



**DEMENTIA: A COMPLETE LITERATURE REVIEW ON
VARIOUS MECHANISMS INVOLVES IN PATHOGENESIS
AND AN INTRACEREBROVENTRICULAR
STREPTOZOTOCIN INDUCED ALZHEIMER'S DISEASE**

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Abstract

Dementia can be defined as loss of multiple components of intellectual function like memory and learning, attention, concentration, orientation, thinking, calculation, language, geographic orientation. Most common cause of dementia is Alzheimer's disease (AD) which is a progressive, irreversible, age-related, neurological and psychiatric disorder characterized by a progressive decline in memory, cognitive performance and loss of acquired skills leading to apraxia, agnosia, anomia and aphasia. AD has been proposed to involve a number of linked pathophysiological mechanisms, such as amyloid β peptides ($A\beta$) toxicity, tau phosphorylation, neuroinflammation, excitotoxicity, oxidative stress and neurotransmitter abnormalities. Various experimental models of AD have been introduced today but not even single model has been found to be truly representative of the SAD. Therefore, considering the fact that AD has been recognized as an insulin resistant brain state, intracerebroventricular (ICV) streptozotocin administered rat has become one of the proposed experimental models relevant to the sporadic type of AD. Intracerebroventricular administration of STZ results in IR desensitization and behavioral, biochemical, histological and neurochemical impairment along with progressive deterioration of cognitive function.

Keywords: - Dementia; ICV; STZ; Alzheimer's disease

Introduction

Dementia is a brain disorder characterized by a decline in several higher mental functions (e.g. memory, intellect, personality) that causes significant impairments in daily functioning (52). The prevalence of dementia rises with age, doubling every 5 years between the ages of 60 and 90 (16). Based on the epidemiological data, dementia is widely recognized as a major medical, social and economic problem in developed countries where the age over 65 accounts for an increasingly high percentage of the dementic population (13). Unfortunately, dementia is now becoming a major problem in developing countries where it did not exist 50 years ago (121). More than 50 million people worldwide have dementia and the most common and irreversible cause of this dementia is

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Alzheimer's disease (AD) (1). AD is a neurodegenerative disorder divided into two forms namely familial (FAD) and sporadic (SAD) cases characterized by cognitive deficits and extensive neuronal loss in the central nervous system (CNS) (70) and at the molecular level by the presence of specific cytoskeletal abnormalities, including intracellular neurofibrillary tangles (NFT) formed by hyperphosphorylated tau protein and the presence of high levels of the 40- and 42-amino acid long amyloid beta ($A\beta$) (115). The early onset form (i.e. FAD) has a strong genetic correlation that exists between characteristic features of AD pathogenesis and mutations in amyloid precursor protein (APP), (8), presenilin (PS-1) and PS-2. Of particular interest, the other form of AD, SAD is a multifactorial disease to which both genetic and epigenetic factors contribute (119). The well confirmed genetic factors for SAD are apolipoprotein E (APOE) epsilon 4 allele and PS-2 promoter polymorphism (60). Accumulating data indicates that disturbances of several aspects of cellular metabolism appear pathologically important in SAD. Among these, increased brain insulin resistance,

decreased glucose utilization and energy metabolism are observed in the early stages of the disease, consequently energy deficit, oxidative stress and inflammation in neuronal tissue which further cause neurodegeneration in SAD.

By understanding some of the pathological aspects of SAD in humans currently, intracerebroventricular (ICV) administration of streptozotocin (STZ) in rats is commonly employed to study experimental dementia. Most importantly, subdiabetogenic doses of ICV -STZ induce alterations of brain insulin receptor (IR) and its signaling and consequently insulin resistant brain state and behavioral, neurochemical, biochemical, morphological, and histological changes similar to aging brain (85). Further, it has been well demonstrated that ICV -STZ rat model is targeting the functioning of brain IR signaling cascade. In brain, decreased levels of glucose/energy metabolism particularly in cerebral cortex and hippocampus regions have been reported starting from 3 weeks following ICV -STZ administration and consequently mitochondrial dysfunction (2). Additionally, a progressive trend towards oxidative stress has also been found starting as early as 1 week following the ICV -STZ administration (75). In addition to reduced energy metabolism and mitochondrial dysfunction, increased free radical generation and subsequent oxidative and nitrosative stress which are well reported to impair learning and memory leading to cognitive dysfunction (46). Furthermore, decreased cholinergic transmission (decreased choline acetyltransferase and increased acetylcholinesterase activity) has started to be persistently found later on in the hippocampus of ICV -STZ treated rats. ICV -STZ administration has also been associated with certain brain morphological changes followed by extensive cell loss and neurodegeneration by induction of specific damage to myelinated tract and astrogliosis found 1 week following the treatment regardless the age of animals. Further, ICV -STZ induced reduction in energy availability may also results in increase in cytoplasmic calcium (Ca^{2+}) ions confirmed by pharmacological use of calcium channel blocker (lercanidipine) that markedly attenuated behavioral and biochemical alterations in ICV -STZ rats. It is well known that ATP dependent brain functions are markedly affected in energy failure and reduced glucose metabolism states. Relevant to this, all these neurochemical and structural changes have been observed as early as 2 weeks after ICV -STZ administration and reported to still persist 12 weeks

accompanied by long term progressive deficits in learning and memory (55) and play a major role in the pathogenesis of SAD.

Dementia: A background

Dementia is a syndrome that in most cases is caused by an underlying disease of brain disorder characterized by a decline in several mental functions e.g. memory, intellect, personality that significantly impair daily functioning. Dementia is a clinical syndrome with multiple etiologies that particularly affects older people (16). Up till now, there is a lack of full understanding of the underlying causes and molecular mechanisms leading to this progressive form of dementia. Given the seriousness of the impact of dementia, the ageing of the world's population, and that the prevalence of dementia increases with age, a lot of attention is understandably now focused on the treatments, care services and support arrangements needed by people with dementia and their families, both today and over the coming decades.

