Molecular Basis of Role of Insulin Resistance in Pathophysiology of Alzheimer's Disease

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ABSTRACT

Background:*The older population in the world is more predisposed to development of diseases linked to oxidative stress, mitochondrial dysfunction and endoplasmic reticulum stress including neurodegenerative disease and insulin resistance. Alzheimer's disease (AD) is the progressive neurodegenerative disease. It contributes to major cause of dementia in older population. Ageing is the most predominant factor in the pathology of AD with 65 years or older age group is more prone to disease. The cognitive impairment is mild in the initial stage of Alzheimer disease but the severity of dementia exacerbates with the progression of AD.*
The insulin resistance is marked by hyperinsulinemia contributing to glucose intolerance manifesting as chronic hyperglycemia. The cascade of molecular events further triggers reactive oxygen species-mediated oxidative damage of biomolecules. These events subsequently precipitate inflammatory response by immune cells leading to irreversible injury to cells and neurons.
Aim & Objective: *The aim of the paper is to find out molecular basis of insulin resistance in pathophysiology of Alzheimer's disease. Present paper reviews various molecular events in insulin resistance that are associated directly or indirectly with the pathophysiology to Alzheimer's disease.*
Research Methodology: *Research design encompassing critical analysis, qualitative analysis and retrospective research study is followed using secondary data from books, monographs, journals, conference proceedings for the evaluation leading to conclusions beneficial either for future research study or in understanding intricate molecular events between insulin resistance and Alzheimer's disease.*
Result: *Based on the research design, study revealed several common stressors involved in the pathogenesis of insulin resistance and Alzheimer's disease. Drug designing targeting stressors could help to ameliorate the severity of Alzheimer disease*
Originality of Paper: *Comprehensive approach was adopted to include papers related to the topic within frame-work of research design to deduce conclusion.*
Paper Type: *Critical analytical review paper*
Keywords: Alzheimer disease, Amyloid beta peptide, Dementia, Diabetes mellitus type 2, Glucose intolerance, Insulin resistance, Insulin sensitivity

1. INTRODUCTION :

1.1 Overview Insulin Resistance

Under normal health condition, rising blood glucose level activates pancreatic beta cells and releases insulin into blood circulation. Insulin promotes glucose uptake in the insulin sensitive cells (skeletal muscle, adipose tissue and liver cells) and it enhances the utilization of glucose in the body tissues. Glucokinase constitutes the glucose sensing molecule in pancreas, intestine, and brain cells [1]. Glucokinase amplify insulin secretion in the beta cells in response to rising glucose plasma levels. Owing to its main role in regulation of secretion of insulin in beta cells, it is described as beta-cell sensor in pancreas. Its importance is further substantiated by the mutations of genes encoding glucokinase enzyme culminating into either hypoglycemia or hyperglycemia in the affected population [1]. Additionally, intake of meal initiates cascade of physiological events including absorption of glucose by mucosal cells of small intestine, release of gastrointestinal hormones, secretion of insulin, de novo

lipogenesis, glucagon action, and glucose catabolism in tissues synchronously operate for the control of postprandial rise in blood glucose level in body [2].

Insulin resistance is non-response or attenuated biological response by the insulin sensitive cells to the action of either normal or raised levels of insulin implicated into dysregulated glucose homeostasis in body [3]. Insulin secretion from beta cells in pancreas increases in state of insulin resistance leading to hyperinsulinemia that is compensatory mechanism to control postprandial hyperglycemia. The compensatory hyperinsulinemia regulate glucose homeostasis in early stage that eventually fails to regulate plasma glucose level leading to fasting and or postprandial hyperglycemia [4]. Prolonged and untreated state of hyperglycemia is implicated into myriad of clinical manifestations including neurodegenerative diseases owing to oxidative stress, mitochondrial dysfunction, liberation of proinflammatory cytokines, activation of Caspases, activation of microglia, failure of synapse and neuronal apoptosis [5]. The insulin resistance is associated with raised levels of triglyceride-rich lipoprotein (TRL) along with apolipoprotein B-48–containing TRL (derived from intestine) in the fasting plasma glucose as well as in postprandial plasma glucose [6]. The intestinally derived apolipoprotein B-48–containing TR lipoprotein may exert oxidative injury on the endothelial wall leading to start of atherosclerotic changes in the capillaries [7]. Thus, these remnant lipoprotein particles due to their oxidative potential, might be insinuated in the pathology of cardiovascular diseases, and hypertension [7].
Insulin resistance is strongly linked to central obesity, dyslipidemia, hyperglycemia, hyperinsulinemia involving rise in triglycerides, and low-density lipoprotein cholesterol in plasma and reduced levels of high-density lipoprotein cholesterol in plasma [8].
Central obesity mediates release of proinflammatory cytokines involving tumor necrosis factor-alpha (TNF-a), and Interleukin-1 and Interleukin-6 via IKK-beta/NF-kappa-B pathway [9] that might be closely associated with exacerbating peripheral insulin resistance and impending brain insulin resistance and thus initiating cascade of molecular events culminating into pathology of Alzheimer's disease and other neurodegenerative diseases [9].
Insulin resistance impairs glucose homeostasis in body and brain leading to glucolipotoxicity [10] involving glucose hypometabolism and deficit of energy in certain regions of brain. The brain glucose hypometabolism has been reported to develop decades earlier than the clinical manifestations of Alzheimer disease [10].

Conclusively, central metabolic dysfunction owing to insulin resistance plays a role in the pathology of Alzheimer's disease (AD).
Whitmer *et* al [11] have concluded through the cohort study the presence of oxidative potential of visceral obesity higher than the subcutaneous fats in body. Furthermore, central obesity in the middle phase of life is identified as the potential risk factor in pathology of neurodegenerative disease including AD. Although it is difficult to establish precise correlation between metabolic disorders and Alzheimer's disease in patients owing to existence of comorbidities and etiological heterogeneity. The Aho [11] conducted cohort study and proved association among vascular injury in brain, vascular dementia, classical beta-amyloidproteins in brain areas, and metabolic disorders in the pathogenesis of Alzheimer's disease.
Insulin resistance, metabolic disorders and AD might share common causative factor [7]. The systemic mitochondrial dysfunction contribute to impaired bioenergetics and is implicated in the vicious cascade of molecular events leading to development of altered brain energetics and brain energy hypometabolism[9].

2. LITERATURE REVIEW :

A literature review shows the broader view of the works on particular topics published in the past. Literature review can be narrative in which discussion of the earlier works is done, and it can be critical review of the earlier published works in which critical analysis is done related to the work based on the earlier studies which in turn lead to beneficial conclusions which serve either as source for future study or source of knowledge for the implication in the particular field to overcome the present day issue affecting the mankind.
The literature review was performed critically related to Alzheimer's disease and association between insulin resistance and Alzheimer's disease in the present study.

