

Correcting Neurodegenerative Changes in the Brain with Drugs

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Abstract This article provides information about the genetic factors causing Alzheimer's disease and how this disease can be corrected through drug treatments. Amyloid precursor protein (APP), the cause of Alzheimer's disease. Insights into the fourth gene, apolipoprotein E are provided. information about the connection of Alzheimer's disease with diabetes is given.

Keywords Alzheimer's disease, Presenilin, Gene, Diabetes, Polyphenolic substances, Metformin, Antioxidant

1. Introduction

Alzheimer's disease (AD) is a genetically complex illness. Mutations in three genes, such as presenilin 1, the predecessor of amyloid protein, and presenilin 2, lead to early-onset familial Alzheimer's disease in rare families before the age of 65. Specific polymorphisms of Apolipoprotein E are associated with the late phase of Alzheimer's disease occurring after the age of 65. Alzheimer's disease is the most common form of age-related dementia. Although the disease mostly occurs in people aged 65 and over, an estimated 500,000 people have early-onset AD (EOAD) or symptoms that begin before the age of 65. One in every eight individuals aged 65 and older, and nearly one in every two individuals over the age of 85, have AD. The main focus of AD research is to understand the genetic etiology of AD and its connection to neuropathological signs. The main neuropathological features of AD are the extensive presence of neurofibrillary tangles made of tau protein and senile plaques composed of β -amyloid ($A\beta$) [39]. Over 20 years of genetic research have improved our understanding of the pathways leading to the accumulation of the insoluble protein $A\beta$ 42. The accumulation of $A\beta$ 42 is considered a central component of AD pathogenesis and is associated with three autosomal dominant genes known to be involved in EOAD: these are presenilin 1 (PSEN1), presenilin 2 (PSEN2), and amyloid precursor protein (APP). A fourth gene, apolipoprotein E (APOE), has been confirmed as a susceptibility/risk factor for late-onset Alzheimer's disease (LOAD). The APOE gene has three common variants: ϵ 2, ϵ 3, and ϵ 4. The ϵ 2 allele is associated with the lowest risk of LOAD, whereas the ϵ 4 allele is linked to an increased risk of LOAD and a younger

onset period of dementia, depending on dosage. The challenges of sampling and diagnostics, population stratification (due to differences in ethnic origins leading to variations in control and risk allele frequencies), and sample size make it a difficult task to identify other genes related to this severe disease. Despite these challenges, research on monozygotic twins showing a 60% concordance rate, and other studies, suggest that there may be several susceptibility genes that play a role in the development of late-onset AD along with APOE ϵ [3,15]. Comprehensive application of genetic markers through full associative research of genes, advanced statistical methods, and increasing the number of available cases for study through collaborative projects can help overcome some barriers in discovering other genes associated with disease. Moreover, several resources have been created to aid in the identification of genes associated with Alzheimer's disease. Within the Alzheimer's Genetics Initiative, sponsorship has been provided for multi-center research on large families suffering from late-onset AD. Clinical data and biological samples are provided to researchers for inclusion in their genetic analyses. Additionally, the NIA has created several mechanisms to store genetic information obtained from NIH-funded research. Another resource is the AlzGene database, which compiles the latest data on genetic associations for AD and AD phenotypes. To date, it has analyzed over 900 AD associations and nearly 400 genes [37]. The AlzGene database sequences and organizes these results to monitor hundreds of positive and negative studies related to potential genes associated with Alzheimer's disease [8].

As mentioned above, since type 2 diabetes shares a number of pathogenetic features with neurodegenerative diseases, it has been hypothesized that some drugs used in the therapy of type 2 diabetes might offer potential benefits in treating AD [9]. Metformin restores mitochondria, activates AMPK in neurons, and reduces the effects of AGEs [10]. It activates

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insulin signaling and reduces tau phosphorylation in neuronal cells [11]. It stimulates protein phosphatase 2A and reduces tau phosphorylation in neurons of tau transgenic mice [12]. It reduces cognitive impairments in leptin-resistant obese mice [13]. It increases the production of beta-amyloid protein in human cell models (negative effect) [30]. It reduces the risk of cognitive decline in patients suffering from diabetes [15]. It improves cognitive function in patients with depression [14,16]. Studies conducted in patients with AD have shown an increased risk of cognitive impairment (negative effect) [18].