Dementia prevalence

Number of older people (taking the conventional definition as aged 65 or over), particularly the number of very old people (aged 80 and above) will increase substantially over the next fifty years in all countries, although rates of ageing varies greatly between countries. Currently 8% of western population is affected from dementia. By 2025 this figure is expected to double with 71 per cent of these likely to live in developing countries, making the need for prevention of an incurable disease crucial. In U.K 20% of the population is 65 and older, particularly in England, 16% of the population was aged 65 or over and 4% aged 80 or over in 2005. By 2050 it is expected that the number of people aged 65 or over will grow from 8 million to almost 15 million (by which time this number will represent 25% of the projected total population), while the number aged 80 or over will grow from 2 million to just over 6 million (equivalent to 10% of the total population) and 10-15% have mild, early and borderline demented states (51).

Dementia symptoms and etiology

Dementia is caused by a disease that damages tissues in the brain causing disturbed brain functioning. Dementia is characterized by reversible and irreversible causes. There are several things which could results reversible dementia and these dementia are treatable. These include dementia due to long-term substance abuse, tumors that can be removed, subdural hematoma, accumulation of blood beneath the outer covering of the brain that result of head injury, normal

pressure hydrocephalus, hypothyroidism, toxic reactions like excessive alcohol or drug use, and nutritional deficiencies like vitamin B12 and folate deficiencies. Some of the irreversible and non-treatable cause of dementia includes diseases that cause degeneration or loss of nerve cells in the brain such as AD, PD (107), and HD, multi-infracts dementia (dementia due to multiple small strokes, also known as vascular dementia), infections that affect the brain and spinal cord, such as acquired-immune deficiency syndrome (AIDS) dementia complex and Creutzfeldt-Jakob disease. Some people have a combined type of dementia involving both AD and vascular dementia.

The most common symptoms that are mostly associated with dementia are delirium from a sudden medical problem, psychosis, aggression, anger, insomnia or “sundowning” (confusion in late afternoon or early evening), anxiety, depression, and pain from arthritis (53).

1. Alzheimer’s Disease: A type of dementia

Alzheimer’s disease is the most common dementia in the elderly population (> 65 years) associated with progressive neurodegeneration of the central nervous system (CNS). Clinically, AD typically begins with a subtle decline in memory and progresses to global deterioration in cognitive and adaptive functioning (111). The majority of AD cases occur sporadically, what suggested that they could arise through interactions among various genetic and environmental factors. Current epidemiological investigations show that midlife hypertension, cardiovascular diseases, hypercholesterolemia, diabetes, obesity, inflammation, and viral infections can significantly contribute to the development and progression of AD, whereas active engagement in social, mental and physical activities may delay the onset of the disease (120).

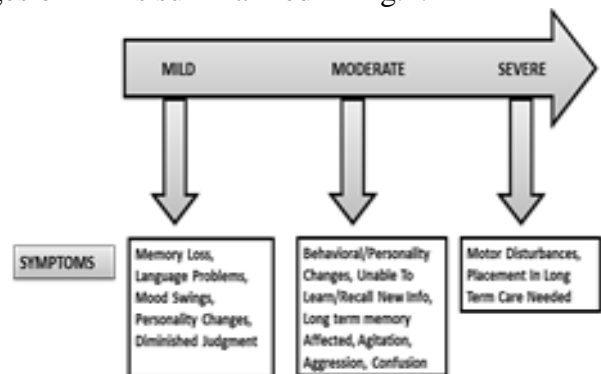
AD prevalence

AD is the sixth leading cause of all deaths in the United States, and the fifth leading cause of death in Americans aged 65 and older. Whereas other major causes of death have been on the decrease, deaths attributable to AD have been rising dramatically. Between 2000 and 2006, deaths attributable to AD increased 47%. An estimated 5.3 million Americans have AD; the approximately 200,000 persons under age 65 years with AD comprise the younger-onset AD population. The prevalence of AD increases with age from 4% in the 65 to 75 years age group to 19% in the 85 to 89 years age group, and the incidence of AD increases from 7/1000 in the 65 to 69 years age

group to 118/1000 in the 85 to 89 years age group (28). Every 70 seconds, someone in America develops AD; by 2050, this time is expected to decrease to every 33 seconds. Over the coming decades, the “baby-boom” population is projected to add 10 million people to these numbers. In 2050, the incidence of AD is expected to approach nearly a million people per year with a total estimated prevalence of 11 to 16 million people (Alzheimer’s disease Facts and Figures, 2009). A minority of around 400 families worldwide can be grouped as familial in origin, whereas the majority of all Alzheimer cases (approx. 25 million worldwide) are sporadic in origin whose clinical manifestation appear in old age and ultimately affects almost half of the population over age 85 (40).

Symptoms and Stages of AD

AD can affect different people in different ways, but the most common symptom pattern begins with gradually worsening difficulty in remembering new information. This is because disruption of brain cells usually begins in regions involved in forming new memories (83). In early mild and moderate stages of the disease, people may experience irritability, anxiety or depression. In later severe stages, other symptoms may occur including sleep disturbances, physical or verbal outbursts, emotional distress, restlessness, pacing, shredding paper or tissues and yelling, delusions (firmly held belief in things that are not real), and hallucinations (seeing, hearing or feeling things that are not there). As damage spreads, individuals also experience confusion, disorganized thinking, impaired judgment, trouble expressing themselves and disorientation to time, space and location, which may lead to unsafe wandering and socially inappropriate behavior. In advanced AD peoples need help with bathing, dressing, using the bathroom, eating and other daily activities. Those in the final stages of the disease lose their ability to communicate, fail to recognize loved ones and become bed-bound and reliant on care. Various symptoms and stages of AD is summarized in Fig.1.



