Hyperinsulinemia or Insulin Resistance: What Impacts the Progression of Alzheimer’s Disease?

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Abstract. Type 2 diabetes mellitus (T2D), which is often accompanied by hyperinsulinemia and insulin resistance, is associated with an increased risk for developing mild cognitive impairment and Alzheimer’s disease (AD); however, the underlying mechanisms for this association are still unclear. Recent findings have shown that hyperinsulinemia and insulin resistance can coexist or be independent events. This makes it imperative to determine the contribution of these individual conditions in impacting AD. This literature review highlights the recent developments of hyperinsulinemia and insulin resistance involvement in the progression and pathogenesis of AD.

Keywords: Alzheimer’s disease, amyloid plaques, hyperglycemia, hyperinsulinemia, insulin resistance, tau phosphorylation

INTRODUCTION

Alzheimer’s disease (AD) is a progressive neurodegenerative disorder and one of the most common causes of dementia, cognitive decline, and eventual death [1]. Worldwide, 46.8 million people are estimated to be living with AD or related dementias and this number is expected to almost double every 20 years, reaching 74.7 million in 2030 [2]. Even though the majority of AD cases have a sporadic origin, genetic background strongly determines the risk of AD [3]. Currently, very little is known about the triggering factors for this damaging neurodegenerative disease [4], apart from aging, which is an important risk factor in the manifestation of late-onset AD [5]. Besides aging, several longitudinal studies have identified Type 2 diabetes (T2D) as a major risk factor for developing dementia and ultimately leading to dementia attributable to AD [6–13]. However, the underlying mechanisms responsible for this association have still not been fully elucidated. Clinical studies report that AD patients often exhibit altered peripheral glucose regulation, characterized by either hyperinsulinemia and insulin resistance [14–20], hypoinsulinemia alone [18], or impaired insulin secretion [21].

In contrast to T2D, there is very little data available on associations between Type 1 diabetes (T1D) and AD, although hypoinsulinemia also evokes an impaired insulin signaling response...
Additionally, cognitive defects have also been recognized as being more common in T1D subjects [22], which suggests cerebral hyperglycemia and/or hypoinsulinemia having a detrimental effect. Along with these deficits, increased GSK3 activity, increased tau phosphorylation, and increased Aβ protein levels have been reported in the brain of a mouse model of T1D [23]. Insulin therapy in this model partially prevented behavioral and biochemical changes, suggesting that insulin deficiency could play a pathogenic role for AD-like features in the brain [23]. Collectively, AD could be regarded as a brain disorder that has features of T1D (insulin deficiency) and T2D (impaired insulin signaling). The role of T1D in AD is not discussed in detail as the focus of this review is to understand the role of clinical features of T2D in AD pathology.

Hyperinsulinemia is a state of excessive blood insulin levels or excessive insulin secretion or response to food or a glucose load [24–27]. Insulin resistance indicates decreased sensitivity to insulin action in insulin signaling pathway [28–30]. It is conventionally considered that resistance to insulin action leads to greater insulin secretion attempting to achieve effective action of insulin. This sequence suggests that insulin resistance leads to hyperinsulinemia. However, recent findings suggest that insulin resistance and hyperinsulinemia can be dissociated, exist in isolation from one another, and play different pathogenic roles in the genesis of the clinical syndromes associated with the two abnormalities [31–34]. These findings raise an important question about the contribution of these states to AD development. Are insulin resistance and hyperinsulinemia both linked with AD, or is it one of the two that is associated with AD? This would be an important question to address, in order to better understand the link between T2D and AD. In the current article, we reviewed the literature for available evidence that may possibly clarify the issue and may help in focusing on developing approaches for impacting the progression of AD. We also discuss recent research on E4orf1 protein (derived from Ad36) and its effects on glycemic control in T2D and possible role in AD.