2.1 Alzheimer's disease:

Alzheimer's disease (AD) is the chronic neurodegenerative disease that progresses with age [11]. Alzheimer's Association Report[12]postulated "2020 Alzheimer's Disease Facts and Figures" that is a statistical reserve for United States data pertaining to Alzheimer's disease. It is a frequent cause of dementia in population. The report portrays that nearly 5.8 million [12] Americans of age sixty five years and older age group [12] suffer from Alzheimer's dementia in 2020. By 2050, the prevalence of Alzheimer's dementia might affect 13.8 million [12] Americans aged 65 years and older population.

Alzheimer disease manifests clinically into two forms namely familial or early-onset AD (FAD), and Sporadic or late-onset-AD (LOAD) [13]. The former form of AD represents nearly 5% of the total patients of AD[13]. The genetic mutations substantially contribute to the pathology of FAD that manifests earlier in life prior to 65 years of age. The implicated genetic mutations in FAD are amyloid precursor protein (APP gene) [14], presenilin 1 (PSEN1gene) [14] and presenilin 2 (PSEN2 gene) [14].
The latter form of Alzheimer's disease constitutes around 95% of the total AD cases [14]. It is mostly manifests clinically after age of sixty five years and constitutes major form of Alzheimer's disease in the affected population. Advancing age is the prominent predisposing factor for the pathogenesis of LOAD [15].
Although precise genetic involvement in the pathogenesis of LOAD is still to be decoded, moreover, Apolipoprotein-Eepsilon-4 allele [16] (APOE4) is mutated gene and is closely implicated in the development of impaired cholesterol metabolism and dyshomeostasis of altered beta-amyloid peptide (Ab) in brain regions [17] exhibiting neurotoxicity as in figure1.

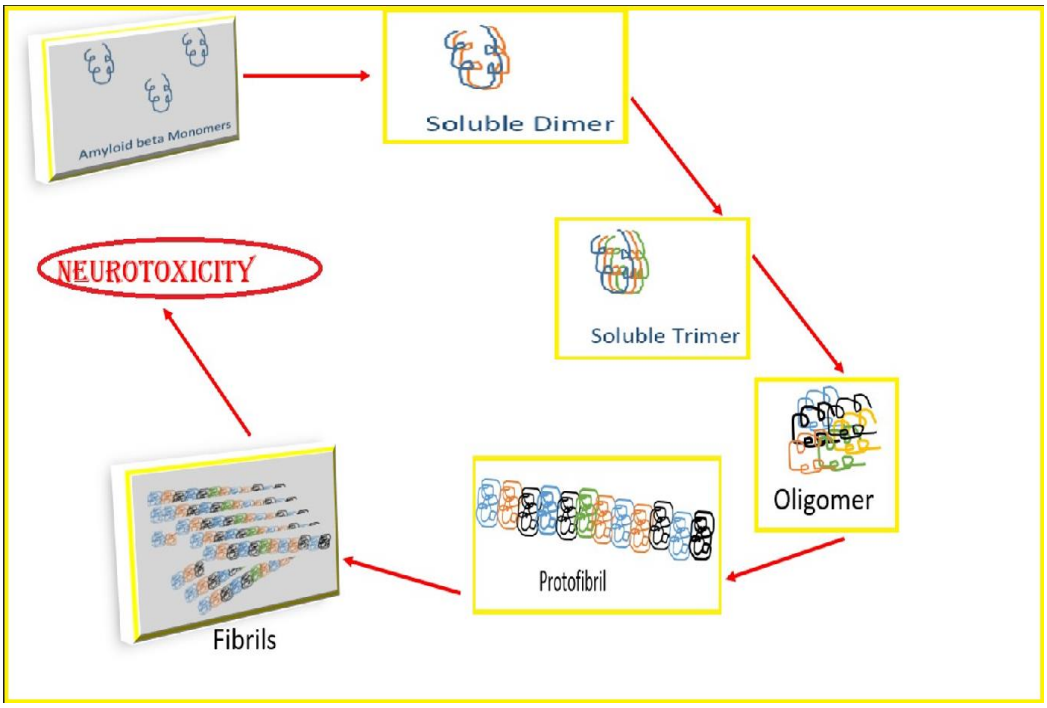

Fig. 1: Hypothetical Diagram Showing Amyloid Beta Neurotoxicity in Brain

The Alzheimer's disease is marked with consistent decline in memory characterized by recalling latest events in initial stage of development of AD [18]. The neuropathological feature in AD is the neurofibrillary tangles (NFTs) that constitute a hallmark in AD [19]. These are made up of hyper-phosphorylated microtubule-associated protein tau in brain region. Braak and Braak [20] identified the NFTs initially in medial temporal lobes and subsequently infiltrated cortex.
Hardy and Higgins [21], Hardy and Selkoe [22] further more substantiated the involvement of amyloid beta protein in mediating oxidative damage of biomolecules, mitochondria leading to failure of synapses and apoptosis of neurons in the areas of brain in the pathology of AD. These molecular events can be described by Amyloid Cascade Hypothesis of AD.The clinical course of AD is the continuous progression manifested with asymptomatic phase without any cognitive impairment and behavior

alteration [22]. Additionally, Sperling *et al* [23], Sridhar *et al* [24] documented microscopic changes in the anatomy of brain in patients suffering from Alzheimer's disease even during the clinically dormant phase of AD. The continuity of pathological changes in brain finally lead to progression of clinical manifestations of AD [23]. The disorientation, speech problem, lack of motivation, changes in behavior, self-neglect and mood changes become evident in patients in later phase of AD [25].
Despite the discussed above namely amyloid beta protein, hyper-phosphorylation of TAU protein [25], genetic mutations in FAD [25] and role of Apolipoprotein-Eepsilon-4 allele [25] in LOAD have been proved as the causative factors in the pathogenesis of AD. However, the precise etiology of AD is still more complex than what we have decoded by the time. Glenner *et al* [26] commented on the challenges in understanding the AD including research gap in grasping the complexity of the pathophysiology of the LOAD and not the FAD form of disease, and paucity of well-established biomarkers to mark the onset of disease, course of disease and the end-point criteria.

