New advances in the treatment of Alzheimer's disease with antidiabetic drugs

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Abstract: Alzheimer's disease (AD) is a persistent neurological disorder characterized by increasing cognitive impairment and is the most prevalent type of dementia. The most common pathological features are amyloid plaques due to amyloid-β (Aβ) deposits and neurofibrillary tangles (NFTs) consisting of hyperphosphorylated tau proteins that accumulate abnormally in the brain. Nearly a decade of clinical studies and preclinical data have demonstrated that AD shares common pathologic mechanisms with type 2 diabetes mellitus (T2DM), including insulin resistance, oxidative stress, and inflammatory responses. Since they share a common pathological mechanism and AD lacks an effective treatment, it is of great clinical significance to investigate whether AD can be treated with existing T2DM drugs.

Keywords: Alzheimer's disease, Diabetes mellitus, Dipeptidyl peptidase IV inhibitors

1. Introduction

AD is a chronic neurodegenerative disease that is characterized by cognitive and memory impairment. It usually occurs in people over the age of 65 and is the most common form of dementia. T2DM is known to be the strongest risk factor for AD[1], and patients with T2DM have an approximately twofold increased risk of developing AD compared to normal subjects [2]. The epidemiological link between T2DM and dementia represents a major public health challenge, but also an opportunity to further our understanding of these diseases. Based on these observations, several biological and clinical studies have provided compelling evidence that AD can be considered a metabolic disorder in which glucose utilization and energy production in the brain are compromised. Therefore, many studies and clinical trials have been conducted to evaluate the potential neuroprotective effects of antidiabetic drugs and to assess their direct and indirect mechanisms of action. After summarizing the mechanisms linking T2DM and AD, this paper will focus on the main glucose-lowering drugs as suitable candidates for AD treatment.

2. Pathological links between AD and T2DM

2.1. Impaired insulin signaling pathway

Insulin is a major regulator of energy metabolism, food intake, and brain activity. The insulin signaling pathway exerts its protective effects on neurological and cognitive functions by activating phosphatidylinositol 3-kinase (PI3K), inducing phosphorylation of serine/threonine protein kinase (AKT), and inhibiting phosphorylation of glycogen synthase kinase 3β (GSK-3β). When insulin is reduced or signaling is impaired in the brain, it leads to enhanced GSK-3β activity and Tau phosphorylation, which results in impaired neuronal synaptic plasticity [3]. Thus, under normal conditions, the insulin signaling pathway leads to GSK-3β inactivation. Whereas, insulin resistance leads to GSK-3β dephosphorylation and activation, which in turn leads to more Aβ production and subsequently increased tau phosphorylation associated with NFT formation.

2.2. Neuroinflammation

Neuroinflammation is defined as the inflammatory response inherent in the nervous system, mediated by cytokines, chemokines, reactive oxygen species and related molecular processes. There is ample

evidence that neuroinflammation is involved in the pathogenesis of AD[4]. In addition, inflammation exacerbates insulin resistance and ceramide accumulation, i.e., lipotoxicity, while insulin resistance, lipotoxic injury and cell death in turn exacerbate inflammation[5]. Insulin resistance, in turn, is a major feature of T2DM and is associated with elevated levels of many serum cytokines, such as IL-6, IL-1β, IL-18, tumor necrosis factor-α (TNF-α), c-reactive protein, and α-1 antichymotrypsin[6].

2.3. Oxidative Stress

Oxidative stress is a state in which oxidation and antioxidant effects are out of balance in the body, and can cause lipid peroxidation damage to membranes, including mitochondrial membranes, or oxidation of structural and enzymatic proteins, resulting in irreversible alterations in their structure and function. ATP required for normal cell and neuronal function is mainly supplied by mitochondria, and mitochondrial damage can lead to cell and neuronal damage [7]. Oxidative stress and mitochondrial dysfunction play an important role in the pathology of both AD and diabetes, with high levels of reactive oxygen species and reactive nitrogen species detected in both diabetic and AD patients [4]. Oxidative stress also leads to the production of advanced glycosylation end products (AGEs). The receptor for advanced glycosylation end products (RAGE) interacts with Aβ peptides to exacerbate oxidative stress and inflammatory responses, leading to cognitive impairment [8].

