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Glucose Metabolism and Insulin Action in Alzheimer's Disease Pathogenesis

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1. Introduction

Alzheimer's disease (AD) is a neurological disorder characterized by profound memory loss and progressive dementia. The pathological and histological hallmarks of AD include amyloid plaques, neurofibrillary tangles and amyloidal angiopathy, accompanied by diffuse loss of neurons and synapses [1]. Environmental and genetic factors interact in the development of disease. Type 2 diabetes mellitus (DM) appears to be a significant risk factor for vascular dementia and AD in several epidemiological studies [2, 3]. Recent longitudinal studies have shown that AD and disorder of glucose metabolism are related [4, 5]. One explanation could be that vascular complications of diabetes result in neurodegenerative disease [6]. On the other hand, in addition to its peripheral metabolic effects, insulin also appears have important outcome on brain functions. A recent commentary offers two models of the link between type-2 DM and AD, 1. "central insulin resistance" and 2. inflammation. Both mechanisms influence insulin sensitivity in the brain, finally leading to β-amyloid accumulation and, consequently, to AD [7]. Complex molecular mechanisms, referring to insulin and/or insulin like growth factor-1 (IGF-1) signaling could link DM and AD [8]. In fact, there is evidence that altered insulin and/or IGF-1 signaling to brain cells is probably responsible of amyloid accumulation in AD [9] and several independent effects of insulin on brain functions and cognitive performance have been described [10]. Insulin resistance with associated hyperinsulinemia are the mechanisms suggested to explain the increased AD risk in diabetes [11]. Subsequent investigations demonstrated reduced blood glucose levels and increased insulin levels in patients with late onset AD compared to aged controls or patients with vascular dementia. Although the authors concluded that these findings did not support an association between diabetes and AD [12], the same data were reinterpreted as an increased prevalence of insulin resistance in AD. The latter conclusion contradicts the finding that glucose administration could both increase plasma insulin levels and improve cognition in AD. Working under the assumption that increased insulin rather than glucose was responsible for the improvement in memory, further studies were used to demonstrate that the administration of insulin significantly improved memory performance in AD [8, 13]. Hyperinsulinemic euglycemic clamp studies in humans showed improvement

of attention in AD patients and neuroelectric changes in evoked potential induced by insulin [14]. In contrast, increases in plasma glucose that were not accompanied by increases in insulin levels did not influence cognitive performances [15]. The Rotterdam Study was one of the first epidemiology surveys to provide convincing evidence on a relationship between DM and dementia based on a significantly higher prevalence of dementia in patients with insulin-dependent (Type 1) DM compared to non diabetic aged controls [3]. In addition, the possible association between DM-insulin resistance and degree of hippocampal and amygdala atrophy was investigated in vivo by magnetic resonance imaging [16]. The study showed that: 1. Individuals with DM had greater degree of hippocampal and amygdala atrophy compared with subjects who did not have DM; 2. Severity of insulin resistance associated with degree of amygdala atrophy. The inability to convincingly demonstrate a correlation between DM and AD, or find evidence that DM causes neuropathology, led to the alternative hypothesis that diabetes may serve as a co-factor in the pathogenesis of dementia and possibly AD. In this regard, epidemiological studies showed that hyperinsulinemia in patients with APO E_4-negative genotype was correlated with AD-type dementia, whereas in the absence of diabetes, APO E_4+ genotype was also correlated with AD [17], suggesting that APO E_4 genotype and DM contribute independently to the pathogenesis of AD. Correspondingly, post-mortem studies have shown that individuals with DM and APO E_4 genotype had significantly more abundant Aβ deposits and neurofibrillary tangles compared with diabetics who did not have an APO E_4 allele [18]. In this review, we will summarize current evidences supporting the association between insulin action, insulin receptors, IGF-1 and AD, and we will describe the underlying mechanisms.

2. Insulin, IGF-1: Secretion, transport and distribution in human brain

Insulin is almost exclusively synthesized and secreted into the plasma by pancreatic β-cells and has important role in metabolic homeostasis. Although accumulated evidence indicate that insulin is derived from peripheral insulin and transferred by a transporter regulated way through the blood-brain-barrier (BBB), [19, 20] there is also evidence consistent with local synthesis of insulin in the brain. In fact, Schechter et al. demonstrated that insulin can be produced locally in rabbit neuronal cells from culture [21]. besides, Devaskar et al. revealed localization of insulin expressing neurons involved in associative areas of limbic system and areas regulating olfaction [22]. On the other hand, it is now generally thought that insulin synthesis in the brain is restricted is not synthesized to any significant amount in adult developed brain [20]. Over the past few years, it has become clear that insulin and IGF-1 also have intense effects in the central nervous system (CNS), regulating key processes such as energy homeostasis, neuronal survival, longevity, as well as learning and memory. Insulin and IGF-1 bind to tyrosine kinase receptors, the insulin receptor (IR) and IGF-1 receptor (IGF-1R), which share a high degree of identity in their structure and function. Insulin and IR are abundant but selectively distributed in the brain. Rodent studies have shown that insulin binding is highest in the olfactory bulb, cerebral cortex, hippocampus, hypothalamus, amygdala and septum [23, 24]. In the adult mammalian brain, two types of IR were found: a peripheral type and a neuron-specific type [25]. Insulin signaling within the cell is mediated, in general, by two functional cascades, one acting through the phosphatidylinositol-3 (PI3) kinase pathway, and other acting through the mitogen-activated protein kinase pathway [26]. Binding of insulin or IGF-1 induces a conformational

