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Review

Insulin resistance and amyloidogenesis as common molecular foundation for type 2 diabetes and Alzheimer's disease

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ABSTRACT

Characterized as a peripheral metabolic disorder and a degenerative disease of the central nervous system respectively, it is now widely recognized that type 2 diabetes mellitus (T2DM) and Alzheimer's disease (AD) share several common abnormalities including impaired glucose metabolism, increased oxidative stress, insulin resistance and amyloidogenesis. Several recent studies suggest that this is not an epiphenomenon, but rather these two diseases disrupt common molecular pathways and each disease compounds the progression of the other. For instance, in AD the accumulation of the amyloid-beta peptide (Aβ), which characterizes the disease and is thought to participate in the neurodegenerative process, may also induce neuronal insulin resistance. Conversely, disrupting normal glucose metabolism in transgenic animal models of AD that over-express the human amyloid precursor protein (hAPP) promotes amyloid-peptide aggregation and accelerates the disease progression. Studying these processes at a cellular level suggests that insulin resistance and Aβ aggregation may not only be the consequence of excitotoxicity, aberrant Ca^{2+} signals, and proinflammatory cytokines such as TNF-α, but may also promote these pathological effectors. At the molecular level, insulin resistance and Aβ disrupt common signal transduction cascades including the insulin receptor family/PI3 kinase/Akt/GSK3 pathway. Thus both disease processes contribute to overlapping pathology, thereby compounding disease symptoms and progression.

1. Introduction

In the United States, Type 2 diabetes mellitus (T2DM) and Azheimer's disease (AD) place huge burdens on our healthcare system and society. In 2004, complications related to diabetes was the sixth leading cause of death, while AD was seventh (http://www.infoplease.com/ipa/A0005110.html). A more recent estimate, has placed AD as the sixth-leading cause of death (http://www.actionalz.org/sixth_leading_cause.asp), with more dire projections as the average age of the population in first world countries continue to increase.

Abbreviations: AD, Alzheimer's disease; Aβ, Amyloid-beta peptide; Aβ1-40, Amyloid beta peptide 1-40; Aβ1-42, Amyloid beta peptide 1-42; ADDL, Aβ derived diffusible ligand; AMPA, α-Amino-3-hydroxy-5-methylisoxazole-4-propionic acid; AGE, Advanced glycation end-product; α7nAchRs, alpha-7-nicotinic acetylcholine receptors; ApoE4, Apolipoprotein E4; APP, Amyloid precursor protein; APV, (±)-2-amino-5-phosphonovaleric acid; BACE-1, β-site amyloid precursor protein cleaving enzyme-1; BAPTA-AM, 1,2-bis-(o-Aminophenoxy)-ethane-N,N,-N',N'-tetraacetic acid tetraacetoxy- Methyl ester; CaMKII, Calcium/calmodulin-dependent kinase II; CNS, Central nervous system; CSF, Cerebrospinal *fluid*; EOAD, Early onset Alzheimer's disease; EphB2, Eph receptor B2; Eph receptors, erythropoietin-producing human hepatocellular carcinoma; FFA, Free fatty acid; *f*MRI, Functional magnetic resonance imaging; GABA, Gamma-Aminobutryic Acid; GLUT1, Glucose transporter 1; GSK3, Glycogen synthase kinase-3; hIAPP, Human islet amyloid polypeptide; IDE, Insulin degrading enzyme; IGF-1R, Insulin-like growth factor-1 receptor; IL-1, Interleukin-1; IL-6, Interleukin-6; IR, Insulin receptor; IRS-1, insulin substrate-1; JNK, c-Jun N-terminal kinase; LFS, Low frequency stimulation; LOAD, late onset Alzheimer's disease; LRP, lipoprotein receptor-related protein; LTD, Long-term depression; LTP, Long-term potentiation; MCI, Mild cognitive impairment; mIPSC, Miniature inhibitory postsynaptic currents; NFT, Neurofibrillary tangles; NIDDM, non-insulin dependent diabetes mellitus; NIRKO, Neuronal insulin receptor knockout; NMDA, N-methyl-D-aspartic acid; NEP, Neprilysin; NF-κB, Nuclear factor kappa B; NR2B, NMDA receptor type 2B; PI3K, Phosphoinositide 3-kinase; PET, Positron emission tomography; PP1, Phosphatase 1; PSD, postsynaptic density; PTP1B, protein tyrosine phosphatase -1B; pTyr, Phosphorylated tyrosine receptor; RAGE, Receptor for advanced glycation end products; Ser/Thr, Serine/threonine; T2DM, Type 2 diabetes mellitus; Tg2576 mouse, Transgenic mouse expressing human mutant APP ($HuAPP_{695}$ SWE); TNF-α, Tumor necrosis factor-alpha; TGN, Trans-Golgi Network

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T2DM, a disorder of glucose regulation, is characterized by hyperinsulinemia, hyper-glycemia and hypo-responsiveness of the insulin receptor (IR). Yet, T2DM has a clear cognitive component that includes impaired attention, memory and in the extreme, neurodegeneration [1]. Impaired memory performance becomes particularly evident in elderly T2DM patients [2]. With respect to epidemiology, each aspect of insulin resistance in T2DM (e.g. hyperinsulinaemia, hyperglycemia, glucose intolerance, adiposity, atherosclerosis, and hypertension) is an independent risk factor for AD [3]. Thus clinical studies reveal that patients who suffer from T2DM have a two- to three fold increased relative risk for AD, independent of the risk for vascular dementia [4–12].

AD is an age-related degenerative disease of the brain which is characterized by progressive dementia and loss of other cognitive abilities necessary for maintaining an independent living style. Notably, greater than 80% of AD patients have T2DM or show abnormal blood glucose levels [13]. Many excellent reviews have covered the historical framework for the hypothesis that neuronal insulin pathway is disrupted in both AD and T2DM [14–20]. The goal of this article is to place more recent experimental data in the context of this model, and underscore how each disease can contribute to the progression of the other. The first part of the article reviews the major common cellular/molecular pathologies in T2DM and AD. The second part summarizes experimental results illustrating interactions between the CNS insulin receptor signaling and neuronal/synaptic activities under physiological conditions, and the mechanistic bases for potential development of neuronal insulin resistance. Finally, the third part discusses the molecular interplay between neuronal insulin resistance and amyloid β (Aβ) aggregation, a central molecular pathology of AD. In this section, we will present experimental evidence and theoretical foundation for a pathological loop formed between insulin resistance and amyloidogenesis that drives AD and T2DM progression.

1.1. Common pathological features between type 2 diabetes mellitus (T2DM) and Alzheimer's disease (AD)

1.1.1. Glucose and energy metabolism impairment in T2DM and AD

The biological basis of T2DM is a systemic and chronic impairment in glucose metabolism and utilization. Glucose metabolism is vital to the brain, since glucose oxidation is nearly the exclusive energy source required for neurons [21]. While representing only 2% of the body weight, the brain consumes 18–30% of total body glucose [22]. Therefore, disruptions of glucose supply, transport, and utilization result in neuronal damage and functional deficits. Indeed, in the developing human brain, hyperinsulinemia and hypoglycemia are accompanied by neuronal death and excitotoxic process such as seizure [23]. Severe chronic hypoglycemia can lead to permanent brain damage and mental retardation [23]. T2DM has long been shown to be associated with dementia [2,24–26]. The fact that significant cognitive disruptions are evident in elderly, but not middle- or younger-aged T2DM patients [2,25,27] suggests T2DM-originated pathologies (e.g. energy metabolism impairment and microvascular lesion) interact particularly with aging. Experimental diabetes in animal models shows a clear association of abnormal glucose metabolism and impaired memory and synaptic plasticity [25,28–36]. Thus disruptions in glucose metabolism can directly affect cognitive function.