Types of AD

AD is classified into two types based on etiology, onset of symptoms, pathophysiological, biochemical and genetic alterations into familial (FAD) and sporadic (SAD) cases (Reed et al., 2009).

Early Onset Familial Type AD

The first one is the very rare autosomal dominant early-onset familial type (FAD) is caused by missense mutations in the amyloid precursor protein (APP) gene on chromosome 21, in the presenilin (PS)-1 gene on chromosome 14 and in the PS -2 gene on the chromosome 1. The genetic abnormalities on chromosomes 1, or 14, or 21 are all characterized by the permanent generation of amyloid beta (Aβ) 1–40 and in particular Aβ1–42, beginning early in life. Both these derivatives of APP reduce the binding of insulin to its receptor and receptor autophosphorylation. The disruption of autophosphorylation by ATP may result in a decrease/lack of receptor tyrosine kinase activity and, thus, in a failure of postreceptor effects exerted via insulin receptor substrate (IRS)-1 (17). This dysfunction of the insulin signal transduction cascade may cause a drastic fall in the cerebral metabolism of glucose in FAD (31). Regardless the primary cause and clinical form of AD, the amyloid cascade hypothesis proposes that both conditions lead to Aβ 1-42 accumulation, oligomerization and plaque formation, which further initiates a whole range of pathological cascade effects; microgliosis and astrocytosis, inflammatory response, oxidative and nitrosative stress, Ca⁺ dysregulation (98), mitochondrial dysfunction, neuronal/neuritic dysfunction, cell death, neurotransmitter deficits, and finally, memory loss (27). In parallel, oxidative stress and neurotransmitter deficits induce kinase/phosphatase activity imbalance which at the level of tau protein (microtubule-associated protein that stimulates the generation and stabilization of microtubules within cells, and control axonal transport of vesicles results in accumulation of hyperphosphorylated tau protein and formation of NFT which contribute to memory loss (68).

Late-Onset Sporadic Type AD

In contrast to early onset FAD, aging is the main risk factor for late-onset SAD. Aging of the brain is associated with a multitude of inherent changes in cerebral glucose/energy metabolism, its control, and related pathways at cellular, molecular and genetic levels (79). Numerous changes are accentuated by stress particularly functional imbalances of regulative systems, such as (1) energy production (reduced) and

energy turnover (increased), (2) insulin action (reduced) and cortisol action (increased) due to a shift in the hypothalamic pituitary–adrenal axis to an increased basal tone, (3) acetylcholine action (reduced) and noradrenaline action (increased), indicating sympathetic tone, obviously also reducing insulin secretion after glucose stimulation and (4) shift in the gene expression profile from anabolic (reduced) to catabolic (increased) in distinct brain areas such as cortex, hippocampus and hypothalamus (118) (Fig.2).

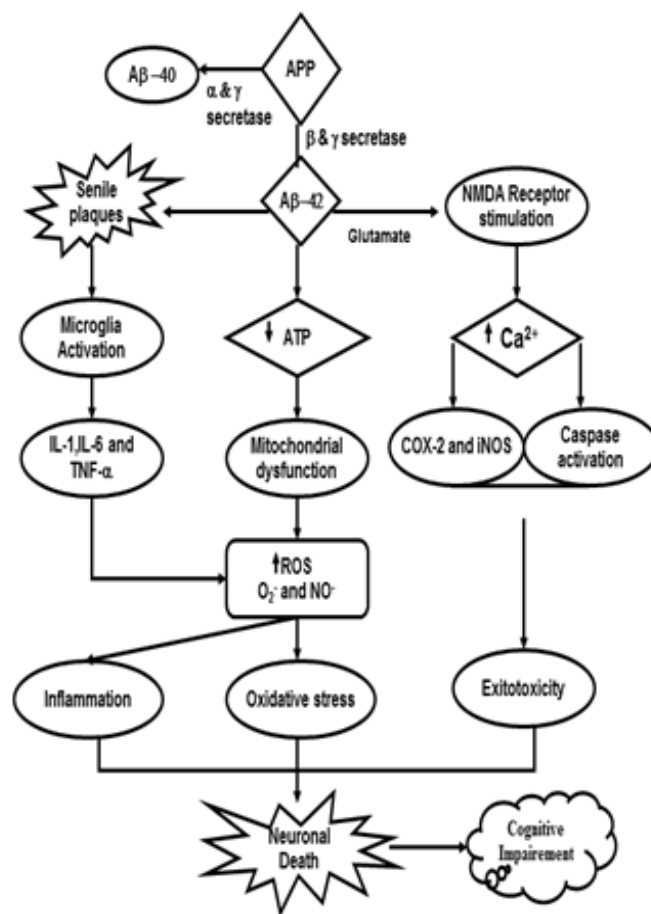


Fig.2: Various neurochemical alterations in AD brain

Sporadic Type AD associated alterations

Changes of the Brain Insulin Signaling Cascade

Research of the brain insulin system has been more pronounced in the last decade, particularly regarding its function in the brain. There is a growing interest in finding the role of neuronal insulin signaling cascade in the brain, and off course in the brain of SAD. Recent data indicate that brain insulin deficiency and insulin resistance brain state are related to the late onset SAD. In line with this decreased brain insulin protein and its mRNA levels were found post mortem in the brain (frontal cortex, hippocampus (70), while IR density was found to be increased and tyrosine -

kinase activity decreased (35). Interestingly, strikingly reduced expression of genes encoding insulin like growth factor-1 (IGF-1) and IGF-1 receptor has also been found in the frontal cortex, hippocampus and hypothalamus of patients with AD post mortem. Regarding the downstream IR signaling pathways, reduced levels of PI3-K have been found (26). Regional specificity of changes and difference in AD severity stage probably account for some inconsistency in results reported in relation to Akt/PKB and GSK-3 α/β alterations, whose phosphorylated form were mainly found to be decreased. In line with this, increased activity of GSK-3 found in hippocampus and hypothalamus could be related to decreased activity of Akt/PKB found in the same regions (65). Recent data have pointed to another important enzyme, involved in tau dephosphorylation, the protein phosphatase 2A (PP2A), which can directly dephosphorylate tau. It has been revealed a significant reduction in the total amount of PP2A in frontal and temporal cortices of SAD patients. Thus, it seems likely that hyperphosphorylated tau formation is the consequence of increased GSK-3 β (78) (Fig.3).

diphospho-N-acetylglucosamine (UDP-GlcAc) necessary for protein-O-GlcNAcylation is decreased. Another pathophysiological consequence of the markedly perturbed glucose metabolism is the fall of ATP production from glucose by around 50% in the beginning of SAD, declining thereafter throughout the course of the disease.

