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Research Article

Calcineurin: A Ca^{2+}-Activated Protein Phosphates Therapeutic Strategies and Involvement in ICV STZ Induced Alzheimer's type Dementia

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Abstract

Sporadic type of Alzheimer's Disease (SAD) is associated with various neurodegenerative and metabolic alterations. Among these, Insulin downstream Phospho-Inositol-3 Kinase (PI3K/Akt) signaling pathway showed drastic abnormalities of Akt/Protein Kinase B (PKB) level, activation of both glycogen synthase kinase 3α and 3β and deregulating phosphorylated/non-phosphorylated GSK-3α and 3β, imbalance between kinases and phosphatases particularly marked decrease in Protein Phosphatase-2A (PP2A), responsible for tau dephosphorylation and significant increase in Mitogen Activated Protein Kinase (MAPK), Extracellular Regulated Kinase (ERK) and c-JUN-N-Terminal Kinase (JNK) implicating in SAD pathogenesis. Moreover, Ca^{2+}/calmodulin-dependent protein serine-threonine phosphatase 2B (PP2B) also known as Calcineurin attracted attention as a potential modulator of both learning and memory function and cell degeneration. Furthermore, PP2B is over expressed in AD and have been linked to Aß deposition and Tau tangle formation. Favorable modulator of PP2B found to beneficial in a variety of experimental models of SAD. In this review, we provide an overview on PP2B and its implication in the pathogenesis of SAD.

Keywords: PP2B; MAPK; Alzheimer's disease; ICV-STZ; Memory; Oxidative Stress

Introduction

Prevalence of Dementia

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 vary greatly between countries. Currently 8% of western population is affected from dementia [1,2]. 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 [3].

Types and Causes of Dementia

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 dementias 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, hypothyriodism, toxic reactions like drug use and nutritional deficiencies like vitamin B12 and folate deficiencies [4]. 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 [5], PD [6], and HD [7], multi-infracts dementia (dementia due to multiple small strokes, also known as vascular dementia) [8], excessive alcohol use [9], infections that affect the brain and spinal cord, such as Acquired-Immune Deficiency Syndrome (AIDS) dementia complex [10] and Creutzfeldt-Jakob disease. Some people have a combined type of dementia involving both AD and vascular dementia [11].

Symptoms of Dementia

The most common symptoms that are mostly associated with dementia are delirium from a sudden medical problem,

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psychosis, aggression, anger, insomnia or "sundowning" (confusion in late afternoon or early evening), anxiety, depression, personality and behavior changes, apathy and withdrawal, progressive and frequent memory loss [12,13].

Alzheimer's Disease

Alzheimer's disease is the most common dementia in the elderly population (> 65 years) associated with progressive neurodegeneration of the Central Nervous System (CNS) [14]. Clinically, AD typically begins with a subtle decline in memory and progresses to global deterioration in cognitive and adaptive functioning [15]. 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 [16].

Prevalence of AD

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 [17]. 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 [18]. 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 [19,20].

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 [21]. In early stages of the disease, people may experience irritability, anxiety or depression. In later 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 [17].

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 [22].

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 [23]. 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 [24]. Both these derivatives of APP reduce the binding of insulin to its receptor and receptor autophosphorylation [25]. The disruption of autophosphorylation by ATP may result in a decrease/lack of receptor tyrosine kinase activity and, thus, in a failure of post receptor effects exerted via insulin receptor substrate (IRS)-1 [26]. This dysfunction of the insulin signal transduction cascade may cause a drastic fall in the cerebral metabolism of glucose in FAD [27,28]. Regardless the primary cause and clinical form of AD, the amyloid cascade hypothesis proposes that both conditions lead to Aß 1-42 accumulation, oligomerization and plaque formation, which further initiates a whole range of pathological cascade effects; microgliosis and astrocytosis [29], inflammatory response [17], oxidative [30], and nitrosative stress [31], Ca^{2+} dysregulation [32], mitochondrial dysfunction [26], neuronal/neuritic dysfunction, cell death [33], neurotransmitter deficits [34], and finally, memory loss [35]. In parallel, oxidative stress and neurotransmitter deficits induce kinase/phosphatase activity imbalance [36] 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 [37].

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 [38]. 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 [39], (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 [40].

Neurochemical Changes in SAD

(A) 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 [41]. In line with this decreased brain insulin protein and its mRNA levels were found post mortem in the brain (frontal cortex, hippocampus [42], while IR density was found to be increased and tyrosine kinase activity decreased [43]. 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 [42]. Regarding the downstream IR signaling pathways, reduced levels of PI3K have been found [44]. 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-3α/β alterations, whose phosphorylated form were mainly found to be decreased [45,46]. 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 [43]. Recent data have pointed to another important enzyme, involved in tau dephosphorylation, the protein phosphatase 2A (PP2A), which can directly dephosphorylate tau [47]. 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-3β [48,49].

(B) Reduced Glucose and Energy

Early and severe abnormalities were found in cerebral glucose metabolism which worsened in parallel with the dementia symptoms [50,35]. It includes the diminished activity of the pyruvate dehydrogenase complex yielding reduced levels of acetyl-CoA [51]. 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-OGlcNAcylation is decreased [52]. Another pathophysiologic 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 [8].

(C) 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 [53]. 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 [54]. A depletion of cellular ATP prevents the dissociation of chaperone/protein complexes and thus blocks secretion of these proteins [55]. Additionally, ATP depletion results in the degradation of membrane phospholipids [56].

(D) 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 [57]. 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 [58].

