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Dementia – A Complete Literature Review on Various Mechanisms Involved in Pathogenesis and an Intracerebroventricular Streptozotocin Induced Alzheimer's Disease

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1. 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 (Kuljis, 2007). The prevalence of dementia rises with age, doubling every 5 years between the ages of 60 and 90 (Corrada et al., 2008). 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 (Breitner et al., 2009). Unfortunately, dementia is now becoming a major problem in developing countries where it did not exist 50 years ago (Zilkens et al., 2009). More than 50 million people worldwide have dementia and the most common and irreversible cause of this dementia is Alzheimer's disease (AD) (Adlard et al., 2009). 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) (Michon et al., 2009; Reed et al., 2009) 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 ($A\beta$) (Woodhouse et al., 2009). 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), (Bernardi et al., 2009), presenilin (PS-1) and PS-2 (Huang et al., 2009). Of particular interest, the other form of AD, SAD is a multifactorial disease to which both genetic and epigenetic factors contribute (Zawia et al., 2009). The well confirmed genetic factors for SAD are apolipoprotein E (APOE) epsilon 4 allele (Wharton et al., 2009) and PS-2 promoter polymorphism (Liu et al., 2008). Accumulating data indicates that disturbances of several aspects of cellular metabolism appear pathologically important in SAD. Among these, increased brain insulin resistance (Salkovic-Petrisic, 2008), decreased glucose utilization and energy metabolism are observed in the early stages of the disease (De la Torre, 2008),

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consequently energy deficit, oxidative stress (Droge and Kinscherf, 2008) and inflammation (De la Monte, 2009) 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 (Salkovic-Petrisic, 2008; Ishrat et al., 2009 a, b). 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 (Pathan et al., 2006) and consequently mitochondrial dysfunction (Agrawal et al., 2009). Additionally, a progressive trend towards oxidative stress has also been found starting as early as 1 week following the ICV -STZ administration (Pathan et al., 2006). 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 (Ishrat et al., 2009 a, b; Tiwari et al., 2009). 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 (Blockland and Jolles 1993, Terwel et al., 1995). 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 (Sonkusare et al., 2005). Further, ICV -STZ induced reduction in energy availability may also results in increase in cytoplasmic calcium (Ca^{2+}) ions (Muller et al., 1998) confirmed by pharmacological use of calcium channel blocker (lercanidipine) that markedly attenuated behavioral and biochemical alterations in ICV -STZ rats (Sonkusare et al., 2005). 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 (Lannert and Hoyer, 1998, Grunblatt et al., 2007) and play a major role in the pathogenesis of SAD.

2. 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 (Ferri et al., 2005). Dementia is a clinical syndrome with multiple etiologies that particularly affects older people (Corrada et al., 2008). 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.

2.1 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 (Zilkens et al., 2009). 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 (Knapp et al., 2007).

2.2 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 (Tanev et al., 2008), and nutritional deficiencies like vitamin B12 and folate deficiencies (Maccioni et al., 2009) 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 (Tong et al., 2009), and HD (Wang et al., 2009), multi-infracts dementia (dementia due to multiple small strokes, also known as vascular dementia) (de la Torre et al., 2008), infections that affect the brain and spinal cord, such as acquired-immune deficiency syndrome (AIDS) dementia complex (Varatharajan and Thomas, 2009) and Creutzfeldt-Jakob disease. Some people have a combined type of dementia involving both AD and vascular dementia (Tsuno, 2009).

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 (Kuller et al., 2008).

3. 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) (Blennow et al., 2006). Clinically, AD typically begins with a subtle decline in memory and progresses to global deterioration in cognitive and adaptive functioning (Watson and Craft, 2004). 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 (Zawia et al., 2009).

3.1 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 (Fernandez et al., 2008). 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 (Hoyer and Jannert, 2007).

3.2 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 (Ramani et al., 2006). 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