change of the receptor and activates tyrosine-kinase which leads to auto-phosphorylation of the intracellular β-subunit [27]. Tyrosine-phosphorylate IR and IGF-1R β-subunits recruit and subsequently phosphorylate tyrosine residues of the intracellular insulin receptor substrates (IRS). The IRS protein family has at least four members, IRS-1 to -4 [28]. IRS proteins are homologue in structure and function but show distinct tissue distribution: IRS-1 and IRS-2 are widely distributed throughout different tissues and the brain, whereas IRS-3 is only expressed in rodent adipose tissue, and IRS-4 is predominantly localized in hypothalamus, thymus, skeletal muscle, heart, kidney, and liver [29]. IR and IGF-1R are also expressed on brain capillaries and mediate the high efficiency translocation of insulin and IGF-1 into the brain across the BBB [30, 31]. Several studies have shown the highest IR density in olfactory bulb, hippocampal formation, hypothalamus, and cerebral cortex [32, 33]. In fact, in postmortem studies in adult humans, Adem et al. showed the highest IGF-1R density in hippocampus, amygdala and parahippocampal gyrus [33]. Whereas the density of brain IR decreases during age, IGF-1R increases, suggesting that specific insulin mediated signals are involved in aging and possibly cause age associated cognitive decline [34, 35]. Insulin has been shown to cross the BBB by different mechanisms: extracellular pathways, non-saturable transmembrane diffusion or saturable active transport [36]. Currently, the majority of studies suggests that the largest proportion of insulin crosses the BBB by receptor-mediated transport [37]. In contrast, insulin IGF-1 is formed within the CNS during the development and, to a lesser extent, in the mature brain [38]. However, Rotwein suggests that IGF-1 might cross the BBB via an analogous mechanism like insulin [39].

3. Insulin and IGF-1 signaling in Alzheimer's disease

In normal physiology, insulin facilitates memory as demonstrated when administration at optimal doses and in contrast of sufficient glucose availability [15]. Type-2-diabetic patients are insulin resistant and have chronic hyperinsulinemia. The peripheral utilization of insulin reduces insulin transport into the brain, ultimately producing brain insulin deficiency [40], and abrogating the beneficial influences of insulin on the brain functions [15]. Different insulin levels have been observed in different brain regions [30, 41], probably linked to multiple insulin actions in CNS. Studies on type-2-DM animal models have shown a reduced uptake of insulin into the brain. It was observed that obese diabetic Zucker rats have a decreased insulin transport into the brain, reduced brain levels of insulin and peripheral hyperglycemia [30, 36, 41]. Recent studies linked diabetes with AD [8, 9, 18] and suggested that the brain may be influenced by changes in insulin levels and sensitivity. The observations that insulin, insulin receptors and C-peptide levels in cerebrospinal fluid (CSF) appears to be reduced in aging [42], along with the finding that AD patients have lower levels of insulin in the CSF, suggest impaired transport of insulin into the brain [43]. However the salutary effect of insulin on brain functions are reserved under conditions that impair its functioning, such as insulin resistance [44]. Frolich et al. found that neuronal tyrosine-kinase activity is decreased in AD patients compared to age-matched controls [35]. The overall expression of IGF-1R is reduced in AD brains dependent on the severity of the disease. Brain IGF-1 mRNA levels diminish in severe AD, whereas IGF-1 serum levels are increased in early stages of the disease, suggesting that IGF-1 resistance plays a role in the pathogenesis of AD [35]. IRS-1/2 protein expression is reduced in AD brains, and inactivating Serine-phosphorylation of IRS-^{312} and Ser^{616} is improved, leading to impaired insulin resistance and IGF-1R signaling [45]. Given that IRS are widely expressed in the hippocampus, the most studied brain region for learning and memory, it seems to be

plausible that decline of insulin resistance signaling leads to cognitive impairment [46]. Experiments with adult mice lacking liver IGF-1 production with an up of 85% reduction in circulating IGF-1 showed impaired spatial memory in the Morris water maze task compared to wild type litter mates [46]. These findings might explain the reduction of cognitive functions during aging, since IGF-1 serum levels diminish under physiological conditions [47]. Unpredictably, studies in neuronal-IR-knockout mice (NIRKO) did not provide evidence for impairment in learning and memory, proposing that insulin resistance alone is not a key feature in dementia and neurodegeneration [17].

3.1 Glucose metabolism and Alzheimer's disease

Some of the earliest work on senile dementia, which probably corresponded to AD, vascular dementia, or a combination of both, documented the development of altered brain metabolism soon after the onset of clinical symptoms [48, 49]. The metabolic abnormalities consisted of impaired glucose utilization and energy metabolism, with features that resemble type-2 DM [48]. In addition, several studies confirmed that cerebral metabolism declined prior to the deterioration of cognitive functions, suggesting that energy failure is one of the earliest reversible hallmarks of AD. These observations led to the hypothesis that AD-associated abnormalities in energy metabolism are caused by IR action in the brain, i.e. brain diabetes [49].

3.2 Insulin therapy and Alzheimer's disease

There are conflicting findings regarding the effects of antidiabetic therapy on clinical and neuropathology of AD. The Honolulu-Asia Aging Study demonstrated improvement of cognitive function and memory following induced hyperinsulinemia in patients with AD [2]. Conversely, the Rotterdam Study [3] observed increased risk of dementia in subjects with diabetes treated with insulin. In fact, in this prospective study, DM almost doubled the risk of dementia [Relative Risk (RR) 1.9] and patients treated with insulin were at higher risk of dementia [RR 4.3]. In opposition, recent studies suggest that the combination of insulinic therapy with other diabetes medications is associated to a lower neuritic plaques [50] and to slower cognitive decline in patients with AD [13]. Besides, studies in animals have revealed the beneficial effects of peripheral and cerebroventricular injections of insulin on memory and learning [51]. Several studies have recognized that increasing plasma glucose levels improves memory in patients with AD [14, 15, 30]. Increasing plasma glucose levels also increases endogenous insulin levels, raising the query whether memory improvement is due to changes in insulin, independently of hyperglycemia [14], although the exact mechanism remains unclear. Dense IR distributions have been documented in the dentate gyros, CA1, and CA3 fields of the hippocampus [52]. These regions are known to play a role in declarative memory and they are affected earlier and most severely by the neuropathologic changes of AD [53]. Increased plasma insulin levels result in amplified insulin binding in hippocampus. In turn, increased brain insulin levels results in enlarged glucose utilization in the entorhinal cortex [54]. In contrast to the traditional notion that the brain is not an insulin-sensitive organ, insulin-promoted glucose utilization also results in glycolytic production of acetyl-CoA and subsequent increase in acetylcholine [55], a neurotransmitter closely linked to memory function and severely reduced in AD. Craft et al. confirm that elevated insulin without hyperglycaemia enhances memory in adults with AD, when endogenous insulin was suppressed by concomitant infusion of somatostatin analogues [14]. Moreover, the beneficial effect of insulin appears to be reduced when insulin resistance

is present [17]. Craft et al. showed acute effect of hyperinsulinemia in older adults and in patients with AD using a hyperinsulinemic-euglycemic clamps [15]. Low doses of insulin improve memory in normal subjects; AD patients with insulin resistance required higher insulin doses to obtain memory improvement. To date, no genetic risk factors have been identified for these patients, raising the possibility that factors relating to insulin resistance may be important for AD pathogenesis [15].