Neuropathological Hallmarks of AD

Two main neuropathological hallmarks are found in the brain of patients with familial and sporadic AD are (1) NFT and (2) amyloid plaques [48,59].

Tau Protein

NFT consist of intracellular protein deposits made of hyperphosphorylated tau protein [60]. 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 [61]. 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 nonphosphorylated tau protein [48,62].

Amyloid Beta

Extracellular amyloid plaques predominantly consist of aggregates of neurotoxic Aβ 1-42 generated in vivo by specific, proteolytic cleavage of APP [63,23]. 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 [64].

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 [65,51]. 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 [66]. Although learning and memory are impaired within 4 weeks in all experimental models of AD [67], 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 [68].

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 [69] and consequently ICV-STZ impairs the insulin-IR system [70]. 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 [65,68]. The stated metabolic abnormalities, as well as several of the classical histopathological lesions of AD, could be attributed in part to reduced

Table 1: Similarities between ICV-STZ model and human SAD [53].

Brain pathology	ICV-STZ 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)

insulin levels and reduced IR function in AD. Siegfried 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 [58,20,57]. A comparison and correlation of various pathological changes observed in human SAD and ICV-STZ rat model are summarized in Table 1.

(A) ICV-STZ and 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 [71]. 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 (PI3K) pathway and the Mitogen Activated Protein Kinase (MAPK) pathway [72]. 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 [73]. 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 (PI3K). After being activated, PI3K 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 Figure 1.

It has been reported that changes in the brain insulin and tau-Aβ 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 [74,68,42). Since treatment with very low to moderate doses of STZ in short term experiments causes insulin resistance [75] via a decrease in autophosphorylation [76] and decrease in total number of IRs, but with little change in phosphorylated IR-β subunit [77]. Indeed, the activity of the protein tyrosine phosphatase decreased after long-term STZ-damage [78] and induced a drastic reduction of IR dephosphorylation [79]. Regarding the enzymes downstream of the IR-PI3K pathway, experiments have shown alterations of hippocampal GSK-3ß however, observed changes were of a greater extent in the phosphorylated than in the non-phosphorylated form of GSK-3 [42]. The IRβ protein was decreased in the frontoparietal cortex and hypothalamus, but the levels of phosphorylated IRβ (p-IRβ) were increased and tyrosine kinase activity was unchanged in these regions, whereas in the hippocampus IRβ protein levels were decreased, but p-IRβ levels, as well as tyrosine kinase activity were increased [113]. Downstream from the PI3K 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 [74]. In this regard, many molecular abnormalities that characteristically occur in AD, including increased GSK-3β activation, increased tau phosphorylation, and decreased neuronal survival, could be mediated by downstream effects of impaired insulin and IGF signaling in the CNS. This altered insulin signaling mechanisms are summarized in Figure 2.

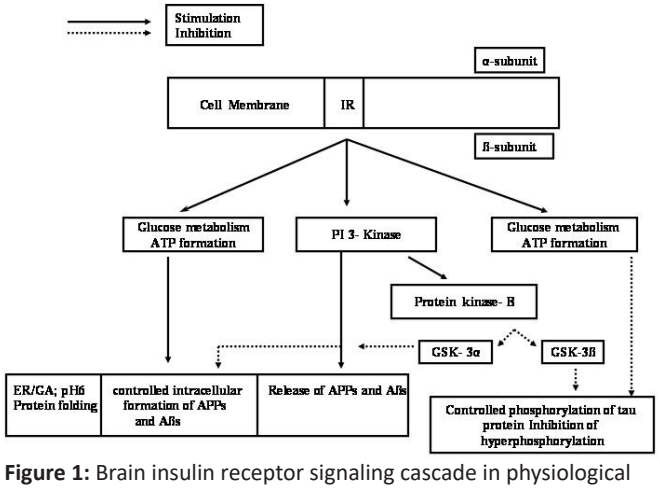

Figure 1: Brain insulin receptor signaling cascade in physiological conditions.

(B) ICV-STZ and glucose and 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

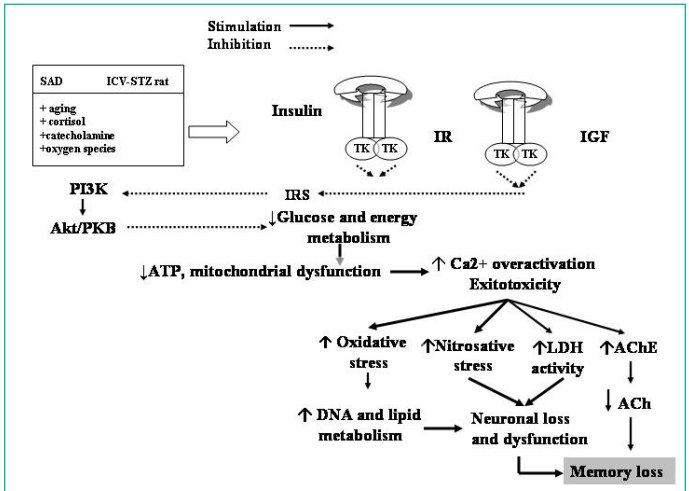

Figure 2: Brain insulin receptor signaling cascade in the insulin resistant brain state induced by the intracerebroventricular streptozotocin treatment. Akt/PKB: protein kinase B; IR: Insulin receptor; IGF-1R: insulin-like growth factor-1 receptor; IRS: insulin receptor substrate; tau: tau protein; tau-P: phosphorylated tau protein; PI3K: phosphatidylinositol- 3 Kianse; TK: tyrosine kinase; kinase; SAD: human sporadic Alzheimer's disease; ICV-STZ intraverebroventricularl streptozotocin [115].