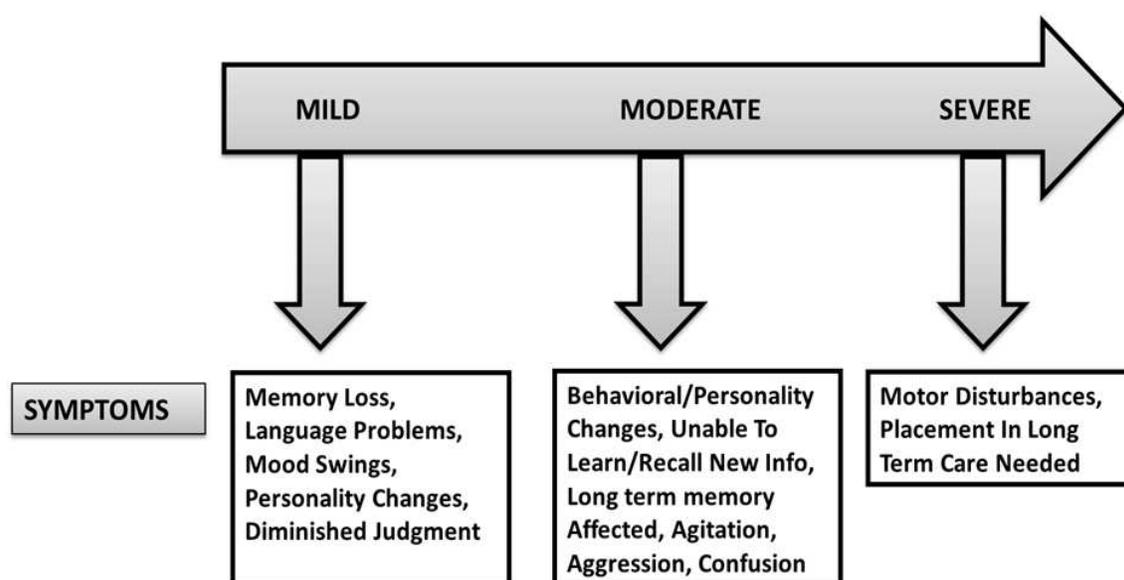


Fig. 1.

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.

3.3 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).

3.3.1 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 (Bernardi et al., 2009). The genetic abnormalities on chromosomes 1, or 14, or 21 are all characterized by the permanent generation of amyloid beta ($A\beta$) 1–40 and in particular $A\beta$ 1–42, beginning early in life (Patterson et al., 2008). Both these derivatives of APP reduce the binding of insulin to its receptor and receptor autophosphorylation (Xie et al., 2002). 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 (de la Monte, 2008). This dysfunction of the insulin signal transduction cascade may cause a drastic fall in the cerebral metabolism of glucose in FAD (Gandy, 2005). Regardless the primary cause and clinical form of AD, the amyloid cascade hypothesis proposes that both conditions lead to $A\beta$ 1-42 accumulation, oligomerization and plaque formation, which further initiates a whole range of pathological cascade effects; microgliosis and astrocytosis (Norris et al., 2005), inflammatory response (Kamer et al., 2008), oxidative and nitrosative stress (Mangialasche et al., 2009), Ca^{+} dysregulation (Small et al., 2009), mitochondrial dysfunction (de la Monte, 2008), neuronal/neuritic dysfunction, cell death (Wang et al., 2008), neurotransmitter deficits (Ding et al., 1992), and finally, memory loss (Erol et al., 2008;). In parallel, oxidative stress and neurotransmitter deficits induce kinase/phosphatase activity imbalance (Gella and Durany, 2009) 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 (Mckee et al., 2008).

3.3.2 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 (Placnica et al., 2009). 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 (Cizza et al., 1994), (3) acetylcholine action (reduced) and noradrenaline action (increased), indicating sympathetic tone, obviously also reducing insulin secretion after glucose stimulation (Erol et

al., 2008) and (4) shift in the gene expression profile from anabolic (reduced) to catabolic (increased) in distinct brain areas such as cortex, hippocampus and hypothalamus (Xu et al., 2006) (Fig.2).

