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Insulin: An Emerging Treatment for Alzheimer's Disease Dementia?

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Abstract

Accumulating evidence indicates a role for metabolic dysfunction in the pathogenesis of Alzheimer's disease (AD). It is widely reported that Type 2 diabetes (T2D) increases the risk of developing AD, and several postmortem analyses have found evidence of insulin resistance in the AD brain. Thus, insulin-based therapies have emerged as potential strategies to slow cognitive decline in AD. The main methods for targeting insulin to date have been intravenous insulin infusion, intranasal insulin administration, and use of insulin sensitizers. These methods have elicited variable results regarding improvement in cognitive function. This review will discuss the rationale for targeting insulin signaling to improve cognitive function in AD, the results of clinical studies that have targeted insulin signaling, and what these results mean for future studies of the role of insulin-based therapies for AD.

Keywords

Insulin; Dementia; Alzheimer's disease; Apolipoprotein E; Amyloid; Rosiglitazone; Pioglitazone; Insulin signaling; Cognition; Memory; Intranasal; Thiazolidinedione; Diabetes

Introduction

The discovery of insulin as a therapy for diabetes in the early 20th century led to the recognition of insulin as a key regulator of energy metabolism. In the periphery, insulin's primary role is to clear blood glucose by increasing cell glucose uptake. Approximately 75 % of insulin-stimulated glucose transport occurs in skeletal muscle (reviewed in [1]), and insulin's metabolic effects on muscle have been widely studied and are well described. The study of insulin-mediated effects in the central nervous system (CNS) has predominately been overlooked for many years. In the mid-1980s, several studies were published that characterized insulin receptors in the CNS and suggested that insulin may play a role in glucose uptake and neurotransmission in the brain [2–5]. These studies ignited interest in the

role of insulin in the CNS and led the way for later research confirming insulin as an important hormone for CNS function [6–9].

In recent years, the study of insulin and insulin signaling in neuronal tissues has gained momentum. Proteins involved in transmission of the insulin signal have been detected in many brain regions, including areas affected in Alzheimer's disease (AD), such as the hippocampus and temporal lobes [10, 11]. Because insulin signaling is impaired in postmortem brain tissue from AD patients [10–13], and because it is known that insulin positively influences cellular processes such as growth and survival [14], improving insulin action in neurons has emerged as a treatment target for improved cognitive function.

Interest in insulin as a potential therapy for AD has also stemmed from a number of clinical studies that indicate that individuals with Type 2 diabetes (T2D) have an elevated risk of mild cognitive impairment and AD [15–24]. In fact, a recent meta-analysis of longitudinal clinical studies found that T2D significantly increased AD risk independently of obesity [25]. T2D is defined by an insulin-resistant state, where the usual effects of insulin on glucose uptake are attenuated. Normally, insulin receptor binding activates an intracellular signaling cascade called the phosphoinositide-3-kinase (PI3K) pathway. Insulin resistance occurs due to a postreceptor signaling defect, which means that although insulin can bind to its receptor, the signal is not properly transduced through the PI3K pathway. This results in decreased activity of downstream proteins, such as AKT. In T2D, insulin resistance is associated with hyperglycemia as a result of decreased glucose uptake. Insulin resistance in T2D is also associated with decreased expression or activation of several intracellular proteins involved in insulin signaling. Interestingly, decreased expression and activation of these same proteins is observed postmortem in AD [10–13]. Thus, studies linking AD and T2D indirectly suggest that insulin resistance may play a role in AD.

