PI3 K isoforms and other major nodes in the pathway including AKT and mTOR hit clinical trials, there are still major problems. Here we highlight recent developments in our understanding of the PI3 K pathway and address both the opportunities and obstacles for the therapeutic production of cancer-centric drugs.

A turning point was the discovery that receptors for metabolism derived hormones were found in brain regions other than the hypothalamus. Insulin signaling has been shown to have an effect on the hippocampal plasticity, learning and memory underlying molecular cascades. Here, we summarize the molecular evidence that connects hippocampal insulin sensitivity alterations with improvements in both adult neurogenesis and synaptic plasticity. We also study the epidemiological research and experimental models illustrating the crucial role of brain insulin resistance at the intersection of metabolic and neurodegenerative disease.

Protein concentrations were determined by the biuret method.

Cholinergic activity was evaluated by acetyl cholinesterase assay to assess the cholinergic dysfunction which is one of the core pathologies of dementia and AD. Inflammatory cytokines like TNF-α, IL-6 was determined by ELISA method to evaluate the neuroinflammation which is aggravated by insulin resistance. C-reactive protein, a marker of neuroinflammation and neurodegeneration was also determined by ELISA. Mitochondrial dysfunction was evaluated estimating mitochondrial enzyme complex-I, II, III, IV depicting picture of viable and non-viable neuronal cells. Histopathology was done by H&E staining to find out apoptotic cells, neuroinflammation, and neurodegeneration. Molecular technique like RT-PCR for IRS-1, PI3-K, AKT, GSK 3-β and BDNF was performed for gene expression analysis.

Key Words

ICV-STZ; PI3-K/AKT/GSK3-β; Insulin resistance; neuroinflammation; Cognition