Enzyme Engineering
ISSN: 2329-6674

Mushtaq, et al., Enz Eng 2015, 4:1
DOI: 10.4172/2329-6674.1000124

Review Article Open Access

Impaired Glucose Metabolism in Alzheimer's Disease and Diabetes

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Rec date: May 27, 2014, **Acc date:** October 3, 2014, **Pub date:** October 5, 2014

Abstract

Several epidemiological studies provide evidence that type 2 diabetes mellitus increases the risk of developing Alzheimer's disease significantly. Both disorders share certain abnormal biological mechanisms such as impaired glucose metabolism, insulin resistance, increased β-amyloid formation, oxidative stress, and the presence of advanced glycation end products. This review focuses on glucose metabolism impairment as a common clinical and biochemical feature shared by Alzheimer's disease and type 2 diabetes. With better knowledge of the common molecular and cellular pathways involved in the progression of these two disorders, researchers may have the opportunity to design effective therapeutic interventions to treat or control type 2 diabetes mellitus and, consequently, delay the onset or progression of Alzheimer's disease.

Keywords: Alzheimer's Disease; β-Amyloid Cognitive Impairment; Dementia; Hyperinsulinemia; Impaired Glucose Metabolism; Neurofibrillary Tangles, Type 2 Diabetes Mellitus

Introduction

Alzheimer's disease (AD) is a disorder that mainly takes its toll on the elderly population of the world with its global prevalence close to 50% among 85 years and older people. On the other hand, the population of the world suffering from type 2 diabetes mellitus (T2DM) currently is 150 million based on a report by CDC and this number will climb to 300 million by the year 2025 [1]. The Rotterdam study in the year 1999 [2] and several epidemiology studies since then have reported that T2DM significantly increases the risk for developing memory and cognitive impairment, dementia and AD [3,4]. Some studies have concluded that there is a 65% increased risk for developing AD in diabetic patients compared to non-diabetes, healthy individuals while other studies have demonstrated that the risk of developing AD is doubled in diabetic patients [5,6]. Likewise, a recent community cohort study from Cache County found AD patients more vulnerable to developing T2DM than non-AD individuals, hence establishing a close association between AD and T2DM [7]. Recently, there have been some clinical trials of anti-diabetic drugs going on in AD patients [8].

Impaired Glucose Metabolism in T2DM and AD

Numerous *in vitro* and *in vivo* animal and human clinical studies have provided evidence that T2DM is a major risk factor in the pathology of AD. Hence, abnormal glucose metabolism is not limited to diabetes, but it is also a pathophysiological phenomenon observed in AD [9]. Studies have shown that insulin levels of AD patients change substantially after they drink sugared sodas, hence classifying those individuals as insulin resistant [10]. Significant decline in cerebral glucose utilization is seen in dementias of AD type. It has been suggested that the irregularities in oxidative and energy metabolism in AD type dementias are caused as a result of metabolic disturbances in glycolytic glucose breakdown and pyruvate oxidation [11]. In an attempt to probe into the areas of decreased glucose metabolism in cerebral regions in AD patients, Fukuyama et al. conducted PET studies on AD patients as well as healthy controls. They found that oxygen consumption, glucose utilization and regional blood flow were significantly lower in the frontal, parietal and temporal regions of AD sufferers. It was suggested that abnormal glucose metabolism in the parietotemporal region in AD could be the main contributor towards the synoptic dysfunction which afflicts the brains of AD patients [12].

When regional cerebral metabolic rate of glucose (rCMRGI) was studied in patients with presenile dementia of AD type (DAT) and the ones with senile DAT in comparison to normal subjects, it was observed that glucose metabolism impairment was concentrated in the frontal and temporo-parietal cortex in presenile DAT while it was more global in the case of senile DAT. This implies that late-onset AD is characterized by impaired glucose metabolism spread all over the cortical areas, in addition to more localized areas of the brain [13,14]. It has been proposed that the glial cells detect reduced glucose availability when there is decreased glucose utilization in brain in the early stages of AD. This results in higher ketone body production and triggering of the NFκB pathway. Hence, central insulin deficit and hyperleptinemia aid in the inflammatory process via the inhibition of AMP-activated protein kinase. As a result of energy deficit and inflammation, the resulting neuronal cell damage may be contributing to neurodegeneration in AD [15].