In addition to studies that indicate that T2D is a risk factor for AD, additional studies specifically implicate insulin. A recent population-based, longitudinal study showed that impaired insulin response during midlife is associated with an increased AD risk [26]. Cell-culture-based studies have reported a relationship between insulin and amyloid beta ($A\beta$), a pathological hallmark of AD. In culture, exposure of neurons to soluble $A\beta$ oligomers caused a decrease in insulin receptors [27], and it has been shown that insulin signaling can protect $A\beta$ oligomer-mediated insulin receptor loss and synaptic deterioration [28]. Moreover, another study showed that insulin promotes $A\beta$ trafficking to the cell membrane and promotes $A\beta$ release [29]. This molecular mechanism is supported by clinical literature that shows that insulin infusion (1.0 mU/kg $\times$ min) increases $A\beta_{42}$ levels in CSF and plasma of nondemented subjects [30, 31]. However, AD subjects require higher doses of insulin to raise plasma $A\beta$ levels, as compared with normal adults, suggesting reduced insulin-provoked $A\beta$ elevation [32]. AD patients also exhibit higher fasting plasma insulin [31], an early sign of insulin resistance, and a decreased CSF/plasma glucose ratio [31]. Moreover, our group has shown that insulin is differentially related to cognitive function in AD patients and nondemented elderly adults. In nondiabetic subjects with AD, increased insulin response during an intravenous glucose tolerance test was associated with less 2-year cognitive decline. However, in nondemented subjects, increased insulin response was associated with greater 2-year cognitive decline. [33]. It is possible that the effects of insulin on cognitive function may differ between non-demented subjects and individuals with AD, potentially due to differences in brain insulin sensitivity. Together, these studies indicate a role for peripheral insulin in the modulation of plasma and CSF $A\beta$ levels and cognitive function in AD.

Because clinical evidence suggests that insulin and insulin-mediated signaling are associated with risk of AD, several studies have sought to increase the effect of insulin in the brain. A

review of clinical literature reveals that three primary methods for improving insulin action in the brains of AD patients have been investigated. These include studies of infused insulin, intranasal insulin, and insulin sensitizers. The goal of each study was similar: to determine whether increasing insulin action would produce cognitive benefit. This article will review recent studies that have analyzed the effect of insulin and insulin signaling on the brain and will address the promise of insulin as a emerging therapy for AD.

Insulin as a Therapy for Alzheimer's Disease

Intravenous Insulin

The first clinical studies to address the effect of insulin on the brain in the context of cognition were performed with intravenous insulin infusion. Insulin infusion is achieved using the hyperinsulinemic-euglycemic clamp method, where circulating insulin levels are raised by a controlled infusion of insulin while glucose levels are monitored and maintained constant through glucose infusion [34]. Several small studies demonstrate that intravenous insulin infusion exerts beneficial effects on memory. One study of young, cognitively normal subjects tested two different infusion rates of insulin (1.5 mU/kg×min and 15 mU/kg×min), which resulted in “low” and “high” serum levels of insulin. Individuals with high infusion rates and serum insulin levels exhibited improved memory performance and attention during intravenous insulin infusion [35]. Two additional studies found that in elderly subjects with AD, insulin infusion (1.0 mU/kg×min) improved declarative memory in cognitively impaired individuals, but not in the healthy control group [36, 37]. However, another study using the same infusion rate (1.0 mU/kg×min) in nondemented older adults found that insulin did result in increased memory performance across all individuals [31].

Intranasal Insulin

Infusion of peripheral insulin is not a viable long-term therapy for AD, due to the dangers of hypoglycemia when insulin is infused peripherally. Recently, direct drug delivery to the CNS has been investigated using intranasal administration. Delivery of substances to the brain through intranasal administration is thought to occur primarily through olfactory and trigeminal pathways. Delivery begins quickly (less than 10 min after administration) and, thus, is thought to occur extracellularly rather than axonally (reviewed in [38]). Intranasal administration of 40 IU insulin results in a peak in CSF insulin concentration after 30 min, without any effect on insulin or glucose levels in the bloodstream [39]. Thus, intranasal delivery of insulin is attractive because it is less invasive than intravenous infusion and circumvents potential side effects of intravenous insulin infusions, such as hypoglycemia. Initial studies of intranasal insulin's effects on memory show some promise.

Although the acute effects of intranasal insulin in non-demented subjects are limited [40, 41], chronic administration of intranasal insulin in cognitively normal young adults is associated with increased memory performance. In these subjects, 8 weeks of intranasal insulin (4× per day, 40 IU/dose) enhanced performance on delayed word recall tests [42]. In a follow-up study, 8 weeks of intranasal insulin (3×/day, 40 IU/dose) also resulted in improved delayed word recall in young, cognitively normal subjects [40]. Intranasal insulin has also been studied in cognitively impaired patients. A 2008 study reported that intranasal insulin (20 IU, 2×/day) for 21 days improved story recall, attention, and caregiver-rated functional status in cognitively impaired subjects or individuals with AD [43•]. Another study involving individuals with AD or mild cognitive impairment found that 4 months of intranasal insulin (20 IU, 2×/day) preserved cognition as measured by ADAS-cog, improved delayed memory, and improved caregiver-rated functional ability [44•]. Additionally, some studies using intravenous and intranasal insulin have shown that the effect of insulin on memory differs on the basis of APOE genotype. These studies are discussed below.

