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How does brain insulin resistance develop in Alzheimer's disease?

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Abstract Compelling preclinical and clinical evidence supports a pathophysiological connection between Alzheimer's disease (AD) and diabetes. Altered metabolism, inflammation, and insulin resistance are key pathological features of both diseases. For many years, it was generally considered that the brain was insensitive to insulin, but it is now accepted that this hormone has central neuromodulatory functions, including roles in learning and memory, that are impaired in AD. However, until recently, the molecular mechanisms accounting for brain insulin resistance in AD have remained elusive. Here, we review recent evidence that sheds light on how brain insulin dysfunction is initiated at a molecular level and why abnormal insulin signaling culminates in synaptic failure and memory decline. We also discuss the cellular basis underlying the beneficial effects of stimulation of brain insulin signaling on cognition. Discoveries summarized here provide pathophysiological background for identification of novel molecular targets and for development of alternative therapeutic approaches in AD.

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Keywords: Alzheimer's disease; Amyloid-β oligomers; Insulin resistance; Insulin therapy; GLP-1R agonists

1. Introduction

Understanding the molecular basis of neuronal dysfunction and memory loss in Alzheimer's disease (AD) has become a major research and public health challenge because the number of cases is predicted to increase exponentially during the next few decades, and effective treatments capable of halting disease progression are still lacking [1,2]. With only a small subset of cases attributed to inherited genetic causes [3], the mechanisms of pathogenesis and etiology of sporadic, late-onset AD are still not elucidated fully. Thus, identification of molecular components and pathways that contribute to this complex neurological disorder has been the focus of intense research efforts during the past few years.

Recent evidence indicates that AD is a brain-specific form of diabetes [4,5]. The intriguing connection between diabetes and AD was identified initially in the Rotterdam study, which revealed that diabetes increases the risk of dementia [6,7]. Subsequent clinical and epidemiologic studies have confirmed this association (reviewed in [8]) and demonstrated that impaired metabolic parameters, such as hyperglycemia and hyperinsulinemia, correlated positively with development of AD-related pathology in humans [9–11]. Moreover, AD brains exhibit defective insulin signaling, altered levels and/or aberrant activation of components of the insulin signaling pathway, and, more importantly, decreased responsiveness to insulin [12–14].

In peripheral tissues (e.g., liver and muscle), insulin signaling stimulates glucose uptake and promotes metabolic reprogramming after feeding [15]. Although the brain was once considered an insulin-insensitive organ, and the source of brain-acting insulin is still a matter of debate [16], it is now established that insulin actions are important for neuronal survival and brain function [17]. Although at that time broader roles of brain insulin signaling were still unknown, early studies demonstrated that insulin regulates brain metabolism and body energy balance by acting on the hypothalamus [18]. In addition to its role in hypothalamic metabolic control, insulin signaling has now been shown to play important roles in other brain regions. Insulin receptors and downstream

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components of canonical insulin signaling are present and active in various forebrain areas important for memory formation, consolidation, and retrieval [19], including the hippocampus [17]. Insulin actions were shown recently to be required for synaptic plasticity, learning, and memory [17,20–22]. Furthermore, in vitro and in vivo evidence supports the notion that insulin has neuroprotective [23,24] and memory-enhancing properties [25,26], indicating a permissive role for insulin in cognition [27]. Thus, it is likely that defects in brain insulin signaling may give rise to neuronal dysfunction and cognitive deficits that are characteristic of AD.