3.3 Insulin and oxidative stress mechanisms in Alzheimer's disease

Insulin promotes cell membrane expression of N-methyl-D-aspartate (NMDA) receptors, with increased neuronal Ca^{2+} influx [56]. Ca^{2+} influx presumably activates Ca^{2+}dependent enzymes, including α-dependent enzymes and strengthens neuronal synaptic association [10]. A recent study identified a molecular mechanism that protects CNS neurons against β-amyloid-derived-diffusible ligands (ADDL), responsible for synaptic deterioration underlying AD memory failure. The authors found ADDL binding to particular synaptic sites, and the resulting oxidative stress on synapses loss are markedly decreased by the presence of insulin. The protection mechanism does not involve simple competition between ADDLs and insulin, but rather is signaling-dependent down regulation of ADDL binding sites [57]. Another metabolic disturbance of emerging importance in AD involves insulin signaling in the brain. Levels of insulin receptors, glucose-transport proteins, and other insulin pathway components are reduced in some studies of AD brain (central resistance) [30]. Han et al. proposed a central insulin resistance together with decreased brain insulin levels might lead to accumulation of β-amyloid and consequently AD [7]. Insulin and brain derived IGF-1 instigate signals in the brain by activating the phosphatidylinositol-3-kinase-Akt pathway and the mitogen-activated protein kinase-extracellular signal-regulated kinase pathway [58], but it is unclear whether signaling is up-regulated (compensatory) or down-regulated (pathologic) in AD. Aging and life span are also influenced by insulin. Both in AD and in normal aging process mtDNA sustains high levels of oxidative damage **(Figure 1)** [59]. In fact, it was observed the accumulation of Aβ within structural damaged mitochondria isolated from the brains of AD patients [59, 60] and transgenic brains [61], which impair critical mitochondrial enzymes. Dysfunctional mitochondria release oxidizing free radicals, with peroxidation of membrane lipids and output of toxic aldehydes that cause considerable oxidative stress in AD and in normal aging brains [62]. Other essential proteins resulted oxidized, yielding carbonyl and nitrated derivatives, in neuronal cytoplasm in cerebral regions of neurodegeneration, in human brain affected by AD [63]. Subsequently, increased membrane permeability to calcium, and impaired glucose transport aggravate the energy imbalance [64]. Experimental model show that markers of oxidative damage precede pathological changes [65]. Destruction of mitochondria by the oxidation of a dynamic like transporter protein may cause synapse loss in AD [66]. The "receptor for advanced glycation end products" (RAGE) mediates Aβ's pro-oxidant effects on neural, microglial, and cerebrovascular cells [67]. The RAGE receptor is a multi-ligand receptor, and one of its ligands is Aβ [67]. RAGE regulates several intracellular pathways [68], such stimulates expression of b-site Amyloid Precursor Protein (APP)-cleaving enzyme 1 (BACE1) [69], an enzyme that is necessary for Aβ production. Moreover RAGE seems to negatively affect the long term potentiation (LTP) synaptic process of learning and memory [70]. RAGE also exists in a soluble form, structured by alternative splicing [71] or proteolytic cleavage by the metalloprotease 10 (ADAM 10) [72]. Soluble

RAGE (sRAGE) contains the ligand-binding site, but does not have the signaling properties of full-length RAGE (flRAGE). It was observed that flRAGE is engaged in positive feedback mechanisms, enhancing its own production, and limiting sRAGE proposed protective actions. This notion is supported by the finding that flRAGE expression is increased in AD brains [73]. Indeed, studies have shown that sRAGE can inhibit the accumulation and aggregation of Aβ in mice brains [74]. In addition, it has been shown that sRAGE is present at lower levels in the blood and brain of AD patients [75]. Abnormal expression of RAGE in AD brain suggests that it is relevant to the pathogenesis of neuronal dysfunction and death.