Table 2: Pharmacological modulators of Calcineurin.

Pharmacological modulator	Example
Immunosuppressant	Endogenous inhibitor AKAP79, cain/cabin 1.
	Natural inhibitors Okadaic acid, microcystin LR endothal derivative, dibefurin, tautomycin, Metal- ligating phosphonates, Inhibitor protein I-1 and I-2.
	Synthetic inhibitors Cyclosporin A, tacrolimus (FK506), cypermethrin, deltamethrin, PD 144795, cantharidin, fenvalerate.
Non- immunosuppressant Analogue of FK506	GPI- 1046, GPI- 1085,V- 13667, V-13669, FK-1706, Lie-120.
Analogue of cyclosporine-A	NIM811, UNIl025.

the hippocampus regions [81]. 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 [81,82). This pathologic condition, obviously sparing the metabolism in the Tricarboxylic Acid (TCA) cycle, seems to be characteristic of SAD [20] resulting in diminished concentration of the energy rich compounds ATP and creatine phosphate [51] Interestingly, the extent of the shortage in energy production was the same in the STZ-damaged brain as in incipient SAD [58,51,83].

(C) ICV-STZ and oxidative stress

ICV-STZ treatment causes marked reduction in brain glucose/energy metabolism and shows a progressive trend towards oxidative stress [81,65,51]. 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 [84,85] 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 nitrosative stresses. Relevant to this oxidative-nitrative stress has been found 1 and 8 weeks following a single ICV-STZ dose (3 mg/kg) with involvement of NO [86,87,88]. Besides oxidative stress was also found in the brain of one year old rats, 3 weeks after administration of single/low doses ICV-STZ dose (1.5 mg/kg) [89].

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 [86,84,79,90]. 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 [79]. This is also supported by the use of naringenin [91], gugulipid [92], melatonin [93], ascorbic acid [94], mefenamic acid [95], transresveratol [96], lipoic acid [89], Centella asiatica [97], Ginko biloba [98], CoQ10 [83], ladostigil [85], melatonin and donepezil [76], curcumin [99], tocotrienol [100] and selenium [90] 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 the possible therapeutic potential of antioxidant strategies in ameliorating SAD.

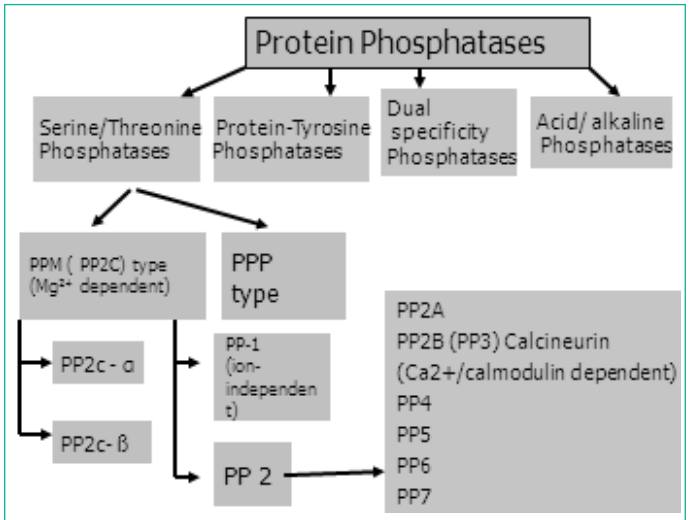

Figure 3: Protein Phosphatase subtypes.

(D) ICV-STZ and 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 [101]. ICV-STZ treated rats showed an impaired learning and memory performance, possibly as a result of cholinergic dysfunction [102]. 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 [103,104]. 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 [105]. This is followed by a significant increase in Acetylcholinesterase (AChE) activity [106, 83, 76]. 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 [102,103]. 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 [106,85,76].

ICV injections of STZ affects not only the cholinergic system but also the concentration of different monoaminergic neurotransmitters (noradrenaline, dopamine, and serotonin) in the rat brain differently [107,76,108]. It has been reported that the content of whole brain monoamine (dopamine, noradrenaline, serotonine (5-hydroxy tryptamine) and 5-HT metabolite 5-hy-

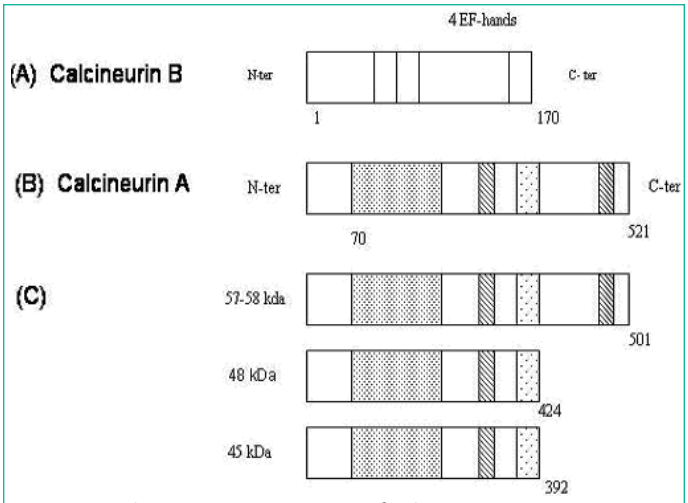

Figure 4: Schematic representation of calcineurin structure.