Reduced ATP availability

A decisive pathophysiological consequence of the markedly perturbed glucose metabolism is a decrease in ATP production from glucose by around 50% in the beginning of SAD. The oxidative utilization of substrates other than glucose restores ATP formation to 80% of normal, but thereafter ATP levels decrease throughout the course of the disease. This energy deficit may compromise ATP-dependent processes in a hierarchical manner including cellular and molecular mechanisms in particular in the endoplasmic reticulum and Golgi apparatus (34). A depletion of cellular ATP prevents the dissociation of chaperone/protein complexes and thus blocks secretion of these proteins. Additionally, ATP depletion results in the degradation of membrane phospholipids (102).

Acetylcholine neurotransmission changes

Oxidative energy metabolism is important for the undisturbed function and structure of the brain. Both the neurotransmitter acetylcholine (ACh) and the membrane sterol constituent cholesterol are derived from the glucose metabolite, acetyl-CoA. As a result of the deficits in glucose and energy metabolism and due to the reduced activity of choline acetyltransferase (ChAT), the synthesis of ACh in the presynaptic neuron is markedly diminished (38).

Neuropathological hallmarks of AD

Two main neuropathological hallmarks are found in the brain of patients with familial and sporadic AD is (1) NFT and (2) amyloid plaques (101) (Fig.4).

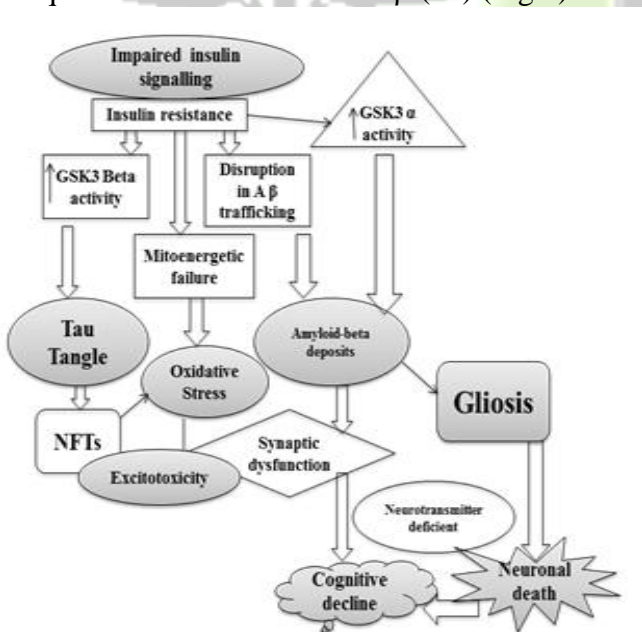


Fig.3: Impairment of Insulin signaling in Alzheimer's disease

Reduced glucose and energy

Early and severe abnormalities were found in cerebral glucose metabolism which worsened in parallel with the dementia symptoms. It includes the diminished activity of the pyruvate dehydrogenase complex yielding reduced levels of acetyl-CoA. As a consequence, the reduced glycolytic glucose breakdown, the formation of fructose-6-phosphate may be diminished so that the availability of uridine-



Fig.4: Neuropathological hallmarks of Alzheimer's

Tau Protein

NFT consist of intracellular protein deposits made of hyperphosphorylated tau protein (13). Tau protein is a microtubule-associated protein which is involved in stabilization and promotion of microtubules but when hyperphosphorylated it gains a toxic function which is lethal for the neurons (43). There is a growing body of evidence that changes in insulin and insulin receptor (IR) signaling cascade in the brain of people with AD and have an influence on the metabolism of APP and Aβ accumulation and in maintaining of balance between phosphorylated and non-phosphorylated tau protein (114).

Amyloid Beta

Extracellular amyloid plaques predominantly consist of aggregates of neurotoxic Aβ 1-42 generated in vivo by specific, proteolytic cleavage of APP. Classical and also leading amyloid cascade hypothesis assumes that pathological assemblies of Aβ are the primary cause of both AD forms and all other neuropathological changes (cell loss, inflammatory response, oxidative stress, neurotransmitter deficits and at the end loss of Cognitive function are downstream consequences of Aβ accumulation (7).

Intracerebroventricular streptozotocin induced neurotoxicity: An Animal Model of SAD

Considering the presence of insulin (from both periphery and brain) and IRs in the brain, an experimental rat model was developed by using streptozotocin (STZ) administered intracerebroventricularly (ICV) in doses of up to 100 times lower (per kg body weight) than those used peripherally to induce an insulin resistant brain state. ICV -STZ rodent model is produced by a single or multiple (up to 3 times within one month) injections of a cytotoxic drug STZ, bilaterally into the lateral cerebral ventricle of an adult rat, first reported in 1990. Although learning and memory are impaired within 4 weeks in all experimental models of AD (114), however, no single model was determined to be truly representative of SAD characterized by abnormalities in neuronal IRs signaling. ICV -STZ reproduces a number of important aspects of SAD-type neurodegeneration within 1 month of ICV -STZ injection(s) and therefore provides supportive evidence that SAD may be caused in part by neuronal insulin resistance, i.e. brain diabetes (87).