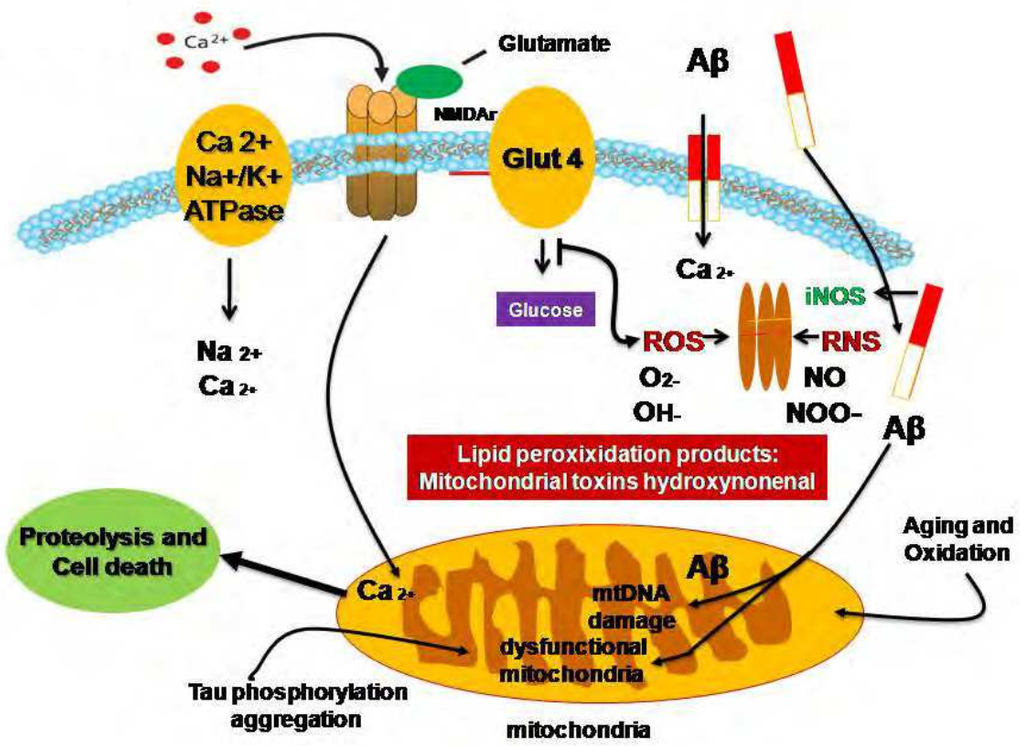

Fig. 1. Oxidative distress

Dysfunctional mitochondria release oxidizing free radicals, and in Alzheimer's disease (AD), they cause significant oxidative stress. Oxidative damage precede pathological changes. Aβ, a strong generator of reactive oxygen species (ROS) and reactive nitrogen species (RNS), is a prime author of this damage. The receptor for advanced glycation end products (RAGE) mediates Aβ's pro-oxidant effects on neural, microglial and cerebrovascular cells. Mitochondrial hydrogen peroxide readily diffuses into the cytosol to contribute in metal-ion-catalyzed hydroxyl radical development. Moved microglia are a major source of the highly diffusible nitric oxide radical. These reactive oxygen species and reactive nitrogen species damage several molecular targets. Peroxidation of membrane lipids yields toxic aldehydes, which impair critical mitochondrial enzymes. Other essential proteins are directly oxidized, yielding carbonyl and nitrated derivates. Consequently, increases in membrane permeability to calcium, other ionic imbalances, and impaired glucose transportation worsen the energy imbalance.

4. The insulin and IGF-1R signaling and Tau phosphorylation

Soluble tau proteins assemble with tubulin to constitute cross bridge between adjacent microtubule and promote stability of microtubules and vesicle transport [76]. Hyperphosphorylation of tau induces abnormal insoluble tau protein [77]. Neurofibrillary tangles are hyperphosphorilated, intracellular polymers of tau proteins. Neurofibrillary tangles are intracellular polymers of tau proteins, observed in cytoplasm of neurons [76] in AD and in other neurodegenerative disorders, such as frontotemporal dementia, Pick's disease, corticobasal degeneration, supranuclear palsy. Several studies [78, 79] supposed that the interaction between Aβ and tau proteins is necessary to cause neuronal loss. When hyperphosphorylated, tau aggregates and interferes with intraneuronal metabolism and transport, leading to neurodegeneration. IR/IGF1 R mediated might be involved in regulation of tau phosphorilation, amyloid precursor protein cleavage, β amyloid transport and degradation, in memory and aging [8]. The phosphorilation of tau is mainly promoted by glycogen syntase kinase (GSK)3β and cyclin dependent kinase(Cdk5).GSK3β is a serine-treonine kinase,regulated by insulin/IGF-1 signaling pathway. GSK-3β is functionally main for regulating glycogen metabolism, proliferation survival, and cell migration [77]. When the IR/IGF-1cascade is activated, GSKβ is phoshorilated by protein kinase AKT at serin leading to its inactivation [80-82] **(Figure 2).** PP2A dephosphorylates tau maintaining an equilibrium of phosphorylation and dephosphorilation of tau [82, 83]. Protein phosphatases 2A (PP2A) is the major phosphatases with 70% activity in human brains [84]. This implies a protective role of PP2A in neurodegeneration which is consistent with the finding that PP2A activity is reduced in AD brains [85]. In vitro studies it was found that insulin influences a regulatory interaction between PP2A and GSK 3β, inducing in activity of both enzymes change in the same direction. This balanced response seemed to preserve equilibrated tau phosphorilation [86, 87]. Several studies on different animal models of insulin resistance showed that impaired IR /IGF-1 signaling and hyperinsulinemia increased tau phosphorylation.[88-89]. In streptozotocina treated mice, model of type 1 diabetes, hyperphosphorilation of tau has be shown, which was reversible after peripheral insulin treatment [90]. Another important physiological role of insulin and IGF-1 in the brain is the regulation of gene transcription by MAP kinase cascade. This pathway leads to activation of extracellular signal-regulated kinase (ERK)-1/-2, involved in long lasting neuronal plasticity, memory consolidation and apoptotic neuronal death [91-93]. Thus, altered IR/IGF-1 signaling as well as lack of insulin might lead to hyperphosphorylation of tau protein and an increased formation of neurofibrillary tangles. These findings suggest that hyperphosphorylation of tau follows an imbalance of insulin regulated tau kinases and phosphatases [94].

Protein phosporylation/dephosphorylation imbalance is generate, at least in part, by a decrease in the activities of tau phosphatases (PP2A), and increase the activities of tau kinase (i.e. cdk5, GSK-3, etc.) affected by insulin. Impaired insulin signaling stimulates GSK-3β activity that increases oxidative stress and tau hyper-phosphorylation, by Cdk-5. Severe or sustained oxidative injury leads to mithocondrial DNA damage, mithocondrial dysfunction, apoptosis and the attendant cell loss and impaired neuronal function lead to dementia. Age reduces membrane fluidity inducing mutations in transmembrane proteins, (i.e. PS1, PS2,..), and vulnerability of the cell membrane to variation in pathological signal transduction.