Damaged neurons, neurofibrillary tangles and extremely insoluble Aβ peptide deposits in the brain are the hallmarks of AD. Aβ peptide plays a pivotal pathological role in AD [16]. Postmortem analysis of the brains of AD patients reveals plaques containing excess amounts of Aβ peptide. It is interesting to note that both Aβ peptide and insulin are substrates for the same insulin degrading enzyme (IDE), an enzyme belonging to zinc-metalloprotease class. Hence, IDE degrades insulin as well as Aβ peptide. Hyperinsulinemia is characterized by higher than normal levels of insulin in the body. This happens due to

abnormal insulin metabolism as seen in T2DM. Hyperinsulinemia diminishes the ability of IDE to degrade Aβ, which eventually causes deposition of amyloid plaque in the brain [17]. It has been suggested that elevations in Aβ levels in older subjects caused by peripheral hyperinsulinemia, may in turn be contributing to age-dependent memory dysfunction and the subsequent development of AD [18].

Furthermore, clinical studies have also demonstrated that those human subjects, who developed acute hyperinsulinemia after receiving insulin infusion, also showed elevated levels of insulin and Aβ in the cerebrospinal fluid. This effect was more pronounced in the older subjects. These effects were not observed in the control group which was administered saline via infusion. Furthermore, elevated levels of Aβ in response to hyperinsulinemia were accompanied by a decrease in insulin's ability to facilitate declarative memory [19]. Hence, the decline in memory functions is associated with the buildup of Aβ peptide in the brain. In vivo animal studies conducted on Tg2576 (transgenic) mice by Kohjima et al. further support this contention. Among the transgenic mouse models used to study Alzheimer's disease, Tg2576 mice are the most common. Around the age of 6 months or more, Tg2576 mice begin to display increasing degeneration in their memory functions because this is about the time when Aβ peptide levels begin to rise in their brains [20]. Recent experimental evidence suggests that Aβ peptide competes with insulin for binding to insulin receptors, hence causing inhibition of insulin receptor autophosphorylation. Thus, Aβ interferes with insulin receptor function in the neurons and halts the rapid activation of certain kinases essential for long term potentiation [21,22]. This suggests that Aβ acts as a competitive inhibitor of insulin binding and action in the brain and elevated levels of Aβ in AD may be linked to insulin resistance in the brain.

Therapeutic Strategies Targeting Both T2DM and AD

In light of several human and experimental animal model studies as well as in vitro studies, it appears that T2DM may be the strongest risk factor other than old age that contributes to the pathogenesis or progression of AD [23,24]. Impaired glucose metabolism is one of the most important pathological mechanisms underlying both AD and T2DM. Therefore, one approach to control T2DM and delay the progression of AD at the same time is by effectively controlling the glucose levels [25,26]. Thus, ant-diabetic drugs that increase cerebral energy metabolism and, thus improve insulin sensitivity may be beneficial in the treatment of AD.

Intranasal insulin restores brain insulin levels in AD patients due to its ability to have direct access to the brain without having an effect on peripheral insulin levels. Clinical data on intranasal insulin- treated AD patients provides evidence for improved cognition, memory enhancement and stabilization of cognitive impairment [27,28]. Facilitation of memory has also been observed in animal studies when insulin is administered via direct intracerebroventricular route [29,30]. Another promising treatment in this regards is intravenous administration of insulin to AD patients. Insulin delivered via intravenous route has the ability to reach the central nervous system by crossing the blood-brain barrier (BBB) [31,32].

Glucagon-like peptide-1 (GLP-1) analogs are novel drugs used in the treatment of T2DM mainly due to their anti-inflammatory action and ability to facilitate insulin signaling by stimulating insulin release while it also inhibiting glucagon secretion. Presently, exendin-4 and liraglutide are among the two GLP-1 receptor agonists approved for T2DM treatment [33]. Besides their role in the treatment of T2DM, in vitro studies have provided evidence that GLP-1 analogs also carry the potential to treat or delay the early onset of AD [34]. GLP-1 plays a pivotal role in inducing neurite growth in the brain, protects against oxidative injury in cultured neuronal cells and lowers the endogenous levels of Aβ in the brain [35,36]. The effect of GLP-1 and certain GLP-1 analogs on the brain is facilitated by their ability to cross the BBB as demonstrated by permeability studies across the BBB [37,38]. In fact, when liraglutide was peripherally injected in an Alzheimer's mouse model (APP/PS1) for 8 weeks, memory impairment and deterioration of synaptic plasticity in the hippocampus were prevented. In addition, liraglutide dosing resulted in significant reduction of the amount of overall β-amyloid plaque in the cortex of liraglutide-treated APP/PS1 mice [39].