Extensive clinical studies have demonstrated that glucose metabolism is also severely impaired in the cerebral cortex of the AD patients using the PET tracer fluoro-2-deoxy-D-glucose. The hypometabolism is most prominent in the posterior cingulate and parietotemporal regions in early stages, but spreads to the prefrontal cortex as the disease progresses[37–46]. The reduced glucose metabolism can be detected in pre- or early stages of AD such as mild cognitive impairment (MCI) cases [47,48]. More interestingly, similar hypometabolism is detected in young and middle aged individuals carrying the apolipoprotein ApoE4 allele (who are at higher risk for developing AD [49] prior to the ability of neuropsychological tests to detect differences from normal individuals [38,39,50,51] and thus may not only be attributable to neuronal loss. While neither ApoE4 nor brain glucose metabolism has been validated to predict AD progression, results from these studies reveal an association between abnormal glucose metabolism and an AD genetic risk factor. Similarly, in transgenic animal models of AD, glucose metabolic reduction is found in the posterior cingulate regions of the mouse brain [52]. Disruptions of the amyloid precursor protein (APP), the protein central to the molecular pathology of AD, either by deletion [53] or expression of a human mutant [54,55] have been shown to affect glucose metabolism and tolerance [56,57]. Finally, the glucose transporter 1 (GLUT1), a major glucose transporter selectively expressed in the endothelium of the blood brain barrier [58], is significantly reduced in aged humans and in transgenic mice and coincides with hippocampal atrophy [59], suggesting impaired glucose transport from the periphery into the CNS is correlated with neuordegeneration. These data demonstrate that impaired glucose distribution and utilization is a characteristic of AD.

1.1.2. Insulin resistance as a common molecular feature in both T2DM and AD

Insulin resistance is a critical feature of T2DM that may be detected 10–20 years before the clinical onset of hyperglycemia [60–62]. Insulin resistance is due to the reduced ability of the insulin receptor to respond to insulin stimulation [62]. Under this condition, the islet β-cells in the pancreas secrete higher levels of insulin to compensate for the declined receptor function making hyperinsulinaemia a common characteristic in T2DM patients. Although insulin receptors in the brain have distinct structure and functions from their peripheral counterpart [63], evidence indicates that excessive insulin levels are associated with functional decline in the central nervous system (CNS). For example, insulin levels usually rise with aging and are strong predictors of cognitive impairment in adults without diabetes [7,8,64]. Studies conducted with elderly subjects reported that elderly men with the highest insulin levels made 25% more errors on the Mini-Mental State Examination than men with the lowest insulin levels [7,8,65]. In their study with postmortem brain tissues, Frolich and colleagues first reported an increase in insulin binding activity in the brain regions of sporadic AD [66]. It is important to note, that despite the increased insulin binding, insulin receptor activity was reduced in the AD brain [67], consistent with insulin insensitivity. Recently a study conducted by Steen et al [68] showed that gene expression of a variety of molecules involved in insulin and insulin-growth factor signaling pathways were altered in the AD brain. Based on their findings, the investigators proposed that AD could be the type 3 diabetes [68]. Apart from the postmortem findings, Craft et al [69,70] compared, in a clinical study, the plasma and CSF insulin levels between 25 AD patients and 14 age-matched controls. Plasma hyperinsulineamia was found in AD patients but not the age-matched controls, providing compelling evidence for an association of insulin resistance with AD. The association was further supported by transgenic AD mouse models. At age of 13 month, Tg2576 mice develop hyperinsulineamia in the plasma, which can be prevented by treating the mice with an insulin sensitizer, rosiglitazone [57]. A follow up study further showed that the rosiglitazone-corrected euinsulinemia was accompanied by improved cognitive performance in Tg2576 mice [71]. In addition, rosiglitazone also showed memory preserving effect in mild AD patients reported by Watson et al in a small scale clinical study [72]. Finally, factors that contribute to T2DM accelerate Aβ deposition in AD mouse models [73] while improved diet reduces Aβ deposition [74,75]. These data indicate that both hyperinsulinemia and impaired insulin receptor function which typify T2DM, are also commonly found in AD.

1.1.3. Amyloidogenesis is a common pathological feature in both AD and T2DM

Both AD and T2DM are amyloid forming diseases. Extracellular amyloid plaque in the brain is one of the principal pathological hallmarks of AD, in which the primary component is made by the amyloid beta peptide1-42 (Aβ) originated from the amyloid precursor protein (APP) via proteolytic cleavage [76,77]. Similarly, deposits of an amyloidogenic peptide are found in the pancreatic islets of Langerhans of T2DM patients. Although it was less well characterized compared to other diabetic pathological changes such as hyperglycemia and hyperinsulinaemia, the islet amyloid was found by ultra structural study, to contact β-cells of the T2DM islet [78]. The component of the islet amyloid deposit was subsequently identified as a 37-amino acid peptide and thus named islet amyloid polypeptide (IAPP) or amylin [79,80]. Under physiological conditions, IAPP is made in islet β-cells and co-secreted with insulin in a fixed ratio. It acts as both an adiposity and a satiety signal, combining functional aspects of insulin and glucagon in regulation of food intake and body weight [81,82]. Both human Aβ and IAPP exhibit sequence differences from their respective counterparts in mice [83]. While the human Aβ1-42 and IAPP are highly prone to aggregation, the mouse Aβ peptides and IAPP do not form polymers [84]. As with AD mouse models that overexpress human APP and develop amyloid plaques, mice transfected with human IAPP together with diabetic traits develop IAPP oligomers and fibrils in the islet and show more severe diabetic symptoms [85]. This subject will be discussed in further details in section 3.4.

The evidence of Aβ oligomer toxicity on neurons together with multiple common features of IAPP with Aβ suggested that aggregates of IAPP could generate toxicity to islet β-cells in a way similar to Aβ oligomers do to neurons. Extensive studies in the past years have found that like Aβ1-42, IAPP also forms early intermediate assemblies as spherical oligomers [86,87] that are recognized by a soluble Aβ oligomer antibody [88] implicating that these oligomers possess a common folding pattern or conformation. The behavior of IAPP oligomers toward cultured β cells is similar to Aβ oligomers to neurons [89–93]. While the *in vivo* "true" IAPP oligomers remain to be isolated from the T2DM islets, these *in vitro* and *ex vivo* studies suggest a potential role of IAPP soluble oligomers in degeneration of the insulin producing β-cells in T2DM. Thus, although the nature of the toxic oligomer species and the mechanism by which they cause target cell damage have not been clearly understood, current evidence supports the notion that amyloid formation might be a basic cause for both AD and T2DM, as well as other protein deposition diseases [94–97].