Our understanding of the molecular underpinnings of why AD is a memory disorder has increased significantly during the past 15 years. For decades, it was thought that neuritic or senile plaques, neuropathological hallmarks of AD mainly composed of large aggregates and amyloid fibrils of the amyloid-β (Aβ) peptide, triggered neuronal death and caused memory impairment in patients with AD [28]. However, despite the demonstrated in vitro neurotoxicity of Aβ fibrils, a puzzling observation resulting from careful neuropathological examination of post mortem AD brains was that amyloid burden did not correlate well with premortem cognitive decline [29,30]. Instead, those studies showed that cognitive deficits were highly correlated with synapse loss [30–32], and suggested that an as-yet-unidentified toxin, but not amyloid plaques, was responsible for triggering memory loss in AD. Identification of soluble amyloid-β oligomers (AβOs) as synaptotoxins that accumulate in AD brains [33–36] stimulated a paradigm shift in the field, with AβOs now considered the proximal toxins responsible for synapse dysfunction and memory failure in AD (for recent reviews, see [1,37–39]).

In the following sections, we review recent findings linking the neurotoxic impact of AβOs and defects in brain insulin signaling in AD. Because these data indicate a close similarity between pathways that drive peripheral insulin resistance in diabetes and brain insulin dysfunction in AD, we summarize further and discuss the molecular bases for using antidiabetic agents as novel therapeutic approaches in AD.

2. Deregulated brain insulin signaling in AD

In peripheral metabolic disorders, such as type 2 diabetes, prolonged metabolic stress and proinflammatory signaling lead to attenuated insulin signaling and decreased cellular responsiveness to insulin [40]. This pathological state is referred to as insulin resistance and it impairs acutely the ability of cells to maintain energy homeostasis. Interestingly, AD brains present similar abnormalities, including metabolic stress and neuroinflammation [12–14,41–43]. Thus, it is conceivable that similar mechanisms account for peripheral insulin resistance in type 2 diabetes and impaired brain insulin signaling in AD. Indeed, recent studies have linked neuropathogenic mechanisms triggered by AβOs to mechanisms involved in peripheral insulin resistance in diabetes [41,44,45].

Physiologically, insulin binds to its cell surface receptor (insulin receptor [IR]) and triggers intrinsic IR tyrosine kinase activity. Activated IRs then phosphorylate members of a conserved family of adaptor proteins called insulin receptor substrates 1 through 4 (IRS-1 through IRS-4) [15]. Once phosphorylated at tyrosine residues, IRS proteins act as scaffolds that couple IR stimulation to downstream effectors, such as phosphoinositide 3-kinase (PI3K), murine thymoma viral oncogene homolog (or Akt)/protein kinase B, and mammalian target of rapamycin complex 1 [15], allowing metabolic and transcriptional reprogramming of cells [46]. On the other hand, IRS-1 and IRS-2, the best-studied components of the IRS family, can undergo inhibitory serine phosphorylation (pSer), which causes their dissociation from the IR and decreases tyrosine phosphorylation (pTyr) [46]. Therefore, an intricate balance between IRS phosphorylation at serine or tyrosine residues (IRS-1pSer vs. IRS-1pTyr) determines the extent of insulin actions [47].

In type 2 diabetes, aberrant tumor necrosis factor-α (TNF-α) signaling leads to activation of the stress kinase c-Jun N-terminal kinase (JNK) [48]. Activated JNK phosphorylates IRS-1 at serine residues (IRS-1pSer), blocking downstream insulin signaling and causing peripheral insulin resistance [40]. Similarly, it was shown recently that AβOs instigate aberrant activation of the TNF-α/JNK pathway and IRS-1 inhibition in primary hippocampal neurons [41,44], and in the hippocampi of cynomolgus monkeys that received intracerebroventricular infusions of AβOs [41]. IRS-1 inhibition was also demonstrated in the brains of a transgenic mouse model of AD [41]. Most important in establishing the clinical relevance of these findings was the demonstration of elevated IRS-1pSer [14,41] and activated JNK [41] in postmortem AD brains. Because AβOs trigger internalization and redistribution of neuronal IRs [49], it is possible that removal of IRs from the cell surface facilitates IRS-1pSer, a view that is consistent with our finding that insulin blocks both neuronal IR downregulation [50] and IRS-1pSer induced by AβOs [41].