T2D IS A RISK FACTOR FOR AD AND IMPROVING T2D CAN IMPROVE AD

Given that T2D is a potentially modifiable risk factor for dementia, significant interest exists in the mechanism underlying the association between the two conditions, with the hope that a common intervention might begin to address both problems. Numerous clinical, animal model, and postmortem studies have suggested that treatment with anti-diabetic medication of persons suffering from dementia may have beneficial effects on cognitive function and on AD-related neuropathology [20, 35, 36]. However, the association is complex. Certain anti-diabetic drugs like Metformin, an insulin sensitizer, seem to contribute to worsening of AD risk [37–39]. Therefore, in order to establish mechanistic links between comorbid diseases, we need to systematically examine molecular mechanisms potentially shared by these diseases. One shared mechanism between T2D and AD is increased endogenous insulin or hyperinsulinemia and insulin resistance, which are involved in the clinical development of T2D. As mentioned above, even though the two can be dissociated, most anti-diabetes agents reduce both insulin resistance and hyperinsulinemia, making it harder to separately investigate their relative roles in AD development and/or prevention. Additionally, hyperinsulinemia precedes hyperglycemia and hence early detection of hyperinsulinemia and therapeutic agents that selectively treat hyperinsulinemia might have better outcomes against AD.

HYPERGLYCEMIA, INSULIN RESISTANCE, AND HYPERINSULINEMIA ARE INVOLVED IN THE CLINICAL DEVELOPMENT OF T2D

The balance between glucose production and utilization is regulated by a network of hormones, neural pathways, and metabolic signals [19]. Insulin plays a pivotal role in this process. The main metabolic actions of insulin are to stimulate glucose uptake in skeletal muscle and the heart and to suppress the production of glucose and very-low-density lipoprotein in the liver. Other metabolic effects of insulin include inhibition of glucose release from the liver, inhibition of the release of free fatty acids (FFAs) from adipose tissue, and stimulation of the process by which amino acids are incorporated into protein [40].

Hyperglycemia is a condition of higher than optimum blood glucose levels, which occurs with insulin resistance, having deleterious effects on organs and tissues in the body [41]. Insulin resistance is a condition when normal levels of insulin do not trigger the signal for glucose absorption due to defects in the action of insulin. This results in increased secretion
of insulin from the pancreatic beta cells, leading to hyperinsulinemia to maintain euglycemia [42]. This compensation by the pancreas continues until reserve capacity is exceeded by metabolic demands and insulin secretion is no longer adequate [43]. With continued hyperglycemia (rise in blood glucose levels) impaired glucose tolerance develops into T2D. Thus, there is a continuous spectrum of insulin responsiveness, ranging from normal insulin sensitivity to severe insulin resistance [44].

However, conflicting information exists regarding the underlying mechanisms of T2D. Basal hyperinsulinemia, reduced sensitivity to insulin, and disturbances in insulin release are often associated with T2D, while hyperinsulinemia has also been postulated to be a cause rather than a consequence of insulin resistance [45, 46]. It has been hypothesized that several factors could contribute to the development of insulin resistance with age, such as increased adiposity, decreased muscle mass, and a reduction in physical activity [47]. In this case, hyperinsulinemia would come later as a compensatory response to insulin resistance. It is known that high plasma insulin concentrations may chronically reduce the number and activity of the insulin receptors, leading to insulin resistance [48]. In support of these findings, in an animal model of high fat diet-induced hyperinsulinemia, it was shown that the ablation of the insulin gene (Ins2 gene deletion), protected these mice from diet induced obesity in the absence of hyperinsulinemia and its complications such as insulin resistance [49], pointing to a new concept associated with T2D pathogenesis. These interesting observations indicate that pathological circulating hyperinsulinemia drives diet-induced obesity and its complications. There have been several attempts to differentiate between the relative roles of insulin resistance and hyperinsulinemia in the development of clinical syndromes associated with insulin metabolism [31–34]. Therefore, it appears that hyperinsulinemia and insulin resistance can exist independent of each other.

