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Insulin Resistance and Alzheimer's Disease

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1. Introduction

Alzheimer disease (AD) is known as a form of type III diabetes due to its similar cellular responses and pathogenesis. Insulin alters normal brain function and peripheral glucose metabolism, and conditions that are related to insulin dysregulation, such as obesity, diabetes mellitus, and cardiovascular disease, have potentially harmful effects on brain function. Many reports have demonstrated that insulin resistance increases age-related memory impairments and is a risk factor for AD. The molecular and cellular link between insulin resistance and AD, however, is unknown. We discuss the potential mechanisms of these metabolic disorders in the pathogenesis of AD. Glucose homeostasis is critical for energy maintenance, neurogenesis, neuronal survival, and synaptic plasticity, which are required for learning and memory. During insulin resistance, one develops reduced sensitivity to insulin, resulting in hyperinsulinemia, and this impairment in insulin signaling mediates the pathogenesis of AD, which manifests as brain inflammation, oxidative stress, alterations in amyloid beta (Aβ) levels, and cell death. Human and experimental animal studies have noted that drugs that modulate insulin resistance decrease the accumulation of Aβ in the brain and the cognitive impairments that are associated with AD. Therapeutic strategies that target the link between insulin resistance and AD might benefit the development of future AD drugs.

2. Insulin signaling

2.1 Introduction

Insulin is a peptide hormone that comprises 51 amino acids and is synthesized in and secreted from pancreatic β-cells in the islet of Langerhans (Huang et al., 2010). Its rapid release is generally triggered by increased levels of glucose in the blood, despite other mechanisms that release insulin; normal blood glucose levels range from 4.4 to 6.1 mmol/L (82 to 110 mg/dL).

Of its many functions, the most significant effects of insulin are its promotion of cellular growth and differentiation, activation or repression of transcription, and regulation of protein kinases and phosphatases (Saltiel and Pessin, 2002). Defects in insulin signaling can affect many diseases, such as type 2 diabetes mellitus (T2DM), metabolic syndrome, and Alzheimer disease (AD). Although most studies have examined the function of insulin and the dysregulation of insulin secretion or insulin receptor signaling in peripheral tissue, it has recently been reported to cause serious mental illness (Huang et al., 2010).

2.2 General effects of insulin signaling

Insulin increases glycogen and lipid synthesis in liver and muscle cells and simultaneously inhibits glycogenolysis and gluconeogenesis in the liver during feeding (Saltiel and Kahn, 2001). These actions are mediated by its binding to membrane-bound insulin receptors (IRs), members of the tyrosine kinase receptor family (Saltiel and Pessin, 2002). The binding of insulin to the alpha subunit of IR induces a conformational change, resulting in the autophosphorylation of tyrosine residues in the beta subunit of the receptor (Van Obberghen et al., 2001). This ligation leads to the subsequent tyrosine phosphorylation of insulin receptor substrates 1-4 (IRS1-4), Shc, Gab-1, Cbl, and APS (Saltiel and Pessin, 2002), and activates downstream cytoplasmic effectors, such as the lipid kinase phosphatidylinositol 3-kinase (PI 3-kinase) and mitogen-activated protein kinase (MAPK) (Cole et al., 2007; Plum et al., 2005).

During insulin-mediated glucose uptake, the phosphorylated residues of insulin receptor and IRS1, 2, and 3 are recognized by the Src homology 2 (SH2) domain (Bevan, 2001) of the p85 regulatory subunit of PI 3-kinase. The catalytic subunit of PI 3-kinase, p110, phosphorylates phosphatidylinositol (4,5) bisphosphate (PtdIns(4,5)P2), leading to the formation of Ptd(3,4,5)P3 (Lizcano and Alessi, 2002). Ptd(3,4,5)P3 then binds to the plasma membrane and associates with phosphoinositol-dependent kinase-1 (PDK-1) and induces the phosphorylation and activation of protein kinase B (PKB)/Akt, a serine-threonine kinase. Activated Akt enters the cytoplasm, where it evokes the phosphorylation and inactivation of glycogen synthase kinase 3 (GSK3), which promotes glycogen synthesis.

By activating PI3-kinase and AKT (Lizcano and Alessi, 2002), insulin affects the translocation of glucose transporter 4 (GLUT4) from intracellular stores to the plasma membrane: When insulin concentrations are low, GLUT4 exists in cytoplasmic vesicles. After insulin binds to its receptors, GLUT4-containing vesicles fuse with the plasma membrane, and the newly inserted GLUT4 takes up glucose efficiently. In parallel, there is a PI 3-kinase independent pathway that recruits GLUT4 to the plasma membrane, led by the phosphorylation of the proto-oncogene Cbl, which is associated with the adaptor protein c-Cbl-associated protein (CAP) (Saltiel and Kahn, 2001).

Insulin promotes the uptake and synthesis of fatty acids in the liver and prevents lipolysis by inhibiting the intracellular lipase that hydrolyzes triglycerides to release fatty acids. Although insulin promotes the synthesis of glycogen in the liver, further synthesis is suppressed when the liver is saturated with glycogen. Any additional glucose that is taken up is then shunted into pathways that lead to fatty acid synthesis (Saltiel and Kahn, 2001).

One study has indicated that lipid synthesis requires increased expression of the transcription factor steroid regulatory element-binding protein (SREBP)-1c (Shimomura et al., 1999), which is synthesized as a membrane protein in the endoplasmic reticulum (ER) (Sato, 2010). Insulin is believed to induce SREBP-1c proteolytic activity and, consequently, insulin-mediated lipogenesis (Sato, 2010). Further, insulin inhibits lipid metabolism by decreasing cellular concentrations of cAMP through activation of a cAMP-specific phosphodiesterase in adipocytes (Kitamura et al., 1999).