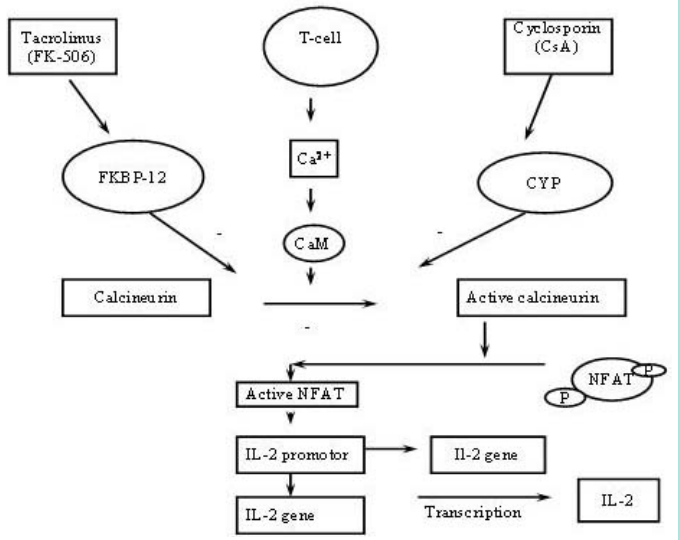

Figure 5: Immunophilin-mediated inhibition of T-cell activation.

droxyindoleacetic acid dose-dependently increased and decreased, respectively, 1 week following ICV-STZ treatment [107].

(E) ICV-STZ and behavioral alterations

ICV-STZ treated rats consistently demonstrate deficits in learning, memory, and cognitive behavior. It is well known that ICV-STZ reduced cerebral metabolism of glucose and caused impaired cognitive performance in the delayed non-matching task [102,104], passive avoidance [51,84,83,99] and Morris water maze escape task 2 weeks after its administration [66,71,105]. These behavioral alterations were observed regardless of age in both 1–2 year [66,51] and 3-month-old rats [77,79,74,85] 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 [105,102,77] 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 [51,77,74,85]. 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 [105]. Chronic treatment with acetyl-L-carnitine attenuated both the STZ induced impairment in spatial bias and the decrease in hippocampal ChAT activity [102]. 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 [85,84], where no signs of neuronal damage or any reduction in specific cholinergic markers were detected in the cortex or hippocampus [85]. Concordingly, memory deficits were reported to be prevented by chronic treatment with several types of drugs with diverse mechanisms of action [67]. Adding to this, (a) drugs generating alternative energy sources such as acetyl-L-carnitine [102], (b) cholinesterase inhibitors such as donepezil and ladostigil (possess monoamine oxidase B inhibition and neuroprotective activity) which also prevent gliosis and oxidative stress [106,85] (c) estradiol which prevents reduction in cerebral ATP [109] (d) antioxidants such as melatonin, resveratrol, and CoQ10 which prevent an increase in free radical generation [84,96,83], dose-dependently improved learning and memory thereby restoring cognitive function without affecting CNS functions.

(F) ICV-STZ and 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 [85] and in the brain and in both ≥ 1 year and 4-month-old rats [103,86,110,85]. 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 subcorical structures including septum, fornix, and fimbria, striatum, and hippocampus, over a period of 3 weeks following ICV-STZ administration [65,104] suggesting that altered hippocampal function could result from direct damage to this region [86,110]. 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 [103,110,67]. These pathological features are all present in the brain of SAD patients [111,112] 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 βAPP generated in endoplasmic reticulum and in the golgi complex which accumulated in AD brain [113].

(G) ICV-STZ and Aβ and tau hyperphosphorylation

Regarding brain immunohistochemical analysis of tau pro-

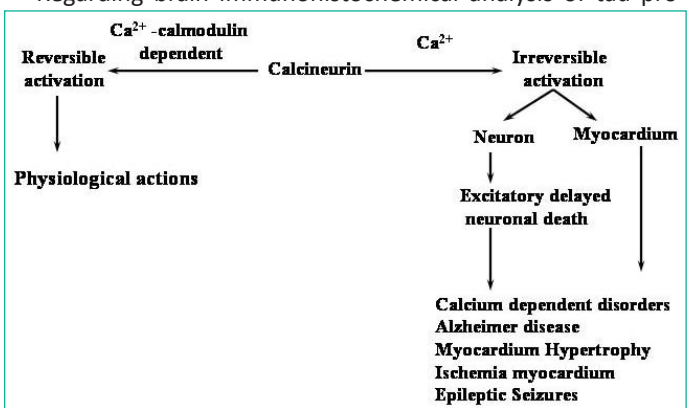

Figure 6: Schematic representation of calcineurin signaling in the pathogenesis of calcium dependent disorders. Under physiological conditions, calcineurin activity is regulated by Ca2+/calmudulin in a reversible manner, under pathophysiological conditions calcineurin is overactivated in a reversible manner mediating pathology of several neurological and myocardial disorders [136].

tein and A 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 [114,42,80,115,116] due to insulin depletion by STZ, or caused by activation of multiple kinase by inhibition of Phosphatase (PP2A) that dephosphorylate these sites [117].

