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Brain insulin resistance: Targeting PI3K/AKT/GSK3 pathway in intracerebroventricular-streptozocin induced rat model of Alzheimers disease

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Alzheimer???s disease (AD) featuring dementia, cognitive deficits and behavioral alterations is one of the most common prevalent neurodegenerative diseases affecting majorly elderly people termed as sporadic AD. Global prevalence of AD is sharply increasing, expected to affect almost 115 million people by 2050. Down regulation of insulin signaling pathway of PI3K-AKT plays a significant role in the pathophysiology of AD. Intracerebroventricular streptozocin as a model of sporadic Alzheimer???s disease is being established. Animals are divided into various groups comprising normal control, sham control, diseased and drug treated groups. Protocol lasts for 21 days, sacrificing animals on the 22nd day followed by isolation of serum and dissection of cortex and hippocampus, preserving the same for further analysis. Behavioral studies, biochemical estimations and molecular techniques are done for evaluating several parameters of control, diseased and treated groups of animals. Behavioral studies like Morris water maze, novel object recognition and actophotometer are performed for cognition, memory and locomotor activity. Biochemical estimations for antioxidant activity are performed by glutathione reductase assay, catalase assay, glutathione S-transferase assay, lipid peroxidation assay, superoxide dismutase assay and protein carbonylation assay. Protein concentrations are determined by biuret method. Cholinergic activity is determined by acetylcholinesterase assay. Inflammatory cytokines like TNF-? and IL-6 are determined by ELISA method. Mitochondrial dysfunction is evaluated by estimating mitochondrial enzyme complex I, II, III and IV. Histopathology is done. Molecular techniques like western blotting for Akt protein and RT-PCR for PI3-K, AKT, p-AKT, NF-?? and GSK 3-? is performed for gene expression analysis.

We review non-pharmacological and pharmacological approaches to managing behavioral and psychological symptoms of dementia (BPSD). We examine methods for assessment and evidence for interventions, focusing on recent findings and innovations. Finally, we recommend an algorithm for management of BPSD.

Training of formal caregivers is the most effective intervention for BPSD; other non-pharmacological interventions are also beneficial. Antidepressants and antipsychotics remain a mainstay of pharmacological treatment for BPSD. There is limited evidence supporting the use of stimulants, cognitive enhancers, dextromethorphan/quinidine, benzodiazepines, anticonvulsants, and pimavanserin. The management of BPSD is highly individualized. Following thorough assessment, the initial step is addressing contributing medical problems. Non-pharmacological interventions should be tried prior to pharmacological interventions. Antipsychotics should be prescribed only when behaviors pose a significant safety risk or if the person with dementia is very distressed. New approaches will be needed to address an increasing population of people with dementia.

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Alzheimer disease and other dementias are a major and increasing global health challenge. In 2010 there were 35.6 million individuals living with dementia and their numbers are expected to double every 20 years and reach approximately 115.4 million by 2050. A behavioral and psychological symptom of dementia (BPSD) is used to describe a group of diverse non-cognitive symptoms and behaviors that are frequently seen among individuals with dementia. BPSD affects approximately 90% of individuals at some point during the course of the illness, with greater prevalence noted among individuals receiving skilled care.

Common BPSD include apathy, anxiety, depression, agitation, psychosis, sleep disturbances, dysphoria, aberrant motor activity, hallucinations and delusions. There is emerging evidence that specific symptom patterns can be identified in different types of dementias. One recent study found that hallucination, abnormal motor behavior, and anxiety were significantly more frequent in Alzheimer disease (AD) and mixed dementia (MD) compared with vascular dementia (VD).3 Hallucinations and delusions were significantly more severe in AD and MD . Disinhibition was significantly more frequent and severe and agitation was significantly more severe in patients with VD.

BPSD is associated with faster cognitive decline, greater functional impairment, reduced quality of life for patients and their caregivers. BPSD is also a risk factor for earlier institutionalization among individuals with dementia. Moreover, BPSD adds to the overall cost of caring for individuals with dementia.

This spectrum of symptoms is thought to occur due to the complex interaction between biological, psychological, social, and environmental factors. These factors include structural, functional, and neurochemical changes in the brain, underlying medical or psychiatric disorders, preexisting personality traits, caregiver distress/depression, and misleading or lack of stimuli from the environment.