1.1.4. Elevated advanced glycation end products (AGEs) and oxidative stress are commonly shared by T2DM and AD

Another common molecular pathology share by both T2DM and AD is elevated levels of advanced glycation end products (AGEs) and the related oxidative stress. In late stage T2DM, chronic intermittent hyperglycemia leads to acceleration of AGEs generated by non-enzymatic glycation and oxidation of cellular proteins, lipids and nucleic acids by reducing sugars [98–103]. Both clinical and animal studies have shown that elevated blood glucose levels result in marckedly increased accumulation of AGEs in tissues of diabetic subjects [98,104–107]. Besides hyperglycemia, aging and increased oxidative stress contribute significantly to AGE formation [101,108]. Accumulated AGEs bind to the cellular receptor (RAGE), a member of the immunoglobulin sperfamily that is expressed on multiple cell types including endothelial cells, mononuclear phagocytes, vascular smooth muscle cells and microglia [109]. Interactions of AGEs with RAGE trigger signaling cascade involving upregulation of transcription factor NF-κB [110]. This process leads to further increased oxidative stress and production/secretion of high levels of inflamtory cytokines such as IL-6 and TNF-α [98]. Thus the AGE-RAGE interaction represents an important source of inflamation and oxidative stress, and is associated with diabetic complications such as diabetic retinopathy, neurophathy, and cardiovascular lesions [98].

Accumulation AGE is not unique to diabetes, but is closely associated with aging and neurodegenative disease such as Alzheimer's disease [101–103,108,111–113]. Modification of Aβ by AGE markedly accelerates Aβ aggregation [114]. Glycation of tau stabilizes neurofibrillary tangles [115–117]. High levels of AGE immunoreactivity are present in AD plaques and neurofibrillary tangles [101,114,118–121]. This evidence indicates that accumulation of AGE in the brain contributes to amyloidosis and neurofibrilarry tangle formation. Moreover, present in brain endothelium, microglia and neurons, RAGE has been found to be a receptor for Aβ [122,123] and mediates Aβ induced microglia activation and subsequent inflammation in AD [124–129]. Interaction of Aβ with RAGE in neurons has been reported to mediate Aβ-induced disruption of LTP [130]. These data implicate elevated glucose levels in AGE-associated neurodegenerative processes.

2. Current understanding of the brain insulin receptor functions

Because neurons do not require insulin for glucose transport, the brain was considered a non-insulin targeting organ until approximately 30 years ago when widespread distribution of insulin receptor (IR) was detected in the brain [131,132]. A specific regional expression of IR mRNA with situ hybridization [133,134] and insulin binding with autoradiography [135] revealed that IRs are distributed in discrete areas including the olfactory bulb, pyriform cortex, hippocampus, amygdala, and hypothalamus. The highest concentrations of IR mRNA expression was found in the choroid plexus and cerebellum [100–102]. Interestingly, while the cerebellum has high levels of IR mRNA, only low levels of protein are detectable [101,102], presumably due to a high protein turnover rate of the receptor. At cellular/subcellular levels, IRs are enriched in neurons relative to the glia, and concentrated in synaptic membranes [135,136]. There is some evidence that insulin itself is expressed in the CNS [137–141] [352], albeit at low levels. Nevertheless, the role of CNS produced insulin is poorly understood.

Biochemical characterization of brain IRs indicates that by multiple criteria they are similar to the peripheral IR [142], yet they display a couple of key differences. First, due to alternative splicing, brain IRs have a lower molecular weight [143,144]. This is caused be deletion of the exon 11 encoding a sequence of 12 amino acids at the distal end of the α subunit [145–148]. IRs lacking exon 11 (A type) show a higher insulin binding affinity, differential glycosylation and a higher internalization rate than the exon 11-containing IR [149,150]. Moreover, a prominent functional difference between the brain and peripheral IRs is that brain IRs are dispensible as the primary and direct regulator of glucose transport and metabolism [151–153]. Instead, brain IRs exert diverse functions determined by the brain region where they are localized. The preponderance of evidence suggest that major functions of brain IR signaling include the central regulation of body energy homeostasis, modulation of synaptic plasticity and cognition, and involvement in aging-related neurodegeneration.

2.1. Central control of food intake and energy homeostasis

One of the most extensively studied and so far best defined functions of the CNS IR is its central role in governing the body energy homeostasis exerted by insulin signaling from hypothalamus. Although the role of CNS insulin signaling in regulation of food intake, body weight control and reproduction has long been proposed [154–156], it has only been clearly confirmed recently that mice with selective deletion of neuronal insulin receptor (NIRKO) display food intake-dependent obesity and impaired reproduction [157]. While

this aspect of brain IR function is beyond the scope of the present review, readers are referred to excellent review articles for detailed information [158–163].

2.2. Insulin receptor in cognition

Less understood are roles of CNS IRs in learning and memory. The abundant distribution of IRs in hippocampus, amygdala and cerebral cortex suggests that they play a role in synaptic activity and cognitive process. Indeed, animals experiencing spatial learning show an increased amount of insulin receptor [101] and insulin substrate-1 (IRS-1) [119] in synaptic membranes of the hippocampus. On the other hand, rats with deficits in β cell insulin production resulting from experimental diabetes show reduced insulin receptor in their hippocampus [32]. Insulin, when given to healthy human adults under euglycemic clamp to maintain normal blood glucose levels, results in activation of medial temporal lobe including the hippocampus revealed by functional MRI (*f*MRI) [164], a structure critically required for processing declarative memory [165]. Consistent with the induced brain activation, insulin was shown to exert cognition-enhancing effects in both human and experimental animals [166–169]. In recent years, a new delivery method of insulin has been tested, in which insulin is administered via an intranasal route to avoid insulin's peripheral effects. Individuals receiving insulin via this method show an elevated CSF insulin level, but unaffected plasma insulin levels [170] together with enhanced declarative memory such as recalling previously learned words [170,171]. Intranasal insulin administration improves attention and verbal memory of AD patients and individuals with MCI [172]. However, the treatment was shown to be only beneficial to non-ApoE4 carriers [173]. Involvement of insulin signaling in learning may be evolutionarily conserved in C elegans [174]. Insulin-1 was found to be localized in AIA interneurons of C elegans and required for chemotaxis learning [141].

2.3. Insulin signaling in synaptic plasticity — a modulator of the membrane excitability homeostasis?

Precisely how insulin signaling is involved in memory processing has been a topic of research for the past decade. Electrophysiology studies have revealed a role of synaptic signaling in long-term potentiation (LTP) and long-term depression (LTD), two primary well characterized forms of activity-dependent synaptic plasticity in the mammalian CNS [175–177]. Using a streptozotocin-induced experimental diabetic animal model, several studies have shown that both spatial learning and hippocampal LTP are inhibited in diabetic animals [29,145]. The LTP deficit was prevented by insulin treatment [178]. Also observed in these animals was a marked decrease in the NR2B subunit of NMDA receptor [179]. While the severity of LTP deficits was related to hyperglycemia [29] implicating an indirect effect, direct inhibition of IR activity via the IR tyrosine kinase inhibitor AG1024 disrupts LTP in hippocampal brain slices [180]. However, a recent study by Stranahan et al suggests that diabetes-associated memory and LTP deficits may be mediated by a glucocorticoid-mediated mechanisms [36].