HYPERINSULINEMIA AND HYPERGLYCEMIA

Fasting hyperinsulinemia is a widely used surrogate measure of insulin resistance and predicts T2D in various populations. Whether fasting hyperinsulinemia predicts diabetes independent of insulin resistance is unknown. There are several lines of evidence to suggest that fasting hyperinsulinemia itself may be a primary metabolic defect and not simply a secondary consequence of insulin resistance [50–57]. Based on the above findings, it has been suggested that basal hypersecretion of insulin may be an independent abnormality in the pathogenesis of diabetes [51, 53, 58, 59] and that in some populations, primary (not compensatory) hyperinsulinemia, rather than insulin resistance, may be the primary genetic defect [58, 59]. The fasting hyperglycemia that defines T2D is largely secondary to inadequate action of insulin, and hyperinsulinemia has been shown to precede hyperglycemia [60–62], by up to 24 years [63]. During the progression of hyperglycemia into diabetes the initial step is compensation, where insulin secretion increases to maintain normal glucose levels in the face of insulin resistance that might result from obesity, physical inactivity, and genetic predisposition [60]. At the beginning, the fasting plasma levels increase from normal levels to higher values; however, this change in glycemia is not recognized as being clinically abnormal because the compensatory hyperinsulinemia does not allow it to reach the category of impaired fasting glucose [60]. Therefore, hyperinsulinemia could exist for long before hyperglycemia is detected [63] and might be an important target in prevention of pathogenesis of hyperglycemia mediated T2D.

HYPERINSULINEMIA IS A HALLMARK OF AD PATHOLOGY

Hyperinsulinemia is strongly linked to decreased insulin signaling within the brain. Several clinical studies have demonstrated that AD patients show evidence of altered peripheral glucose regulation characterized by hyperinsulinemia and insulin resistance [6, 17, 64], and in a number of pathophysiological processes related to AD [65, 66]. The insulin resistance syndrome occurs when tissues become unresponsive to the effects of insulin and are typically accompanied by compensatory hyperinsulinemia in the periphery, which has independent deleterious effects. More specifically, systemic hyperinsulinemia or insulin resistance, affect the insulin receptor and/or insulin receptor substrate mediated Akt signaling, which induces the inhibition of glycogen synthase kinase-3β (GSK-3β) [67–69]. Under normal conditions, insulin signaling via the insulin receptor leads to phosphorylation of GSK-3β, leading to its inactivation. Whereas, in insulin resis-
tance or hyperinsulinemia conditions, GSK-3β is dephosphorylated, leading to its activation [67, 70]. The regulation of GSK-3β in the hippocampus and cortex changes in response to changes in glucose and insulin concentrations [71], and in T2D an increase in GSK-3β activity might lead to insulin resistance by reducing glucose clearance [69]. Increased GSK-3β activation might also lead to an elevation in Aβ production (resulting from a GSK-3β-mediated increase in presenilin 1 activity) [72] and an increase in tau phosphorylation associated with neurofibrillary tangles formation [67] (Fig. 1). In the brain, binding of insulin to its receptors modulates cognitive function. Additionally, insulin also aids the release of amyloid-β peptide extracellularly, and increases the expression of the enzyme which degrades insulin, insulin degrading enzyme [73]. This enzyme also degrades amyloid-β peptide and thus insulin deficiency results in accumulation of amyloid-β peptide (Fig. 1). By contrast, inhibition of GSK-3β attenuates AβPP processing and inhibits hyperphosphorylated tau-associated neurodegeneration in cell-culture and animal models of AD [72, 74]. Therefore, insulin resistance and/or hyperinsulinemia, which are the underlying causes of T2D, are considered a part of the core syndrome that increases the risk of AD.

IS IT HYPERINSULINEMIA OR INSULIN RESISTANCE THAT IMPACTS PROGRESSION OF AD

As mentioned above, hyperinsulinemia and insulin resistance can be dissociated, therefore it is important to test if improving one without affecting the other will be an effective therapeutic approach. Currently several clinical and basic science studies using insulin sensitizers have shown that thiglutzonazones (e.g., pioglitazone, rosiglitazone), and biguanides (e.g., metformin) can improve cognitive function [75]. Particularly, rosiglitazone has been shown to protect cultured neurons from amyloid-β oligomers [76], and in transgenic mice of AD to attenuate amyloid-β expression and tau phosphorylation [77] and decreased learning and memory deficits [78]. Although initial clinical pilot studies with rosiglitazone were promising, three larger follow-up studies have found no effect of rosiglitazone on cognitive function [79–81].