Sulfonylurea drugs: Glimepiride protects neurons from synaptic degeneration induced by beta-amyloid in vitro [19]. Gliclazide displays antioxidant effects in the brains of diabetic rats [20]. Glibenclamide reduces depression and anxiety in AD mice [21]. When combined with metformin, it reduces the risk of dementia in patients with diabetes [22].

Thiazolidinediones (Glitazones): Have neuroprotective effects related to inhibiting inflammation and A β deposition in AD [23]. Pioglitazone prevents the activation of glial cells in AD mice [24]. Pioglitazone enhances Akt signaling and reduces tau hyperphosphorylation in AD mice [25].

Together with leptin, pioglitazone reduces amyloid levels in the brains of AD mice [26]. Pioglitazone improves cognitive functions and local cerebral blood flow in patients with type 2 diabetes [27]. Pioglitazone may improve cognitive functions during the early stages and mild to moderate periods of AD in humans [28].

Glucagon-like peptide 1 agonists: Reduce oxidative stress and apoptosis in brain cells; improve synaptic plasticity in AD mice [29]. They protect neurons and affect cellular mechanisms of mitochondrial function [30]. They reduce tau phosphorylation, prevent synaptic loss, and decrease A β deposition in AD mice. They prevent the decline in glucose metabolism in the brains of patients with AD [31].

DPP-4 inhibitors: Reduction of tau phosphorylation, amyloid burden, and cognitive impairments correlates with improved memory [32]. Improvement in incretin levels, reduction in A β deposition, tau phosphorylation, activation of GSK-3 β , and KASH [33]. They improve glucose control and prevent the deterioration of cognitive functions in elderly patients with type 2 diabetes [34].

Insulin reduces cognitive impairments and improves memory in elderly patients with AD [35]. It inhibits apoptosis in vitro; controls tau phosphorylation, metabolism, and A β [36]. It improves memory, mood, glucose metabolism in the brain, and preserves brain volume in AD patients [3].

Metformin: Metformin is a biguanide that reduces glucose production in the liver via insulin, increases insulin sensitivity, and is considered a first-line therapy for type 2 diabetes. It rapidly crosses the blood-brain barrier, disperses across brain regions [5], and exerts a neuroprotective effect on human nerve core cells due to the activation of the AMPK pathway, restoring mitochondrial functions and reducing the effects of final glycation products [8]. Data on the impact of metformin on neurodegenerative diseases are contradictory.

In vitro studies report that metformin reduces tau phosphorylation in nerve cell lines [15]. In vivo studies have shown that metformin reduces cognitive impairments and AD-like pathology in leptin-resistant obese mice [17]. Conversely, results in cultured cells have shown that metformin increases the production of A β [26]. Observational studies in patients with type 2 diabetes taking metformin have shown a reduction in mild cognitive impairment (MCI) [31] and dementia [24] compared to placebo. Long-term treatment with metformin reduces the risk of cognitive function decline in diabetic patients [37], alleviates depression, and improves cognitive function in patients with depression by altering glucose metabolism [16]. A clinical trial conducted over 12 months in patients with MCI showed that metformin improved cognitive function in non-diabetic individuals compared to placebo [4]. A clinical study examining the impact of various type 2 diabetes treatments on cognition showed that only metformin led to better outcomes in oral learning, working memory, and executive functions compared to other forms of diabetes treatment [7]. On the other hand, a study in patients with Alzheimer's disease showed that the use of metformin was associated with an increased risk of cognitive impairment and the development of AD [8]. This phenomenon is partly related to vitamin B12 deficiency induced by metformin. However, an analysis of cognitive function conducted 8-10 years after metformin therapy in the Diabetes Prevention Program Outcomes Study (DPPOS) showed no negative effects from long-term use of metformin [10]. Currently, planned randomized clinical trials provide the opportunity to assess whether metformin can prevent cognitive decline or improve cognitive function in humans [16].