2.2 Association in Insulin resistance and Alzheimer's disease:

Pathology of Alzheimer's disease is complex and includes additional factors as insulin resistance, dyslipidemia [24], glucose intolerance and obesity that stem in the midlife and subsequently can impair central metabolic functions including the brain glucose metabolism and energetics with higher propensity towards developing neurodegenerative diseases including Alzheimer's dementia [23-26]. Kivipelto *et al* [27] studied the role of metabolic dysfunction in midlife to the risk of developing AD in older life. Haass *et* al [28], de la Monte [29] supported the hypothesis that deficiency of insulin in brain and deficit of insulin-like growth factor (IGF-1) [13] in brain is culminated into impairment of cognitive functions and neurodegeneration. Insulin resistance marked by hyperinsulinemia [8] and hyperglycemia [12] has potential for oxidative damage [22] both upon the peripheral tissues as well as in the brain tissues, thus sharing common causative factors in the pathology of diabetes and Alzheimer's disease.
In the present review paper, cascades of molecular events in the pathology of insulin resistance and its role as predisposing factor in the pathophysiology of Alzheimer's disease shall be discussed.

2.3 Aim of Study:

The study is aimed to identify "Molecular Basis of Role of Insulin Resistance in Pathophysiology of Alzheimer's disease".

2.4 Objectives:

(1) To identify molecular basis of pathophysiology of insulin resistance
(2) To identify molecular basis of pathophysiology of Alzheimer's disease
(3) To identify role of molecular events of insulin resistance in pathophysiology of Alzheimer's disease

2.5 Scope of Study:

Present study has scope in the field of neurology. Study outlines molecular signaling events involved in pathophysiology Alzheimer's disease mediated with insulin resistance. Study helps in understanding the causative potential of insulin resistance in pathophysiology of Alzheimer's disease. Present study has scope in the pharmaceutical field. The insulin resistance's stressors could have role in the pathophysiology of Alzheimer's disease as both diseases are age dependent and might be the target of novel drug molecules helping in amelioration of the clinical symptoms of both diseases and delay the progression of Alzheimer's disease.

2.6 Significance of Study:

Present study significantly furnishes academic and clinical knowledge beneficial to the neurologist and neurosurgeon, moreover, the study provides fundamental knowledge to students and research scholars in the field of life science and medicine.

2.7 Limitations of Study:

- ✓ Paper is focused to include only Alzheimer's disease excluding other neurodegenerative diseases
- ✓ The sources of secondary data are limited. Additional sources could be included.

3. RESEARCH METHODOLOGY :

3.1 Research Design

Critical analytical, Qualitative and Retrospective research design

4. MOLECULAR BASIS OF INSULIN RESISTANCE :

Insulin induces activation of Ras/Raf/MAPK [30] signalling pathway and PI-3K/Akt [30] pathway involved in the actions of insulin on body tissues. (Evans-Anderson et al. 2008). Activation of former signalling pathway regulates mitogenic [26, 30] effect of insulin while the latter signalling pathway controls metabolic and physiological effects [30] of insulin on tissues.

4.1Akt/FOXO1/GSK3b Impaired Signalling in Insulin resistance:

Insulin binding with its cell surface receptor on the target tissue leads to activation of insulin receptor [32].It is a heterotetrameric glycoprotein composed of two α-subunits [31, 15] located on extracellular surface while two β-subunits [31] running across the length of cell membrane. Insulin binding activates the insulin receptor [32]. Insulin attachment to α-subunit leads to activation of tyrosine kinase activity in the β-subunits. It spurts into autophosphorylation at Try1162 [33], Tyr1163 [33] and Tyr1158 [33]. This marks the phosphorylation and activation of insulin receptor that subsequently activates insulin receptor substrate (IRS-1 and 2) [33], and several adaptor (Guo et al. 1999) proteins [32] namely Grb-2-assocated protein (Gab1) [34], adaptor protein Cbl [34], APS adaptor protein [34] and Shc adaptor protein [34] which in turn provides docking sites to many downstream effector molecules [34].

Activated insulin receptor substrate (IRS-1) phosphorylates phosphoinositide 3-kinase which in turn binds with Phosphatidyl-inositol 3,4-bisphosphate (PIP2) [23] and converts it Phosphatidyl-inositol 3,4,5-trisphosphate (PIP3) that serves as 2nd messenger [18] inside the cytosol. The PIP3 activates protein kinase B/Akt and subsequent activation of downstream effector molecules take place for the metabolic effects of insulin [35].

The activated Akt phosphorylates the SNARE proteins [35] inside cytosol and mediates translocation of glucose transporter (GLUT-4) [35] containing storage vesicle (GSV) from the cytosol to the inner surface of cell membrane leading to uptake of glucose from blood circulation and helps to normalize postprandial hyperglycemia [35].

Activated Akt further phosphorylates and inhibits the glycogen synthase kinase 3b that suppresses the glycogen synthase and thus promotes glycogenesis in liver and tends to reduce postprandial hyperglycemia [36].

The forkhead transcription factor (Foxo1) [37] is localized in the nucleus and controls the transcription of protein involved in the regulation of gluconeogenesis in liver [37]. Activated Akt moleculefurther phosphorylates Foxo1 at S^{256}.

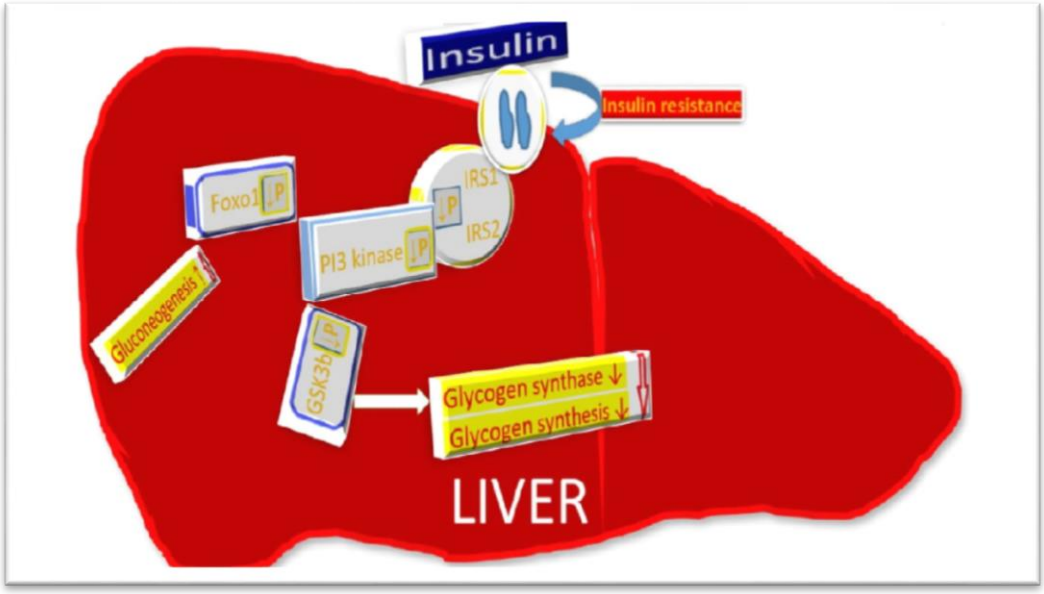

Fig. 2: Hypothetical Diagram Showing Impaired Insuling Signalling In Insulin Resistance

It undergoes nuclear exclusion and is localized in the cytosol. Phosphorylated Foxo1 passes through ubiquitination and proteolysis by the proteasome and thus suppressing the gluconeogenesis in liver [36, 38].