Downstream from IRS-1 and PI3K, AβOs instigate Ser473 phosphorylation of Akt, a molecular hub in the insulin signaling pathway. Elevated pSer473 levels are associated with feedback-dependent Akt inhibition in inflammation and peripheral insulin resistance [51,52]. Interestingly, induction of Akt-pSer473 by AβOs takes place both in the absence and presence of insulin [49], suggesting that it could be mediated by an IR-independent pathway, likely involving TNF-α signaling.

In peripheral insulin resistance, activation of the TNF-α/JNK pathway is linked to major inflammatory/stress signaling networks, including endoplasmic reticulum (ER) stress and the stress kinases IκBα kinase (IKK) and double-stranded RNA-dependent protein kinase (PKR) [53,54]. We recently reported that IκBα kinase and double-stranded RNA-dependent protein kinase appear to mediate AβO-induced IRS-1 inhibition in hippocampal neurons [41]. It is also conceivable that ER stress, which has been reported in AD brains [43,55], further underlies oligomer-induced

deregulation of neuronal insulin signaling. If, indeed, found to be the case, this would reinforce the notion that common mechanisms underlie impaired peripheral insulin signaling in type 2 diabetes and brain insulin resistance in AD [41].

3. A possible crosstalk between deregulated insulin and N-methyl-D-aspartate receptor signaling

AβOs have been documented to cause aberrant activation and deregulation of N-methyl-D-aspartate (NMDA)-subtype glutamate receptors (NMDARs) [56–59]. Deregulated NMDAR function may play a role in the impairment of neuronal insulin signaling in AD, because AβO-induced inhibition of IR signaling is prevented by the NMDAR blocker memantine [49]. Both memantine and an antibody against the constitutive NMDAR subunit 1 (or GluN1) attenuate the rapid increase in intraneuronal calcium and neuronal oxidative stress triggered by AβOs [56,58]. Because excitatory glutamate signaling and neuronal depolarization reduce the responsiveness of IRs to insulin [49], and chelation of intracellular calcium with BAPTA-AM prevents both AβO-induced IR inhibition [49] and oxidative stress [56], it seems plausible that a mechanism involving aberrant NMDAR-dependent calcium influx underlies neuronal insulin resistance in AD.

Under physiological conditions, synaptic NMDAR activity exerts an antioxidant role through suppression of the FOXO1 transcription factor in the hippocampus [60,61]. In AD, however, abnormal NMDAR function and insulin resistance may enable nuclear translocation of FOXO1, culminating in increased generation of reactive oxygen species and, possibly, activation of stress kinases [62]. This, in turn, may exacerbate the impairment of insulin signaling and neuronal dysfunction.

Another possibility is that excessive NMDAR activation and calcium influx triggered by oligomers [57,58,63,64] stimulate the activity of tyrosine phosphatases on IRS-1, as described for glutamate-induced neuronal damage [65], thus attenuating insulin signal transduction. These possibilities are in harmony with described IR regulatory mechanisms and suggest a possible physiological feedback between deregulated neuronal activity and insulin signaling. A schematic outline of this interplay under physiological and pathological conditions is presented in Fig. 1.

Interestingly, defective insulin signaling accelerates Aβ production in the brain by enhancing the amyloidogenic processing of the amyloid precursor protein [66,67], and also increases Aβ aggregation through monosialotetrahexosylganglioside (GM1) clustering and membrane signaling [68]. Thus, oligomer-induced insulin resistance may create a vicious cycle in which oligomers upregulate their own production and aggregation by disrupting insulin physiological actions. Such a mechanism could account in part for AβO buildup in AD brains.

In summary, multiple toxic effects of AβOs may impair proper brain insulin signaling and trigger a feed-forward cascade that disrupts neuronal functions through increased cellular stress (e.g., aberrant cytosolic calcium, oxidative stress, ER stress). This condition, in turn, appears to intensify neuronal insulin resistance and Aβ generation. Because defective neuronal IR/IRS-1 function appears critical for the onset of AD-related neuronal damage, it seems likely that bolstering insulin sensitivity and actions could provide encouraging results in preventing/rescuing memory decline.