Insulin stimulates amino acid uptake into cells, inhibits protein degradation, and promotes protein synthesis (Saltiel and Kahn, 2001) by stimulating components of the translational machinery, including eukaryotic initiation factors (eIFs) and eukaryotic elongation factors (eEFs) (Proud, 2006). This entails the activation of PKB, leading to the phosphorylation and inactivation of GSK3, which in turn promotes phosphorylation and inhibition of a guanine nucleotide exchange factor, eIF2B, to regulate the initiation of translation (Proud, 2006).

Moreover, PKB phosphorylates the tuberous sclerosis complex 1 (TSC1)-TSC2 complex, relieving its inhibition of the mammalian target of rapamycin (mTOR) (Proud, 2006), which promotes protein synthesis through p70 ribosomal S6 kinase (p70S6k) and inhibition of eIF-4E binding protein (4E-BP1), and thereby governs ribosomal protein translation (Proud, 2006).

2.3 Insulin in the brain

The brain is the primary consumer of glucose, requiring two-thirds of total circulating glucose daily (Peters, 2011); thus, the regulation of glucose homeostasis by insulin in the central nervous system (CNS) is paramount for normal brain function. Insulin, by a saturable transport process that is mediated by insulin receptor, can cross the blood-brain barrier (BBB), which governs the transduction between the CNS and peripheral tissues (Neumann et al., 2008). Although insulin is synthesized locally in the brain (Banks et al., 1997; Devaskar et al., 1994; Rulifson et al., 2002), its function is unknown.

IRs in the CNS are widely expressed throughout the brain in neurons and glial cells, at particularly high concentrations in the cerebral cortex, hippocampus, hypothalamus, and olfactory bulb (Neumann et al., 2008). They have disparate functions, molecular weights, and structures from IRs in peripheral organs (Heidenreich et al., 1983), but it is unknown whether the counter effects of insulin in the CNS compared with those in peripheral tissues are attributed to such differences. Insulin increases glucose and inhibits feeding in the CNS, but decreases glucose and stimulates feeding in peripheral tissue (Florant et al., 1991). A recent report observed that impaired brain insulin activity might affect unrestrained lipolysis that initiates and exacerbates type 2 diabetes mellitus in humans (Scherer et al., 2011).

2.4 Role of insulin in cognitive function

In humans, brain insulin enhances learning, memory, and, in particular, verbal memory (Benedict et al., 2004). Insulin signaling in the limbic system and hypothalamus is especially important for cognitive function (Zhao et al., 1999), independent of changes in peripheral glucose (Craft et al., 1999; Kern et al., 1999). These functions have been supported by evidence that insulin modulates the concentrations of neurotransmitters, which influence cognition, such as Ach (acetylcholine) (Kopf and Baratti, 1999). Insulin also alters synaptic plasticity by regulating the endocytosis of 3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor, which causes long-term depression (LTD) of excitatory synaptic transmission in the hippocampus and cerebellum (Huang et al., 2003; Man et al., 2000; Wang and Linden, 2000), and by enhancing N-methyl-D-aspartate (NMDA) receptor-mediated synaptic transmission at hippocampal CA1 synapses (van der Heide et al., 2005).

2.5 Insulin-like growth factor (IGF)

Insulin-like growth factors are polypeptides that are similar in sequence to proinsulin (Clemmons, 2007). Insulin-like growth factor 1, which stimulates cell growth and proliferation, especially in nerve cells, binds to IGF receptor and IRs (Jones et al., 2009). IGF-1 functions similarly to insulin receptor. IGF-1, a tyrosine kinase, initiates signaling cascades through IRS and enhances insulin activity (Clemmons, 2007).

Deficiency of or irresponsiveness to IGF-1 causes not only growth failure but also dyslipidemia (Twickler et al., 2003), insulin resistance (Conti et al., 2002; Twickler et al.,

2003), and obesity (Rasmussen et al., 1995). According to recent longitudinal studies, these phenotypes are closely related to a high risk of neurodegenerative disorders, such as dementia and AD (Luchsinger et al., 2004; Ott et al., 1996; Ronnemaa et al., 2008). Similarly, mice in which IGF-1 has been deleted develop increased Aβ levels in the brain, suggesting that IGF-1 promotes the clearance of Aβ (Carro et al., 2002). Moreover, IGF-1 mediates transient site-selective increases in tau phosphorylation—hyperphosphorylated tau is a pathological hallmark of AD—in primary cortical neurons via GSK-3 pathways (Lesort and Johnson, 2000).
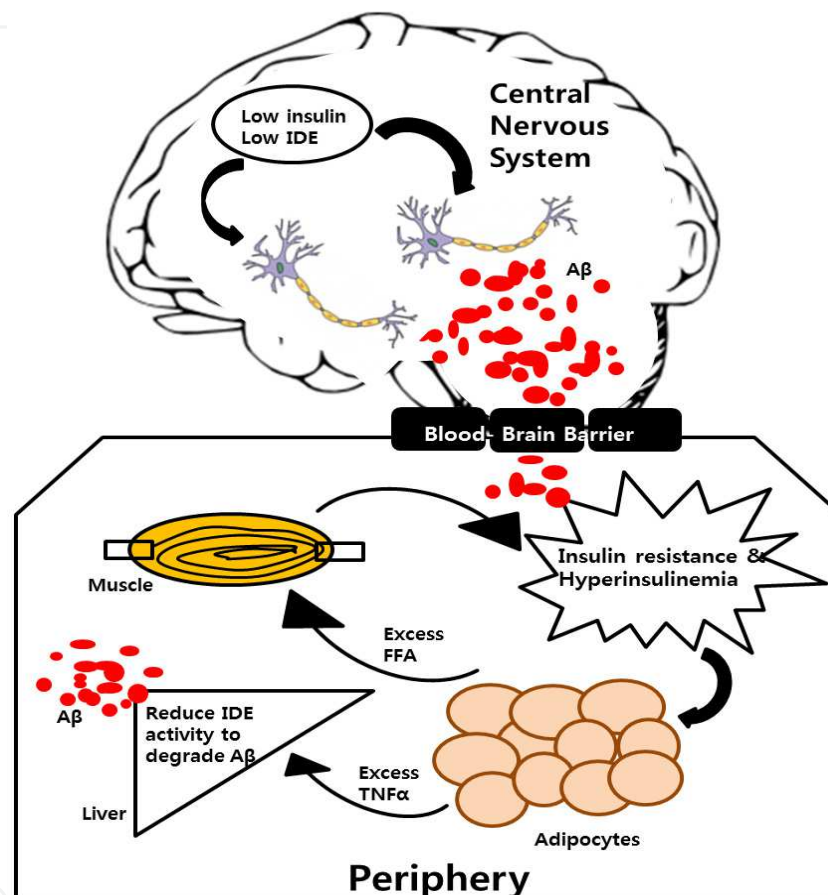