Multiple studies have demonstrated that insulin regulates inhibitory transmission and synaptic depression pathway by regulating AMPA and GABA receptor trafficking. The AMPA-type glutamate receptor mediates the vast majority of fast excitatory transmission at CNS synapses. They are the primary receptors responsible for basal synaptic transmission, activation of NMDA-type glutamate receptors, as well as expression of LTP and LTD [181–184]. Synaptic AMPA receptors are highly dynamic, showing rapid exocytosis and endocytosis [185]. Research over the past decade has reached a general consensus in the field that it is the regulated, rather than constitutive or ligand-induced endocytosis of AMPA receptor mediated via a clathrin-dependent mechanism, that reduces the number of the receptors on synaptic membrane surface and underlies synaptic LTD [186,187]. Using electrophysiology, molecular mutagenesis, pharmacology and confocal immunostaining, several labs have independently shown that application of insulin to neurons induces a rapid internalization of AMPA receptor via a clathrin-mediated pathway [188–191] thereby inducing LTD [152,155,157]. Moreover, insulin-mediated LTD shares the same mechanism as low frequency stimulation (LFS)-induced LTD, since these two types of LTD induction occlude each other [155]. These experiments demonstrate that insulin can regulate AMPA receptor trafficking that underlies synaptic transmission and synaptic plasticity. LTD mediated by AMPA receptor internalization has been shown to regulate extinction of fear conditioned memory process [192], hence linking the insulin-involved synaptic activities to specific aspects of cognition. The paradox that insulin is found to promote both LTP and LTD was addressed in a study by van der Heide et al., in which the authors show that insulin shifts the stimulation frequency threshold for inducing LTD and LTP. Thus in the presence of insulin, 0.033 Hz and 10 Hz frequencies induce LTD and LTP respectively while in the absence of insulin, 1 Hz and 100 Hz frequencies are required [193]. These results suggest that insulin plays a modulatory role in activity-dependent synaptic plasticity via changes in membrane responsiveness to stimulation frequency. Consistent with this finding, Chiu et al [194] reported that transfection of a dominant-negative IR in optic neurons of Xenopus tadpole decreased synaptic density and AMPA currents following visual stimulation. These data indicate that insulin receptors in the CNS play a role in regulating synaptic structure and function.

In addition to AMPA and NMDA receptors, insulin has been shown to be a regulator of type-A GABA receptors. GABA(A) receptors are the principal inotropic GABA receptor in the CNS and mediate inhibitory synaptic transmission throughout the brain including hippocampus and cerebral cortex. Using HEK 293 cells expressing GABA(A) receptors, Wan and colleagues show that insulin causes a rapid recruitment of GABA(A) receptors from cytosol to the plasma membrane [195]. These receptors are functionally integrated into the membrane, since the authors observe enhancement of GABA(A) receptor mediated miniature inhibitory postsynaptic currents (mIPSC) following insulin treatment [162]. Following these findings, it is shown that insulin also affects muscarinic acetylcholine transmission-potentiated GABA currents [196]. Essential to the insulin-mediated effects on GABA neurotransmission and translocation is the PI3 kinase signal transduction pathway [197].

Similar to the effects of insulin on GABA receptors in the CNS, insulin potentiates glycine signaling, another inhibibitory neurotransmitter, in spinal cord neurons [198,199]. In the presence of insulin, the amplitude, but not the frequency of glycine mIPSCs increases three fold compared with untreated cells. As with GABA(A) receptors the PI3K pathway is involved; however, insulin does not appear to cause translocation of glycine receptor in spinal cord primary neurons [165]. While methods vary between laboratories (such as insulin concentration, acute versus chronic application, cell type), the preponderance of evidence obtained so far points to a role for insulin and insulin receptors in the cycling of multiple neurotransmitter receptors into and out of synapses.

While in vitro studies suggest insulin receptors modulate multiple neurotransmitter systems, *in vivo* studies using the NIRKO mice (with selective deletion of neuronal insulin receptor) suggest only a modest role for the neuronal insulin receptors. Schubert et al. reported that these mice showed no deficits in learning tasks such as the Morris water maze or T-maze, nor alteration of brain glucose metabolism despite altered PI3K signaling and GSK3 activity [118]. Although a clear understanding has not been achieved, one explanation is that the hippocampus and the cerebral cortex express the IGF-1 receptor. Under physiological conditions, insulin and IGF-1 cross-react with IRs and IGF-1Rs. Moreover, the IR family shares many intracellular signaling pathways. The IR family is also thought to form heteromeric

receptors containing both IR and IGF-1Rs [200]. Thus even though IGF-1 receptor levels were reported to be unchanged in the NIRKO mice, it is possible that the IGF-1 receptor could compensate for the lack of IRs. Indeed, in diabetic rats with severe insulin deficits, we have observed decreased IR expression accompanied by a slight but significant upregulation of IGF-1R in the hippocampus [32]. Given the amount of tau pathology in the NIRKO mice, it is surprising that these animals appear to be cognitively normal. However it is worth noting that the T2DM-associated cognition impairments mostly are not evident until age 65 or older [2,7,8,25,27,66], and that memory deficits in diabetic animals depend on disease duration [201]. Additional studies, therefore, with aged mice (the NIRKO mice were 7 weeks old) might reveal more evidence of abnormal cognitive functions. Alternatively, an inducible siRNA knockdown of brain insulin and/or IR/IGF-1R could provide complementary data.

2.4. Regulation of insulin receptor activity by synaptic/neuronal activities — implication of excitotoxicity and neuronal insulin resistance

Much effort has been devoted to the effects of insulin signaling on synaptic and neuronal function. In contrast, little is known about how IRs in turn affected by synaptic activity. Studies on peripheral IRs reveal that IR tyrosine phosphorylation is regulated by multiple feedforward and feedback routes at both inter- and intra-molecular levels.

The IR is a membrane receptor tyrosine kinase, activated by tyrosine autophosphorylation of the β subunit upon insulin binding to the α subunit exposed to the extracellular surface [202,203]. The phosphorylated receptor subsequently activates several downstream signaling cascades primarily through insulin receptor substrates 1–6 (IRS1-6). Best studied in the periphery, activated IRs initiate signaling through phosphoinositide 3-kinase (PI3K), PDK-1 and Akt/PKB [204]. Activation of this pathway leads to several responses: 1) GLUT4 translocation to the plasma membrane for glucose transport and uptake [205]; 2) glycogen synthesis-via Akt inhibition of GSK3, a kinase that is constitutively active and negatively regulates glycogen synthase [206]; and 3) lipogenesis via up-regulation of fatty acid synthase gene [207].

Under physiological conditions, deactivation of IRs is regulated by multiple tyrosine phosphatases including the protein tyrosine phosphatase-1B (PTP1B) [208,209]. Secondly, IR activity can be inhibited by serine/threonine (Ser/Thr) phosphorylation at the level of IR itself or on downstream signaling molecules such as IRS-1 [210–219]. For instance calcium has been shown to inhibit IR autophosphorylation subsequent to insulin binding [185], primarily via the activation of Ca^{2+}-dependent Ser/Thr kinases such as PKC, Akt and MAP kinase [220–225]. Thirdly, IRs are regulated by receptor internalization, downregulation and desensitization. Upon insulin binding, IRs undergo rapid internalization to endosomes where they dissociate from insulin and are degraded [226–228] or recycled back to the plasma membrane [229,230].