STZ (2-deoxy-2-(3-(methyl-3-nitrosoureido)-D-glucopyranose) is a drug selectively toxic for insulin producing/secreting cells both in the periphery as well as in the brain and consequently ICV -STZ poly

impairs the insulin-IR system. Reflection on some of the earlier findings in AD, including the impaired glucose utilization, mitochondrial dysfunction, reduced ATP production, and energy dysregulation prompted consideration of the hypothesis that these abnormalities were mediated by desensitization of the neuronal IRs. The stated metabolic abnormalities, as well as several of the classical histopathological lesions of AD, could be attributed in part to reduced insulin levels and reduced IR function in AD. Seigfried Hoyer was among the first to suggest that reduced levels of brain insulin may precipitate a cascade resulting in disturbances in cellular glucose, Ach, cholesterol and ATP levels, impaired membrane function, accumulation of amyloidogenic derivatives, and hyperphosphorylation of tau, i.e. that SAD may represent a brain form of type 2 diabetes mellitus. A comparison and correlation of various pathological changes observed in human SAD and ICV -STZ rat model are summarized in Table 1.

Table.1. Similarities between ICV -STZ Model and Human SAD

Brain pathology	STZ- ICV rat model	Human SAD
Behavioral Cognitive deficits	Decrease memory and learning	dementia
Morphological gliosis and synaptic loss	+ +	+ +
Metabolic Glucose / energy	decrease metabolism	decrease metabolism
Neurochemical Oxidative stress Ach transmission Insulin receptor signailing	+ Decreased brain insulin resistance state	+ Decreased brain insulin resistance state
Neuropathological Tau protein Amyloid beta	+ +	+ + (Salkovic-Petrisic, 2008)

Peripheral mechanism of streptozotocin

In the periphery, STZ causes selective pancreatic β cell toxicity results from the drug’s chemical structure which allows it to enter the cell via the GLUT2 glucose transporter. The predominant site of GLUT2 localization is the pancreatic beta cell membrane (63). Following peripheral administration, STZ causes alkylation of β-cell DNA which triggers activation of

ADP-ribosylation, leading to depletion of cellular NADH and ATP. When applied intraperitoneally in high doses (45-75 mg/kg) STZ is toxic for insulin producing/secreting cells, which induces experimental DM type 1. Low doses (20-60 mg/kg) of STZ given intraperitoneally in neonatal rats damages IR and alters IR signaling and causes diabetes mellitus type 2 (11) (Fig.5).

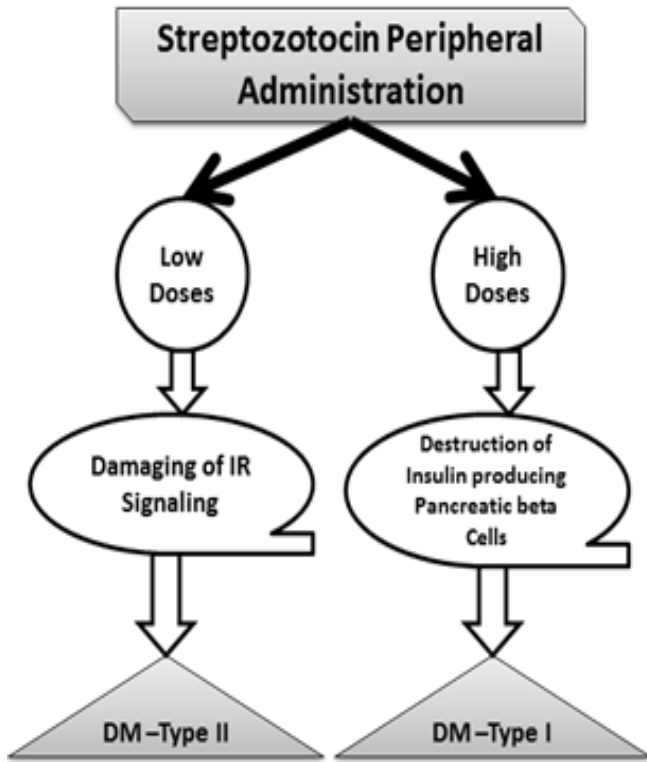


Fig.5: Peripheral mechanism of streptozotocin
Central mechanism of action of streptozotocin

Central STZ administration caused neither systemic metabolic changes nor diabetes mellitus. STZ has been administered mostly in doses ranging from 1–3 mg/kg body weight, injected 1–3 times, either uni- or bi-laterally into the lateral cerebral ventricles. Identical biochemical changes have been found in the left and right striatum after administration of STZ into the right lateral cerebral ventricle only (77). The mechanism of central STZ action and its target cells/molecules have not yet been clarified but a similar mechanism of action to that in the periphery has been recently suggested. GLUT2 may also be responsible for the STZ induced effects in the brain as GLUT2 also is reported to have regional specific distribution in the mammalian brain (4). The chemical structure of STZ also suggests this compound may produce intracellular free radicals, nitric oxide (NO) and hydrogen peroxide and induces behavioral, neurochemical and structural changes that are similar to those found in SAD (Fig. 6).