Fig. 1. Schematic diagram of the effects of peripheral insulin resistance on insulin, insulin-degrading enzyme (IDE) and Aβ levels. Peripheral insulin resistance and hyperinsulinemia triggers an excess release of FFA from adipocytes to liver and muscles. A three-fold increase of FFAs reduce insulin-dependent skeletal muscle glucose uptake by 50% (Roden et al., 1996), thereby hampering further insulin signal transduction (Hotamisligil et al., 1996; Schinner et al., 2005). In addition, Increased peripheral FFA levels invoke elevations in TNFα in the periphery and in the CNS, which may result in increased accumulation of Aβ. Chronic elevations in plasma Aβ may result in increased transport of Aβ into the brain. In contrast, peripheral hyperinsulinemia decrease insulin transport into the CNS. Low insulin level in CNS, and low level of IDE may contribute to the formation of senile plaques via disability to degrade Aβ peptides (Jones et al., 2009), further promoting intraneuronal Aβ accumulation, which is the hallmark of AD. <modified from Craft's paper (Craft, 2007)>

2.6 Insulin-degrading enzyme (IDE)

Insulin-degrading enzyme is the chief enzyme that degrades excess insulin and other substrates, including Aβ, a peptide that is implicated in the pathogenesis of AD (Wang et al., 2010). IDE knockout mice experienced decreased Aβ degradation, hyperinsulinemia, and hyperglycemia (Farris et al., 2003). As insulin levels rise, IDE expression increases to prevent the chronic activation of insulin (Zhao et al., 2004). Reduced IDE activity might contribute to the formation of senile plaques through the inability to degrade Aβ peptides (Jones et al., 2009).

3. Insulin resistance

3.1 Definition of insulin resistance

Insulin resistance is a physiological condition in which one loses or reduces his sensitivity to insulin—that is, it becomes less effective at lowering glucose levels in the blood. There are several representative phenotypes of insulin resistance that are used to diagnose diabetes, such as hyperinsulinemia (elevated levels of insulin that are required to maintain normal glucose levels in the bloodstream) and hyperglycemia (elevated glucose levels in the bloodstream that result from the failure of insulin to mediate glucose uptake or insufficient production of insulin by β-cells). Thus, insulin resistance reduces glycogen storage in muscle and fat cells and decreases hepatic glucose uptake.

High cortisol and uric acid levels and low vitamin D levels (Chiu et al., 2004; Vuorinen-Markkola and Yki-Jarvinen, 1994) are believed to be dietary conditions that precipitate insulin resistance. In addition, insulin resistance is closely related to obesity, hypertension, polycystic ovarian syndrome, dyslipidemia, and atherosclerosis (Saltiel and Pessin, 2002).

3.2 Peripheral effects of insulin resistance

Advanced glycation end products (AGEs) production is a pathological phenotype that results from hyperglycemia (Jager et al., 2007). Activation of the jun-N-terminal kinase (JNK) pathway by the binding of AGEs to their receptor (RAGE) leads to serine phosphorylation of IRS proteins and disrupts the imbalance in glucose levels further (Han et al., 2011). In addition to excess AGE production, prolonged hyperglycemia activates the transcription factor nuclear factor kappa B (NF-kB), which regulates proinflammatory and antiapoptotic pathways by modulating the transcription of cytokine and antioxidant genes (Baeuerle and Baltimore, 1996); it also controls the expression of genes that mediate immune responses and proliferation.

Peripheral insulin resistance mediates the progression to hyperglycemia and affects other functions of insulin. In particular, it affects reduced uptake of circulating lipids and increased hydrolysis of stored triglycerides. Such dysfunctional lipid homeostasis has been identified as a significant trigger of insulin resistance (Jones et al., 2009)

Because insulin resistance is linked to metabolic syndrome, which is generally characterized as overweightedness and obesity, and is often observed in persons with hyperglycemia and visceral adiposity, visceral fat is believed to accelerate insulin insensitivity, since visceral fat is less sensitive to the antilipolytic activity of insulin than subcutaneous fat (Jones et al., 2009), thereby triggering excessive release of free fatty acids (FFAs) (Schulingkamp et al., 2000) into the bloodstream. FFAs increase 3-fold above basal levels, reducing insulin-dependent skeletal muscle glucose uptake by 50% (Roden et al., 1996). This phenomenon, a direct cause of insulin resistance, induces inhibits serine phosphorylation of IRS and decreases its chances of binding to insulin receptor, further hampering insulin signaling (Hotamisligil et al., 1996; Schinner et al., 2005).

3.3 Central insulin resistance

As discussed, an abnormality in peripheral insulin is a risk factor for memory loss and neurodegeneration. In addition, chronic exposure of neurons to high insulin levels has a negative impact on memory, according to animal model studies. Chronic hyperinsulinemia impairs BBB function and IR activity and reduces insulin transport to the brain (Strachan et al., 1997). In contrast, some studies have noted that acute increases in brain insulin enhance memory (Craft et al., 1999; Park et al., 2000).