Based on this evidence, it is likely that IRs in the brain can be negatively regulated by Ca^{2+} influx subsequent to excitatory or excitotoxic neurotransmission. Activation of excitatory glutamatergic receptors such as NMDA receptor induces Ca^{2+} influx at postsynaptic sites, which acts as a second messenger to stimulate an array of Ca^{2+}-dependent Ser/Thr protein kinases such as PKC, Ca^{2+}/calmodulin-dependent kinase II (CaMKII), MAP kinases and Akt [231–241]. Indeed, in the presence of elevated calcium, insulin-stimulated IR tyrosine phosphorylation is markedly reduced in hippocampal synaptic preparations [101]. In hippocampal primary neuronal cultures, both glutamate and high K^+ induced depolarization have been shown to attenuate insulin-stimulated IR tyrosine phosphorylation. The effect is reversed by the NMDA receptor antagonists APV and memantine; neuronal activity blocker tetrodotoxin, and calcium chelator BAPTA-AM[242]. Thus, at hippocampal synapses, IRs not only modulate glutamatergic and GABAergic transmission, but are also regulated by calcium and calcium-dependent kinases arising from synaptic transmission (Fig. 1).

The negative regulation of IR tyrosine phosphorylation by calcium and calcium-dependent kinase activities suggest a testable model for the molecular basis brain insulin resistance under pathological

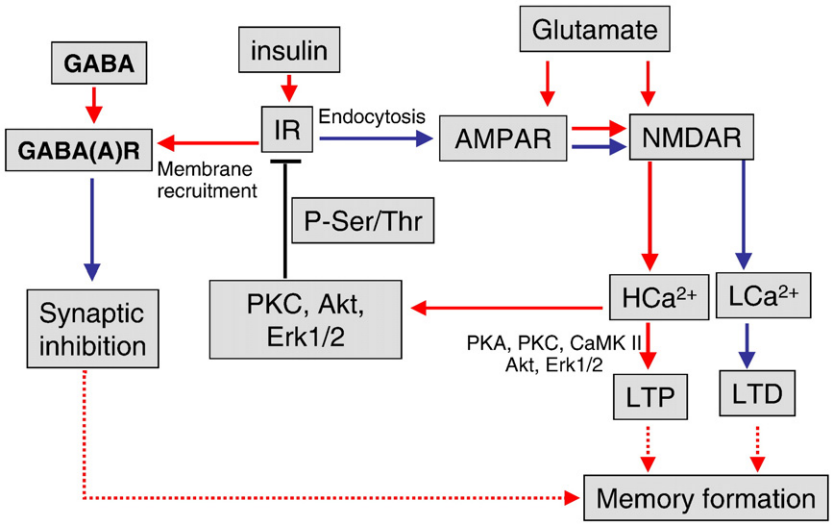

Fig. 1. Hypothetical schematic showing synaptic interactions of insulin receptor with neurotransmitter receptors. Upon binding of the neurotransmitter glutamate, the AMPA-type glutamate receptor triggers a depolarization of the synaptic membrane. In response to the shift in membrane potential, NMDA-type glutamate receptors are relieved of the voltage-dependent Mg^{2+} block and coupled with glutamate binding, results in activation of the NMDA receptor and Ca^{2+} influx. The high concentration of Ca^{2+} (HCa^{2+}) influx acts as a second messenger to trigger activation of a variety of Ca^{2+}-dependent protein kinases that are required for formation and maintenance of long-term potentiation. On the other hand, insulin activation of insulin receptors (IRs) activates endocytotic pathways to internalize synaptic AMPA receptors. Removal of AMPA receptor from the synapses is associated with long-term depression (LTD) similar to that induced by low concentrations of Ca^{2+} (LCa^{2+}). Activation of insulin signaling also potentiates GABA transmission by recruiting GABA(A) receptors to the membrane surface. The balance of glutamatergic and GABAergic transmission are required to maintain proper brain function, while LTP and LTD-like processes are involved in regulating the relative strength of synaptic inputs required for the storage of memory. Therefore, IR signaling may play a role in modulating the excitability of the synaptic membrane as well as synaptic plasticity. At the same time, IR function is affected by synaptic activity. Ca^{2+}-dependent kinases that are activated by synaptic activity can exert a inhibitory effect on IR tyrosine kinase function by increasing serine and threonine phosphorylation of IRs and/or IR substrates. Under conditions of abnormal Ca^{2+} regulation, often found in AD, insulin receptor function may be adversely affected, thereby contributing to decreased insulin sensitivity.

conditions. Excessive and aberrant excitatory transmission and calcium deregulation are thought to be involved in pathogenesis of neurodegenerative diseases such as AD [243–246]. Persistent excitotoxicity caused by high levels of glutamate neurotransmission and abnormally elevated calcium signal could enhance Ser/Thr phosphorylation of the IR and IRS, thereby attenuate IR tyrosine kinase activity and downstream insulin signaling. In return, impairment of insulin signaling could compromise synaptic trafficking of AMPA receptors (endocytosis) and GABA(A) receptors (membrane translocation). Together with disregulation of other insulin-modulated membrane proteins (Na+/K+ ATPase, for example) [247], this feeback loop could adversely affect the maintenance of synaptic membrane potential thereby further exacerbating the cell's control of membrane excitability.

3. Involvement of insulin signaling in AD pathogenesis: Interaction of brain insulin resistance and Aβ aggregation

3.1. Aβ abnormality in AD and the synaptotoxicity of Aβ oligomers

The most evident symptom of AD is a progressive memory loss. Although the etiology and epidemiology for the early onset (EOAD) and late onset AD (LOAD) may be quite different, the clinical symptoms and brain pathologies for both are indistinguishable with deposition of senile plaques in the parenchyma and vasculature accompanied by neurofibrillary tangles (NFT) in the intraneuronal compartment. Because of the common pathology, it is widely believed that Aβ plays a key role in the molecular mechanisms of early disease progression [248–250].

The Aβ1-40 and Aβ1-42 peptides are produced from sequential enzymatic cleavages of APP by the β-site amyloid precursor protein cleaving enzyme-1 (BACE-1) and the γ secretase complex [249]. Early onset AD is caused by mutations of APP [251,252] and presenilins 1 and 2 [253–256], which typically increase the levels of Aβ or propensity of Aβ to aggregate. The mechanism for accumulation of Aβ in LOAD, however, is not clear. It has been suggested that cleavage of the wild-type APP occurs at the endosome and/or along the endocytic pathway, since high efficiency of APP-BACE interactions are found in the endosome but not the trans-Golgi Network (TGN) and cell surface [257,258]. One hypothesis is that additional genetic factors including molecules that affect protein sorting within the endosome-TGN and/or endosome-membrane routes contribute to prolonging APP-BACE interactions which result in increased Aβ production [229]. In many cases, the genetic risk factors for AD are expected to elevate Aβ levels or the propensity for aggregation of Aβ in the brain.