2.4. Cholinesterase

Acetylcholinesterase (AChE) is a key enzyme in the cholinergic nervous system, and its levels continue to decline in the brain during AD development [9]. Its classical function is to hydrolyze acetylcholine and terminate impulse transmission at cholinergic synapses. Indeed, aberrant expression of AChE associated with amyloid plaques and tangles has been found in the brains of AD patients [10]. However, it was found that AChE activity was higher in T2DM patients compared to healthy controls [11]. This implies that abnormal levels of AChE may be involved in the development of T2DM and AD and may serve as a potential therapeutic target[12].

3. Classes of antidiabetic drugs as potential therapeutic agents for Alzheimer's disease

3.1. Insulin

Preclinical studies in rat models have shown that intracerebroventricular streptozotocin (STZ-ICV) injections can cause cognitive dysfunction, and intracerebroventricular administration of insulin analogs successfully restored this impairment in diabetic rats as demonstrated by a significant improvement in learning ability[13]. Another study showed that basal insulin treatment (glucagon) significantly reduced hippocampal Aβ, inhibited neuronal apoptosis, improved memory deficits and increased hippocampal synaptic plasticity in a db / db mouse model suffering from hyperinsulinemia[14]. The first clinical evidence that acute insulin treatment in the absence of hyperglycemia enhances memory in adult AD patients suggests that this hormone plays an important role in memory facilitation[15]. Whereas systemic insulin injections increase the risk of hypoglycemia and affect insulin access to the central nervous system, intranasal insulin injections to the brain can overcome these problems. Preclinical evidence suggests that intranasal administration of insulin counteracts the protective effect of the blood-brain barrier(BBB)[16]. Studies have demonstrated that treatment of a model of brain insulin resistance established by STZ-ICV injection with intranasal insulin resulted in significant recovery of learning and memory functions and elevated insulin levels in the brain of mice [17]. Clinical trials in patients with mild cognitive impairment (MCI) or AD have demonstrated that acute and prolonged intranasal insulin administration enhances memory and suggests that cerebral insulin resistance is a pathophysiologic factor in AD, with or without metabolic dysfunction [18]. In a phase II clinical trial, participants with MCI or AD treated with intranasal insulin had improved cerebrospinal fluid biomarker profiles and slower symptom progression compared to the placebo group[19]. As intranasal insulin is a safe intervention, future studies should be conducted with larger doses after the appropriate selection of patients and insulin type.

3.2. Metformin

It is considered one of the most common antidiabetic drugs for the treatment of T2DM and has been extensively studied and reported to have favorable results compared to other drugs. Metformin treatment was found to significantly reduce hippocampal Aβ levels and inhibit neuronal apoptosis in db/db mice

[14]. However, it has also been reported that in a transgenic mouse model of human tauopathy, P301S, the aggregation-promoting effects of metformin reversed the potential benefits of its dephosphorylation. which may lead to an elderly diabetic patient with an overall increased risk of tauopathy [20]. There is also evidence that metformin decreases the activity of AChE[10], which, as discussed above, AChE degrades acetylcholine, a major neurotransmitter in learning and memory processes. Considering the beneficial effects of metformin, its anti-inflammatory and antioxidant properties cannot be underestimated, as confirmed by numerous in vitro and in vivo studies[21] Some studies have demonstrated that metformin use is associated with a reduced incidence of dementia in patients with T2DM and may reduce the risk of AD in the general population[22]. However, the evidence for the use of metformin in the treatment of AD is controversial, as metformin has little effect on patients with MCI or mild AD in clinical trials [23]. Thus, it is clear from the discussion in this paper that despite the considerable efforts that have been made about metformin, a large amount of conflicting data has emerged from clinical trials of metformin drug therapy.