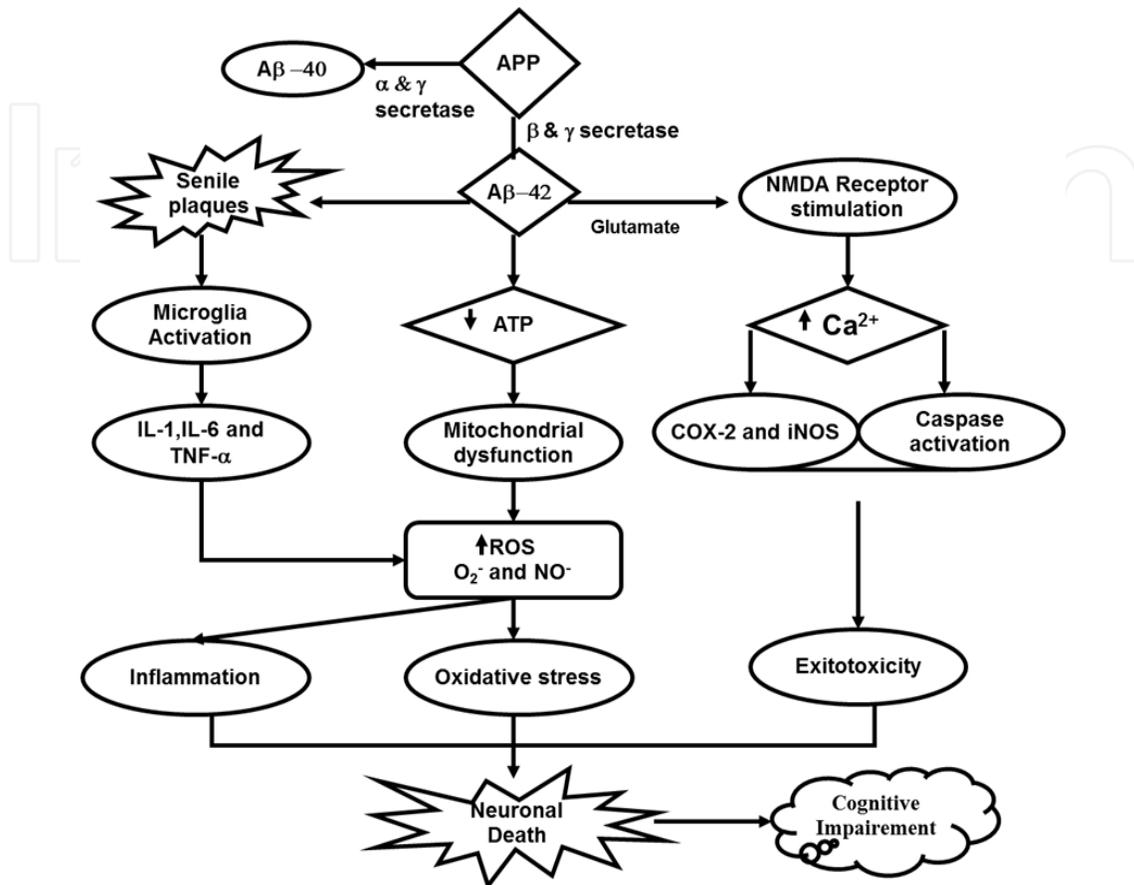


Fig. 2. Various neurochemical alterations in AD brain

4. Sporadic type AD associated alterations

4.1 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 (Shaw and Hoglinger, 2007). In line with this decreased brain insulin protein and its mRNA levels were found post mortem in the brain (frontal cortex, hippocampus (Lester Coll et al., 2006), while IR density was found to be increased and tyrosine kinase activity decreased (Frlolich et al., 1998). 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 (Steen et al., 2005). Regarding the downstream IR signaling pathways, reduced levels of PI3-K have been found (Dong et al., 2009). 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 (Giese, 2009). 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 (Steen et al., 2005). Recent data have pointed to another important enzyme, involved in tau dephosphorylation, the protein phosphatase 2A (PP2A), which can directly dephosphorylate tau (Liang et al., 2009; Martin et al., 2009). 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 (Peineau et al., 2008) (Fig.3).

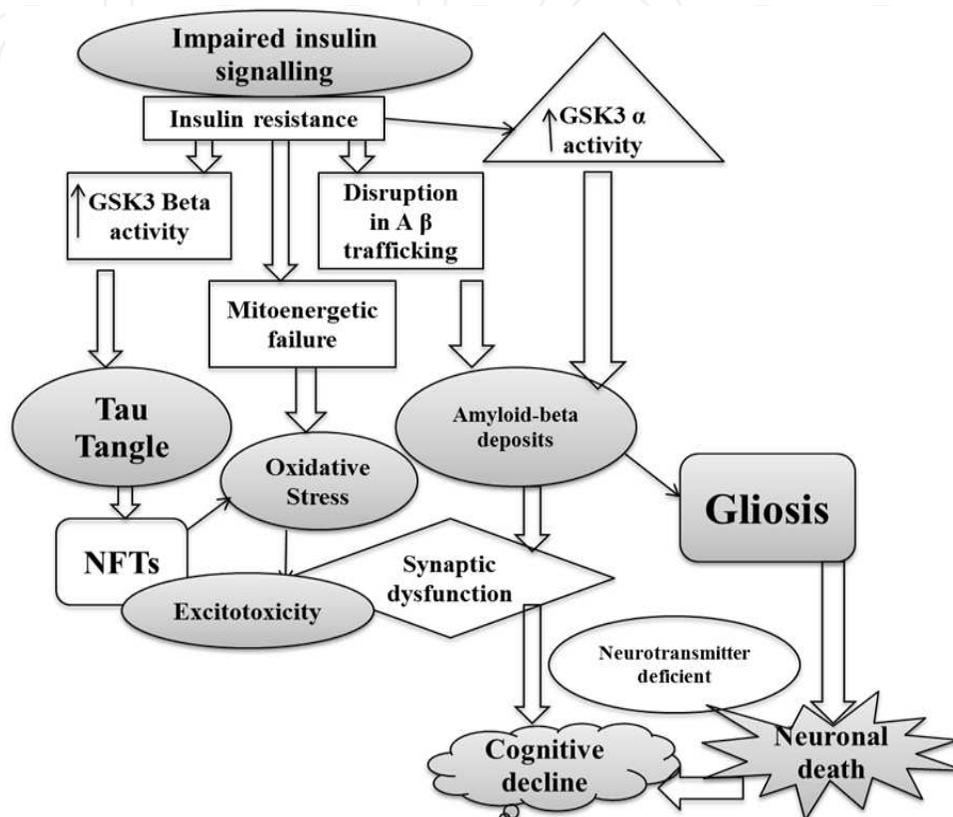


Fig. 3. Impairment of Insulin signaling in Alzheimer's disease

4.2 Reduced glucose and energy

Early and severe abnormalities were found in cerebral glucose metabolism which worsened in parallel with the dementia symptoms (Maurer and Hoyer, 2006). It includes the diminished activity of the pyruvate dehydrogenase complex yielding reduced levels of acetyl-CoA (Lannert et al., 1998). As a consequence, the reduced glycolytic glucose breakdown, the formation of fructose-6-phosphate may be diminished so that the availability of uridine-diphospho-N-acetylglucosamine (UDP-GlcAc) necessary for protein-O-GlcNAcylation is decreased (Gong et al., 2006). 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 (de la Torre, 2008).