(H) ICV-STZ and phosphatase/kinase imbalance

It has been shown that GSK-3 plays a key role in numerous cell functions. It consists of two forms GSK-3α and GSK-3β [48]. GSK-3α regulates the production of Aβ peptides, the Amyloid Precursor Protein (APP) derivatives [116]. The promotion of APP secretion from the intracellular to the extracellular space and the inhibition of its degradation by insulin-degrading enzymes are mediated by insulin and the tyrosine kinase activity of the IR [118]. Furthermore, insulin signaling via activation of PI3K regulates APP release into the extracellular space [119]. GSK-3β isoform is involved in tau-protein phosphorylation [120]. Accumulation of hyperphosphorylated tau protein leads to the formation of NFT. The phosphorylation and dephosphorylation of the tau protein is regulated by several protein kinases, including GSK-3β, and by several protein phosphatases, including PTP-1, -2A, -2B [47]. Prolonged exposure to insulin has been shown to induce down-regulation of GSK-3β activity and, thus, decreased phosphorylation of tau-protein [121,122]. Within 3 days after ICV-STZ treatment after insulin depletion there is decrease in Protein Phosphatase-2A (PP2A) responsible for tau dephosphorylation, physiologically as previously implicated in pathology of AD [182] and significant increase in p38, MAPK and JNK [117]. A recent investigation focusing on the downstream PI3K signaling pathway showed drastic abnormalities of Akt/PKB level and of both phosphorylated GSK-3α/β protein 1 and 3 month after ICV-STZ administration [77,123,115] at dose 1 mg/kg in to lateral ventricle.

Protein phosphatase superfamilies

Phosphatases remove the phosphoryl group and restore the protein to its original dephosphorylated state. The human protein phosphatase has been classified in to five groups; first group: serine/threonine phosphatase, second group: protein tyrosine phosphatase (PTP), third group: dual specificity phosphatase, fourth group: acid/alkaline phosphatase, fifth group: aspartate-based protein phosphatase with a (DXDXT/V) catalytic signature [124,125]. These families are further classified in to subclasses. Serine/threonine phosphatase into Phospho Protein Phosphatases (PPP) and Mg^{2+} and Mn^{2+} dependent protein phosphatase phophatase (PPM) characterized by their requirement for Mg^{2+} and Mn^{2+} ions for their activity [126,127]. PTP superfamily in to class I PTPs (Receptor PTPs, Non receptor PTP) and is also known as DSPs (MAPKP, slingshotes, PRLSs, atypical DSP, CDC14 PTEN, myotubularins), class II PTPs (CDC 25s), class III PTPs (LMWPTP), Asp-based catalysis family include FCP/SCP family- FCP1, SCP, FCP/SCP-like class and Haloacid Dehalogenase (HAD) family [125].

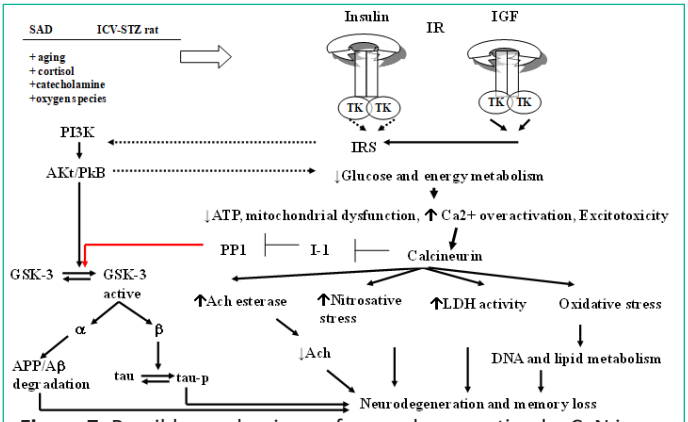

Figure 7: Possible mechanisms of neurodegeneration by CaN in ICV-STZ induced SAD in rats.

Isoforms of Serine- Threonine Phosphatase

The serine/threonine protein phosphatase family members include phospho protein phosphatase (PPP) which further divided into type 1- phospho protein phosphatase 1 (PP1), and type 2- 2A (PP2A), PP2B, PP4, PP5, PP6, PP7 phosphatase [33,128,127]. Type 1 protein phosphatase dephosphorylates the ß subunit of phosphorylase kinase whereas type 2 protein phosphatase dephosphorylates the α subunit of phosphorylase kinase [130]. Most importantly, PP2B also known as Calcineurin (CaN) is regulated by Ca^{2+}/calmodulin. PPM comprises PP2C and pyrovate dehydrogenase phosphotase [126,127] of which PP2C is Mg^{2+} dependent [129].

Immunophilins

Immunophilins are defined as receptors for immunosuppressive drugs including Cyclosporin A (CsA), FK506, also known as tacrolimus, and rapamycin. The CsA receptors are referred to as Cyclophilins (CYPs) and FK506- and rapamycin-binding proteins are abbreviated as FKBPs. These two groups of proteins (collectively called immunophilins) share little sequence homology, but both have peptidyl prolyl cis/trans isomerase (PPIase) activity [131-133]. Small size FKBP family members contain only FK506-binding domain, while FKBPs with large molecular weights possess extra domains such as tetratricopeptide repeat domains, calmodulin binding and trans membrane motifs. FKBPs are a family of immunophilin proteins named according to their molecular weight (in kDa): for example, FKBP-12, -12.6, -13, -25, -38, -51, - 52, -59, -60, and -65. Among these FKBP 12, 38, and 65 are enriched in the CNS [132]. Moreover, therapeutic implications of immunophilin ligands in treating neurodegenerative disorders have been accumulating. FK506 and its derivatives with no immunosuppressive activities bind to the conserved active sites of the canonical FKBP12 is the mediator of immunosuppressive action of FK506. When complexes with the tacrolimus, FKBP12 blocks nuclear import of NFAT and formation of AP-1 heterodimer, due to inhibition of calcium-dependent phosphatase CaN and JNK/p38 pathways. Suppression of these two and possibly some other signaling pathways leads to prevention of (Interleukin) IL-2 expression and T cell activation. FKBP51 and FKBP52 are natural components of glucocorticoid receptor complex and direct regulators of its activity. Upon ligand binding, FKBP51 maintaining glucocorticoid receptor in the cytoplasm is exchanged by FKBP52, which allows translocation of the complex to the nucleus. Thereby, FKBPs participate in the regulation of immune response by glucocorticoids (Kochel and Strzadala, 2004). On the other hand, in the noncanonical FKBP members such as FKBP38, FK506-binding site is not conserved and shows neither PPIase activity nor affinity to FK506 [132].