Therefore, activated protein kinase B/Akt mediated phosphorylation of forkhead transcription factor Foxo1[38] is the centre stage of determining insulin sensitivity and glucose homeostasis **Impaired activation and phosphorylation of Akt mediates dysregulated translocation of GSVs from cytosol, impaired Foxo1 phosphorylation, impaired Foxo1 translocation, activation of gluconeogenesis, de-phosphorylation and over-activity of GSK3b, inhibition of glycogen synthase and suppression of insulin mediated glycogenesis manifesting as insulin resistance, hyperinsulinemia, hyperglycemia, and glucose intolerance as shown in fig. 2.**

Araki *et al* [39] conducted study involving experimental mice with targeted knockout of IRS-1 gene resulted into deficient IRS-1 protein and failure to phosphorylate and activate downstream effector molecules including protein kinase B and Foxo-1 [38] manifesting into peripheral insulin resistance especially in skeletal muscles and retarded growth of mice [30, 39].

Dong *et al* [40] characterized targeted deletion of gene IRS1 and gene IRS2 in the liver cells of transgenic mice (L-DKO mice) led to inhibition of activation of protein kinase B/Foxo1 in liver cells manifesting into glucose intolerance, insulin resistance and diabetes mellitus

Conclusively, inactivation of Akt leading subsequent to suppression of IRS1 and IRS2 leads to failure of phosphorylation and nuclear localization of Foxo1 afford fundamental molecular basis in the pathology of insulin resistance, that might be insinuated in both classical and non-classical insulin sensitive tissues, hence, altering peripheral glucose homeostasis culminating into peripheral glucose intolerance, peripheral hyperglycemia, and cerebral glucose hypo-metabolism which synchronously predispose to pathophysiology of Alzheimer's disease.

4.2 Role of P85 and P110 Subunits of PI3 kinase in Insulin resistance:

The PI3 kinase is made up of two subunits as regulatory subunit (P85) [41] and catalytic subunit (p110) [41]. The former subunit is covalently bound with latter subunit of PI3 kinase. Still, there is free pool of P85 subunits [42] in the cell that is not bound to P110 subunit, thus leading to existence of free P85 monomer to P85:P110 heterodimer [42] which are in dynamic equilibrium in cytosol [42]. The heterodimer p85-p110 [42] controls the enzymatic activity of PI3 kinase. Furthermore, p85 subunit and the p85-p110 heterodimer have competition for similar attachment sites located on the tyrosine-phosphorylated insulin receptor substrate [43, 44]. Thus, increase in concentration or reduction in the concentration of p85-p110 heterodimer could lead to the increase or decrease of PI3 kinase activity leading to alteration in phosphorylation of AKT and downstream effector molecules [45].

4.3 Role of c-Jun N-terminal kinase (JNK) phosphorylation pathway in Insulin resistance and Alzheimer's disease:

Another hypothetical model for insulin resistance manifestation and its involvement in AD is the activation of c-Jun N-terminal kinase (JNK) [46].

Several extraneuronal and intraneuronal stimuli including reactive oxygen species, amyloid beta peptide, hyper-phosphorylated [47] Tau protein, and oxidized mitochondrial DNA segments mtDNA [46] could activate toll-like receptors and tumor necrosis factor alpha R on the cell surface [47].

Activated receptors in turn phosphorylate IκB kinase (IKK enzyme) and c-Jun N-terminal kinases [48] (protein kinases regulating cell stress, inflammation, cell signalling neuronal plasticity) [47]. The activated c-Jun N-terminal kinases [48] mediate phosphorylation of serine residue on the insulin receptor substrate (IRS1) [49] leading to impaired tyrosine phosphorylation of IRS1 which further characterize into decline in activation of PI3 kinase and reduced phosphorylation of downstream Akt and impaired signalling in the cell manifesting as insulin resistance [50].

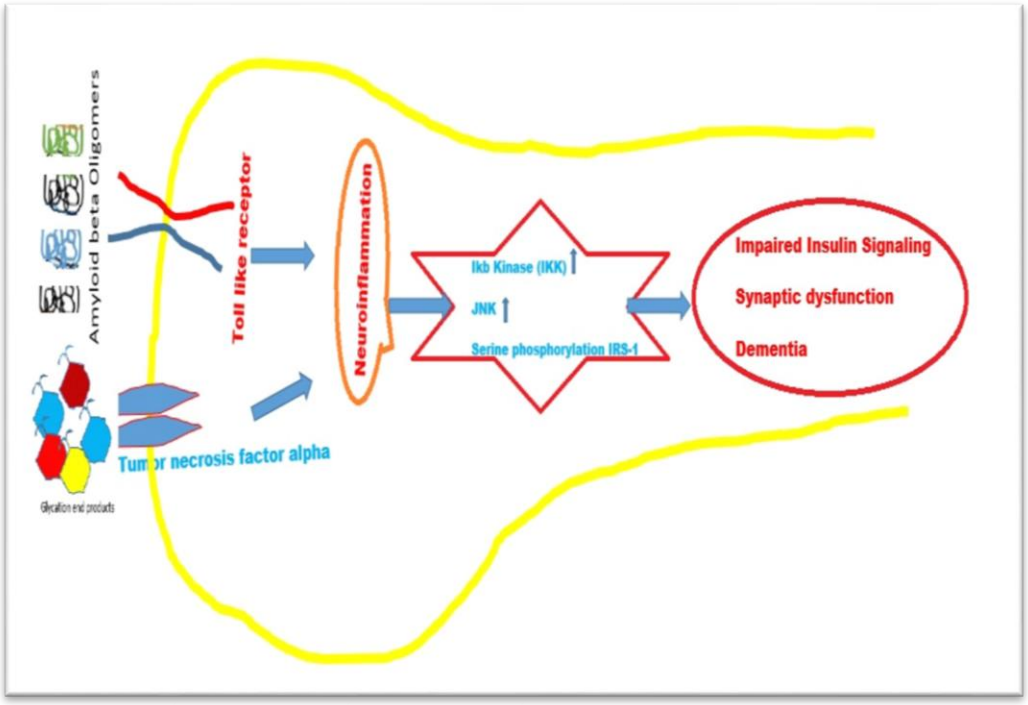

Fig. 3: Hypothetical Diagram Showing Impaired Insulin Signaling In Neuron In Alzheimer's Disease

Moreover, serine phosphorylation of IRS1 suppresses interaction of insulin receptor with IRS1 leading to inhibition of insulin effect on the insulin receptor causing insulin resistance.