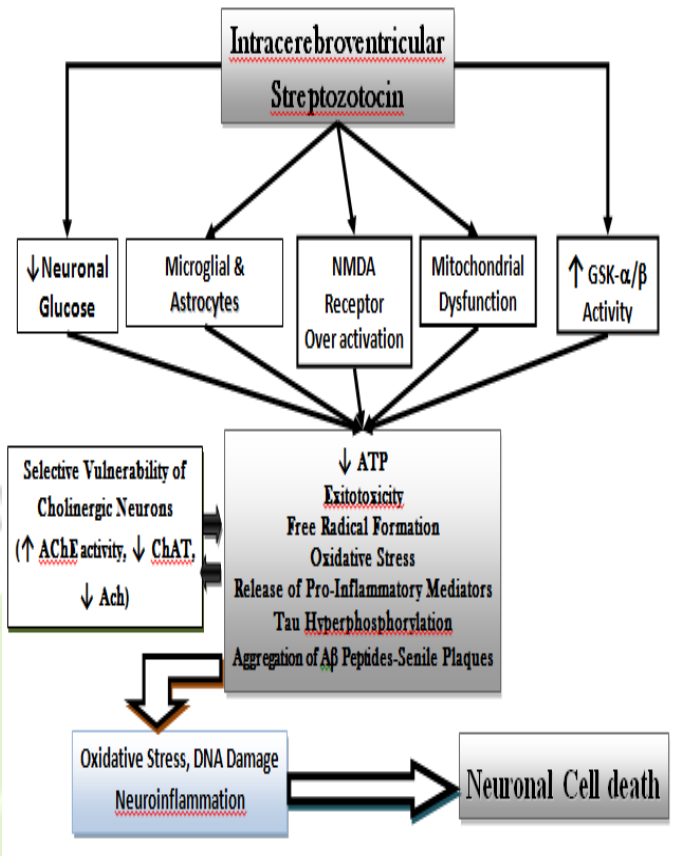


Fig. 6: Central mechanism of action of intracerebroventricularly administered streptozotocin in rats

ICV -STZ induced Insulin signaling alteration

Substantial evidence has been gathered in support of the presence of both insulin and IRs in the brain, and of insulin action. The main source of brain insulin is the pancreas crossing the blood–brain barrier by a saturable transport mechanism. A smaller proportion of insulin is produced in the brain itself (IR signaling cascade in the brain) is similar to the one at the periphery. There are two main parallel IR intracellular pathways, the (PI-3K) pathway and the mitogen activated protein kinase (MAPK) pathway (68,69). When insulin binds to the subunit of IR it induces autophosphorylation of the intracellular α -subunit resulting in increased catalytic activity of the tyrosine kinase. Now activated IR becomes a docking site for the IRS, which then becomes phosphorylated on tyrosine residues. IRS is now ready to bind various signaling molecules with SH2 domains; one of these molecules is (PI-3K). After being activated, PI-3K induces phosphorylation and subsequent activation of protein kinase B (Akt/PKB), consequently activated Akt/PKB triggers glucose transporter 4 (GLUT4) and also phosphorylates the next downstream enzyme glycogen synthase kinase (GSK-3) which then becomes inactive (49) (Fig.7).

Regarding the enzymes downstream of the IR-PI3-K pathway, experiments have shown alterations of hippocampal GSK-3 β however, observed changes were of a greater extent in the phosphorylated than in the non-phosphorylated form of GSK-3 (37). The IR β protein was decreased in the frontoparietal cortex and hypothalamus, but the levels of phosphorylated IR β (p-IR β) were increased and tyrosine kinase activity was unchanged in these regions, whereas in the hippocampus IR β protein levels were decreased, but p-IR β levels, as well as tyrosine kinase activity were increased (29). Downstream from the PI3-K signaling pathway, hippocampal Akt/PKB remained unchanged at 4 weeks and decreased by 12 weeks post-treatment, whereas in the frontoparietal cortex Akt/PKB expression was decreased 4 weeks and increased by 12 weeks post-ICV-STZ treatment. Regarding the phosphorylated GSK-3 (pGSK-3) form, levels in hippocampus were increased after 1 month, but decreased 3 months after the STZ treatment, while in the frontal cortex, pGSK-3 was found to be decreased in both observational periods, 1 and 3 months following the ICV-STZ treatment (47). In this regard, many molecular abnormalities that characteristically occur in AD, including increased GSK-3 β activation, increased tau phosphorylation, and decreased neuronal survival, could be mediated by downstream effects of impaired insulin and IGF signaling in the CNS (Fig. 8).

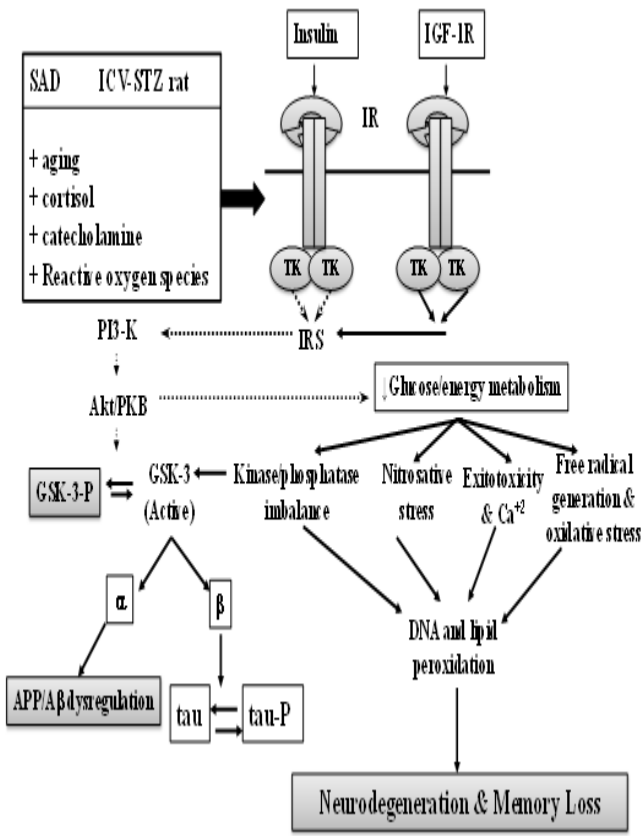


Fig. 7: Brain insulin receptor signaling cascade in the insulin resistant brain state induced by the intracerebroventricular streptozotocin treatment.