Subunit and Domain Structure of Calcineurin

One of the intracellular signaling phosphatase that has recently attracted attention as a potential modulator of both memory function and cell degeneration is the Ca^{2+}/ calmodulin-dependent protein serine/threonine phosphatase (PP2B) also known as CaN, the most abundant phosphatase in the CNS

[134,135]. Purified calcineurin is a heterodimer consisting of catalytic subunit (calcineurin A) with mol. mass (57-59 kDa) and regulatory calcium binding subunit (calcineurin B) with mol. mass (19 kDa) (Figure 4) [136,137]. Structural and functional analysis suggests that the active site of CaN is located on the A subunit the catalytic subunit calcineurin A (521 residues) contains (residues 1-328), a CaN B binding helical domain (348-368 residues), a calmodulin binding region (390-414) & auto inhibitory loop (468 -490 residue) The gene for mammalian CaN B encodes a protein a protein of 170 amino acids containing four Ca^{2+}-binding EF bands. CaN B consist of two Ca^{2+} binding domains, domain 1 (residue 1-84) and domain 2 (residue 86-169), which are arranged linearly along with its binding domain in calcineurin A, a myristoylated binding. Each domain contains two Ca^{2+}-binding EF-hand motifs that are similar to those of calmodulin [136]. Mammalians have three isoforms of CaN A (α, ß, γ) and two of CaN B (B1 and B2) [135-137].

Tissue Expression and Activity of Calcineurin

Previous findings reveal that the immunophilins are much more (10-100 times) abundant in the CNS highly enriched in neurons and glial cells [139] than in immune system led to the research that reveals important roles for the immunophilins in multiple areas of neural function. In the CNS, CaN is highly localized in hippocampus, striatum, substantia nigra, neocortical neurons, in layers, 3, 5, 6, and cerebellum [140]. In T lymphocytes, CaN has been found intracellularly colocalized with one of its substrates NFAT. To date, five separate genes encoding NFATs have been cloned and generally denoted NFAT1/p, NFAT2/c, NFAT3, NFAT4, and NFAT5 [141]. In addition, the presence of both immunoreactivity and enzyme activity of CaN have been reported in many other organs like lung, thymus, heart, kidney, and muscle [142,130].

Various Endogenous and Synthetic Ligands of Calcineurin: There are two types of pharmacological inhibitor of CaN, immunosuppressant and non-immunosuppressant modulators [141,129,143]. The calicineurin modulators are enlisted in Table 2.

Biological functions of Calcineurin

(A) Physiological role of calcineurin

CaN is involved in the regulation of diverse cellular functions as gene expression, [144], cell embryonic development [145], proliferation [146], differentiation [147], migration [148], cell cycle progression [149], meiosis and mitosis [150], ion homeostasis [151], ion channel regulation [152], harmones secretion [153], neuronal transmission [154], signal transduction [155] and dopaminergic-mediated transcription in neurons, [156], embryogenesis [145], muscle differentiation [157] muscle glycogen metabolism, cyclic AMP- activated protein- kinase activity [158] and lymphocyte activation [159].

(B) Calcineurin and immunological disorders:

It is widely accepted that the most likely mechanism for the action of immunosuppressant agents involves inhibition of the activity of CaN [160,161]. By inhibiting the CaN-induced dephosphorylation of a (NFAT), FK506 and CsA prevent NFAT translocation into the nucleus where it induces interleukin-2 (IL-2) secretion, thereby preventing T-cell proliferation [132]. Members of the FKBP family play various functions within the cell. For T cell biology essential is their involvement in the regulation of cytokine genes transcription, mainly at the level of nucleocytoplasmic transport of transcription factors. FKBP12 is the mediator of immunosuppressive action of FK506 [162] When complexed with the drug, FKBP12 blocks nuclear import of NFAT and formation of AP-1 heterodimer, due to inhibition of calcium-dependent phosphatase calcineurin. Suppression of these two and possibly some other signals pathways leads to prevention of IL-2 expression and T cell activation. FKBP51 and FKBP52 are natural components of glucocorticoid receptor complex and direct regulators of its activity. Upon ligand binding FKBP51, maintaining receptor in the cytoplasm, is exchanged by FKBP52, which allows translocation of the complex to the nucleus (Figure 5). Thereby FKBPs take a part in the regulation of immune response by glucocorticoids [163].

C) Calcineurin and mitochondrial dysfunctions

Intracellular Ca^{2+} is a powerful secondary messenger that affects a number of calcium sensors, including calpain, a calcium-dependent cysteine protease, and CaN, a Ca^{2+}/calmodulin- dependent protein phosphatase Deregulation of calpain and CaN has been implicated in the pathogenesis of several calcium dependent disorders (Figure 6) [136). Tacrolimus, unlike CsA, does not interact with the mitochondrial permeability transmembrane pore [164] but prevents the secondary deterioration in mitochondrial respiration and rundown of adenosine triphosphate (ATP) that occurs following establishment of reperfusion [165] Tacrolimus has also been shown to attenuate the loss of mitochondrial calcium during ischaemia challenge and its accumulation following reperfusion [166]. It is of important that tacrolimus has also been reported to prevent the neurodegeneration produced by a variety of mitochondrial toxins including 3-nitropropionic acid (3-NP), a 'suicide' inhibitor of complex II [167] and the complex I inhibitor, 1-methyl-4-phenyl-1,2,3,6-tetradropyridine [168]