It is generally believed that accumulation of Aβ leads to its aggregation, and it is these misfolded Aβ species that are detrimental to neuronal networks [259–262]. Compared to Aβ1-40, Aβ1-42 has high propensity to aggregate rapidly [263–265], forming multi-level intermediates from oligomers, protofibrils to plaque [250]. Among the multi-forms of Aβ1-42, the soluble oligomers have been shown over the past 10 years to be the most toxic species to neurons [266,267]. In the brains of MCI patients that are not contaminated with senile plaques, the Aβ levels correlate with cognitive decline [268]. From the brain and CSF of AD patients, ADDLs, a term describing a combination of Aβ oligomeric species from trimer to 24mer or higher [269,270] are found to be markedly increased compared to age matched non-demented controls [271,272]. Similarly, in AD transgenic mice over-expressing mutated human APP, increases in Aβ production correlate closely with memory deficits in middle aged mice before plaque formation [54]. From both human AD brain and brains of transgenic mice, Aβ oligomeric species around 50–56 kDa (equal to approximately 12 aggregated monomers) have been identified to exert neuronal toxic and memory impairing effects [273–275]. In addition, naturally secreted small Aβ oligomers (e.g. dimers and trimers) are also highly toxic to neurons [262,276]. It has been shown that small oligomers of Aβ, probably formed first as dimers intracellularly [277], are secreted into conditioned medium as stable dimers and trimers [276]. When the isolated oligomers or the conditioned medium containing these oligomers are applied to rat hippocampal slices or given to live animals, they blocked the LTP type of synaptic plasticity and inhibited memory formation [278,279]. These inhibitory effects are prevented by anti-Aβ antibody, gamma-secretase inhibitors and scyllo-inositol that inhibits the stability of Aβ oligomers [246,247]. Furthermore, Aβ dimers were also detected and isolated from human CSF and brains of AD patients [280,281]. When given to animals and hippocampal slices, the dimer-specific CSF and brain tissue extract showed potent LTP and memory disrupting effects [248,249]. With synaptic immunochemical approaches, Aβ oligomers are shown to bind specifically to synaptic spines and cause disruptions to these structures [282,283]. The binding and synaptotoxic effects of these oligomers are blocked by anti-ADDL antibodies [284,285].

It is not yet clear why oligomeric forms of Aβ are particularly toxic to synpases at nanomolar concentrations compared to the monomers. For one thing, these oligomers are unusual structures that appear prominently only in disease. They arise from protein misfolding due to certain cellular mechanistic defects that have not been clearly identified. During oligomerization, Aβ monomers are likely to undergo conformational changes [286] that may confer the ability to interact with surface receptors such as IRs and α7nAchRs [287] which could disrupt normal cellular function. In this scenario, a conformational change in oligomerized Aβ acts as a "gain-of-function' pathogenic ligand [240,313] on surface receptor/proteins leading to interruptions of normal neuronal function such as synaptic transmission and memory formation. Alternatively, oligomeric Aβ may be more toxic than its monomeric form because an enlarged peptide may sterically hinder the function of a membrane-bound protein such as a ligand gated receptor. In either case, synaptic transmission and downstream cellular events required for memory processing are likely to be interrupted (i.e. synaptic failure) and memory formation deficits would occur [95].

3.2. Neuronal insulin receptor impairment as a direct target of Aβ oligomer toxicity

Although the molecular mechanisms by which Aβ and its oligomers induce synaptic degeneration and memory loss have yet been clearly understood, evidence is now emerging that neuronal insulin resistance in the AD brain is a direct consequence of Aβ oligomer toxicity. As described in the previous sections, impaired insulin receptor activity and plasma hyperinsulinemia are found in AD patients and transgenic animal models of AD [57,69,70]. Treating AD patients and transgenic animals with either insulin or insulin sensitizer reduces Aβ level and improves memory performance [71,139,140], suggesting a correlation between insulin resistance and AD. More recent evidence has demonstrated that neuronal insulin resistance is a direct consequence of Aβ oligomer toxicity. It is shown that the low-n Aβ oligomers inhibit the insulin-stimulated IR tyrosine phosphorylation and phosphorylation of several down stream kinases in hippocampal neurons [147]. When applied to hippocampal slices both Aβ oligomers and an IR tyrosine kinase inhibitor block LTP, an effect that is overcome by 1 μM insulin [147]. Lee et al also reported similar results, which showed that Aβ oligomers were significantly more potent than Aβ42 monomer in inhibiting LTP, and that insulin overcame Aβ-induced LTP deficits probably via inhibiting Aβ oligomerization [288]. This synaptic plasticity protection of insulin is consistent with insulin's memory improving function in AD patients [139,140]. Independent results are also obtained with ADDLs. ADDLs at nanomolar concentrations inhibit the insulin-stimulated IR tyrosine phosphorylation in rat hippocampal primary neurons, and in human IR expressing NIH3T3 cells [212]. Under the same condition, ADDLs do not affect IGF-1R tyrosine phosphorylation. Remarkably, ADDLs'

binding to neurons causes a striking loss of IR α-subunit from the dendritic membranes; such that most ADDL bound neurons show the IR immunoreactivity to be translocated to the cell interior and nucleus, whereas neurons without ADDL binding showed intact IR immunoreactivities in dendrites [212]. A similar phenomenon appears to exist in the AD brain. In a recent study Moloney and colleagues [289] show a loss of IR immunoreactivity from neuronal processes and the periphery compartment of the cell body in brains of AD patients. In these AD neurons IR immunoreactivity is localized in the nucleus, whereas in neurons of non-AD brains the IR immunoreactivity is detected in both neuronal processes and the cell body. In correlation, a marked reduction in protein expression of IR and substrates IRS-1 and IRS-2 were found in the brains of both AD patients and transgenic animals [257]. Taking together, the evidence demonstrates IR impairment (insulin resistance) can result directly from Aβ oligomer toxicity, which may also be the situation in the AD brain.

3.3. Mechanisms by which Aβ oligomers induce neuronal insulin resistance

Although it remains to be explored and clearly understood, several mechanisms may underlie the Aβ oligomer-induced IR impairment.

3.3.1. A direct interaction between Aβ oligomers and IR

Aβ oligomers may disrupt IR function via a direct interaction. All Aβ species including monomers [290], low-n oligomers [147], and ADDLs [212] bind IRs. In one scenario Aβ has been proposed to compete with insulin for IR binding thereby hindering IR activation [258]. This is supported by the observation that insulin at a higher dose (1 μM) overcomes the inhibition of LTP by Aβ oligomers [147]. Given the fact that both insulin and Aβ bind to and compete with the same degradating enzyme (IDE) [291], it is possible that they may also compete for binding to the IR. By contrast ADDL binding to IR is dependent on the tyrosine phosphorylation state of the IR [212]. Additional studies will be required to clarify whether and how Aβ affects insulin binding, insulin receptor conformation and/or insulin receptor expression (see below).

3.3.2. Downregulation of IR expression on synaptic membrane surface

Aβ oligomers may also disrupt synaptic IR function via removal of the receptor from synaptic surface [212]. In addition to IR, Aβ has been shown to cause loss of synaptic surface receptors including AMPA [292], NMDA, α7-nicotinic receptors [255], and EphB2 tyrosine kinase receptors [240]. The removal of most of these receptors is via Aβ-triggered endocytosis [255,260], and it accompanies severe loss of spine structures [240,247,249,260]. The IR is known to undergo rapid internalization upon insulin binding, a mechanism is thought to mediate insulin degradation and receptor downregulation [195]. It is not clear whether loss of the synaptic IR is induced by a ligand-like action of ADDLs, or simply an event accompanying synaptic spine removal. However, the fact that insulin overcomes Aβ oligomer-induced LTP inhibition [147] suggest a possible role for insulin signaling in these processes. In any case, persistently suppressing IR expression on neuronal surface may be an important mechanism by which accumulated Aβ oligomers cause insulin resistance in the brain.

3.3.3. Negative regulation by serine/threonine phosphorylation derived from excessive excitatory activity and inflammation

Brain insulin resistance could be enhanced by Aβ oligomer-associated excitotoxicity and inflammation. In the periphery, inflammatory factors such as TNF-α, free fatty acid (FFA) and their downstream effectors such as the c-Jun amino-terminal kinases (JNKs) have been identified as potent mediators for obesity-related insulin resistance and T2DM [293–295] via influences on serine phosphorylation of IR and IRS-1 [296,297]. Activities of PKC, Akt and several other kinases are involved in this pathway [298–301]. TNF-α has been shown to inactivate phosphatase 1 (PP1) [302,303] shifting the phosphorylation-dephosphorylation equilibrium to the left, resulting in enhanced Ser/Thr phosphorylation of IRS-1 and IR.