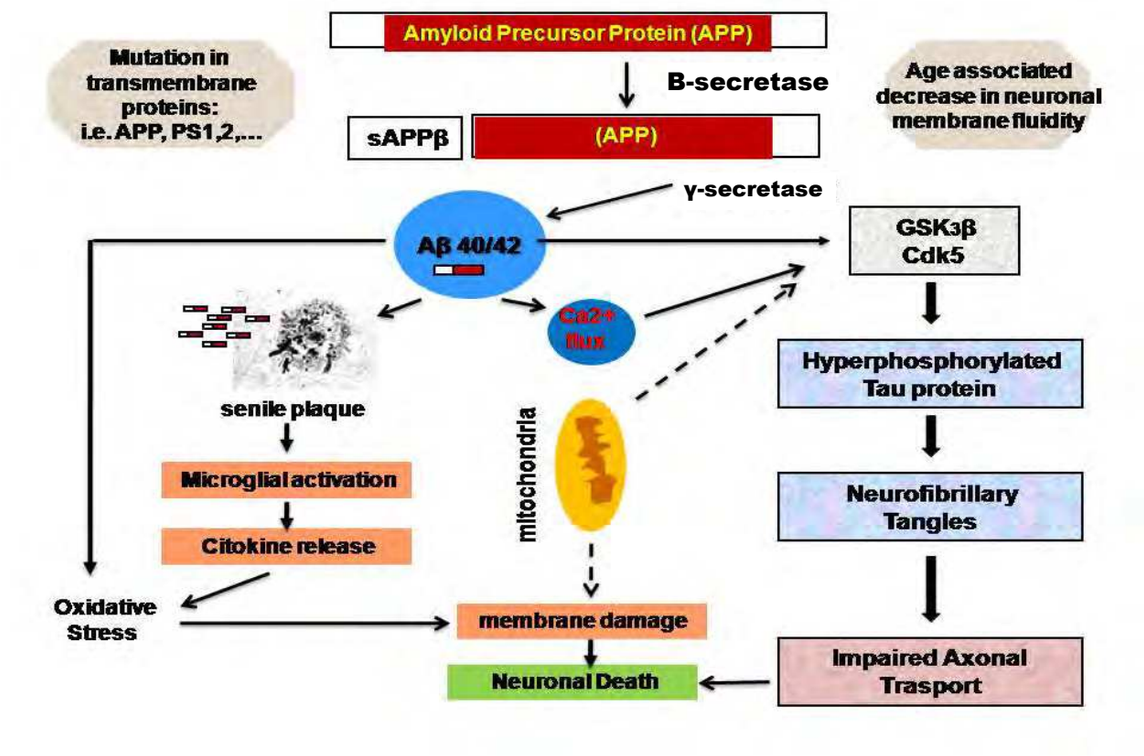

Fig. 2. Dementia and anomalous hyperphosphorylation of tau

4.1 Protein phosphatases A (PPA) processing in Alzheimer's disease

The amyloid plaques is formed by amyloid β (Aβ) peptides organized in fibrils intermixed with non fibrillar forms of this peptide and are surrounded by dystrophic dendrites, axons, reactive astrocytes and activated microglia. Aβ consists of small hydrophobic peptides with N- and C-terminal heterogeneity, i.e. $A\beta_{1\text{-}40}$ and $A\beta_{1\text{-}42}$ which are proteolytically released from a large type 1 integral membrane glycoprotein, the APP, via sequential cleavage by two aspartyl proteases, the β- and γ-secretases [enzymatic complex, containing nicastrina, presenilina, preselin enhancer-2 (PEN-2), CD_{147}] [95]. Initial β-secretase cleavage generates a soluble fragment from the NH_2-terminus of APP, while the c-terminal fragment (β-CTF) stays membrane bound. Full-length APP can undergo alternative processing by α-secretase, generating a soluble APPsα ectodomain and a membrane-bound carboxy-terminal fragment, APP-CTFα. Processing of APP by α-secretase is postulated to be protective in the context of AD, because the enzyme cleaves within the Aβ-sequence, thereby preventing the production of Aβ. APP, αCTF and βCTF are further cleaved by γ-secretase to generate p83 fragment and Aβ respectively [96]. Multiple lines of biochemical evidence have shown γ-secretases activity to reside in a high molecular weight complex, consisting of at least four components: presenilin (PS, PS1, PS2), nicastrin, anterior pharynx-defective (APH-1) and PEN-2 [97]. The p83 fragment is rapidly degraded and widely believed to possess no important function, if any. γ-secretase-mediated cleavage is unique in that the cleavage takes place within the membrane domain, though the exact site can vary. γ-cleavage can yield both $A\beta_{1\text{-}40}$ and to a lesser extent $A\beta_{1\text{-}42}$ [96]. Aβ are toxic, and their accumulation is

currently seen as a key step in the pathogenesis of AD **(Figure 3).** Closer examination of the amyloidogenic β- and γ-secretates discovered the membrane-anchored aspartyl protease β-site BACE-1, which acts as β-secretase and presenelin 1-2, transmembrane proteins involved in formation of the γ-secretase complex, as the responsible cleavage enzymes. Thus, alteration of their activity might be a possible target for AD treatment [98]. It has been shown that BACE-1 levels are increased in post-mortem brain sections from AD patients [99]. During aging changes in the cerebral expression levels of the neurotrophin receptors, TrkA (tyrosine kinase receptor A) and $p75^{NTR}$ (p75 neurotrophin receptor) have been described. In the human neuroblastoma cell line SHSY5Y as well as primary cultured neurons, chronic treatment with IGF-1 leads to a switch from TrkA to $p75^{NTR}$ expression as seen in aging brains [100]. This switch causes increased β-secretase activity indirectly by activation of neuronal sphingomyelinase which is responsible for hydrolysis of sphingomyelin and active liberation of the second messenger ceramide [101]. Ceramide is responsible for the molecular stabilization of BACE-1, the β-secretase which is rate-limiting for generation of Aβ [102]. This process leads to accumulation of Aβ, connecting IGF-1R signaling to neurotrophin action. These data might provide a molecular link between aging, pathogenesis of AD and neuronal insulin-IGF-1 signaling. Lots of research has been done on the formation and accumulation of Aβ, however, in the last years the mechanisms of amyloid clearance came into focus.