Insulin resistance is the cradle of several clinical manifestations through expression of myriads of molecular events leading to manifestations of several disorders including neurodegeneration and AD.

5. INSULIN RESISTANCE, PROTEIN KINASE B/AKT AND TAU PROTEIN IN ALZHEIMER'S DISEASE :

Protein kinase B is the serine/threonine-specific protein kinases. These have significant activity in the regulation of multiple physiological and metabolic functions in body namely glucose metabolism, cell proliferation, apoptosis [51], cell migration and gene transcription [51]. Insulin binding with insulin receptor mediates molecular events cascade resulting into activation of Akt along with downstream molecules [52]. Insulin resistance impair the insulin signaling pathway leading to inhibition of activation of Akt, and increased activation of glycogen synthase kinase 3beta (GSK3β) [52] that is closely related to phosphorylation of Tau protein [46].

6. INSULIN RESISTANCE, GSK3B AND HYPER-PHOSPHORYLATION OF TAU PROTEIN IN ALZHEIMER'S DISEASE :

GSK3 is a proline-directed kinase existing in GSK3**α** and GSK3β. The latter isoform mainly expresses in CNS. It is located in axons. It is the predominant kinase phosphorylating tau protein [47]. Insulin resistance raisesGSK3β activationby insulin mediated PI3K/Akt pathway in which insulin resistance leads to inactivation of protein kinase B [48].

Hyper-activation or overexpression of GSK3β raises the phosphorylation of Tau protein leading to its disengagement from the microtubule terminating into aggregate of Tau protein inside axon which is called as neurofibrillary tangles that is the predominant lesion in Alzheimer's disease [50]. Furthermore, the amount of NFTs formation in brain areas in patients with AD certainly depends on activity of GSK3β [50] as in fig 4.

Muyllaert *et al[47],* Avila *et al* [51]studied the axonal transport of hyper-phosphorylated tau and concluded that altered axonal transport of tau is related to neuronal apoptosis in hippocampus leading to cognitive impairment in AD [52]. Additionally, the GSK3β in AD enhances the transcription of pro-apoptotic factors [53], Bax protein [53] and suppresses the transcription of anti-apoptotic factors [53]

leading to exacerbated neurotoxicity, neuro-inflammation and neuronal apoptosis in brain areas resulting in pathology of AD [52].

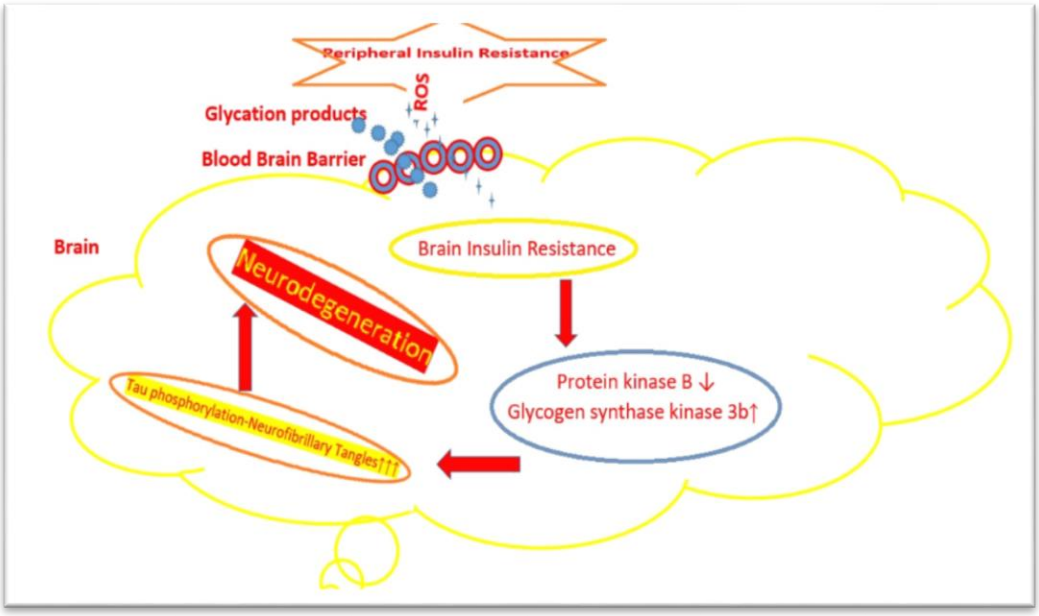

Fig. 4: Hypothetical Diagram Showing Insulin Resistance, Pkb, Gskb3 in Alzheimer's Disease

7. INSULIN DEGRADING ENZYME, AMYLOID B-PEPTIDE AND ALZHEIMER'S DISEASE :

Insulin-degrading enzyme (IDE) is zinc dependent peptidase [54]. It catalyzes degradation of insulin, glucagon, beta-amyloid peptide, atrial natriuretic peptide, and controls proteasomal splitting of proteins [54]. The IDE might be pathological link between insulin resistance and late onset Alzheimer's disease (LOAD) [54] as in fig 5.