4.3 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 (Hoyer, 2004). 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 (Greenfield et al., 1999). A depletion of cellular ATP prevents the dissociation of chaperone/protein complexes and thus blocks secretion of these proteins (Dorner et al., 1990). Additionally, ATP depletion results in the degradation of membrane phospholipids (Sun et al., 1993).

4.4 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 (Hellweg et al., 1992). 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 (Hoyer, 1992).

5. 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 (Woodhouse et al., 2009) (Fig.4).

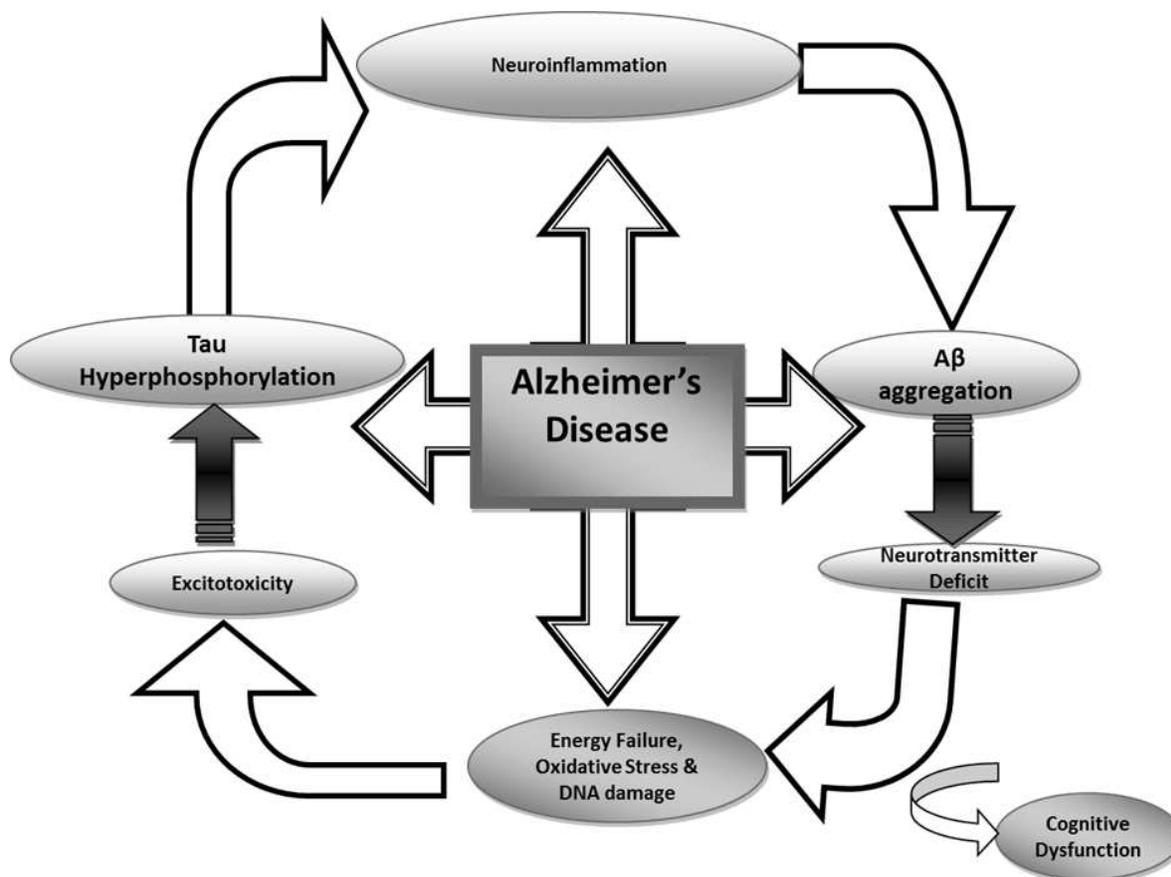


Fig. 4. Neuropathological hallmarks of Alzheimer's Disease

5.1 Tau protein

NFT consist of intracellular protein deposits made of hyperphosphorylated tau protein (Blennow et al., 2006). 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 (Iqbal et al., 2005). 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 (Wegiel et al., 2008).

5.2 Amyloid beta

Extracellular amyloid plaques predominantly consist of aggregates of neurotoxic Aβ 1-42 generated in vivo by specific, proteolytic cleavage of APP (Bernardi et al., 2009). 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 (Bamburg and Bloom, 2009).

6. 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 (Duelli et al., 1994; Lannert and Hoyer, 1998). 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

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 Thau protein Amyloid beta	+ +	+ + (Salkovic-Perisic, 2008)

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

ventricle of an adult rat, first reported in 1990 (Mayer et al., 1990). Although learning and memory are impaired within 4 weeks in all experimental models of AD (Weinstock and Shoham, 2004), 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 (Salkovic et al., 2006).

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 (Hoyer and Nitsch, 1989) and consequently ICV -STZ impairs the insulin-IR system (Blokland and Jolles, 1993). 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 (Duelli et al., 1994; de la Monte et al., 2006). 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 (Hoyer and Riederer, 2007; Li and Holscher, 2007). A comparison and correlation of various pathological changes observed in human SAD and ICV -STZ rat model are summarized in Table 1.