3.3. Thiazolidinediones

Thiazolidinediones are agonists of peroxisome proliferator-activated receptor γ (PPARγ), with anti-inflammatory and insulin-sensitizing effects, which may reduce and delay the risk of neurodegeneration[24]. Currently, only pioglitazone is approved for the treatment of DM. Pioglitazone protects against STZ-ICV injection-induced memory dysfunction in rats[25], which may be related to its anti-inflammatory, antioxidant, and anti-apoptotic effects via the nitric oxide pathway. In contrast, in a recent study[26], long-term pioglitazone treatment was found to have no significant effect on microglia activation and tau pathology in P301S mice. This is inconsistent with previous findings and may be related to the different animal models used [27]. Another phase II study on AD and its previous diabetic indications showed that pioglitazone was safe and well tolerated [28]. Pioglitazone was found to improve cognition in diabetic patients with AD or MCI in 3 clinical trials, but controversy exists because the other 2 studies did not show an effect. In addition, in a phase 3, multicenter, randomized, double-blind, placebo and parallel control group study, pioglitazone did not delay the onset of MCI in the high-risk group compared with the low-risk group for AD, but reduced mortality [29]. Thus, at present, we know that pioglitazone is safe for the treatment of AD, but the effect is controversial.

3.4. Glucagon-like peptide 1 (GLP-1) analogs and GLP-1 receptor agonists

Glucagon-like peptide 1 (GLP-1) is a glucagon peptide secreted by small intestinal L-cells, which has hypoglycemic effects such as inhibition of glucagon secretion, augmentation of insulin secretion, increase in satiety and delay in gastric emptying. Natural GLP-1 is rapidly degraded by Dipeptidyl peptidase IV (DPP-4), and analogs of GLP-1 have been developed and approved for T2DM treatment. These include liraglutide and exenatide. analogs of GLP-1 are injectable and have extended half-lives. Physiologically, one of the advantages of these drugs is that they have a lower risk of hypoglycemia. It has been demonstrated that subcutaneous injection of liraglutide improves cognition in transgenic AD mice by enhancing aerobic glycolysis and decreasing levels of oxidative phosphorylation and oxidative stress in the brain; and protects Aβ-induced astrocytes and promotes neuronal survival and axonal growth[30]. Liraglutide has protective effects against AD both in vivo and ex vivo, mediated by prevention of neuronal apoptosis, inhibition of tau activation and BACE1 expression[31]. Repeated subcutaneous administration of a GLP-1 receptor agonist (NLY01) blocked microglia-mediated neuroinflammation and preserved neuronal viability in two transgenic AD mouse models (5xFAD and 3xTg-AD), resulting in improved spatial learning and memory[32]. The results of preclinical studies are encouraging. In a 26-week randomized, placebo-controlled, double-blind study, liraglutide treatment improved glucose metabolism and cognitive decline in patients with AD compared with the placebo group[33]. However, no differences in Aβ deposition were found between the liraglutide and placebo groups. Moreover, GLP-1 analog treatment was found to restore glucose transport at the BBB in AD patients and was also associated with a reduced risk of AD in T2DM patients [34, 35].

3.5. DPP-4 inhibitors

DPP-4 inhibitors inhibit the degradation of Glucose-dependent insulinotropic peptide (GIP) and GLP-1, and at the same time inhibit glucagon secretion, promote insulin release, and increase the levels of endogenous GLP-1 and GIP, thus lowering blood glucose. It is less likely to induce hypoglycemia and increase body weight, which is the advantage of its possible application in AD treatment. Various oral DPP-4 inhibitors have been developed for T2DM treatment. Commonly used DPP-4 inhibitors include