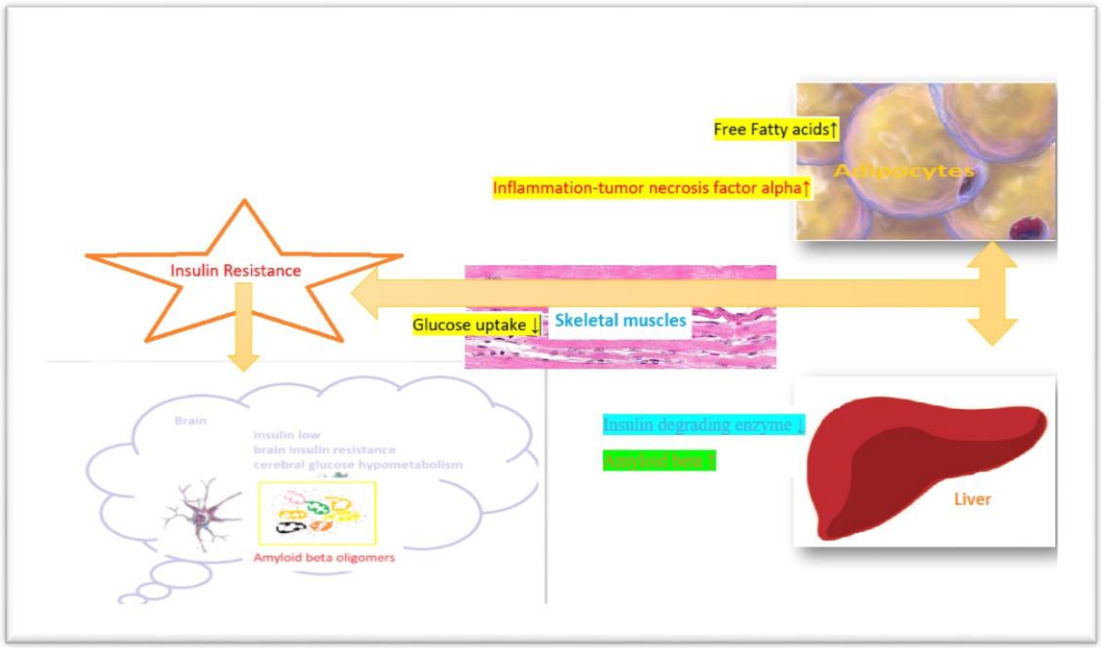

Fig. 5: Hypothetical Diagram Showing Role of Insulin Degrading Enzyme, Insulin Resistance In Alzheimer's Disease

Farris *et al* [55] prepared transgenic mice model [55] of DM2 with homozygous knockout of the IDE gene. It was identified that more than 50% reduced degradation of amyloid beta peptides in primary neuronal cultures and brain membrane fractions. Moreover, nearly same proportion of deficiency in the degradation of insulin was reported [55].

Study clearly proved the essentiality and catalytic role of insulin degrading enzyme (IDE) in the degradation of insulin and amyloid beta [55]. In the similar study, the IDE gene deletion mice showed the surplus accumulation of amyloid beta peptides in the cerebellum that signifies prominent biomarker in the Alzheimer's disease.

Thus, hypo-activity of insulin degrading enzyme could contribute to surplus accumulation of amyloid beta peptides in brain regions due to impaired clearance involving in the molecular pathology of Alzheimer's disease and insulin resistance as shown in figure 4.

8. AMYLOID B-PEPTIDE AGGREGATE AND SYNAPTIC IMPAIRMENT IN ALZHEIMER'S DISEASE :

After the hypo-function of insulin degrading enzyme, the degradation of amyloid beta peptides is decreased significantly leading to their accumulation both inside and outside the neurons in regions of brain [56]. This event is the symbol of Alzheimer's disease leading to severe cognitive dysfunction [57, 58]. The amyloid β peptide aggregates exist either in the soluble for as monomers or dimers or oligomers [54] or in insoluble form as senile plaques [54]. The amyloid beta oligomers inside the neurons can mediate neuro-inflammation [59], oxidative injury, caspase activation [59], release of cytokines and neuronal apoptosis [59] while the senile plaques [54] outside the neurons can impair the permeability of the axonal membrane and alter signalling pathway [59].

Conclusively, cascades of molecular events are implicated in the amyloid beta peptides mediated neurotoxicity, neuronal death, and pathology of Alzheimer's disease with dementia.

9. PERIPHERAL HYPERINSULINEMIA, BRAIN INSULIN RESISTANCE AND IMPAIRED COGNITIVE FUNCTION :

Peripheral insulin crosses the blood brain barrier via saturable transport systems (control peptide entry into brain, respond to both physiological as well as pathological stimuli [60]. Insulin in brain can have peripheral source or central source or both but insulin acts via insulin receptors present in peripheral tissues as well as in brain. The cascades of molecular features by which insulin act in brain as well as in peripheral tissues have similarity [61].

Schwartz *et al* [62] studied the hyperinsulinemic Zucker rats (transgenic mice with obesity) to determine affinity of insulin receptor in brain regions. Schwartz *et al* [62] reported 65% decline in the expression of insulin receptors in capillaries in brain without any alteration in the receptor affinity of insulin in the obese Zucker rats in comparison to the lean Zucker rats.

Thus, insulin receptor expression in obesity, insulin resistance and chronic peripheral hyperinsulinemia is reduced in blood brain barrier. The normal insulin level in brain control metabolism of glucose in the peripheral tissues and brain tissues, regulate synapse functioning, cognitive functions and serve as neuroprotective [63].

These conditions negatively affect the insulin transport across blood brain barrier that leads to decline in insulin transport and reduced insulin level in brain [64, 65] leading to impaired cognitive function and thus implicated in the pathogenesis of Alzheimer's disease [66, 67].

Conclusively, peripheral hyperinsulinemia, and brain insulin resistance negate physiological functions of insulin in brain and enhance neurotoxicity and cognitive impairment in the brain.

10. BRAIN INSULIN RESISTANCE, TAU PROTEIN AND AMYLOID BETA PEPTIDE PATHOLOGY IN ALZHEIMER'S DISEASE :

Peripheral insulin resistance reduces the insulin uptake by blood brain barrier leading to brain insulin resistance that subsequently represents a predisposing factor for the neurotoxicity of amyloid beta peptides in brain in the pathology of Alzheimer's disease [68].

Brain insulin resistance predisposes to overexpression of amyloid precursor protein in brain coupled with impaired cleavage of amyloid precursor protein by β and γ secretases enzymes [69] lead to formation of 40 or 42 amino acids [69] length amyloid β peptides which aggregate into soluble oligomer, insoluble senile plaque and AβPP-Aβ-derived diffusible ligands (ADDLs) [69]. These have

neurotoxicity and mediate oxidative stress and neuro-inflammation in brain regions. The AβPP-Aβ-derived diffusible ligands can mediate over-activity of glycogen synthase kinase 3 beta [70] leading to hyper-phosphorylation of Tau protein in the neurons and their subsequent aggregation into formation of neurofibrillary tangles in neurons [71]. **Conclusively, ADDLs can impair function of insulin-receptors in brain and exacerbate the brain insulin resistance leading to oxidative stress, mitochondrial dysfunction, caspase activation, microglial activation, and neuroinflammation involved in the molecular pathology of Alzheimer's disease.**

11. CEREBRAL GLUCOSE HYPOMETABOLISM IN ALZHEIMER'S DISEASE :

Cerebral glucose Hypometabolism refers to the low uptake and utilization of glucose by brain regions in body. Simpson *et al* [72], Minoshima *et al* [73] involving patients with Alzheimer's disease. The concentration of insulin in CSF and plasma were estimated and reported reduced insulin level in CSF than its concentration in plasma in circulating blood.

Simpson *et al* [74] posited that reduced insulin level in CSF is exacerbated in the progressing Alzheimer disease.

Mosconi [75] estimated the cause of above findings and suggested that insulin resistance in peripheral tissues lead to hyperinsulinemia while decline in insulin in brain results from reduced uptake of insulin by saturable transport system in blood brain barrier from the peripheral source of insulin.