4. Stimulation of brain insulin signaling as a novel therapeutic approach in AD

Our understanding of how sporadic AD develops has increased significantly during the past few years. For example, it is now well established that the onset of AD correlates with synapse failure and metabolic changes in the brain [28]. Moreover, accumulation of soluble Aβ species, notably oligomers, likely accounts for altered brain function [28]. To date, however, most approaches proposed as possible treatments for AD have failed disappointingly in clinical trials [1]. At the same time, insulin-based strategies have emerged as potentially successful therapies for AD [45].

Brain insulin signaling declines with age [69], the major risk factor for AD, suggesting that restoring insulin signaling might be beneficial to patients with AD. Of special interest is the finding that intranasal insulin administration, a preferential route for central nervous system delivery [70], improves memory in healthy adults without affecting circulating levels of insulin or glucose [25,71]. Intranasal insulin also enhanced verbal memory in memory-impaired subjects [72] and improved cognitive performance in patients with early AD [45,73]. In this regard, it is noteworthy that a larger scale clinical trial is now planned to determine the efficacy of insulin in improving memory and cognition in patients with AD [74]. The mechanism of neuroprotection by insulin appears to involve downregulation of neuronal AβO binding sites [50] and increased oligomer clearance [75], consequently preventing IR internalization and synapse loss [50,76,77]. Insulin-mediated synapse protection mechanisms could thus contribute to preserved cognitive function in normal individuals, whereas impaired insulin signaling might render neurons vulnerable to oligomer-induced synaptotoxicity. As pointed out recently, insulin may have important therapeutic implications at early and/or intermediate phases of AD [72,78], preventing oligomer binding to synapses and blocking insulin receptor pathology [13,49,50]. At later disease stages, when surface IRs dwindle, it is possible that insulin may stimulate other receptors (e.g., insulin-like growth factor 1 (IGF-1) receptors) and thus still improve AD-related deficits.

Alternative approaches to boost insulin-related signaling pathways might provide additional therapeutic opportunities in AD [79,80]. In this regard, glucagon-like peptide 1 receptor (GLP-1R) agonists are an attractive option because they activate pathways common to insulin signaling and facilitate hippocampal synaptic plasticity,