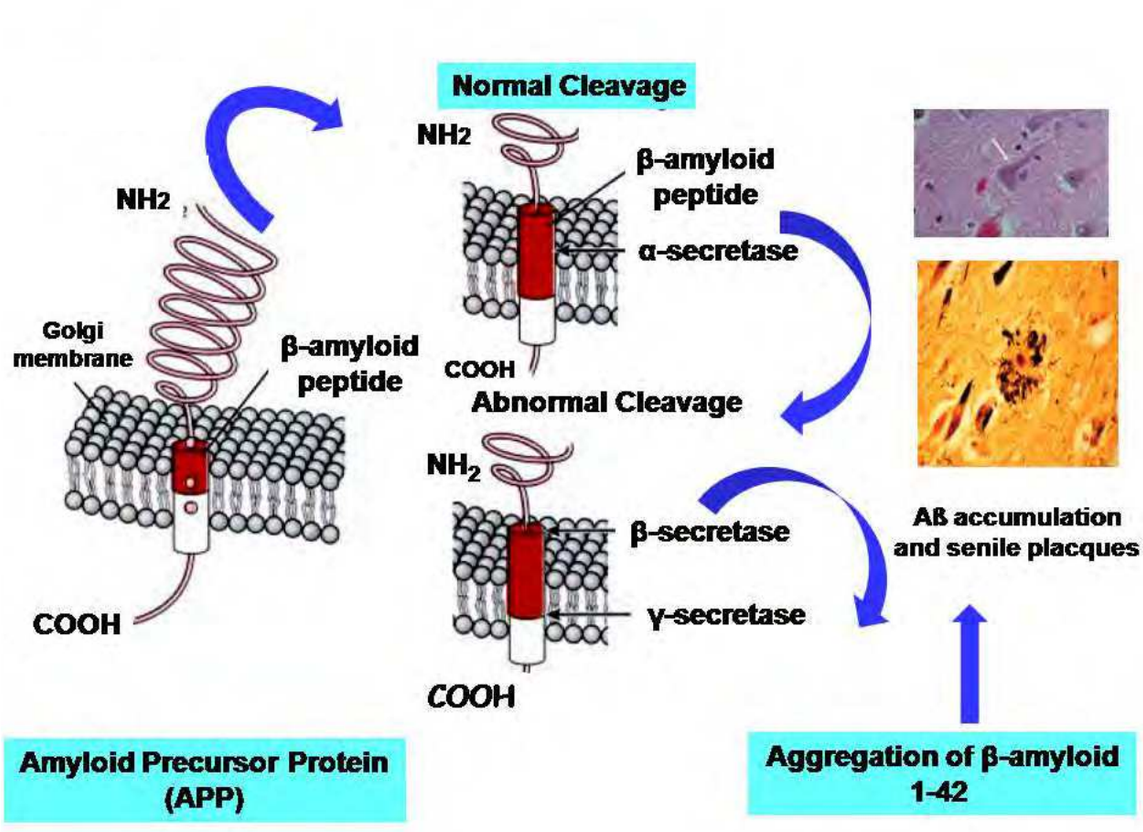

Fig. 3. Amyloid placque formation.

The histological and pathological features of AD are amyloid plaques, neurofibrillary tangles and amyloid angiopathy. The dominant component of the placque core is the the amyloid beta-peptide (Aβ) organized in fibrils of approximately 7-10 nm intermidex with non fibrillar forms of this peptide. Aβ is a a 39-43 aminoacid peptide proteolytically released from a much larger precursor, tha amyloid precursor protein (APP). The generation of Aβ from APP requires the sequential recruitment of two enzymatic activities: β-secretase, also called BACE1 (for beta side APP cleaving enzyme), and γ-secretase , a multicentric protein complex containing presenelin, nicastrina,..Aβ spontaneously self-aggregates into multiple coexisting physical forms, such as oligomers (2 to 6 peptides), transitional assemblies, fibrils that coalesce into β pleated sheets to form insoluble fibers and amyloid plaques. While monomeric Aβ is not neurotoxic, the Aβ oligomers exhibits a marked toxicity (Adapte from Martin JB; 1999).

4.2 Insulin, IGF-1 signaling and β-amyloid in Alzheimer's disease

β-amyloid spontaneously self-aggregates into multiple coexisting physical forms, such as oligomers (2 to 6 peptides), intermediate assemblies, fibrils that coalesce into β pleated sheets to form insoluble fibers and amyloid plaques [103]. While monomeric Aβ is not neurotoxic, the Aβ oligomers exhibits a marked toxicity [104]. Neuronal activation rapidly increase Aβ secretion at the synapse, during the process of neurotransmitters release. Normal levels of Aβ at this site may modulate neuronal transmission and prevent hyperactivity [105]. It was assumed that imbalance between production, aggregation and clearance of peptides, is considered initiating factor in AD [106]. For Aβ clearance several mechanisms have been described: 1. enzymatic degradation by activated microglia or by insulin degrading enzyme (IDE), neprilysin, endothelin converting enzyme (ECE), and angiotensin converting enzyme (ACE); 2. receptor-mediated transport across the BBB by binding to the low-density lipoprotein receptor-related protein (LRP), either directly or after binding to APO E and/or α2-macroglobulin (α2M), to be delivered to peripheral sites of degradation, e.g., liver and kidney [41]. Concerning insulin resistance it has been shown that IDE expression is stimulated by the insulin resistance-IGF-1R cascade [107]. It has been recently reported that membrane associated G protein-coupled receptor kinase-5 (GRK5) deficiency occurs during early AD [108]. In deficient GRK5 mice (tg2576-APPsw) Aß accumulation resulted significantly increased [108]. IGF-1 administration resulted in reduction of cerebral Aβ load in these mice, whereas Aβ was elevated in CSF suggesting an increased Aβ elimination across the BBB or the choroid plexus [109]. Furthermore, it has been shown that the blockade of the IGF-1R in the choroid plexus triggers AD-like pathology. Furthermore, tau phosphorylation did not change significantly following chronic IGF-1 treatment in Tg2576 mice [109]. A possible explanation could be that the chronic increase of IGF-1 by peripheral treatment might down regulate IGF-1R signaling. This hypothesis is supported by the finding that in a cohort of individuals with exceptional longevity serum IGF-1 levels were high but IGF-1R activity was low leading to reduced IGF-1R signaling [110]. However, induction of insulin resistance by high fat diet [111] or intake of sucrose-sweetened water [112] leads to an aggravation of amyloid pathology in mouse models of AD. Furthermore, peripheral injection of supra physiologically high insulin doses but not of physiological doses leads to transient cerebral tau phosphorylation [113], leading to the proposal that there is a dose dependent effect of insulin resistance-IGF-1R signaling in the pathogenesis of AD.