APOE Genotype and Insulin Effects

Several clinical studies have suggested a role for apolipo-protein E (APOE) genotype in mediating effects of both intravenous and intranasal insulin. The e4 allele of APOE (APOE e4) is known to be a risk factor for AD [45]. Although the function of APOE is still debated, several studies indicate that APOE e4-negative subjects exhibit greater insulin-mediated memory benefits. For instance, it has been shown that intravenous insulin improves memory in subjects with mild cognitive impairment or AD who are APOE e4 negative, but not individuals who are positive for the APOE e4 allele [46, 47]. One study using intranasal insulin tested word and story recall in response to two doses of acute insulin (20 or 40 IU) administered on separate occasions. Acute cognitive testing (15 min following insulin) revealed that only APOE e4-negative patients showed improved performance. APOE e4-positive individuals did not improve and actually performed more poorly on word list recall following the 40-IU dose [41]. Two additional studies found that insulin-mediated memory improvement was dependent upon both dose and genotype [48, 49]. Finally, another study that analyzed the APOE e4 genotype as a covariate did not find that the APOE e4 genotype modified the beneficial effects of insulin, although the authors acknowledged that the study was not powered to examine the effects of the APOE genotype [44]. These initial studies are promising, but findings are inconsistent between nondemented and cognitively impaired subjects regarding the acute effects of intranasal insulin on memory, and the role of APOE genotype remains unclear. Additional work needs to be done to further characterize the relationship between intranasal insulin, genotype, and cognitive function.

Insulin Sensitizers

An alternative method for increasing insulin action in the brain is the use of insulin sensitizers. These agents are effectively used in patients with T2D and, thus, are already approved for use in humans. A common class of insulin-sensitizing drugs is thiazolidinediones, which includes rosiglitazone and pioglitazone. These drugs exert effects through nuclear receptor peroxisome proliferator activated receptor-gamma (PPAR- γ) and differ from other diabetic medications, such as sulfonylureas, because they enhance insulin sensitivity, rather than increasing insulin secretion [50]. Thus, thiazolidinediones can be used in concert with first-line diabetic medications, such as metformin. It is interesting that while PPAR- γ agonists are recognized to enhance insulin sensitivity, their mechanism of action is not well understood. Recently, it has been suggested that the insulin-sensitizing effects of PPAR- γ ligands such as rosiglitazone may not be due to direct action on PPAR- γ , as previously thought, but instead may be due to inhibition of PPAR- γ phosphorylation by the kinase cdk5, which normalizes downstream effects on gene expression [51].

A number of preclinical studies have suggested that rosiglitazone may improve cognitive function in AD patients (reviewed in [52]). It has been shown that insulin protects cultured neurons from soluble amyloid beta oligomers and that this effect is potentiated by rosiglitazone [28]. Furthermore, rosiglitazone administration in transgenic mice has been shown to attenuate amyloid beta expression and tau phosphorylation [53] and to decrease learning and memory deficits [54]. However, clinical studies regarding the effect of insulin sensitizers on cognitive function in AD have reported mixed results. Results from early, exploratory clinical studies were promising. Individuals with mild AD or MCI who received rosiglitazone daily for 6 months exhibited improved attention and delayed recall [55]. Another study, conducted on individuals with T2D and mild cognitive impairment, found that subjects receiving rosiglitazone and metformin exhibited less cognitive decline than did individuals receiving only metformin [56].