(D) Calcineurin and apoptotic cell death

CaN has been implicated in direct apoptotic cell death through a variety of mechanisms, namely, activation of nitric oxide synthase (NOS) interaction with the Bcl-2 family of proteins and activation of the CD95 ligand receptor pathway. It has been demonstrated that CaN, through the dephosphorylation of the proapoptotic protein BAD, may be the link between Ca^{2+} homeostasis deregulation and apoptotic neuronal death [169]. In addition, there is involvement of CaN activity in excessisive stimulation of glutamate receptors leads to intracellular Ca^{2+} overload. Furthermore, CaN play a role in apoptosis in neuronal cells via the cytochrome c/caspase 3-pathway [170,171]. Calcineurin and NFAT play a role in programmed cell death of T and B lymphocytes [172] (Figure 6). Alternatively, tacrolimus and cyclosporine could act at the level of the cytosol to suppress the translocation of pro-apoptotic proteins BAX and BAD from the cytosol to the mitochondria by binding to and inhibiting the action of FKBP or calcineurin [173,174] Figure 6.

(E) Calcineurin and epileptic seizures

CaN is involved in the activation of long-term molecular cellular mechanisms leading to sustained recurrent excitatory activity, which induces late spontaneous seizures [175]. It has been reported that CaN in the brain of rats, increases after completion of electrical kindling, and two CaN inhibitors, FK506 and CsA inhibited progression of electrical kindling in rats [176] Several recent studies have demonstrated an inhibitory modulation of GABA-A receptor function by CaN [177]. CaN activity also be involved in the biochemical changes leading to picrotoxin-in-

duced epileptic seizures, because picrotoxin binding to GABA-A receptors results in a net disinhibition of cellular excitability and may lead to increased dephosphorylation. Thus, CaN inhibition might favor GABAA receptor activation antagonizing the effect of picrotoxin [178] demonstrated a significant increase in CaN activity in cortical and hippocampal homogenates during status epilepticus induced by pilocarpine, occurring through a NMDA-dependent mechanism [179]. Importantly, protective mechanism of FK506 involves the reduced formation of free radicals either directly or indirectly by NOS inhibition by CaN inhibition, thereby reducing NO formation in kindling [180].

(F) Calcineurin in ischemia

In inflammation, bacterial products and pro-inflammatory cytokines induce the expression of inducible nitric oxide synthase (iNOS) and formation of high amounts of NO and CaN inhibitors CsA, FK506 and pimecrolimus reduce iNOS expression and NO production in response to inflammatory stimuli by enhancing the decay of iNOS [181]. It has been also demonstrated that the inhibitors of CaN and PP1/PP2A could enhance nNOS phosphorylation at Ser847 site after ischemia, thus CaN inhibitors may serve as a potential and important neuroprotectant in therapy for ischemic stroke [182]. The most cited mechanism for tacrolimus- and CsA-mediated neuroprotection is by attenuation of NO-related free radical production via inhibition of NOS [183] Tacrolimus was shown to have the ability to extend the therapeutic time window for thrombolysis without increasing the risk of hemorrhagic transformation in a clot embolization stroke model [184].

(G) Calcineurin and cardiovascular diseases

CaN also have been implicated in the pathogenesis of cardiac hypertrophy and congenital heart disease [185,186]. One prohypertrophic pathway that has received much attention involves the ubiquitously expressed Ca^{2+}/calmodulin-activated phosphatase CaN. CaN possibly plays a role in the progression of right ventricle myocardial hypertrophy in rats with chronic hypoxia. Blocking L-type Ca^{2+} channels with CsA effectively prevents the development of myocardial hypertrophy possibly by inhibiting calcium influx and suppressing CaN activity [187]. Considering the dominant role of the CaN pathway in cardiac hypertrophy and failure, CaN-inhibitory strategies may lead to the identification of novel therapeutic approaches for patients with cardiac disease [188].

(H) Calcineurin and learning and memory, Alzheimer's disease, Aging

CaN has been implicated in numerous physiological processes including learning and memory (Hernandez-Espinosa and Morton, 2006). Growing body of evidences suggested that upregulation of CaN in aged rats negatively correlates with cognitive functions [189,156] and downregulation of CaN by an autoinhibitory peptide improves memory in rodents [190]. It has been reported that CaN-mediated activation increases in rat hippocampus during aging [191]. During aging in human and rodents, overall PP1 and CaN activity increase in the brain, which might be responsible for learning and memory failures, cognitive decline and altered synaptic plasticity [134,192,154].

Abnormal tau hyperphosphorylation, one of the hallmarks of AD, might results from an imbalance between protein kinases and protein phosphatases, such as PP1, PP2A, PP2B (CaN) and PP5 [193,134,129,47]. In one of the studies in AD affected brains, PP2A, PP1, PP5 and PP2B accounted for approximately 71%, approximately 11%, approximately 10% and approximately 7%, respectively, of the total tau phosphatase activity of human brain [193]. It is also suggested that CaN-NFAT signaling pathway activation increases in intracellular calcium concentration that stimulate BACE1 expression, resulting in accelerated Aβ generation, in Tg2576 and its pharmacological inhibition reverses Aβ dependent associative learning and memory [194,195]. Apart from this, in APP/PS1 doubly transgenic mice CaN trigger inflammatory responses typical of AD [196]. More significantly, inhibition of CaN protects neuronal cells from Aβ-induced cell death [197] and abolishes A-induced perturbations of LTP that are promoted by Aβ in hippocampal slices [198].