Reduced glucose metabolism in the brain has been shown in patients with AD [82] and also observed years before the development of clinical symptoms of dementia and is associated with increased risk for AD [83]. Interestingly, a similar impairment in regional glucose metabolism to that observed in the AD brain has been reported in individuals with T2D. Most of the brain glucose uptake is insulin-independent by glucose transporter subtypes 1 and 3 [84], but the hippocampus region of the brain relies on insulin dependent glucose transporter 4 mediated glucose uptake [85]. These findings would suggest that increasing brain insulin levels to overcome AD associated insulin resistance might be rational treatment for AD. As peripheral administration of insulin automatically leads to hypoglycemia, in animal studies, intranasal administration of insulin has been shown to access the brain along the olfactory and trigeminal pathways at therapeutic levels and improve cognition [86]. Similarly, in clinical trials with both acute and chronic intranasal insulin therapy in individuals with mild cognitive impairment have shown amelioration of multiple aspects of cognition, including verbal memory, memory storage, and selective attention [87–90]. However, intranasal insulin therapy has not been equally effective in all AD patients as reported in the currently ongoing phase II/III (SNIFF) clinical studies (https://www.medpagetoday.com/meetingcoverage/aaic/81116?xid=fb_o&trw=no; Craft S, et al. “Open Label Extension Results from a Phase II/III Trial of Intranasal Insulin” AAIC 2019;
Abstract 35542.). Collectively, these data suggest that improving insulin resistance by anti-diabetic agents or insulin therapy is not an effective treatment option for AD.

Alternatively, agents that improve glycemic control independent of hyperglycemia without affecting insulin sensitivity need to be tested as possible therapeutic treatment for AD (Fig. 2). Our recent data indicate that the E4orf1 protein derived from a human adenovirus could be a novel candidate to prevent glucose intolerance and hyperinsulinemia without affecting insulin sensitivity. Work from ours and others has shown that natural Ad36 infection in humans and experimental Ad36 infection of animals (chickens, rats, mice, non-human primates) is correlatively and causatively linked with obesity [91]. These studies led us to noticing that Ad36 infection improves glycemic control and attenuates hepatic steatosis in rodents, despite a 60% fat diet [92, 93]. In a series of subsequent in vitro studies, we identified the E4orf1 gene of Ad36 as essential for the effect of the virus on glucose disposal [94–97]. A distinct advantage of E4orf1 compared to insulin for treating hyperglycemia is that E4orf1 does not cause severe fasting hypoglycemia [98–100]. Also, during a glucose tolerance test, glucose clearance is rapid in presence of E4orf1, but after the excess glucose is cleared, there is no further drop in glucose. T2D is often associated with resistance to insulin signaling, including impaired response of molecular drivers of insulin signaling, such as IRS [101–104]. However, E4orf1 enhances glucose uptake by bypassing the proximal insulin signaling and independent of insulin [105–107]. Additionally, insulin is involved in the activation of GSK-3β, which in turn phosphorylates tau protein, forming neurofibrillary tangles [108]. Other than tau phosphorylation, insulin may also regulate the metabolism of amyloid-β protein. Therefore increased endogenous insulin secretion may positively influence progression of AD. E4orf1 is not a sensitizer, mimetic, or secretagogue of insulin but has an insulin-sparing action [109]. E4orf1 expressing mice lack the transient insulin spike typically observed in response to a glucose bolus [98–100]. This reduced insulin secretion in response to exogenous glucose is not due to pancreatic beta cell damage [98]. Instead, the better glycemic control coupled with lower insulin levels indicate that in presence of E4orf1, less endogenous insulin is needed to clear glucose from circulation and does not cause hyperinsulinemia. These attributes make E4orf1 an ideal candidate to examine the role of hyperinsulinemia independent of insulin resistance as a possible contributor to AD pathology and progression of the disease (Fig. 2).

CONCLUSIONS

It is well recognized that earliest detection of any disease state allows for the best possible outcomes. Epidemiological data reveal that T2D dramatically increases the risk for developing cognitive impairment and AD. Therefore, to find effective therapeutic options we need to determine if it is hyperglycemia, hyperinsulinemia, or tissue resistance (insulin resistance) to insulin action is linked with AD pathogenesis. Anti-diabetic medications or insulin therapy targeting amelioration of insulin resistance has not yielded the desired results. On the other hand, hyperinsulinemia may develop and exist for years without apparent hyperglycemia or T2D [60–62]. Hence, it would be important to address hyperinsulinemia sooner, if it plays a role in AD development.

DISCLOSURE STATEMENT

Authors’ disclosures available online (https://www.j-alz.com/manuscript-disclosures/19-0808r1).
REFERENCES