4. Link between insulin resistance and Alzheimer disease

Many studies have suggested that patients with diabetes have a higher risk of AD. Luchsinger et al. found that hyperinsulinemia increased risk for AD (Luchsinger et al., 2004). Also, it has been shown that high levels of insulin and insulin resistance are associated with a higher risk of AD in Rotterdam study, a population-based cohort study (Ott et al., 1999; Schrijvers et al., 2010). Although relationship between diabetes and AD remains controversial (Profenno et al., 2010), the abnormalities in insulin metabolism, which influence the onset of AD mechanistically, are believed to mediate AD through their influence on the synthesis and degradation of Aβ, tau hyperphosphorylation, oxidative stress and/or inflammation.

4.1 Impaired insulin/IGF-1 system in the AD brain

By positron emission tomography (PET) of early-stage AD and mild cognitive impairment (MCI), glucose uptake and metabolism decline significantly in the cortex (Jagust et al., 1991). According to another study, cerebral glucose utilization and blood flow fall by 45% and 18%, respectively, in the early stages of AD. In late-stage AD, cerebral blood flow is reduced by 65% (Hoyer and Nitsch, 1989). These data indicate that brain metabolism is altered in the AD brain, resembling T2DM. In addition, AD patients experience decreases in insulin in the CSF, reflecting dysregulation in insulin transport to the brain (Messier and White, 1987).

The AD brain also exhibits reduced expression of IR and IGF-1R, IRS, and trophic factors (Steen et al., 2005). IGF-1R expression decreases in AD brains in proportion to disease severity, and IGF-1 mRNA levels decline in late-stage AD (Frolich et al., 1998). IRS1/2 expression is decreased in the AD brain (Bosco et al., 2011; Squire, 1986). Because IRS1 and 2 regulate insulin and IGF-1 signaling, these findings suggest that insulin/IGF-1 signal transduction is altered in the AD brain.

There is much evidence of altered insulin signaling in AD. Inhibition of insulin/IGF-1 signaling in AD blocks the Wnt pathway (Doble and Woodgett, 2003), which mediates normal physiological processes in animals (Gogolla et al., 2009). Further, decreased PI3K signaling reduces GLUT4 translocation, inhibiting glucose uptake (Johnston et al., 2003). Since the brain depends on glucose as an energy source, altered glucose metabolism reduces the synthesis of acetyl-CoA and, ultimately, acetylcholine, an important neurotransmitter (Gibson et al., 1981). This decrease disrupts synaptic transmission and, consequently, impairs memory (Craft et al., 2003).

4.2 Insulin resistance and APP processing

Recent studies have indicated that abnormalities in insulin metabolism mediate the onset of AD through their influence on the synthesis and degradation of Aβ peptides (Table 1). Insulin significantly upregulates extracellular levels of Aβ40 and Aβ42 peptides through acceleration of amyloid precursor protein (APP)/Aβ trafficking from the Golgi/*trans*-Golgi

network (TGN), a major site of Aβ generation, to the plasma membrane (Gasparini et al., 2001). Also, certain downstream signaling pathways of IR might also regulate the generation of Aβ peptides by modulating the expression or activity of β-secretase or γ-secretase (Phiel et al., 2003; Zhang et al., 2011), major components of APP processing (Edbauer et al., 2003; Vassar et al., 1999).

Under AD-like conditions, the expression levels of the neurotrophin receptors TrkA (tyrosine kinase receptor A) and p75NTR (p75 neurotrophin receptor) change markedly, increasing Aβ production by stabilizing β-secretase through the activation of sphingomyelinase (Puglielli et al., 2003). Chronic treatment of neuronal cells with IGF-1 (which induces insulin resistance) results in alteration in expression of TrkA and p75NTR, as in AD brains, increasing Aβ production (Costantini et al., 2006). Aβ is a ligand of p75NTR (Yaar et al., 1997), and Aβ stimulates p75NTR-mediated cell death in vitro and in vivo (Coulson, 2006; Sotthibundhu et al., 2008).
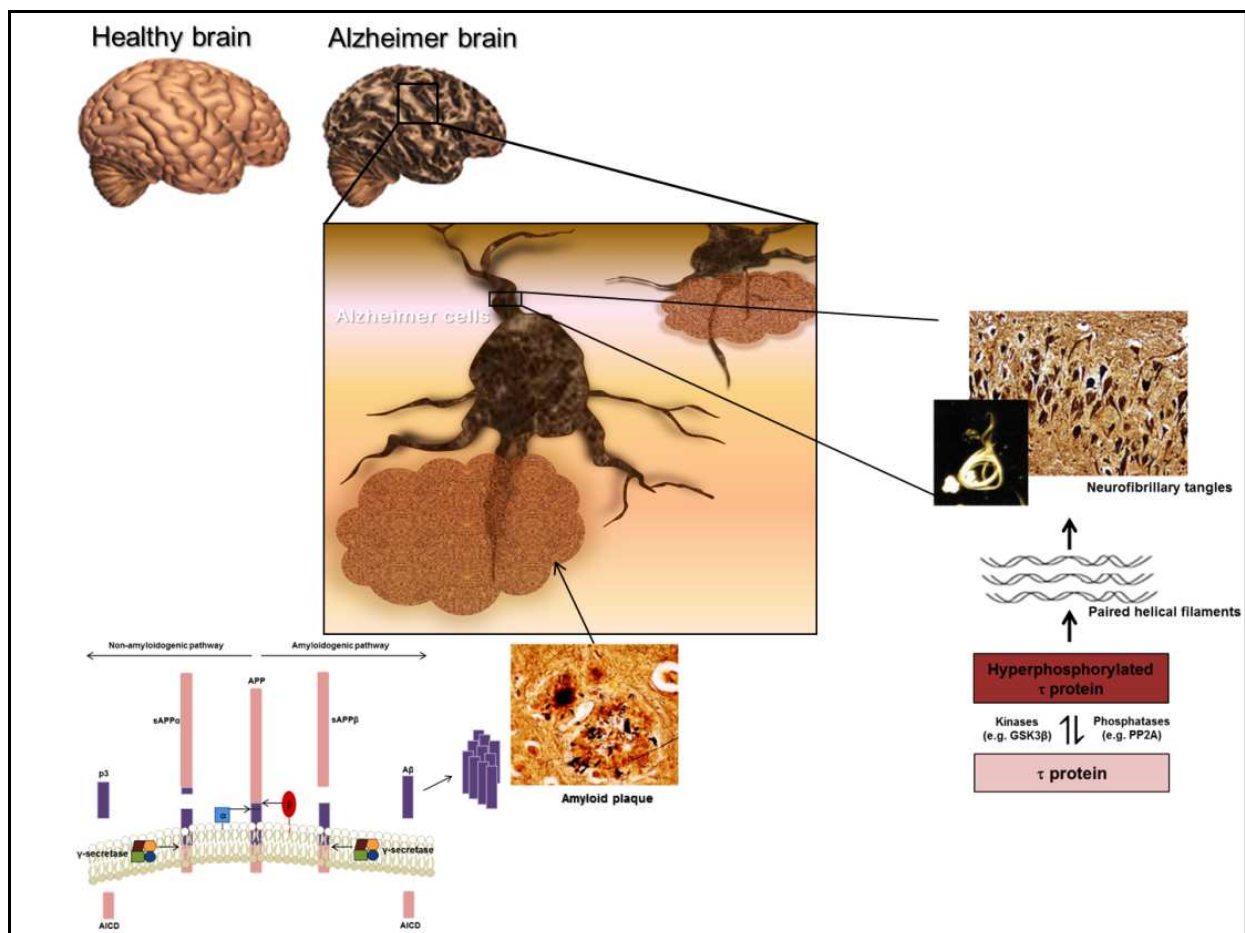