Around 3 decades back, cerebral glucose Hypometabolism was quantitatively estimated by measuring difference in glucose levels in arteries and veins [76, 77, 78].

Chen and Zhong [79], Costantini *et al* [80], Cunnane *et al* [81] posited thatmanifestation of cerebral glucose hypometabolismas a consequence of insulin resistance about 2 decades earlier than the clinical manifestations of Alzheimer's disease. This manifestation could be characterized as pre-symptomatic hallmark of AD.

Glucose transporters GLUT-1 [82] is located in the wall of endothelium in blood brain barrier while GLUT-3 [82] is located in the membrane of neurons for the uptake of glucose in brain.The expression of GLUT 1 and GLUT 3 is reduced in brain regions of patients with AD particularly in the cerebral cortex [82].

Liu *et al* [83] stated that decreased uptake of glucose in brain areas leads to reduction in the O-linked-N-acetylglucosaminylation (O-GlcNAcylation) [83] of intracellular Tau protein in neurons. It represents post-translational modification of Tau protein with β-*N*-acetyl-glucosamine [83]. It is the O-linked glycosylation of Tau protein. Contrarily, phosphorylation of Tau protein is increased that might predispose to the formation of neurofibrillary tangles [83] that are the principle lesion in brain in AD.

Liu *et al* [83] in their study reported the presence of four times lesser O-GlcNAc in the hyper-phosphorylated Tau protein when compared with the non-hyper-phosphorylated Tau.

Thus, negative relationship can be inferred between the O-GlcNAcylation and hyper-phosphorylation of tau protein in brain regions.

Liu et al {83] characterized human embryonic kidney 293 cells (HEK 292 cells, immortal cell line) with targeted deletion of gene O-GlcNAc transferase. The raised phosphorylation of Tau protein was reported in the HEK 293 cell line.

Liu et al [83] selected transgenic mice with brain glucose hypometabolism induced by fasting of rodents. The hexosamine biosynthesis pathway was suppressed in the mice that led to raised phosphorylation of tau protein and reduced O-GlcNAcylation of Tau.

Conclusively, it can be inferred that brain glucose hypometabolism materialize into hyper-phosphorylation of tau protein that certainly has potential for the formation of neurofibrillary tangles, neurodegeneration, mediated through O-GlcNAcylation down-regulation in tau protein that could be implicated into molecular pathophysiology of Alzheimer's disease.

12. GENETIC BASIS OF MOLECULAR PATHOLOGY OF INSULIN RESISTANCE AND ALZHEIMER'S DISEASE :

The cAMP-response element (CRE) is the specific sequence of DNA. It is positioned in the promoter region of genes. The cAMP-response element binding protein (CREB) is positioned in the nucleus. It binds with cAMP-response element (CRE) of promoter gene and serves as transcription factor [83]. Phosphorylation of CREB at Serine residue 133 leads to its activation. So activated and phosphorylated CREB recruits CREB-binding protein (CBP) leading to initiation of transcription of genes [46].

Study [76, 81] provided evidence about the role of CREB in brain neurons involving neurogenesis, plasticity of neurons, synapse transmission, cognition, and memories formation. Study revealed the activity of CREB in the pathogenesis of psychiatric disorders and Alzheimer's disease including neurodegenerative diseases.

12.1 Alzheimer's disease and cAMP-PKA-CREB Signalling Pathway:

In a cAMP-PKA-CREB signalling pathway, cAMP acts as 2nd messenger. The protein kinase A (PKA) is essential for the memory formation and synaptic plasticity.

The adenylyl cyclase is the cytosolic hormone that is activated in response to the hormonal stimulus. Activated adenylyl cyclase further converts ATP into cAMP which in turn phosphorylates and activates the protein kinase A (PKA) inside neuron in brain regions. Activated and phosphorylated PKA phosphorylates and activates nuclear cAMP response element binding protein (CREB) that in turn recruits CREB-binding protein and subsequently bind with CRE located in promoter region of memory promoting genes. Thus CREB mediated transcription of memory promoting genes help in formation of memories [57].

The amyloid beta 42 fragment (Aβ42) in nano-molar concentration could cause reduction in activity of PKA for prolonged period and thus suppressing the phosphorylation of CREB in nucleus in neurons in the hippocampus in culture of cells leading to impaired memory formation, memory deficit and dementia implicated in the pathology of Alzheimer's disease.

12.2 Role of CREB in Insulin resistance:

12.2.1 Chronic Activation of CREB regulated transcription co-activator 2 (CRTC2) in hepatic Insulin Resistance

During fasting state, the plasma levels of glucagon catecholamines are elevated leading to activation of cAMP-PKA induced signalling cascade of molecular events in hepatocytes manifesting into gluconeogenesis. The cAMP-PKA mediated signalling induces de-phosphorylation of the CREB regulated transcription co-activator 2 and activation-phosphorylation of CREB protein in hepatocytes.

SIK2, salt-inducible kinase-2 is the substrate of activated PKA. Activated PKA in turn phosphorylates and inhibits the SIK2 enzyme leading to de-phosphorylation of pCRTC2 and promotes its nuclear localization to act synchronously with phosphorylated CREB. The de-phosphorylation of pCRTC2 occurs either through the action of Calcineurin(Ca2+-calmodulin-sensitive protein phosphatase) or via action of serine/threonine protein phosphatase (PPP4C/PPP4R1) [89, 92].

The phosphorylated CREB is maintained in nucleus along with CREB regulated transcriptional Co-activator (CRTC 2) and recruits the CREB-binding protein. Together, the transcriptional family promotes the transcription of gluconeogenic genes and expression of gluconeogenic enzymes to promote the gluconeogenesis in liver during stage of fasting.

Conclusively, overexpression of CREB and sustained increase in activity of CRTC2 in liver leads to exacerbation of insulin resistance, further leading to hyperglycemia and glucose intolerance.

12.2.2. Obesity, Insulin resistance and Adipose CREB

Obesity refers to raised adipose tissues mass leading to development of proinflammatory environment in adipose tissues and subsequently release of tumor necrosis factor alpha by both adipocytes as well as infiltrated macrophages. Thus, rise in adiposity initiates the inflammatory changes in adipose tissues which further exacerbate the responsiveness of tissues to action of insulin manifesting as insulin resistance [85, 94].

The expression of cAMP Response Element Binding protein is enhanced in adipose tissues under obesity state leading to activation of expression of activating transcription factor-3 (ATF3) that acts as transcriptional repressor and enhances insulin resistance.

In a study involving transgenic mice with adipocytes containing dominant negative CREB transgene led to elevated insulin sensitivity in response to diet and genetic propensity. Conclusively, adipocyte CREB expression is the hallmark in the manifestation of insulin resistance in adipose tissues and should be utilized as a drug target for the management of type 2 diabetes and the prevention of establishment of diabetes in patients with pre-diabetic signs [72, 89].