Although largely unappreciated, Ser/Thr phosphorylation-induced insulin resistance may be particularly relevant to the brain, as neurons are the most polarized and excitable cells in the body and rely critically on Ca^{2+} and Ca^{2+}-dependent kinases for their functions. IR and IRSs are highly concentrated on the synaptic membranes, the primary sites where Ca^{2+} and other excitatory signals are generated, which would subject them to regulation by synaptic activities. As discussed earlier, increased Ca^{2+}, neuronal depolarization and glutamate have been shown to inhibit the insulin-stimulated tyrosine phosphorylation of IR in hippocampal synaptic membranes and primary neurons [101,212]. In addition to Ca^{2+} disregulation, oxidative stress and inflammatory cytokines that are thought to be involved in the pathogenesis of AD [102,302,304–308] could also contribute to the inhibition of IR via increases in IRS and Akt serine phosphorylation. Increased IRS-1 and Akt serine phosphorylation are found in the AD brain and are correlated with decreased surface IR expression and tyrosine phosphorylation [309]. Ex vivo studies show that Akt activity is triggered by Aβ and Aβ oligomers [242,310], and is responsible for mediating Aβ-induced microglia production of inflammatory chemokines [311]. Given the negative feedback effect of IRS-1 and Akt serine phosphorylation on IR Tyr phosphorylation, the Aβ/Aβ oligomer-induced activation of IRS and Akt could contribute to brain insulin resistance in AD. On the other hand, PI3K/Akt pathway is well known as a downstream event to be activated by IR and IGF-1R activities [170], which plays a role in insulin and IGF-1- associated neuron protection [312–314]. Interestingly, Akt activation is involved in both apoptotic and neuroprotective pathways mediated by different TNF receptors [315]. Therefore, depending on whether it is involved in a feedforward or a feedback pathway, its cellular colocalization, and its specific association with upstream signaling cascades, Akt serine phosphorylation may induce different signal transduction outcomes.

3.3.4. Aβ oligomer induced insulin resistance at the blood brain barrier and other brain regions

Aβ oligomers might cause insulin resistance in other brain cells. For example, insulin receptor mRNA is highly concentrated at choroid plexus [101–103] where it is responsible for transport of insulin across the blood brain barrier [316]. Increased circulating Aβ oligomers in the brain may act on IRs that are localized at brain capillaries, particularly those at the choroid plexus. Impairment of IR at these loci would affect central insulin transport. As briefly mentioned earlier, Aβ oligomers can also interact with RAGE in endothelial cells of blood brain barrier to trigger production of inflammatory cytokines such as IL-6 and TNFα [111,317]. Although AD most critically affects brain regions involved in higher cognition, it is possible that at advanced stages more widespread Aβ oligomers distribution in the brain circulation may adversely affect neurons of other brain regions such as those in hypothalamus or neurons with glucose sensing capability. If IRs in these regions are impaired by Aβ oligomers, the result may be disregulation of hypothalamic function, glucose and energy metabolism. This might explain, at least in part, why a high proportion of AD patients develop T2DM [13].

3.4. Insulin resistance as a necessary cofactor for Aβ aggregation – the beginning of the vicious cycle?

While the above evidence shows that neuronal insulin resistance is a result of Aβ oligomer toxicity, a large body of data indicates impairment of brain insulin signaling promotes amyloidogenesis. Insight may be gained from the generation of human IAPP (hIAPP) transgenic mouse model. Although hIAPP is highly aggregable

compared to the rodent IAPP, the transgenic mice overexpressing hIAPP do not produce islet amyloid aggregates despite up to 15-fold increase in plasma hIAPP [318]. Nor do the mice show any abnormality in blood glucose and insulin levels [278]. However, when the hIAPP mice islets are exposed to high concentrations of glucose in culture, extracellular IAPP amyloid aggregates are formed [319]. Similarly, a few years after their first report in 1993 [278], Hoppener and colleagues crossed the hIAPP mice with the *ob*/*ob* mice (mice express a mutant leptin gene and developed insulin resistance, obesity and diabetes) to produce a double transgenic model [85]. Remarkably, a significant amount of islet amyloid aggregation was observed in the islets of double transgenic hIAPP-*ob*/*ob* mice together with additional molecular, cellular and symptomatic alterations [85]. In *ob*/*ob* mice, insulin resistance resulted in an increased insulin secretion that overcomes hyperglycemia. In hIAPP-*ob*/*ob* mice, however, the hIAPP amyloidogenesis is accompanied by exacerbation of insulin resistance: The mice are notably more obese than *ob*/*ob*-only mice; and insulin secretion is reduced resulting in hyperglycemia, indicating loss of β-cell function. It is likely the loss of β-cells is caused by lower molecular weight IAPP oligomers, which show cytotoxic effects by disrupting membrane stability and inducing dell death in cultured islet β-cells [86,88–90,92,93], similar to the neuronal toxic properties of Aβ oligomers. On the other hand, the IAPP mature fibrils are not toxic [87,92]. From these results, it is suggested that increased hIAPP production may be essential but not sufficient for islet amyloidogenesis, whereas insulin resistance and elevated glucose is a necessary cofactor required to triggers the amyloid aggregation. However, whether and when an elevated IAPP level (locally and/or in circulation) occurs in T2DM remains to be clarified.

Similar cases can also be found in AD transgenic mice models. In the Tg2576 AD mouse model, mice fed with normal laboratory diet do not show memory deficits until 6 months of age [54,55]. The mice maintain relatively normal circulating insulin levels and glucose metabolism until 13 months old, when plasma hyperinsulinemia becomes evident [58]. Despite high production of Aβ and plaque disposition, there is lack of neuronal death and neurofibrillary tangles in their brains [54,55]. However, when these mice are fed with a high fat diet, they develop non-insulin dependent diabetes mellitus (NIDDM) insulin resistance, a condition that leads to significantly advanced AD pathology and symptoms [73]. First, there is greater than 2-fold higher blood insulin levels by 9 months of age along with obesity compared to the non insulin resistant Tg2576 mice that do not show hyperinsulinaemia until 13 months of age [57]. Second, at the same age, the levels of Aβ1-40 and Aβ1-42 from the hippocampus and cerebral cortex are also >2-fold higher, correlated with activation of γ-secretase and GSK3α and GSK3β. Third, the tyrosine phosphorylation of cerebral IR is considerably lower, as is the phosphorylation of PI3 kinase and Akt. Fourth, compared to the non insulin resistant controls, the NIDDM insulin resistant Tg2576 mice show severe impairment in water maze spatial learning [73]. Thus, similar to the case of the hIAPP-*ob*/*ob* mice, on the basis of high production of Aβ, development of insulin resistance accelerates brain amyloidogenesis, and facilitates disease progression.