Fig. 2. Amyloid plaque and neurofibrillary tangles as hallmarks of Alzheimer disease (AD). AD is a progressive neurodegenerative disease characterized by senile plaques, neurofibrillary tangles and neuronal loss. Abnormal aggregates of amyloid-beta peptide (Aβ) are found in extracellular senile plaques and associated with neurodegeneration in AD. Neurofibrillary tangles are aggregates of the microtubule-associated protein (MAP) tau protein which is hyperphosphorylated by kinases and accumulated inside the neurons themselves.

In AD brains, Aβ accumulates on not only alterations in Aβ generation but also dysfunction of Aβ clearance. Several mechanisms of Aβ clearance have been examined: 1) Enzymatic degradation by microglia or endopeptidases, such as IDE (Qiu and Folstein, 2006), neprilysin (Iwata et al., 2000), endothelin-converting enzyme (ECE) (Eckman et al., 2003), angiotensin-converting enzyme (ACE) (Lehmann et al., 2005), matrix metalloproteinase-9 (MMP-9), and plasmin (Nalivaeva et al., 2008); 2) Influx into receptor-mediated transport across the BBB primarily via RAGE (Deane et al., 2003; Han et al., 2011); and 3) Receptor-mediated BBB transport by binding to low-density lipoprotein receptor-related protein-1 (LRP1) after ligation with apolipoprotein E (APOE) or α2-macroglobulin (α2M), to be delivered to peripheral sites of degradation (Shibata et al., 2000).

With regard to insulin resistance, insulin induces the accumulation of Aβ by limiting Aβ degradation through direct competition for IDE. IDE is a zinc metalloendopeptidase that preferentially cleaves proteins that tend to form β-pleated sheet-rich amyloid fibrils, such as Aβ peptides (Qiu and Folstein, 2006). IDE activity in the brain correlates negatively with Aβ levels (Farris et al., 2003), and IDE expression is decreased in the AD brain (Cook et al., 2003). Insulin regulates the levels of IDE, and insulin resistance reduces Aβ clearance by down-regulating IDE expression or competing with it for binding (Farris et al., 2003; Ho et al., 2004). A recent report has indicated that Aβ oligomers disrupt IR signaling, resulting from a rapid and substantial loss of neuronal IRs on dendrites by Aβ oligomer (Zhao et al., 2008). There is also evidence that Aβ reduces insulin binding to IRs and induces insulin resistance (Xie et al., 2002).

4.3 Insulin resistance and tau phosphorylation

AD is a multifactorial disease in which protein alterations, oxidative stress, inflammation, dysregulated immunity, impaired neuronal-glial communication, and increase of neurotoxic agents triggering neuronal death. AD is defined by Aβ pathology (Aβ plaques) and tau pathology [neurofibrillary tangles (NFTs)], but whether tau mediates AD pathology has been discussed for many years. Nevertheless, there is increasing evidence that when tau proteins assume pathological forms, they compromise neuronal function and affect cell death. These results suggest that tau is an important mediator of Aβ toxicity and AD pathology (Pritchard et al., 2011).

Microtubule (MT)-associated protein (MAP) tau is the major MT-associated phosphor-protein in normal neuronal cells (Cleveland et al., 1977). Normally, tau proteins assemble with tubulin to stabilize microtubules and vesicular transport. Neurofibrillary tangles are hyperphosphorylated and aggregated forms of tau proteins. When it is hyperphosphorylated, tau becomes insoluble and lacks affinity for microtubules, leading to neurodegeneration (Iqbal et al., 2005).