Akt/PKB: protein kinase B; APP: amyloid precursor protein; A β : amyloid beta; GSK-3: glycogen synthase kinase-3; GSK-3-P: phosphorylated glycogen synthase kinase-3; IR: Insulin receptor; IGF-1R: insulin-like growth factor-1 receptor; IRS: insulin receptor substrate; tau: tau protein; tau-P: phosphorylated tau protein; MAP-K: mitogen activated protein kinase; PI3-K: phosphatidylinositol-3 TK: tyrosine kinase; kinase; SAD: human sporadic Alzheimer's disease; ICV-STZ intracerebroventricular streptozotocin (83).

It has been reported that changes in the brain insulin and tau-A β systems are observed following the bilateral application of a single or multiple 1 mg/kg STZ dose into the lateral cerebral ventricles of adult 3 month old rats (86). Since treatment with very low to moderate doses of STZ in short term experiments causes insulin resistance via a decrease in autophosphorylation and decrease in total number of IRs, but with little change in phosphorylated IR- β subunit (26). Indeed, the activity of the protein tyrosine phosphatase decreased after long-term STZ-damage and induced a drastic reduction of IR dephosphorylation.

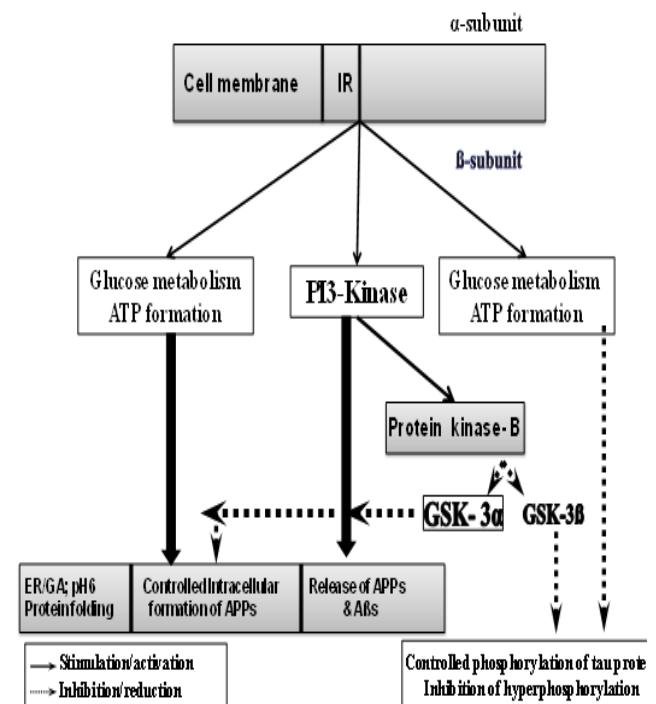


Fig. 8: Brain insulin receptor signaling cascade in physiological conditions.

[A β : amyloid beta; Akt/PKB: protein kinase B; APP: amyloid precursor protein; GSK-3: glycogen synthase kinase-3; GSK-3-P: phosphorylated glycogen synthase kinase-3; IGF-1R: insulin-like growth factor-1 receptor; IR: Insulin receptor; IRS: insulin receptor substrate; MAPK: mitogen activated protein kinase; PI3-K: phosphatidylinositol-3 kinase; tau: tau protein; tau-P: phosphorylated tau protein; TK: tyrosine kinase].

ICV-STZ induced glucose/energy metabolism changes

ICV administration of STZ clearly shows heterogeneous changes in local cerebral glucose utilization after single bilateral injection in to brain ventricles in all region of cerebral cortex, in particular parietal cerebral cortex (-19%) and frontal cerebral cortex (-13%) where concentration of ADP, as well as glycogen and lactate level, were increased in the cerebral cortex and in the hippocampus regions (59). In addition, significantly diminished the activities of glycolytic enzymatic hexokinase and phosphofructokinase by 15 and 28% respectively, in parietotemporal cerebral cortex and hippocampus activity and 10-30% in brain cortex and hippocampus 3 and 6 weeks post ICV -STZ administration. This pathologic condition, obviously sparing the metabolism in the tricarboxylic acid (TCA) cycle, seems to be characteristic of SAD resulting in diminished concentration of the energy rich compounds ATP and creatine phosphate (73). Interestingly, the extent of the shortage in energy production was the same in the STZ-damaged brain as in incipient SAD

ICV-STZ induced oxidative stress

ICV -STZ treatment causes marked reduction in brain glucose/energy metabolism and shows a progressive trend towards oxidative stress. Growing body of evidences indicate that STZ treatment generates reactive oxygen species (ROS) that results in increased oxidative stress and additionally releases NO in brains of ICV -STZ treated rats (92). Estimation of oxidative stress induced by ICV -STZ treatment commonly utilize the measurement of levels of MDA, a product of lipid peroxidation used as an indicator of free radical generation, and GSH levels, an endogenous antioxidant that scavengers free radicals and protect against oxidative and nitrate stresses. Relevant to this oxidative-nitrate stress has been found 1 and 8 weeks following a single 3 mg/kg ICV -STZ dose without involvement of NO. Besides oxidative stress was also found in the brain of one year old rats, 3 weeks following a lower

single ICV -STZ dose 1.5 mg/kg. Significant alteration in the markers of oxidative damage thiobarbituric acid (TBARS), GSH, protein carbonylation (PC), glutathione peroxidase (GPx), glutathione reductase (GR) and decline in the level of ATP were observed in hypothalamus and cerebral cortex, monitored 2-3 weeks after ICV -STZ application. A recent study demonstrated the beneficial effects of pioglitazone in the ICV - STZ induced cognitive deficits, which can be exploited for the treatment of dementia associated with diabetes and age-related neurodegenerative disorder, where oxidative stress and impaired glucose and energy metabolism are involved. This is also supported by the use of naringenin (8), guggulipid, melatonin, ascorbic acid (105), mefenamic acid (56), transresveratrol, lipoic acid, *Centella asiatica* (87), *Ginkgo biloba*, CoQ10, ladostigil, melatonin and donepezil (3), curcumin and selenium (47) which prevented or reduced ICV-STZ induced behavioral, neurochemical and histological alterations via reducing free radical generation, scavenging free radicals, restoring endogenous antioxidant defenses. These data strongly suggest antioxidant strategies in ameliorating SAD.