Although initial clinical pilot studies with rosiglitazone were promising, three larger follow-up studies have found no effect of rosiglitazone on cognitive function [57•, 58•, 59•]. A

2010 phase III trial enrolled nearly 700 subjects and assessed the primary outcome measures of ADAS-Cog and Clinician's Interview-Based Impression of Change plus caregiver input (CIBIC+). Two doses of Rosiglitazone Extended Release (RSG-XR), 2 or 8 mg, were administered once a day for 24 weeks. RSG-XR showed no effect on either primary outcome measure [57•]. A larger, longer phase III trial followed, and similar results were reported. This study, which involved almost 1,500 subjects, analyzed the effect of once daily 2- or 8-mg RSG-XR after 48 weeks. The primary outcome measures were ADAS-Cog and Clinical Dementia Rating scale–Sum of Boxes (CDR–SB). No differences were observed between treatment groups in any outcome measures [58•]. Neither phase III rosiglitazone study found any effect of APOE e4 genotype on primary outcome measures. Finally, a multicenter clinical trial tested the effect of 12 months of RSG-XR (4 mg daily during months 1 and 8 mg daily for the remainder of the study) on the primary outcome measure of Fluorodeoxyglucose positron emission tomography (^{18}F FDG-PET). Participants were scanned at baseline and after 1, 2, 6, and 12 months of RSG-XR. No significant differences were shown between groups in the primary outcome measure (^{18}F FDG-PET) after 12 months of treatment, although there was a nonsignificant trend for increased glucose metabolism after 1 month of RSG-XR. There was also no difference between groups for secondary outcome measures (ADAS-cog and CIBIC+) [59•]. The failure of rosiglitazone to elicit effects in several large, well-performed clinical trials does not support RSG-XR as a viable AD therapeutic agent. However, the authors of the latter study pointed out that more “CNS-penetrant” therapeutics targeting metabolic processes cannot be ruled out, since RSG-XR did exhibit a nonsignificant trend for increasing cerebral glucose metabolism after 1 month of treatment [59•].

Despite the negative effects of rosiglitazone in larger trials, a different thiazolidinedione, pioglitazone, is still being investigated. Pioglitazone has exhibited beneficial effects in preclinical studies. In mice, pioglitazone attenuated streptozotocin-induced memory deficits [60] and improved cognitive impairment in MPTP-treated monkeys [61]. However, the use of this drug in humans with AD is very limited. The first study of pioglitazone in AD patients examined individuals with comorbid AD and T2D. Pioglitazone (15–30 mg, $n=15$) was administered daily for 6 months in addition to normal diabetic medication. Treated subjects were compared with a control group ($n=17$) that did not receive pioglitazone. Six months of treatment was found to increase logical memory and improve performance on ADAS-Cog [62]. A follow-up study by the same group again found that 6 months of daily pioglitazone improved measures of cognitive function in individuals with comorbid AD and T2D [63]. In the latter study, pioglitazone was administered at two doses, 15 mg ($n=19$) and 30 mg ($n=2$). Subjects were compared with a control group ($n=21$) that did not receive pioglitazone. These studies included small sample sizes and assessed only individuals with comorbid AD and T2D; thus, additional studies are needed to assess the use of pioglitazone to improve cognitive function in AD.

Why Target Insulin in AD?

To understand why insulin treatment may improve cognitive function, it is important to understand the mechanism of insulin signaling and how it is affected in AD. Although insulin signaling is most widely characterized in peripheral tissues, the components of this pathway appear highly conserved in the brain [64]. Insulin signaling requires interactions between the insulin receptor and insulin receptor substrate (IRS) protein, which occurs via tyrosine phosphorylation of IRS [65]. This provides a docking site for proteins with Src Homology 2 domains, such as phosphoinositide-3-kinase (PI3K) [66]. Activation of the catalytic subunit of PI3K catalyzes conversion of PI(4,5)-bisphosphate (PIP2) to PI(3,4,5)-triphosphate (PIP3) at the plasma membrane. This allows proteins that contain pleckstrin-homology domains, such as phosphoinositide-dependent kinase-1 (PDK-1) and AKT, to be

activated [67]. It is widely recognized that AKT is a crucial player in the transmission of the insulin signal.

In recent years, insulin signaling has been characterized in postmortem brains from AD patients [10–13]. These studies report many deficiencies in insulin signaling, such as decreased insulin receptor expression [11], insulin receptor substrate (IRS) expression [10, 11], AKT activation [11, 12], PI3K expression [13], and AKT expression [13]. Taken together, these studies provide strong molecular evidence of deficient insulin signaling in AD patients. These deficiencies are outlined in Fig. 1. Because many of the proteins involved in insulin signal transmission are downregulated or less active in AD, it is possible that increasing insulin levels in the brain or increasing insulin sensitivity can help compensate for decreased signaling.