5. Insulin, inflammation and Alzheimer's disease

In recent years inflammatory pathway have been linked to type 2 diabetes mellitus, metabolic syndrome (MS) and neurodegenerative diseases, including AD. Inflammation as able to accelerates the development type2 DM, through its influence on peripheral insulin sensitivity and pancreatic islet function; on the other hand, in addition to impaired insulin signaling, diabetes accelerated the appearance of cerebrovascular inflammation and Aβ deposition, as evidenced by increased levels of proinflammatory cytokines IL6 and TNFα, as well as dense amyloid deposits in blood vessels. [7, 114]. Cerebrovascular and central inflammation, along with increased accumulation of β amyloid, disrupts normal synaptic function, a starting point of AD progression. It was hypothesized the mutual interaction between AD and DM. Takaeda observed increased severity of diabetic phenotype in AD animal models. The reciprocal actions between AD and type-2 DM thus form a vicious cycle, further illustrating the possibility that AD and type-2 DM may share common cellular and molecular mechanisms [114] **(Figure 4).** Peripheral and central inflammation might affect pathogenesis of DM and AD. Elevated concentrations of interleukin (IL) 6 E_2–isoprostane have been observed in CFS of patients with AD [115]. Furthermore, in vitro and animal studies suggest that inflammation interacts with processing and deposit of Aβ [116]. Insulin exerts multiple effects involved in inflammation. In peripheral tissues insulin modulates many aspects of inflammatory network. Low doses of insulin exert anti-inflammatory effects [117]; however, during chronic hyperinsulinemia, insulin may exacerbate inflammatory responses and increase markers of oxidative stress [118]. In human, co-administration of insulin and lipopolysaccharide produces a synergist increase in plasma concentrations of C-reactive protein and proinflammatory cytokines IL-1β, IL-6, TNFα [119]. TNFα has both neurotoxic and neuroprotective effects mediated respectively by two receptor subtypes, TNF-R1 and TNF-R2. TNF-R1 contains a death receptor domain, and has been implicated in pro-apoptotic events, whereas TNF-R2 promotes cell survival. Increased levels of TNF-R1 and decreased levels of TNF-R2 have been observed in AD brain [120]. Abnormal levels of soluble TNF-R1 and R2 have been documented in adults with diabetes and impaired glucose tolerance [121], which reportedly normalize after a 3-weeks low calorie diet [122]. Insulin may also modulate levels of eicosanoids such as F2-isoprostane via regulation of prostaglandin production in adypocites [123]. For example, elevated eicosanoid concentrations have been observed in hyperisulinemic Zucker rats [41]. Furthermore, excessive or chronic hyperinsulinemia inhibits degradation of protein damaged by oxidation and leads to formation of superoxide anions [124]. Insulin may also contribute to inflammation in the CNS, partially through effects on Aβ. In fact, $Aβ_{42}$ interacts with inflammatory agents in a cyclically reinforcing manner, such that Aβ elevations increase pro-inflammatory cytokines [125]. In vitro, soluble Aβ oligomers rapidly increase IL-1β and TNFα levels [126]. Conversely, IL-6 and IL-1β can regulate processing of the APP from which Aβ is derived and increase production of $Aβ_{42}$ [127]. The mutually reinforcing effects of Aβ, TNFα, IL-1β and IL-6 may thus create a "cytokine cycle" [125]. In the periphery, insulin reduces hepatic production of Apo E and regulates its uptake by low-density lipoprotein receptor-related protein [128]. Fishel et al. showed that insulin reduced plasma Apo E levels, an effect that increased with age. In contrast, insulin increased CSF Apo E concentrations for older subjects [129]. Increased brain APO E levels have been reported in AD in association with polymorphisms in the promoter region of the APO E gene that influence protein expression [130]. Recent studies showed that insulin-induced

elevations of CSF APO E levels were associated with attenuated increase IL6 and TNFα levels and with higher anti-inflammatory cytokine, IL-1α concentration. This pattern suggests multiple insulin effects that modulate the role of APO E in response to inflammation in CNS [129] .Insulin can regulate CNS norepinephrine [131], an endogenous anti-inflammatory neuromodulator that blocks IL-1β expression [132]. Increased Aβ plaque load in AD has been linked to neuronal loss in the locus coeruleus, the primary source of brain norepinephrine [133]. In human, raising plasma insulin levels while maintain euglycemia increases CSF norepinephine levels [134].Thus, these findings support the notion that insulin action is involved in neutrasmitter modulation and insulin abnormalities might contribute to CNS inflammation.

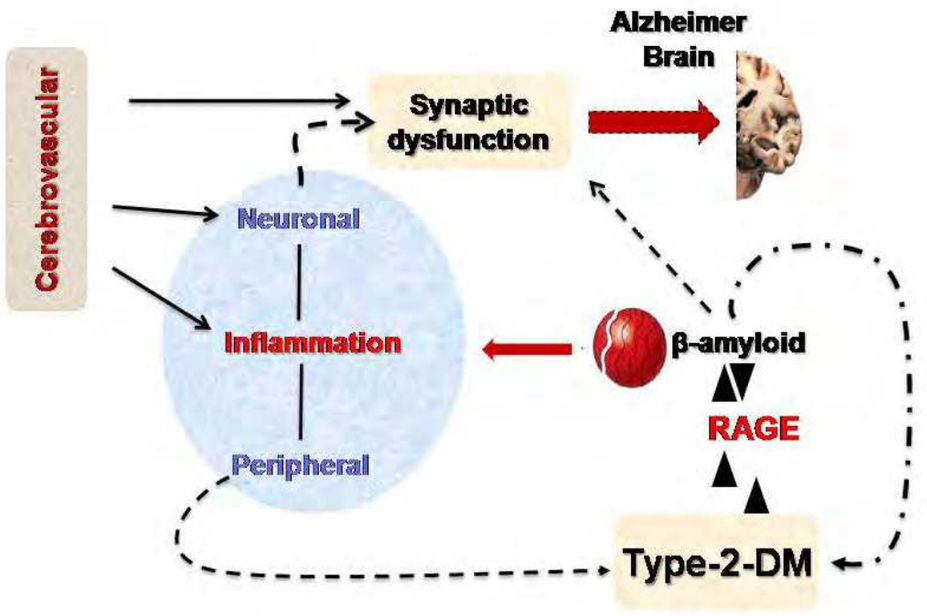

Fig. 4. The underlying link between Alzheimer's disease (AD) and type-2 Diabetes Mellitus (DM).
Inflammation influences islet function and peripheral insulin sensitivity. Besides, inflammation accelerates the development of type-2 DM. Cerebrovascular and central inflammation, along with increased accumulation of β-amyloid, disrupts normal synaptic function, a starting point of AD pathological progression.