6.1 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

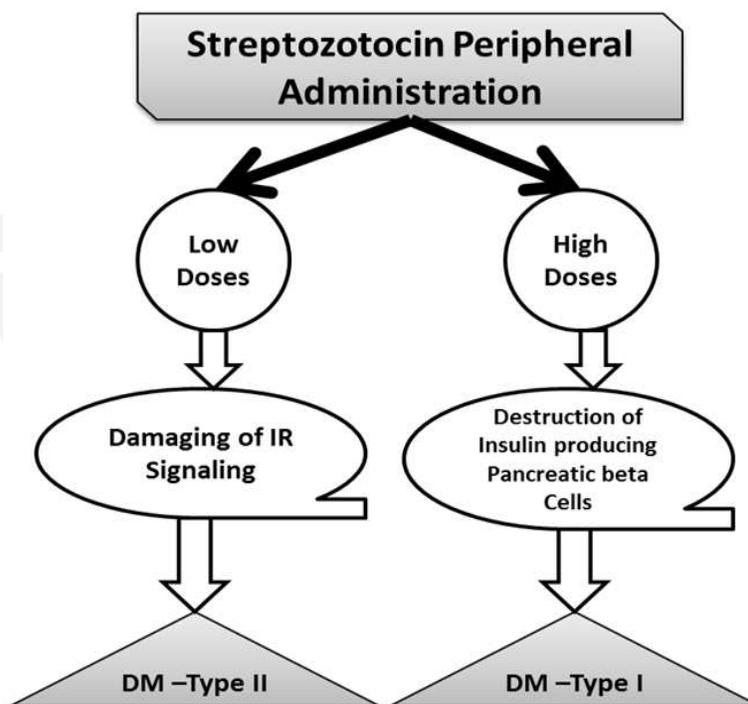


Fig. 5. Peripheral mechanism of streptozotocin.

predominant site of GLUT2 localization is the pancreatic beta cell membrane (Szkudelski, 2001). Following peripheral administration, STZ causes alkylation of β -cell DNA which triggers activation of poly ADP-ribosylation, leading to depletion of cellular NADH and ATP (Szkudelski, 2001). 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 (Blondel and Portha, 1989) (Fig.5).

6.2 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 (Prickaerts et al., 2000, Deshmukh et al., 2009). 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 (Arluison et al., 2004a, b). The chemical structure of STZ also suggests this compound may produce intracellular free radicals, nitric oxide (NO) and hydrogen peroxide (Szkudelski, 2001) and induces behavioral, neurochemical and structural changes that are similar to those found in SAD (Fig. 6).

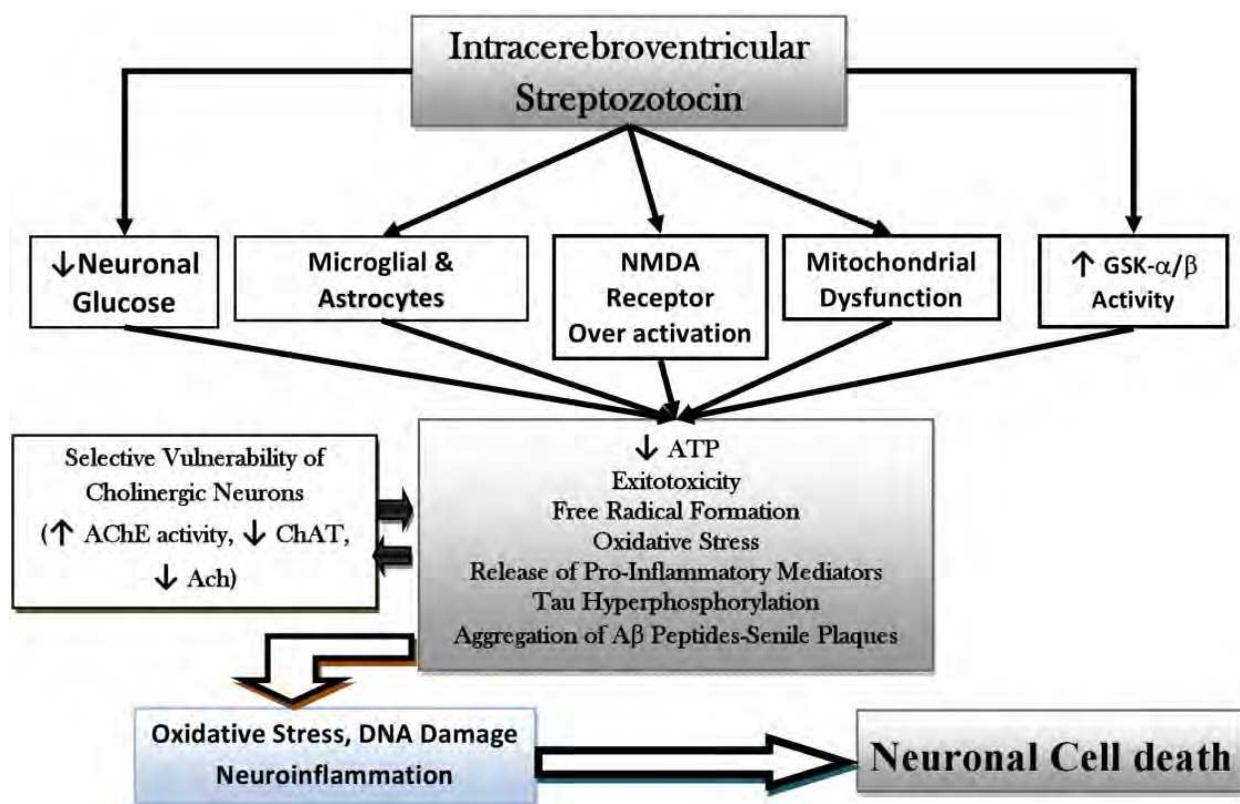


Fig. 6. Central mechanism of action of intracerebroventricularly administered streptozotocin in rats.