The kinases that regulate tau phosphorylation are grouped according to specificity: 1) proline-directed protein kinases, such as cyclin-dependent kinase 5 (CDK5), glycogen synthase kinase 3β (GSK3β), MAPK1, p38, JNK, and ERK2; and 2) nonproline-directed protein kinases, such as cAMP-dependent protein kinase A (PKA), PKC, CaMKII, CKII, and MAP/microtubule affinity-regulating kinase (MARK) (Baudier et al., 1987; Drewes et al., 1992; Goedert et al., 1997; Hanger et al., 1992; Morishima-Kawashima et al., 1995).

Tau hyperphosphorylation can also be induced by decreased dephosphorylation. Several protein phosphatases (PPs), including PP1, PP2A, PP2B, and PP5, catalyze tau dephosphorylation (Drewes et al., 1993; Liu et al., 2005). The appearance of tau hyperphosphorylation in the brain reflects an early stage of AD (Maccioni et al., 2010).

Insulin and IGF-1 are related to the phosphorylation state of tau (Table 1). Transient insulin treatment increases tau phosphorylation temporarily, correlating with the sequential activation and deactivation of GSK3β in SH-SY5Y cells (Lesort et al., 1999). Further, tau phosphorylation in primary cortical neurons is regulated by insulin and IGF-1 (Lesort and Johnson, 2000). In IRS-2 knockout mice, defects in IRS-2 signaling promotes neuronal death and induces the hyperphosphorylation of tau, suggesting that tau-mediated neurodegeneration is regulated by the IRS-2 branch of the insulin-IGF signaling pathway (Schubert et al., 2003).

Neuron-specific deletion of insulin receptor (neuronal/brain-specific insulin receptor knockout (NIRKO)) in mice leads to tau hyperphosphorylation (Schubert et al., 2004). However, the patterns of phosphorylation in NIRKO mice and IRS-2 knockout mice differ, suggesting that tau phosphorylation is regulated not only by insulin resistance, but also by other factors (e.g., hyperinsulinemia, hyperglycemia, inflammation) (Schubert et al., 2003; Schubert et al., 2004). There are other evidences on the relationship between insulin signaling and tau hyperphosphorylation. In IGF-1 knockout mice, tau is hyperphosphorylated at Ser202 and Ser396, implicating IGF-1 as protective against tau hyperphosphorylation (Cheng et al., 2005). Separately, the peripheral administration of insulin induced site-specific tau phosphorylation (at Ser202), which occurred rapidly after acute insulin administration but prolonged (Freude et al., 2005).

4.4 Insulin resistance and oxidative stress

The increase in oxidative stress and the resulting activation of many signaling pathways are associated with AD (Markesbery and Carney, 1999; Nunomura et al., 2001).

Oxidative stress is manifested by damage to proteins (Smith et al., 1991; Smith et al., 1996), lipids (Sayre et al., 1997), and nucleic acids (DNA, RNA) (Gabbita et al., 1998; Mecocci et al., 1994; Nunomura et al., 1999). In AD, neurons that show increased oxidative damage have significantly more mtDNA, indicating that mtDNA sustains high oxidative stress in AD (Hirai et al., 2001).

Mitochondria from the brains of AD patients experience structural damage and are the site of Aβ accumulation (Gouras et al., 2005; Hirai et al., 2001). Further, important mitochondrial enzymes become impaired in the brains of AD transgenic mice (Caspersen et al., 2005). Dysregulated mitochondria release oxidizing free radicals, with peroxidation of membrane lipids and the output of toxic aldehydes that cause considerable oxidative stress in AD (Smith et al., 1996).

Oxidative stress is a common feature in AD and insulin resistance. In Drosophila, oxidative stress increases signaling through c-Jun N-terminal kinase (JNK), which is a related pathway of AD and insulin resistance (Ozcan et al., 2004). Hydrogen peroxide-induced JNK activation induces γ-secretase activation, and increases Aβ generation (Shen et al., 2008). Insulin resistance leads to greater oxidative stress, DNA damage, mitochondrial dysfunction, and, ultimately, cell death (de la Monte, 2009). In AD patient brains, the expression of pro-oxidant enzymes that catalyze the generation of reactive nitrogen (RNS) and oxygen species (ROS), such as nitric oxide synthase (NOS) and NADPH oxidase (NOX), rises significantly, which accelerates insulin resistance in the brain (de la Monte and Wands, 2006).

4.5 Insulin resistance and inflammation

There are many reports that inflammation mediates the progress of AD. In brains of AD model mice and AD patients, Aβ plaque and NFTs activate astrocytes and microglia,