Although the exact mechanism by which insulin improves cognitive function is unknown, there are several possibilities. Molecularly, relationships have been reported between insulin signaling, amyloid beta, and tau phosphorylation. It has been shown that amyloid can inhibit insulin signaling. Amyloid beta expression decreases AKT phosphorylation and disrupts insulin signal transmission, likely by inhibiting the interaction between AKT and PDK1 [12], and amyloid beta can also directly compete with insulin to decrease its binding to insulin receptor [68]. Furthermore, impaired insulin signaling in AD has been linked to increased activation of glycogen synthase kinase beta [11]. GSK3 beta is recognized as the major tau kinase [69] and has been implicated in tau hyperphosphorylation [70]. The interplay between insulin signaling, amyloid beta, and tau phosphorylation will likely contribute to any long-term benefits of insulin.

Additional Considerations

The role of APOE genotype in mediating the cognitive effects of insulin is unclear. In fact, this relationship may have more to do with A β itself than with APOE genotype. As has been mentioned, A β may inhibit insulin signaling. In targeted replacement mouse models, animals expressing human APOE e4 exhibited higher brain A β -42 levels, as compared with mice expressing other forms of human APOE [71]. This relationship seems to hold true in humans as well, since a higher percentage of APOE e4-positive individuals exhibit increased amyloid load [72]. If A β does modulate insulin signal transmission, this may explain why some studies using intranasal insulin show that insulin is most effective at improving cognitive function in APOE e4-negative individuals. An additional possibility may be differential levels of LDL cholesterol in APOE e4-positive subjects. In healthy young adults, it has been shown that LDL levels differ on the basis of APOE genotype, with APOE e4-positive subjects exhibiting the highest levels and with the lowest levels in APOE e2-negative individuals [73]. Although speculative, LDL levels may be important when considering response to insulin, since oxidized LDL has been shown to impair insulin signaling in cell culture [74, 75].

It is interesting that while it is widely recognized that T2D is associated with increased AD risk, studies have shown that individuals with comorbid T2D and AD exhibit slower cognitive decline than do those with only AD [76]. Although there are numerous factors that could contribute to this finding, one possibility is the use of diabetic medications in this group. As has been mentioned, a recent study showed that individuals with comorbid T2D and mild cognitive impairment who were treated with metformin and rosiglitazone exhibited relative cognitive stability, when compared with counterparts treated with metformin only [56]. It has also been shown that improved glycemic control is related to improved memory in patients with T2D [77, 78].

Conclusions

The relationship between metabolism, insulin, and cognitive function is complex. Although studies using intravenous insulin provide a foundation for understanding the cognitive effects of insulin, this is not a viable method of treatment going forward, due to potential secondary effects, such as hypoglycemia. Results from human studies on the effect of intranasal insulin and cognitive function remain difficult to interpret; differential effects based upon genotype and dosing have been reported, and the reason for these effects is not understood. Insulin sensitizers have also shown success in small studies, but the results of larger, more definitive clinical trials of rosiglitazone have been consistently negative. Nevertheless, there are clear molecular mechanisms by which insulin could affect cognitive function. This possibility is supported by clinical studies showing improved cognition both in response to intravenous or intranasal insulin and with use of diabetic medications in subjects with comorbid T2D and AD. Of the therapies discussed here, it is our opinion that intranasal insulin shows the most promise, due to positive findings from several clinical studies, a known safety record, and ease of use. However, additional studies must be performed to further demonstrate the effects of intranasal insulin before it can be considered as a therapy for AD.

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Fig. 1.

Insulin signaling deficits in AD brain. Several studies have compared insulin signaling in nondemented and AD subjects in postmortem brain tissue. Deficits in insulin signaling associated with AD include decreased expression of insulin receptor, insulin receptor substrate (IRS), phosphoinositide 3-kinase (PI3K), and AKT and decreased AKT activity (phosphorylation). Preclinical studies have also shown that amyloid beta ($A\beta$) can compete with insulin for insulin receptor binding and impair interaction of AKT and phosphoinositide-dependent kinase (PDK1). Because glycogen synthase kinase-3 (GSK-3) lies downstream of AKT, it is possible that these effects could influence tau phosphorylation