6.2.1 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 (Hoyer, 2004). 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 (Johanston et al., 2003, Mehan et al., 2010a,b). When insulin binds to the subunit of IR induces autophosphorylation of the intracellular α -subunit resulting in increased catalytic activity of the tyrosine kinase (Johanston et al., 2003). 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 (Johanston et al., 2003) (Fig.7).

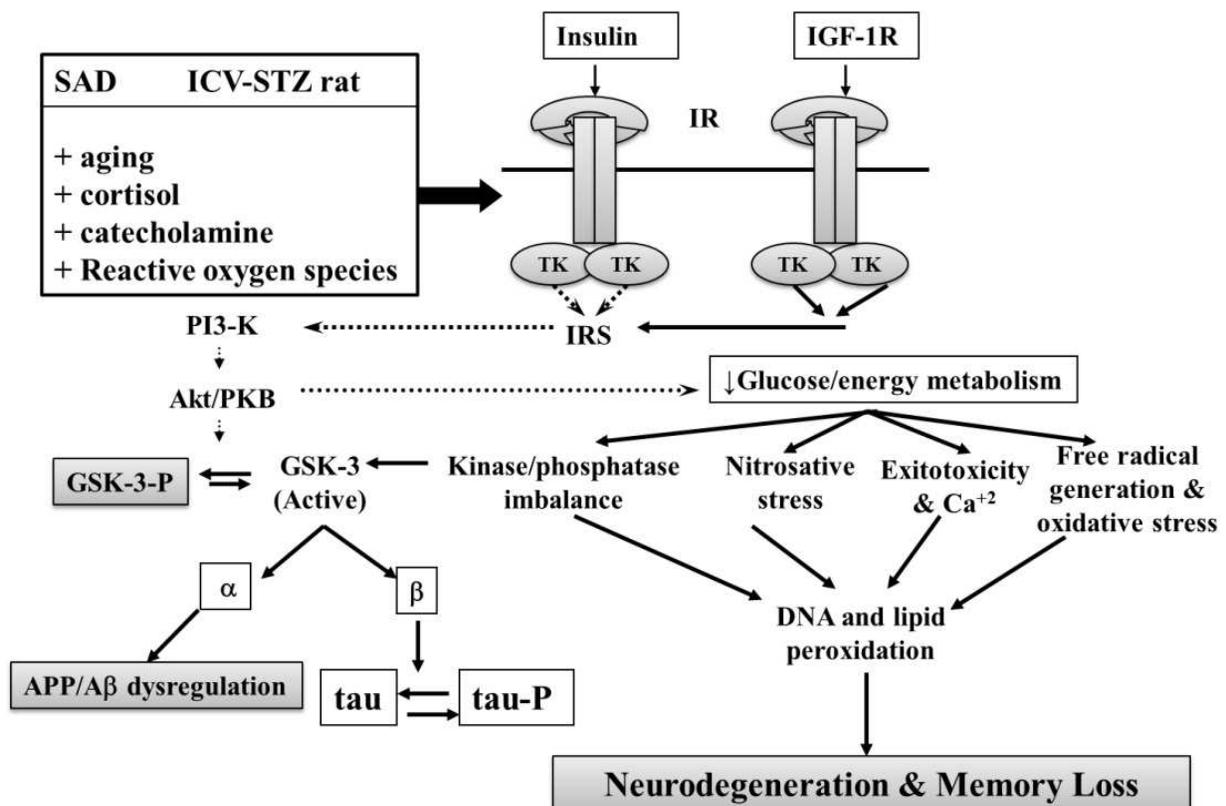


Fig. 7. Brain insulin receptor signaling cascade in the insulin resistant brain state induced by the intracerebroventricular streptozotocin treatment.

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 (Salkovic-Petrisic and Hoyer, 2007).

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 (Salkovic-Petrisic et al., 2006). Since treatment with very low to moderate doses of STZ in short term experiments causes insulin resistance (Blondel and Portha, 1989) via a decrease in autophosphorylation and decrease in total number of IRs, but with little change in phosphorylated IR- β subunit (Droge and Kinscherf, 2008). Indeed, the activity of the protein tyrosine phosphatase decreased after long-term STZ-damage (Mayerovitch et al., 1989) and induced a drastic reduction of IR dephosphorylation (Pathan et al., 2006).