gliptin, Linagliptin, saxagliptin, vildagliptin, and Sitagliptin. Experimental studies examining the effects of gliptin on cognition have proven beneficial. Linagliptin has been shown to significantly reverse motor and cognitive deficits in an Aβ-induced rat model, reducing the level of soluble Aβ$_{42}$ in the hippocampus, which is achieved through insulin receptor substrate alteration of neurodegeneration and brain insulin resistance[36]. The same phenomenon was recently found in a rat model induced by STZ-ICV injection[37]. One study demonstrated the anti-inflammatory effect of a newly developed type of nanoparticles (selegiline-loaded yeast cell wall vesicles) on TNF-α in a mouse model of neuroinflammation[38]. A recent study showed that DPP-4 inhibitors exhibited a protective effect against the risk of Alzheimer's dementia compared to treatment with other antidiabetic drugs[39]. And it was found that the use of DPP-4 inhibitors may reduce the rate of memory loss in T2DM patients with AD[40].

3.6. Sodium-glucose cotransporter (SGLT-2) inhibitors

SGLT-2 Inhibitors inhibit glucose reabsorption by the kidneys, resulting in increased glucose excretion, which lowers blood glucose. This is a new class of antidiabetic drugs and carries no risk of hypoglycemia because SGLT-2 increases renal glucose excretion without affecting insulin secretion in the presence of hyperglycemia. Currently, the U.S. Food and Drug Administration (FDA) approves three SGLT2-selective inhibitors for use in mono-, dual-, and triple-therapy: canagliflozin, Dapagliflozin, and empagliflozin. It was found that in an AD-T1DM mouse model, engeletin reduced neuronal loss, decreased senile plaque load, and ameliorated cognitive deficits in mice[41]. In the STZ-ICV-injected rat model, engeletin was found to ameliorate cognitive deficits and inhibit hippocampal AChE activity, which may be related to the inhibition of tau hyperphosphorylation induced by disruption of insulin signaling[42]. Recent studies explored the molecular interactions of human brain AChE with these antidiabetic drugs and suggested that canagliflozin and Dapagliflozin may have an inhibitory effect on AChE[43]. SGLT2 inhibitors were found to show an association with a lower risk of dementia in elderly T2DM patients in a population-based cohort study[44]. Recent clinical studies have found that empagliflozin reduces the excitatory neurotransmitter glutamate in the brains of non-diabetic patients, and the finding that glutamatergic excitotoxicity has been associated with AD pathology[45] is encouraging. There are still few studies and further research is needed to address the question of its dual inhibitory effects on T2DM and AD.

4. Conclusion and outlook

People with diabetes are at a higher risk of developing AD than healthy people. We now know that AD and diabetes share common pathophysiological mechanisms, including impaired insulin signaling pathways, neuroinflammation, oxidative stress, etc., and all of the above theories may contribute to the development of diabetes and AD. As a result, researchers have been investigating the role of diabetes medications in preventing or slowing the progression of AD. The findings reviewed in this article are highly clinically relevant and discuss whether antidiabetic medications have an effect on brain function including memory, cognition, and attention. Based on preclinical studies, insulin sensitizers including DPP-4 inhibitors, GLP-1 analogs, or GLP-1R agonists are promising targets for neuroprotection, especially in elderly subjects. DPP-4 inhibitors are generally safe and well tolerated, reducing fasting and postprandial glucose orally with little effect on body weight or gastric emptying. DPP-4 inhibitors also have a lower risk of hypoglycemia compared with other agents (e.g., GLP-1 analogs or GLP-1R agonists), which is another advantage for their possible application in AD treatment given their physiologic mechanism of action. However, there are still few clinical studies. On the contrary, intranasal administration of insulin for the treatment of AD has yielded encouraging results without major side effects after several clinical trials, making it an effective way to prevent or treat AD. More clinical trials and research in this area are needed to limit the progression of AD, find better therapeutic outcomes, and improve the quality of life of AD patients.

Acknowledgements

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