13. ROLE OF AMYLIN IN PATHOLOGY OF ALZHEIMER'S DISEASE :

Amylin [84] is the islet amyloid polypeptide hormone. It is composed of 37-amino acid residues and secreted by beta cells in pancreas along with insulin secretion. Locally in pancreas, it suppresses

secretion of insulin and glucagon [84]. Possibly, it has binding sites in regions of brain and lowers gastric emptying and enhance satiety, and thus suppresses the post-prandial spurts in plasma glucose levels. Its secretion in insulin resistance is increased [85].

Kawahara *et al* [86], Kandimalla *et al* [87] described that amylin peptide hormone and amyloid β peptide could have similarity in the molecular pathology in brain.

The amylin hormone and amyloid β peptide are involved in formation of oligomers and amyloid fibrils perpetuating their neurotoxicity in brain regions. The amylin oligomers can alter membrane permeability and result into disruption of blood brain barrier and might find entry into brain [87].

Despa *et al* [88] identified additional molecular mechanism of amylin oligomers where these attach on receptors of advanced glycation endproducts [88] located on the endothelium of blood brain barrier thus inducing inflammation and further compromising the health of blood brain barrier.

Amylin oligomers accumulate in the brain regions. The hyperamylinemia could lead to cerebral inflammation.

Jackson *et al* [89] pointed that amylin oligomers in the regions of brain could react directly with the neurons that was proved by the authors through their study on the cultured neurons where elevated calcium levels was reported and this effect had similarity with the findings induced by amyloid β oligomers in the Alzheimer's disease.

14. ROLE OF CERAMIDES IN NEURODEGENERATION IN ALZHEIMER'S DISEASE :

Ceramides [90] are the compound lipids composed of sphingosine alcohol and long chain saturated fatty acids [90]. These are structural components of plasma membranes of the microglial cells and neurons in brain.

These control cell growth, proliferation, and aging of neuronal cells. The hyperinsulinemia and insulin resistance are hallmark of lipid mobilization in adipose tissues and hydrolysis of triglycerides and release of excess of free fatty acids in circulation leading to ceramides surplus synthesis [91].

The ceramides can easily cross the blood brain barrier and exert neurotoxic injury on the endothelium and induce cerebral inflammation [92].

Conclusively, diet with high fat content induced insulin resistance and so peripheral hyperinsulinemia could be involved in the excessive ceramides synthesis due to surplus availability of free fatty acids and hence, can cross blood brain barrier inducing irreversible injury to endothelial cells of BBB causing its disruption, cerebral inflammation, cerebral insulin resistance, oxidative stress, neuronal apoptosis and neurodegeneration together involved in the molecular pathology of AD.

15. ADVANCED GLYCATION END PRODUCTS AND MITOCHONDRIAL DYSFUNCTION IN ALZHEIMER'S DISEASE :

Insulin resistance promote peripheral hyperinsulinemia and chronic hyperglycemia [93] leading to rapid oxidation of intermediates of glucose metabolism imparting high concentration of endogenous advanced Glycation end products contributing to raise concentration of AGE adducts in blood circulation in patients with glucose intolerance [94].

High reactive free glucose or carbonyl containing moieties react with the free amino terminals in protein molecules leading to non-enzymatic synthesis of advanced glycation end-products [95].

The AGE adducts in blood circulation are highly reactive and can interact with receptor for AGE (RAGEs) located on the several cell surfaces and initiate deleterious molecular events in the tissues [96].

The interaction could lead to formation of excessive reactive oxygen species, proinflammatory cytokines release and inflammation in tissues and neurons [97].

Conclusively, insulin resistance could result into formation of AGEs and AGE adducts involved in release of proinflammatory cytokines and might be correlated with dysfunction of mitochondria in cells and neurons.

15.1 Whether AGEs and AGE adducts are implicated into the impaired working of mitochondria?:

The RAGE is the multi-ligands cell surface receptor [98] located on several cell types including the membrane of mitochondria. The interaction between AGE and RAGE on mitochondrial membrane

surface initiates molecular events leading to activation of NADPH2 that donates 2 protons to reduce molecular oxygen in mitochondrial matrix to generate super-oxides and H_2O_2 [99] in mitochondria characterizing into larger levels of reactive oxygen species inflicting oxidative injury on the Electron transport system enzymes.

The ROS reduce the mitochondrial membrane potential leading to opening of mitochondrial permeability transition pores [99] (mPTP) which serves as gatekeeper of the apoptosis of cell. There is release of large amount of calcium ions and pro-apoptotic proteins from the mitochondria into the cytosol inducing degenerative changes in cells and neurons probably implicated in the molecular pathology of AD.

Thus, AGE and AGE adducts mediate oxidative stress in mitochondrial implicated in the molecular changes in the mitochondrial membranes and release pro-apoptotic proteins into cytosol for degenerative changes of cells and neurons

Release of large amount of ROS by mitochondrial dysfunction in tissues and brain could damage almost all types of macromolecules.

Butterfield and Halliwell [100] studied patients with AD and reported that macromolecules like proteins, lipids, sugars, nucleic acids were damaged in the brain of AD patients.

It was provided evidence by estimating raised levels of protein carbonyls and 3-nitrotyrosine modification representing the biomarkers of protein oxidative damage in brain.

Additionally, reports submitted that presence of intermediates of oxidation of sugars in the brain of AD patients

Butterfield and Halliwell [100] identified presence of elevated levels of 8-hydroxydeoxyguanosine s biomarker for DNA damage including damage to mtDNA, while elevated levels of acrolein, aldehydes, 4-hydroxynonal, malondialdehyde were reported in the brain regions of AD patients signifying the presence of large levels of oxidative stress in the AD patients.

16. CONCLUSION :

Central stage in insulin resistance and molecular pathology of AD is the defunct insulin signalling that impair functions of downstream effector molecules leading to glucose intolerance and its associated oxidative stress influencing physiology of almost all the macromolecules in peripheral tissues and brain provoking release of pro-apoptotic proteins, secretion of proinflammatory cytokines, thus inducing inflammation, that further exacerbate the oxidative stress and health of cells and neurons in brain, especially disrupting functions of blood brain barrier resulting into formation of amyloid beta oligomers and hyper-phosphorylated Tau protein mediated neurofibrillary tangles characterizing into neurodegeneration, synapse failure, cognitive impairment involved in the molecular pathology of Alzheimer's disease.

Impaired insulin signalling could be a drug target to normalize in peripheral and cerebral insulin mediated signalling and helps to promote insulin induced neuroprotective, and neurotropic roles in brain regions including improvement in synapse transmission and cognitive functions in the patients with AD.

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