A growing body of evidence implicates impairment in brain insulin signaling in early SAD pathology. ICV-STZ treatment causes impairment in PI3K/Akt IR signaling which further leads to decreased cerebral uptake and hypometabolism of glucose [81,80], reduced synthesis of acetyl CoA ultimately result into cholinergic deficiency [85,76] and thereby memory deficit [104,99,90]. Accumulated data indicate that CaN is negatively regulates learning and memory [134,199,200]. In addition, acute inhibition of CaN with pharmacological inhibitor FK506 restores associative learning and memory in Tg2576 APP mice [201,194]. Moreover, in a recent study, FK506 significantly improved memory performance against 3-nitropropionic acid-induced neurotoxicity [167].

Accumulating data explains the etiology of SAD that is postulated on neurochemical alterations comprise the insulin resistance, impaired glucose and mitochondrial energy metabolism [26] that lead to neuronal excitotoxicity (Shoham et al., 2007), Ca^{2+} overactivation [106], and consequently leads to kinase-phosphatase imbalance [115]. It is important to note that L-type calcium channel blockers have shown beneficial effects on learning and memory in AD patients (202) as well as in various animal models of dementia [203]. Further, reduced energy metabolism in neurons results into depolarization-induced release of glutamate causing glutamate excitotoxicity, which is blocked by L-type Ca^{2+} channel blockers. Its addition, ICV-STZ administration increased intracellular Ca^{2+} leading to consequent development of neurotoxicity which is blocked by lercanidipine, a L-type Ca^{2+} channel blocker [106,138]. Adding to this, the activities of PI3K/Akt decrease and MAPK, JNK and ERK increased following ICV-STZ administration [111]. Of particular interest, phosphatase activation is suggested to be major culprit for development of SAD and CaN a Ca^{2+}/calmodulin dependent enzyme is among the first postsynaptic phosphatase to be activated after Ca^{2+} influx [159]. Thus, CaN being a phosphatase may be involved in pathogenesis of SAD.

Oxidative stress has been implicated in the pathogenesis of AD in humans (Pratico, 2008; 204]. Importantly, central STZ-induced impaired IR signaling is responsible for ATP depletion and mitochondrial disturbances that causes increased intracellular Ca^{2+} influx and generation of reactive oxygen species (ROS) leading to oxidative stress [85,138]. It has been reported that oxidative stress regulates Ca^{2+} dependent serine-threonine phosphatase, CaN [205]. In addition, mitochondrial dysfunction and oxidative stress has been observed in CaN transgenic mice indicate CaN induced oxidative stress [206]. However, the exact mechanisms of antioxidant effect of FK506 are not clear, but several possibilities can be proposed. First, FK506 possess direct radicals scavenging properties (207) and improved antioxidant defense mechanisms. It has been reported that CaN by dephosphorylation NFAT, a substrate of CaN, produces free

radicals [208] whereas FK506, inhibitor of CaN, prevented NFAT-dephosphorylation and subsequent free radical generation demonstrating the role of CaN and reduces the formation of free radicals and oxidative stress [180,209,210].

It has been reported that FK506 provide neuroprotection in haloperidol-induced orofacial dyskinesia and pentylenetetrazol-induced kindling possibly by antioxidant mechanism [180,209]. Of particular relevance to this, it has been previously shown that FK506 negatively regulates Ca^{2+} channel and inhibiting Ca^{2+} dependent release of glutamate from presynaptic vessels [211] and also inhibits the mitochondrial permeability transition opening triggered by increase in Ca^{2+} level in mitochondrial matrix [212]. In addition, FK506 is reported to protect dopaminergic and GABAergic neurons by decreasing free radical generation [180,209,213] without affecting inflammatory mechanism [214,215]. Further, ICV-STZ administration also results Ca^{2+} dependent production of NO. Further, NO as a precursor for free radicals reacts with superoxide anions to form peroxynitrite causing nitrosative stress following ICV-STZ administration [85,167]. The strongest support that CaN dephosphorylate NOS resulting in increase of NO [215]. It has been observed that FK506 by CaN inhibition and blockade of Ca^{2+} channel inhibits the free radical generation and NOS activity [217,218].

In brain, STZ causes neurodegeneration accompanied by increase in LDH activity [53]. In neurons of CNS, Ca^{2+} mobilization following glutamate stimulation of NMDA receptors is strongly implicated in cell death. The Ca^{2+} sensitivity for NOS makes Ca^{2+} dependent phosphatase CaN an obvious candidate for affecting cell death in neurons [219] and therefore, CaN may be a material factor in Ca^{2+} activated cell death in neurons [220,189]. In addition, increase in LDH level is due to the overactivation of CaN has also been reported [221,22]. It has been suggested that GSK-3 activation (GSK-3α/β) which is activated by inhibition of inhibitor-1 (I-1) via CaN contribute towards various neuropathological changes [49]. It has been speculated that that overactivity of CaN increase the activity of GSK-3α/β leads to memory loss [115]. Indeed, GSK-3K enhances calcineurin signaling [223]. These potential findings associate the linkage of CaN to cognitive dysfunction, impairment of cellular oxidant/antioxidant defenses, cholinergic deficits and neuronal damage following ICV-STZ administration [224].

Conclusion

In conclusion, the present findings associate the linkage of CaN to cognitive dysfunction, impairment of cellular oxidant/antioxidant defenses, cholinergic deficits and neuronal damage following ICV-STZ administration.

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