Angiotensin converting enzyme (ACE) inhibitors have also been shown to delay the onset of T2DM owing to their ability to reduce certain markers of inflammation [40,41]. Likewise, ACE inhibitors have been shown reported to delay AD progression perhaps due to their ability to penetrate the brain and reduce inflammation [42]. In the Ginkgo Evaluation of Memory Study, reduced risk of AD dementia was reported for individuals with normal cognitive abilities [43]. In another 4-year cohort study from 16 different hospitals in France, older adults with AD receiving ACE inhibitors experienced slower cognitive decline [44].

Drugs from the peroxisome proliferator-activated receptors (PPARs) class also possess the ability to prevent and/or delay the progression of both T2DM and AD at the same time. Among the PPAR drugs, the most important ones are the compounds of the sub-class PPAR-gamma (PPAR-γ), used as a treatment for T2DM for more than a decade. PPAR-γ is expressed not only in the pancreatic beta cells but also in the adipocytes, where it regulates adipogenesis and increases the uptake of fatty acids into adipocytes [45,46]. In the brain, PPAR-γ is involved in the regulation of cell survival and inflammatory responses and it is to be found most notably in the neurons and astrocytes [47]. Thiazolidinediones (TZDs) are a class of drugs that work by activating PPAR-γ. TZD drugs have been shown to reduce the risk of developing T2DM [48]. Troglitazone, a TZD-derivative, is a PPAR-γ agonist used in the treatment of T2DM. Clinical studies have demonstrated that T2DM patients receiving troglitazone treatment had lowered fasting plasma glucose and HbA1c levels [49]. Troglitazone has also been reported to delay the onset of T2DM in high-risk subjects in a double-blind study [50]. Rosiglitazone, another PPAR-γ agonist and a member of TZD class has been shown to lower glucose and lipid levels in T2DM patients [51]. Furthermore, clinical evidence suggests that both pioglitazone and rosiglitazone increase peripheral insulin sensitivity and lower concentrations of insulin [52].

On the other hand, PPAR-γ agonists possess therapeutic potential for the treatment of AD. In vivo studies have demonstrated the ability of PPAR-γ agonists to inhibit β-amyloid-stimulated expression of IL-6 and TNFα [53]. For instance, glimepiride, a TZD-derivative, is an oral anti-diabetic drug with PPAR-γ-stimulating activity. It has been reported that glimepiride has been shown to attenuate Aβ production in primary cortical neurons by suppression of BACE1 activity, hence making it a promising drug for the treatment of AD associated with T2DM [54]. Likewise, a small clinical study of 30 patients with mild AD or mild cognitive impairment found that patients treated with rosiglitazone for 6 months demonstrated memory enhancement and enhanced attention [55]. In a larger study of more than 500 patients with mild to moderate AD, 6 months of treatment with rosiglitazone resulted in statistically significant cognitive improvement in patients

that did not possess an Apo-epsilon-4 allele [56]. In an animal study, it has been shown that 9-14% of rosiglitazone crosses the BBB after oral treatment [57]. Pioglitazone is another TZD-derivative with PPARγ-receptor agonist properties. Continuing use of pioglitazone in the mouse model of AD has been reported to improve visuo-spatial and long term memory [58]. In a recent randomized, open-controlled trial of T2DM patients with mild AD, pioglitazone-dosed patients exhibited cognitive and functional improvements compared to the controlled, no-treatment group. Pioglitazone caused reduction in their fasting plasma insulin levels lowered and those patients experienced improvement in their cognition and regional cerebral blood flow in the parietal lobe [59]. Since both T2DM and AD share common molecular mechanisms such as impaired glucose metabolism, PPAR-γ-receptor agonists such as TZD-derivatives may prove beneficial for the treatment or management of both of the disorders [60].

Conclusion

In conclusion, biological mechanisms common to both AD and T2DM may provide us a clue to the development and progression of AD. Currently, various therapeutic agents have already been clinically shown to prevent or delay the onset of T2DM and AD and this clinical evidence in itself confirms the association of T2DM and AD. However, there is still a need to further study the inter-connected cellular and molecular mechanisms between T2DM and AD. Better understanding of the impairment of glucose metabolism as a pathophysiological link between AD and T2DM is crucial because this knowledge will guide the researchers in designing future therapeutic strategies targeting both of the pathologies at the molecular level.

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