Sulfonylurea drugs: Sulfonylureas are hypoglycemic drugs that stimulate insulin release by blocking ATP-sensitive potassium channels in pancreatic beta cells. In vitro, glimepiride protects neurons from synaptic degeneration induced by beta-amyloid [19]. Gliclazide has shown antioxidant effects in the brains of streptozotocin-induced diabetic rats [13]. Additionally, glibenclamide reduces depression and anxiety in mice with Alzheimer's disease [11]. Eight-year prospective clinical studies in patients with type 2 diabetes have indicated that the combination of sulfonylureas and metformin reduces the risk of developing dementia [12], but other randomized controlled trials have shown that long-term use of sulfonylurea drugs does not affect the risk of developing dementia [17]. This calls for further research to validate the potential therapeutic role of this class of drugs.

Thiazolidinediones (glitazones): Thiazolidinediones (TZDs) (pioglitazone and rosiglitazone) are potent and selective activators of the peroxisome proliferator-activated receptor gamma (PPAR gamma) in muscle, fat, and liver tissues, which improves insulin sensitivity and reduces systemic insulin resistance. TZDs may play a role in enhancing neuron function and memory formation. These drugs have shown neuroprotective effects in Alzheimer's disease by inhibiting

gene expression related to inflammation and altering the formation and accumulation of A β [23]. Pioglitazone can enter the brain, suppress glial activation, and reduce the clinical manifestations of AD [14]. In AD mice, pioglitazone administered for four months enhanced Akt signaling, improved spatial learning, and reduced tau hyperphosphorylation [23]. When used in conjunction with leptin, it reduces memory deficits and amyloid levels in the brain [46]. Initial studies conducted over six months in patients with type 2 diabetes treated with pioglitazone showed improvements in cognitive functions and local brain blood flow [17].

Glucagon-like peptide-1 (GLP-1) receptor agonists: Another category of hypoglycemic drugs are GLP-1 receptor agonists. GLP-1 is an incretin peptide secreted in the gut that enhances glucose-dependent insulin secretion and inhibits glucagon secretion. GLP-1 also has trophic properties such as stimulating neogenesis, growth and differentiation of β -cells, inhibiting β -cell apoptosis, and enhancing cell survivability [11]. GLP-1 and most of its analogs cross the blood-brain barrier and are expressed in areas of the brain such as the frontal cortex, hypothalamus, thalamus, hippocampus, cerebellum, and substantia nigra [11]. GLP-1 likely plays a neuroprotective role in the brains of AD mice by reducing apoptosis, protecting neurons from oxidative stress, and shielding synapses from the deleterious effects of A β -induced synaptic plasticity in the hippocampus [9]. Natural GLP-1 has a short half-life because it is easily degraded by dipeptidyl peptidase-4 (DPP-4). Several more stable analogs of natural GLP-1 have been developed, including exenatide, liraglutide, and lixisenatide, which cross the blood-brain barrier and, regardless of their impact on glucose control, affect neuronal protective pathways, mitochondrial functions, apoptosis, and oxidative stress [14].

Dipeptidyl Peptidase-4 (DPP-4) inhibitors: DPP-4 inhibitors are hypoglycemic drugs that stabilize the level of GLP-1 by inhibiting the proteolytic enzyme DPP-4 responsible for its degradation, thereby extending its plasma half-life and enhancing its hypoglycemic effect [42]. DPP-4 inhibitors have shown neuroprotective effects, potentially mediated by the action of GLP-1 in the brain. In animal models of Alzheimer's disease, treatment with DPP-4 inhibitors (saxagliptin, vildagliptin, sitagliptin) reduces tau phosphorylation, amyloid burden, and inflammation markers, as well as alleviates cognitive deficits by improving memory [40,44]. In human neuronal cells, linagliptin reduces the accumulation of A β , decreases tau hyperphosphorylation, prevents the activation of GSK3 β , and reduces the intracellular production of reactive oxygen species by stimulating the 5' AMP-activated protein kinase (AMPK) - Sirt1 signaling pathway [6]. All these effects help improve cognitive functions. Treatment with a DPP-4 inhibitor in elderly patients with type 2 diabetes and mild cognitive impairments improves glucose control and prevents the deterioration of cognitive functions [7]. A prospective clinical study assessing six months of treatment with sitagliptin in elderly patients with type 2 diabetes reported improvements in cognitive function [32].

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