An impaired IR signaling may exacerbate Aβ accumulation in several ways. Perhaps the most important effect of an impaired IR signaling is reflected by a weakened inhibition on glycogen synthase kinase 3 (GSK3), an important downstream node of IR signaling [320]. GSK3, including both the α and the β subunit, are thought to be critically involved in AD pathogenesis with activated GSK3α triggering APP γ-secretase activity [321–324] thus increases Aβ production, and GSKβ phosphorylating Tau [325–328] thereby promoting formation of NFT. Activation of IR signaling inhibits both GSK3α and SKG3β via the PI3 kinase pathway [171]. Impairment of IR function, therefore, would result in high activity of GSK3 that leads to enhanced Tau phosphorylation and Aβ production, exacerbation of both would certainly facilitate the disease pathologies. Indeed, specific knockout of brain IR revealed activation of GSK3 in the mouse brain [118]. Secondly, brain insulin resistance could interrupt Aβ clearance. Aβ is reported to be transported across the blood brain barrier and/or taken into microglias for clearance, a process depending on the low-density lipoprotein receptor-related protein (LRP) and its ligands ApoE and α2-macroglobulin [329–332]. In addition Aβ is also cleared through local enzymatic digestion by insulysin (IDE), neprilysin (NEP) and other metalloenzymes [333–335]. Insulin signaling has been reported to stimulate α2M binding to LRP and their expression [336] and expression of IDE [337]. Furthermore, APP processing and Aβ transport between TGN and plasma membrane in neurons has been reported to involve IR signaling [338]. Insulin resistance, therefore, would add to accumulation of Aβ via interruption of both clearance and production processes (Fig. 2).

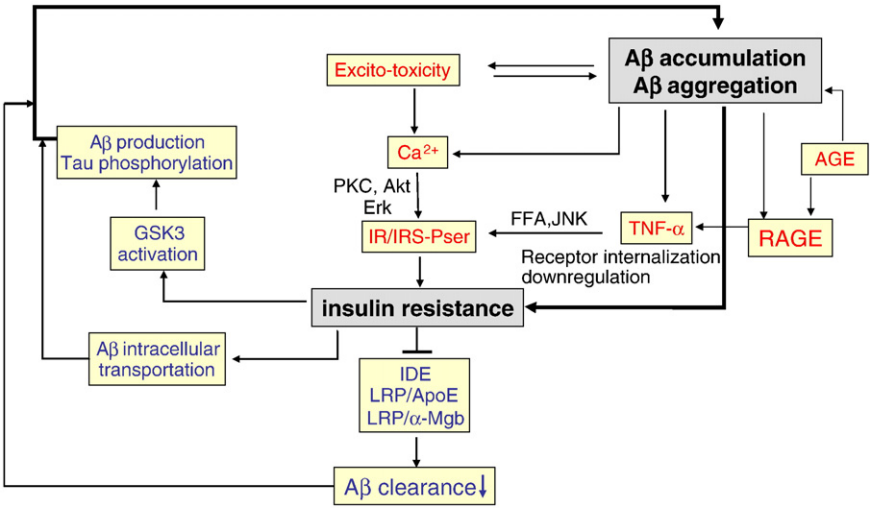

Fig. 2. A hypothetical pathological loop of insulin resistance and Aβ accumulation: Increased Aβ and Aβ oligomers in the brain may cause neuronal insulin resistance at multiple levels. First Aβ may disrupt insulin receptor function by downregulating membrane surface IR via internalization, desensitizating the receptor or by direct substrate competition. Second, Aβ may inhibit of IR tyrosine kinase signaling by increasing intracellular Ca^{2+}, thereby activating select serine/threonine kinases, which in turn phosphorylate IRs and IRS. Third, Aβ may induce microglia to produce inflammatory cytokines such as TNFα as well as its effectors free fatty acids (FFA) and JNK. The consequences of impaired IR signaling include accelerating disease progression, perhaps by activation of GSK3 leading to hyperphosphorylation of tau. Impaired IR function could also promote Aβ aggregation by increasing Aβ production and impeding ransport and clearance of Aβ. Thus brain insulin resistance and Aβ aggregation/accumulation reinforce each other to drive the disease to more advanced stages.

4. Concluding remarks

Emerging evidence in the past decade from the diabetes and AD research fields, as well as from basic neuroscience research has made great strides in understanding the molecular pathogenesis of these two degenerative diseases. It is becoming clear that T2DM and AD are linked by two common molecular pathologies, namely insulin resistance and amyloidogenesis that are associated with impaired glucose metabolism and increased oxidative stress. When they co-occur in the brain, these two factors appear to form a pathological loop, in which they interact with and reinforce each other to generate cellular toxicity that leads to energy metabolism impairment and cognitive deficits. While IR impairment may result from actions of Aβ oligomers at multiple levels, IR desensitization accelerates Aβ aggregation and disease progression. Evidence supporting this loop include that IR tyrosine kinase activity and its membrane surface expression are markedly inhibited in the AD brain [67,289], and in rat primary hippocampal neurons by Aβ oligomers [147,212]. Conversely, T2DM is a risk factor for AD [339,340] . Insulin resistance is a trigger/accelerator for amyloidogenesis[319] as transgenic mice on a insulin resistance-inducing diet show more advanced Aβ deposition and memory deficits [73]. Therefore, not only do these diseases compound each other's pathologies, but interact on the same molecular pathways.

However, much is still unknown about the relationship between an essential role of insulin signaling in normal cellular function and development of T2DM and AD. One of the main issues that remains to be reconciled is that deletion of the key IR/IGF-1 signaling (IIS) genes in species including c. elegans [341,342], drosophila [343,344] and rodents [345,346] during the embryonic development results in a longer and disease-resistant life span [347], whereas diminished insulin response of IR in later age is associated with metabolic/degenerative diseases that cause high mortality. One possible explanation is that with deletion of the key insulin pathway genes throughout life, the body adopts a starvation strategy, upregulates compensatory mechanisms and lengthens lifespan to improve reproductive success. In contrast, insulin resistance in T2DM and AD is a late onset dysfunction of glucose homeostasis. To clarify this issue, novel animal models with inducible IR phosphorylation mutants (either Ser/Thr or Tyr) may mimic the late onset insulin resistance and thus provide a model to test this issue.

Another test of the hypothesis that insulin receptor signaling plays an important role in AD, is the identification of familial mutations in the IR pathway that would increase the risk of developing AD. Point mutations in IR are associated with insulin resistance, obesity and diabetes [348–350]. Although one isolated study has identified polymorphism of PI3K, a major downstream kinase of IR, in AD patients [351], to date, no genetic defect of IR has been identified in AD.

Additional questions include: How and why does insulin resistance promote Aβ aggregation? Apart from influencing Aβ production and Tau phosphorylation, does insulin resistance play a role in protein misfolding on the neuronal surface? Does insulin resistance interfere with Aβ turnover in the brain? To address these questions might require development of appropriate animal models such as inducible knockdown (or dominant negative) of IR in specific brain regions of AD transgenic mice at specific age windows, from which the specific molecular connection between brain insulin resistance and amyloidogenesis relevant to disease progress of AD may be identified. If the IR can affect synapses of the CNS, what is the source of endogenous insulin (i.e. transport from the periphery, or locally synthesized and secreted by neurons)? Is the mechanism of action direct through insulin receptor signal transduction or perhaps indirect through glucose metabolism and mitochondrial function? Lastly, while future studies are required to validate the pathological feedback loops of insulin resistance and amyloidogenesis, one can speculate that brain insulin resistance may contribute to abnormal Aβ turnover thereby contributing to disease progression in at least a subtype of LOAD. Thus, it may be reasonable to hypothesize that while the peripheral insulin resistance likely to proceed into T2DM (some might take more than 10 years), the neuronal insulin resistance might proceed AD. In this context, AD could be seen as a brain type of diabetes.

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