resulting in the release of inflammatory molecules (cytokines and chemokines) and the production of complement, and ultimately causing neuroinflammation (Eikelenboom et al., 2002; Hoozemans et al., 2002; McGeer and McGeer, 2003; Tansey et al., 2007). In fact, in AD, neurons themselves induce the production of inflammatory molecules, such as interleukin (IL)-1, IL-6, TNF-α, and complement proteins (Li et al., 2000; Tchelingerian et al., 1996; Yu et al., 2002).Further, Aβ can attract and activate microglia, affecting the recruitment of microglia to Aβ plaques, and increase the secretion of proinflammatory molecules, such as IL-1, IL-6, and IL-8 (Rogers and Lue, 2001). Astrocytes are also activated by Aβ peptide to produce proinflammatory cytokines and chemokines in AD (Smits et al., 2002). Conversely, inflammatory cytokines, such as IL-6, regulate APP processing, resulting in elevation of Aβ42 levels (Papassotiropoulos et al., 2001).
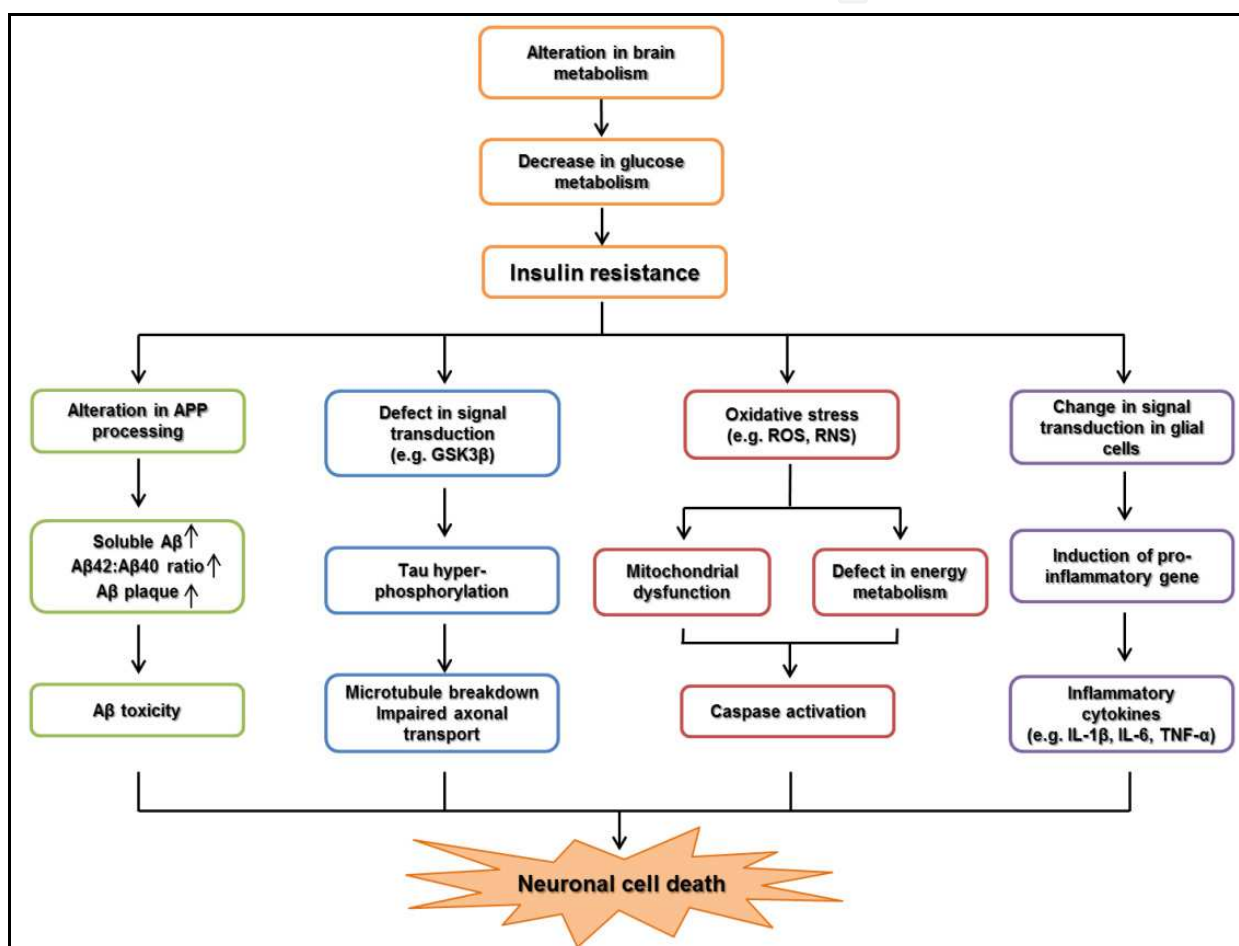

Fig. 3. Schematic representation of molecular pathways linking insulin resistance and Alzheimer disease. Peripheral insulin resistance leads to decrease insulin signaling in CNS, followed by alteration in brain metabolism. Increased Aβ toxicity, Tau hyperphosphorylation, oxidative stress and neuroinflammation are attributed to central insulin resistance, which leads to neurodegeneration.

Chronic administration of insulin induces inflammatory responses, although low doses of insulin is anti-inflammatory (Krogh-Madsen et al., 2004), suggesting that insulin contributes to inflammation. Several reports have noted that insulin modulates many inflammatory networks. Co-administration of insulin and lipopolysaccharide has a synergistic effect on

the release of inflammatory cytokines, such as IL-1β and IL-6 (Soop et al., 2002). Insulin can regulate norepinephrine uptake in the locus coeruleus by modulating the expression of norepinephrine transporter protein (NET) (Figlewicz et al., 1993). Because norepinephrine is an endogenous anti-inflammatory neuromodulator that prevents IL-1β expression (Heneka et al., 2002), chronic administration of insulin might have abnormal inflammatory effects.

5. Clinical studies on insulin resistance and AD

Much evidence suggests that insulin resistance and peripheral hyperinsulinemia are risk factors for AD, implicating them as novel targets (Craft, 2005; Watson and Craft, 2003). For example, optimal doses of insulin and glucose in patients with AD improve declines in cognition (Watson et al., 2005). Using hyperinsulinemic-euglycemic clamps, intravenous insulin infusion in older subjects and in AD patients improves memory (Craft et al., 2003). Recently, intranasal administration of insulin was shown to improve cognitive function and modulate APP processing, resulting in increased Aβ40/Aβ42 ratio (Reger et al., 2008).