6. Conclusion

Mild to moderate impairments of cognitive functioning has been reported both in patients with DM-type1 and in patients with DM-type2. The potential impact of DM on cognitive functions in the elderly is further emphasized by several large epidemiological surveys that report an increased incidence of dementia among DM patients. Several mechanisms may be

involved in accelerated cognitive decline in patients with DM. Insulin may affect the metabolism of Aβ and tau, two proteins that represent the building blocks of amyloid plaques and neurofibrillary tangles, the neuropathological hallmarks of AD. Moreover, insulin and its receptor are widely distributed throughout the brain, with particular abundance in defined areas, such as the hypothalamus and the hippocampus. In addition, insulin appears to act as "neuromodulator", that influences the release and reuptake of neurotransmitters, and improves learning and memory. These findings could provide insights to develop a strategy for prevention and treatment of AD. Insulin therapy plays an important role in cognitive processes and could slow dementia in patients with AD and DM. This could be explained by: 1.*molecular mechanisms*, insulin promotes cell membrane expression of NMDA receptors, which increases neuronal Ca2+ influx [56], that activates Ca^{2+}-dependent enzymes, including α-dependent enzymes and strengthens neuronal synaptic association [10]; 2. *glucose metabolism,* low concentrations of exogenous insulin may increase cerebral glucose metabolism and then modulate brain functions such as memory [135]. In fact, insulin has shown a significant effect on global brain glucose metabolism and this effect is mainly expressed in the cerebral cortex; 3. *neurotransmitter modulation*, low doses of insulin can reverse the amnestic effects of cholinergic blockade [136]**.** Although the concepts of "Cerebral Insulin Resistance" and "insulin-induced amyloid pathology" are an attractive explanation for some of the effects of DM2 on the brain, there are still many loose ends. It is important to point out that definitive conclusions about the value of insulinic treatment in course of AD cannot be established at this time.

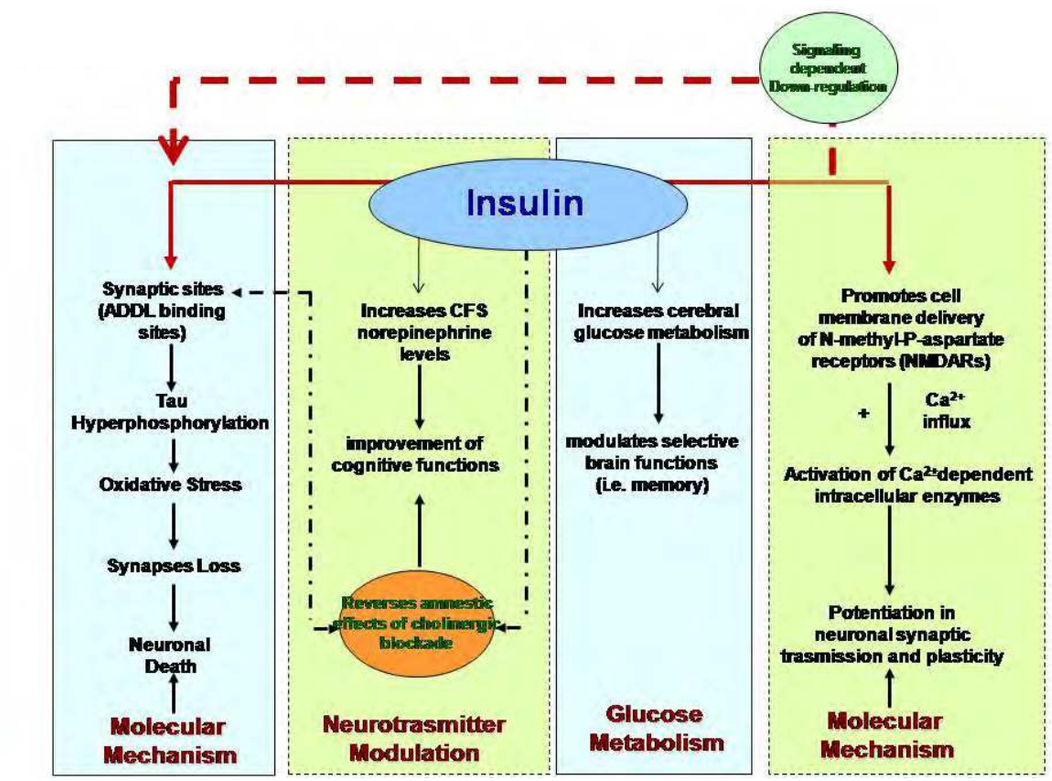

Fig. 5. Schematic representation of molecular mechanism, glucose metabolism and neurotransmitter modulation

Insulin promotes cell membrane expression of NMDA receptors, which increases neuronal Ca^{2-} influx, that activates Ca^{2-} dependent enzymes and strengthens neuronal synaptic association. Besides, diffusible ligands (ADDL) binding to particular synaptic sites and the resulting oxidative stress and synapse loss are markedly decreased by the presence of insulin. This mechanism is associated with a signal dependent down regulation of ADDL binding sites. Low peripheric insulin level may increase cerebral glucose and modulate cognitive functions. Besides, low levels of insulin contributes reverse the anamnestic effects of cholinergic blockade.

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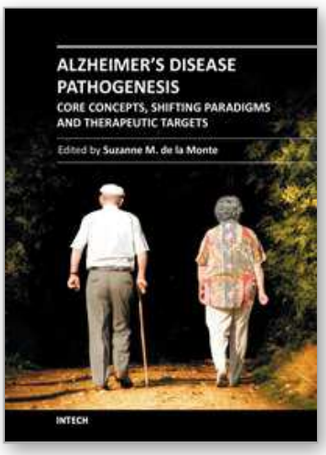

Alzheimer's Disease Pathogenesis-Core Concepts, Shifting Paradigms and Therapeutic Targets

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Alzheimer's Disease Pathogenesis: Core Concepts, Shifting Paradigms, and Therapeutic Targets, delivers the concepts embodied within its title. This exciting book presents the full array of theories about the causes of Alzheimer's, including fresh concepts that have gained ground among both professionals and the lay public. Acknowledged experts provide highly informative yet critical reviews of the factors that most likely contribute to Alzheimer's, including genetics, metabolic deficiencies, oxidative stress, and possibly environmental exposures. Evidence that Alzheimer's resembles a brain form of diabetes is discussed from different perspectives, ranging from disease mechanisms to therapeutics. This book is further energized by discussions of how neurotransmitter deficits, neuro-inflammation, and oxidative stress impair neuronal plasticity and contribute to Alzheimer's neurodegeneration. The diversity of topics presented in just the right depth will interest clinicians and researchers alike. This book inspires confidence that effective treatments could be developed based upon the expanding list of potential therapeutic targets.

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