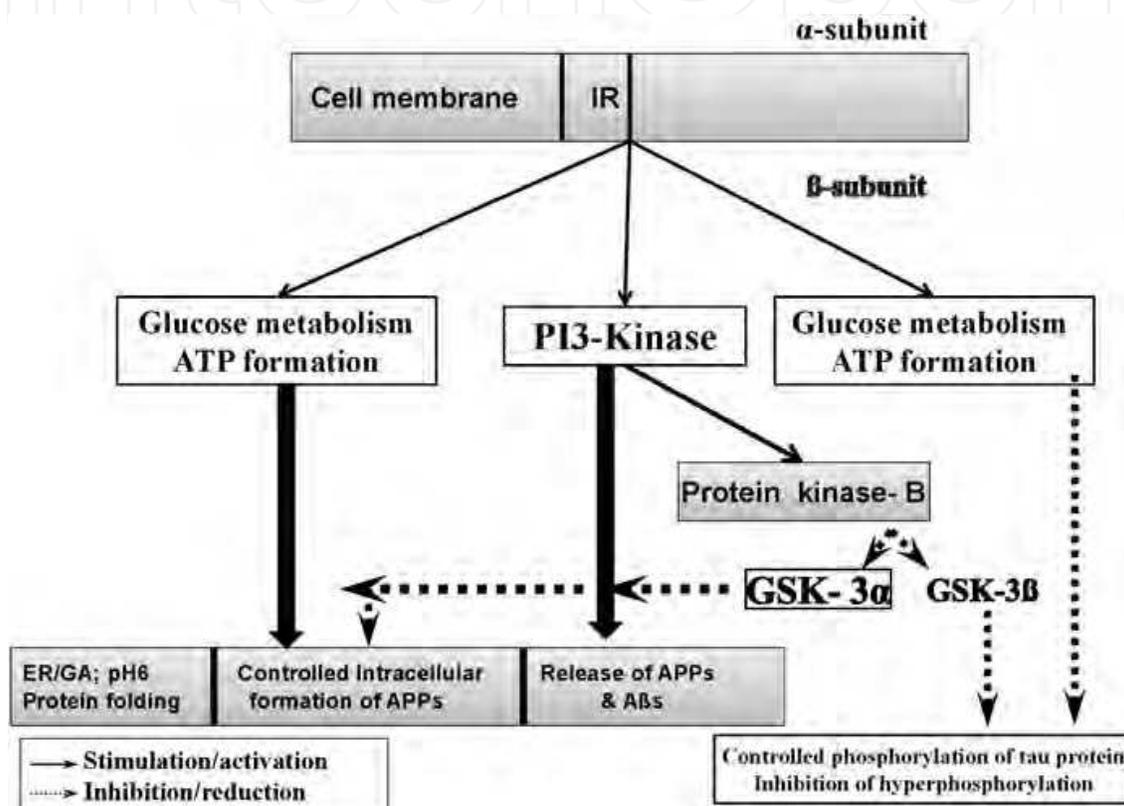


Fig. 8. Brain insulin receptor signaling cascade in physiological conditions.

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 (Lester Coll et al., 2006). 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 (Grunblatt et al., 2007). 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 (Salkovic-Petrisic and Hoyer, 2007). 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).

[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].

6.2.2 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 (Nitsch and Hoyer, 1991). 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 (Plaschke and Hoyer, 1993). This pathologic condition, obviously sparing the metabolism in the tricarboxylic acid (TCA) cycle, seems to be characteristic of SAD (Plaschke and Hoyer, 1993) resulting in diminished concentration of the energy rich compounds ATP and creatine phosphate (Lannert and Hoyer., 1998). Interestingly, the extent of the shortage in energy production was the same in the STZ-damaged brain as in incipient SAD (Ishrat et al., 2006).

6.2.3 ICV-STZ induced oxidative stress

ICV -STZ treatment causes marked reduction in brain glucose/energy metabolism and shows a progressive trend towards oxidative stress (Lannert and Hoyer 1998). 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 (Shoham et al., 2007). 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 nitrative stresses. Relevant to this oxidative-nitrative stress has been found 1 and 8 weeks following a single 3 mg/kg ICV -STZ dose without involvement of NO (Shoham et al., 2003). 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 (Ishrat et al., 2009 a,b). 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 (Pathan et al., 2006). This is also supported by the use of naringenin (Balchenejadmojarad and Roghani, 2006), guggulipid (Saxena et al., 2007), melatonin (Sharma

and Gupta 2001a), ascorbic acid (Weerateerangukul et al., 2008), mefenamic acid (Mojarad et al., 2007), transresveratrol (Sharma and Gupta, 2002), lipoic acid (Sharma and Gupta, 2003), *Centella asiatica* (Kumar and Gupta., 2003), *Ginkgo biloba* (Hoyer et al., 1999), CoQ10 (Ishrat et al., 2006), ladostigil (Shoham et al., 2007), melatonin and donepezil (Agarwal et al., 2009), curcumin (Ishrat et al., 2009a) and selenium ((Ishrat et al., 2009 b) 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.

6.2.4 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 (Spencer and Lal, 1983). ICV -STZ treated rats showed an impaired learning and memory performance, possibly as a result of cholinergic dysfunction (Nitsch and Hoyer, 1991). Apart from this, Blokland and Jolles (1993, 1994), found spatial learning deficit and reduced hippocampal ChAT activity in rats one week after ICV -STZ injection (Prickaerts et al., 1999). 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 (Hellweg et al., 1992). This is followed by a significant increase in acetylcholinesterase (AChE) activity (Agarwal et al., 2009). 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 (Terwel et al., 1995). 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 (Sonkusare et al., 2005).