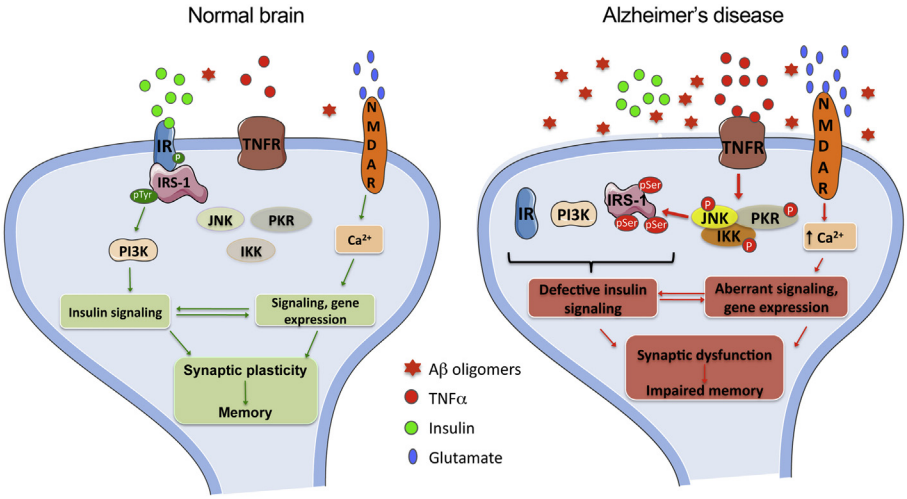

Fig. 1. Impaired neuronal insulin signaling in Alzheimer's disease (AD). Schematic outline of neuronal insulin signaling in normal brain (left) and AD brain (right). Under physiological conditions, insulin binding to its cell surface receptor (insulin receptor [IR]) triggers IR autophosphorylation and subsequent tyrosine phosphorylation of insulin receptor substrate 1 (IRS-1). This results in phosphoinositide 3-kinase (PI3K) activation and downstream cellular responses that facilitate synaptic plasticity and memory. Activity-dependent calcium (Ca^{2+}) influx via N-methyl-D-aspartate receptors (NMDARs) activates signaling and expression of genes involved in synaptic plasticity and memory. A crosstalk between NMDAR- and IR-dependent signaling may modulate the actions of insulin on memory. In AD, accumulation of amyloid-β (Aβ) oligomers leads to increased tumor necrosis factor-α (TNF-α) levels and activation of stress kinases (c-Jun N-terminal kinase [JNK], double-stranded ribonucleic acid [RNA]-dependent protein kinase [PKR], and IκBα kinase [IKK]), resulting in inhibitory serine phosphorylation of IRS-1. Aβ oligomers instigate additional removal of IRs from the cell surface and redistribution to the cell body. These combined events block neuronal insulin signaling. Aberrant activation of NMDARs by Aβ oligomers results in excessive Ca^{2+} influx, neuronal oxidative stress, and disrupted signaling, leading to impaired synaptic plasticity. Under these conditions, putative activation of protein tyrosine phosphatases may inhibit IRS-1 signaling further, ultimately leading to synapse impairment and memory failure. pSer, phosphoserine; pTyr, phosphotyrosine; TNFR, TNFa receptor.

cognition, and cell survival [81–84]. Exendin-4 and liraglutide are two such agonists that have been approved for treatment of type 2 diabetes. GLP-1 analogs are stable in blood and exhibit good brain penetration [85]. Exendin-4 was found recently to block AβO-induced impairment in insulin signaling in hippocampal neurons [41]. Exendin-4 also restored impaired brain insulin signaling in a transgenic mouse model of AD, decreasing Aβ accumulation and improving cognition [41]. More significant, liraglutide has been shown to counteract Aβ-induced memory deficits in mice [86] and to reduce neuropathology and improve cognitive performance in AD transgenic mice [87].

The complete cellular machinery recruited by GLP-1R activation to mediate neuroprotection and cognitive enhancement is still not fully understood, but the recent finding that exendin-4 reduces JNK activation and improves insulin signaling in an AD mouse model provides initial clues on this issue [41]. One may further speculate that neuroprotection involves both cyclic adenosine monophosphate (cAMP) production and PI3K activation, mechanisms that ultimately favor neuronal survival, enhanced synaptic plasticity, and memory formation. GLP-1R activation may thus provide a novel strategy to resensitize impaired brain insulin signaling and to prevent or halt neurodegeneration in AD.

5. Conclusions

AD is still a disorder in search of mechanisms that fully explain memory loss and lead the way to development of effective therapies. Recent reports demonstrating shared clinical and pathophysiological traits between AD and diabetes raise the possibility that antidiabetic agents might provide cognitive benefit. This notion finds support in evidence that AβOs, increasingly viewed as key synaptotoxins in AD, disrupt normal brain insulin signaling via proinflammatory mechanisms, similar to what happens in peripheral tissue in diabetes. The resulting scenario of cellular stress and synapse dysfunction appears to be counteracted by stimulating brain insulin signaling, either using insulin itself or antidiabetic drugs such as GLP-1R agonists.

In conclusion, establishing a molecular link between AD and diabetes may have important implications for elucidating the mechanisms underlying neuronal dysfunction in AD. It is conceivable that novel therapeutic options for AD may arise from efforts aimed at unraveling mechanisms accounting for brain insulin resistance [45,73]. We look forward to results from recently implemented clinical trials using both insulin [88] and GLP-1R agonists [89,90] in AD. Hopefully, results from those trials will favor the emergence of novel therapeutic opportunities for this devastating disease.

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