ICV-STZ induced neurotransmission deficits

The most studied neurochemical alteration in ICV -STZ injected rats is cholinergic deficit in the brain, without morphological changes in cholinergic neurons important for learning and memory (84). ICV -STZ treated rats showed an impaired learning and memory performance, possibly as a result of cholinergic dysfunction (71). Apart from this, Blokland and Jolles (11), found spatial learning deficit and reduced hippocampal ChAT activity in rats one week after ICV -STZ injection. A decrease in ChAT activity has been consistently found in the hippocampus of ICV -STZ treated rats as early as 1 week following STZ treatment and is still present 3 weeks post-injection (37). This is followed by a significant increase in acetylcholinesterase (AChE) activity. A decrease in hippocampal ChAT activity was completely prevented by 2-weeks of orally administered acetyl-L-carnitine, which acts by enhancing the utilization of alternative energy sources (109). Chronic administration of cholinesterase inhibitors Donepezil, Ladostigil and Donepezil along with melatonin reduced AChE activity in a dose-dependent manner in ICV-STZ treated rats regardless of whether treatment began 1 week prior to, in parallel or 13 days after ICV -STZ administration.

ICV injections of STZ affect not only the cholinergic system but also the concentration of different

monoaminergic neurotransmitters (noradrenaline, dopamine, and serotonin) in the rat brain differently. It has been reported that the content of whole brain monoamine (dopamine, noradrenaline, serotonin (5-hydroxy tryptamine) and 5-HT metabolite 5-hydroxyindoleacetic acid (5HIAA) dose-dependently increased and decreased, respectively, 1 week following ICV -STZ treatment (88).

ICV-STZ induced behavioral alterations

ICV-STZ treated rats consistently demonstrate deficits in learning, memory, and cognitive behavior (Table.2). It is well known that ICV -STZ reduced cerebral metabolism of glucose and caused impaired cognitive performance in the delayed non-matching task, passive avoidance and Morris water maze escape task 2 weeks after its administration. These behavioral alterations were observed regardless of age in both 1–2 year and 3-month old rats (36) and also after either a single 1 or 3 mg/kg injection or multiple 1 mg/kg ICV -STZ injections. It is well documented that ICV -STZ shows dose-dependency in causing neurotoxicity with lower STZ doses induces less severe cognitive deficits. Most importantly, cognitive deficits are long-term and progressive, observed as early as 2 weeks after ICV -STZ administration and are maintained up to 12 weeks post treatment. The correlation between spatial discrimination performance in the Morris water maze task and the decrease in hippocampal ChAT activity which resembles the relationship between cognitive and biochemical cholinergic changes observed in SAD has been found in ICV -STZ treated rats (12). Chronic treatment with acetyl-L-carnitine attenuated both the STZ induced impairment in spatial bias and the decrease in hippocampal ChAT activity. Interestingly, it has also been demonstrated that ICV -STZ induces development of reactive gliosis and oxidative stress 1 week post-treatment, preceded the induction of memory deficits at 3 weeks post-treatment, where no signs of neuronal damage or any reduction in specific cholinergic markers were detected in the cortex or hippocampus. Concomitantly, memory deficits were reported to be prevented by chronic treatment with several types of drugs with diverse mechanisms of action. Adding to this, (a) drugs generating alternative energy sources such as acetyl-L-carnitine (79), (b) cholinesterase inhibitors such as donepezil and ladostigil (possess monoamine oxidase B inhibition and neuroprotective activity which also prevent gliosis and oxidative stress (98) (c) estradiol which prevents reduction in cerebral ATP (d) antioxidants such as melatonin, resveratrol,

and CoQ10 which prevent an increase in free radical generation (79), dose-dependently improved learning and memory thereby restoring cognitive function without affecting CNS functions.

ICV-STZ induced structural changes, inflammation and neurodegeneration

ICV -STZ administration has also been associated with certain brain structural changes in the brain as early as 1 week following a single dose and in the brain and in both ≥ 1 year and 4 month old rats. In preliminary studies, glial fibrillary acidic protein (GFAP), a marker of gliosis has been found to be increased in three different protein fractions (soluble, triton X-100 soluble in cortical and subcortical structures including septum, fornix, and fimbria, striatum, and hippocampus, over a period of 3 weeks following ICV -STZ administration suggesting that altered hippocampal function could result from direct damage to this region (80). A direct histopathological evidence caused by STZ by its specific neurotoxic damage to axon and myelin in some brain region responsible for learning and spatial memory including the fornix, anterior hippocampus and periventricular areas independent of its action on glucose metabolism have been reported (114). These pathological features are all present in the brain of SAD patients (21). The most prominent change, seen 3 weeks following ICV -STZ injection was a significant enlargement of golgi-apparatus, caused by expansion of trans-golgi segment of cellular protein secretory pathway in the rat cerebral cortex was found, which did not resemble Golgi atrophy found in the brain of SAD patients. Trans part of Golgi complex may influence proteolytic processing of β APP generated in endoplasmic reticulum and in the golgi complex which accumulated in AD brain.

ICV-STZ induced A β and Tau Hyperphosphorylation

Regarding brain immunohistochemical analysis of tau protein and A β expression, 3 weeks following ICV -STZ treatment both the overexpression of tau protein in the leptomeningeal vessels at all of epitopes examined in both cerebral cortex and hippocampus were demonstrated 3 weeks after ICV -STZ (Chu and Qian, 2005; Lester-coll et al., 2006;) due to insulin depletion by STZ, or caused by activation of multiple kinase/by inhibition of phosphatase (PP2A) that dephosphorylate these sites (63).

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