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 (Salkovic-Petristic and Lackovic, 2003; Levine et al., 1990). 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 (Salkovic-Petristic and Lackovic, 2003).

6.2.5 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 (Prickaerts et al., 1995, 1999), passive avoidance (Ishrat et al., 2006, 2009 a, b) and Morris water maze escape task 2 weeks after its administration (Blokland and Jolles et al., 1993, 1994). These behavioral alterations were observed regardless of age in both 1–2 year (Mayer et al., 1990; Lannert and Hoyer, 1998; and 3-month old rats (Grunblatt et al., 2006) 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 (Blokland and Joles, 1994; Prickaerts et al., 2000; Grunblatt et al., 2006). 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 (Shoham et al., 2003). 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 (Blokland and Jolles, 1994). Chronic treatment with acetyl-L-carnitine attenuated both the STZ induced impairment in spatial bias and the decrease in hippocampal ChAT activity (Prickaerts et al., 1995). 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 (Sharma and Gupta, 2001b), where no signs of neuronal damage or any reduction in specific cholinergic markers were detected in the cortex or hippocampus (Shoham et al., 2003). Concomitantly, memory deficits were reported to be prevented by chronic treatment with several types of drugs with diverse mechanisms of action (Weinstock and Shoham, 2004). Adding to this, (a) drugs generating alternative energy sources such as acetyl-L-carnitine (Prickaerts et al., 1995), (b) cholinesterase inhibitors such as donepezil and ladostigil (possess monoamine oxidase B inhibition and neuroprotective activity which also prevent gliosis and oxidative stress (Sonkusare et al., 2005) (c) estradiol which prevents reduction in cerebral ATP (Lannert et al., 1998) (d) antioxidants such as melatonin, resveratrol, and CoQ10 which prevent an increase in free radical generation (Sharma and Gupta, 2001c, 2002), dose-dependently improved learning and memory thereby restoring cognitive function without affecting CNS functions.

6.2.6 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 (Shoham et al., 2003) and in the brain and in both ≥ 1 year and 4 month old rats (Terwel et al., 1995). 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 (Prickaerts et al., 1999, 2000) suggesting that altered hippocampal function could result from direct damage to this region (Prickaerts et al., 2000; Shoham et al., 2003). 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 (Weinstock and Shoham, 2004). These pathological features are all present in the brain of SAD patients (Frlolich et al., 1998). 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 A β generated in endoplasmic reticulum and in the golgi complex (Greenfield et al., 1999) which accumulated in AD brain.

6.2.7 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 leptomenigeal

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 (Martin et al., 2009).

7. Acknowledgement

Authors express their thankfulness to his late guide Prof. Manjeet Singh, Director Academics, ISF College of Pharmacy, Moga (Punjab) for always being with us.

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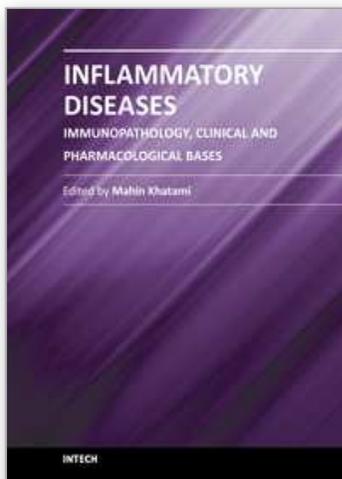
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Inflammatory Diseases - Immunopathology, Clinical and Pharmacological Bases

Edited by Dr Mahin Khatami

ISBN 978-953-307-911-0

Hard cover, 396 pages

Publisher InTech

Published online 10, February, 2012

Published in print edition February, 2012

This book is a collection of comprehensive reviews contributed by experts in the diverse fields of acute and chronic inflammatory diseases, with emphasis on current pharmacological and diagnostic options. Interested professionals are also encouraged to review the contributions made by experts in a second related book entitled "Inflammation, Chronic Diseases and Cancer"; it deals with immunobiology, clinical reviews, and perspectives of the mechanisms of immune inflammatory responses that are involved in alterations of immune dynamics during the genesis, progression and manifestation of a number of inflammatory diseases and cancers, as well as perspectives for diagnosis, and treatment or prevention of these disabling and potentially preventable diseases, particularly for the growing population of older adults around the globe.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Sidharth Mehan, Rimpi Arora, Vandana Sehgal, Deepak Sharma and Garuav Sharma (2012). Dementia – A Complete Literature Review on Various Mechanisms Involves in Pathogenesis and an Intracerebroventricular Streptozotocin Induced Alzheimer's Disease, *Inflammatory Diseases - Immunopathology, Clinical and Pharmacological Bases*, Dr Mahin Khatami (Ed.), ISBN: 978-953-307-911-0, InTech, Available from: <http://www.intechopen.com/books/inflammatory-diseases-immunopathology-clinical-and-pharmacological-bases/alzheimer-s-disease-an-updated-review-on-pathogenesis-and-intracerebroventricular-streptozotocin-ind>

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