1. Aβ metabolism	
Insulin increases the extracellular level of Aβ by promoting its secretion.	(Gasparini et al., 2001)
Insulin increases the extracellular level of Aβ by inhibiting its degradation via insulin-degrading enzyme (IDE).	(Gasparini et al., 2001)
Chronic treatment with IGF-1 increases Aβ production by switching from TrkA to p75NTR.	(Costantini et al., 2006)
IGF-1 reduces BACE-1 expression in PC12 cells via activation of PI3K and ERK1/2 signaling pathways.	(Zhang et al., 2011)
IGF-1 enhanced APP phosphorylation at Thr668, contributing to the neuronal degeneration in AD.	(Araki et al., 2009; Chang et al., 2006)
Infusion of insulin under glucose clamp originated a rapid increase in CSF Aβ levels in older subject	(Watson and Craft, 2003)
Systemic administration of IGF-1 increases CSF Aβ levels.	(Carro et al., 2002)
IGF-1 increases neuronal excitability and release of Aβ is enhanced by neuronal activity.	(Gomez, 2008)
2. Tau hyperphosphorylation	
Insulin and IGF-1 treatment results in increase in tau phosphorylation in primary cortical neurons.	(Lesort and Johnson, 2000)
Peripheral administration of insulin induces site-specific tau phosphorylation (Ser202).	(Freude et al., 2005)
In IGF-1 knockout mice, tau is hyperphosphorylated at Ser202 and Ser396.	(Cheng et al., 2005)
In IRS-2 knockout mice, IRS-2 regulates tau-mediated neurodegeneration.	(Schubert et al., 2003)
Neuronal/brain-specific insulin receptor knockout (NIRKO) in mice leads to tau hyperphosphorylation.	(Schubert et al., 2004)

Table 1. The direct role for insulin or IGF-1 as a possible mediator of AD.

In addition to insulin, insulin-sensitizing compounds have been used as pharmacological treatments. Thiazolidinediones (TZDs) act as agonists of nuclear receptor PPAR-γ (peroxisome proliferator-activated receptor-gamma) and improve insulin sensitivity by reducing circulating insulin, FFA levels, and glucose uptake. TZDs are also anti-

inflammatory drugs that decrease the levels of many inflammatory mediators (Jiang et al., 2008; Neumann et al., 2008; Rojo et al., 2008). Pioglitazone and rosiglitazone are some of the TZDs that are available for clinical use. The dual function of TZDs also affects hallmarks of AD pathogenesis, such as Aβ levels and tau hyperphosphorylation. PPAR-γ agonists, such as pioglitazone and indomethacin, can regulate Aβ42 levels and Aβ plaque loads (Heneka et al., 2005; Sastre et al., 2003).

Troglitazone decreases tau phosphorylation at Ser202 and Ser396/404 through a PPAR-γ-dependent/independent mechanism (d'Abramo et al., 2006). In a recent report, rosiglitazone reduced tau phosphorylation through JNK inhibition (Yoon et al., 2010).

TZDs improve memory in animal models and patients with AD. Rosiglitazone, a TZD, attenuates learning and memory deficits in Tg2576 mouse, an animal model of AD (Pedersen et al., 2006). Recently, pioglitazone was noted to preserve cognitive function in AD (Sato et al., 2009). This pilot study on 42 patients who were treated with 15-30 mg pioglitazone daily or placebo observed cognitive improvement in the pioglitazone groups. In another study, 511 AD patients were assigned to receive 2, 4, or 8 mg rosiglitazone (rosiglitazone group) or nothing (control group) (Risner et al., 2006); the rosiglitazone group improved cognition significantly, and this result was restricted to non-APOE ε4 carriers.

Insulin-sensitizing hormones, such as ghrelin, also affect AD pathogenesis. Ghrelin is a 28-amino-acid endogenous hormone that is a ligand of growth hormone secretagogue receptor 1a (GHSR-1a) (Kojima et al., 1999). Several studies have shown that ghrelin reduces tau hyperphosphorylation in high-glucose-induced neurons (Chen et al., 2010), and ghrelin enhances hippocampus-dependent memory in rodents (Carlini et al., 2010). Recently, Moon et al. observed that ghrelin ameliorates cognitive dysfunction in oligomeric Aβ42-injected mice (Moon et al., 2011). These and other reports demonstrate that brain insulin resistance leads to AD pathologies and thus suggest that insulin-sensitizing agents, such as the TZDs and ghrelin, are useful therapeutic agents.

6. Conclusion

Insulin resistance is characterized by chronic peripheral insulin elevations, central reduction of insulin levels and abnormality of insulin activity. Insulin modulates not only peripheral glucose metabolism but also normal brain function, and thereby conditions related to insulin dysregulation, such as obesity and diabetes mellitus, have deleterious effects on brain function. According to recent longitudinal studies, insulin resistance increases the risk of memory deficit and AD. Potential mechanisms linking insulin resistance to AD pathogenesis include the alteration in APP processing, defects in signal transduction related to both neuronal function (e.g. GSK3β) and cellular toxicity including oxidative stress and inflammation. Identification of underlying mechanisms for relevance of insulin resistance to AD is exigent goal to develop effective therapeutic strategies targeting AD. Many evidences have noted that agents modulating insulin resistance, including TZDs and insulin-sensitizing hormones, alleviate cognitive impairments associated with AD. Therapeutic strategies focused on preventing or regulating insulin resistance may thus benefit the development of drugs for AD.

7. Acknowledgement

8. References

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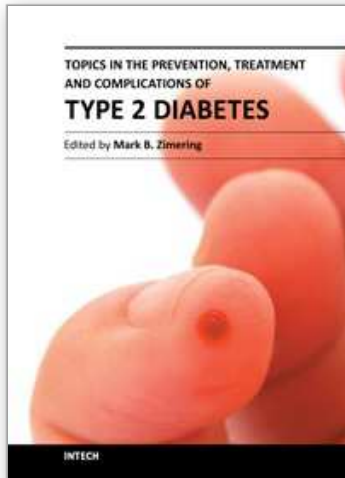
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Type 2 diabetes is estimated to affect 120 million people worldwide- and according to projections from the World Health Organization this number is expected to double over the next two decades. Novel, cost-effective strategies are needed to reverse the global epidemic of obesity which is driving the increased occurrence of type 2 diabetes and to less the burden of diabetic vascular complications. In the current volume, Topics in the Prevention, Treatment and Complications of Type 2 Diabetes, experts in biology and medicine from four different continents contribute important information and cutting-edge scientific knowledge on a variety of topics relevant to the management and prevention of diabetes and related illnesses.

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