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Review

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Pathology and Treatments of Alzheimer's Disease Based on Considering Changes in Brain Energy Metabolism Due to Type 2 Diabetes

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Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disorder with cognitive dysfunction, memory decline, and behavioral disturbance, and pathologically characterized by the accumulation of amyloid plaques and neurofibrillary tangles in the brain. Although various hypotheses have been proposed to explain the pathogenesis of AD, including the amyloid beta hypothesis, oxidative stress hypothesis, and abnormal phosphorylation of tau proteins, the exact pathogenic mechanisms underlying AD remain largely undefined. Furthermore, effective curative treatments are very limited. Epidemiologic studies provide convincing evidence for a significant association between type 2 diabetes and AD. Here, we showed energy metabolism using glucose, lactate and ketone bodies and lipids as energy substrates in normal brain, and changes in such energy metabolism due to type 2 diabetes. We also showed the influences of such altered energy metabolism due to type 2 diabetes on the pathology of AD. Furthermore, we comprehensively searched the risk factors related with type 2 diabetes for AD, and showed possible therapeutic interventions based on considering risk factors and altered brain energy metabolism due to type 2 diabetes for the development of AD.

Keywords: Alzheimer's disease; amyloid beta; glucagon-like peptide 1 receptor agonists; insulin resistance; oxidative stress; type 2 diabetes

1. Introduction

Alzheimer's disease (AD) is the leading cause of cognitive impairment in older individuals (aged 65 and above) and one of the key factors of disability and mortality in later life throughout the world [1]. AD is a progressive neurodegenerative disorder characterized by the accumulation of amyloid plaques and neurofibrillary tangles in the brain, and this disease is an incurably neurodegenerative disorder with cognitive dysfunction, memory decline, and behavioral disturbance [2]. Various hypotheses have been proposed to explain the pathogenesis of AD, including the amyloid beta (Aβ) hypothesis [3], oxidative stress hypothesis [4], and abnormal phosphorylation of tau proteins [5]. However, the exact pathogenic mechanisms underlying AD remain largely undefined. The accumulation of soluble and insoluble aggregated Aβ may initiate or potentiate pathologic processes in AD. Aβ vaccines that are significantly capable of reducing amyloid plaques were unable to prevent AD progression [6]. Unfortunately, to date, almost all the clinical trials targeting at eliminating Aβ deposit have done little to improve cognitive function [6,7]. Recently, lecanemab, a humanized IgG1 monoclonal antibody that binds with high affinity to Aβ soluble protofibrils, was developed and tested to treat patients with early AD [8]. Lecanemab reduced brain amyloid burden in patients with early AD and resulted in moderately less decline on measures of cognition and mental function than placebo at 18 months [8]. However, longer trials are warranted to determine the efficacy and safety of lecanemab in early AD. Furthermore, the effective therapy based on tau pathology is lack [9–11].

The Rotterdam Study, a prospective population-based cohort study among 6,370 elderly subjects showed that diabetes almost doubled the risk of AD (relative risk [RR], 1.9; 95% confidence interval [CI], 1.2 to 3.1) [12]. The Hisayama study, Japanese cohort study,

showed that the age- and sex-adjusted incidence of AD was significantly higher in subjects with diabetes than in those with normal glucose tolerance. This association remained robust even after adjustment for confounding factors for AD (adjusted hazard ratio [aHR], 2.05; 95% CI, 1.18 to 3.57, p = 0.01). The risk of developing AD significantly increased with elevated 2-hour post-load glucose levels, but no such association was observed for fasting plasma glucose levels [13]. These studies suggest that impaired glucose metabolism is associated with the development of AD. Here, we show energy metabolism using glucose, lactate and ketone bodies and lipids as energy substrates in normal brain, and changes in such energy metabolism due to type 2 diabetes. We showed the influences of such altered energy metabolism due to type 2 diabetes on the pathology of AD. Furthermore, we comprehensively searched the risk factors related with type 2 diabetes for AD, and showed possible therapeutic interventions based on considering risk factors and altered brain energy metabolism due to type 2 diabetes for the development of AD.

2. Glucose Metabolism and Insulin Signaling in Normal Brain

Glucose transporters (GLUTs), insulin receptor (IR), insulin receptor substrate (IRS), and monocarboxylate transporters (MCTs) in normal brain were shown in Figure 1.
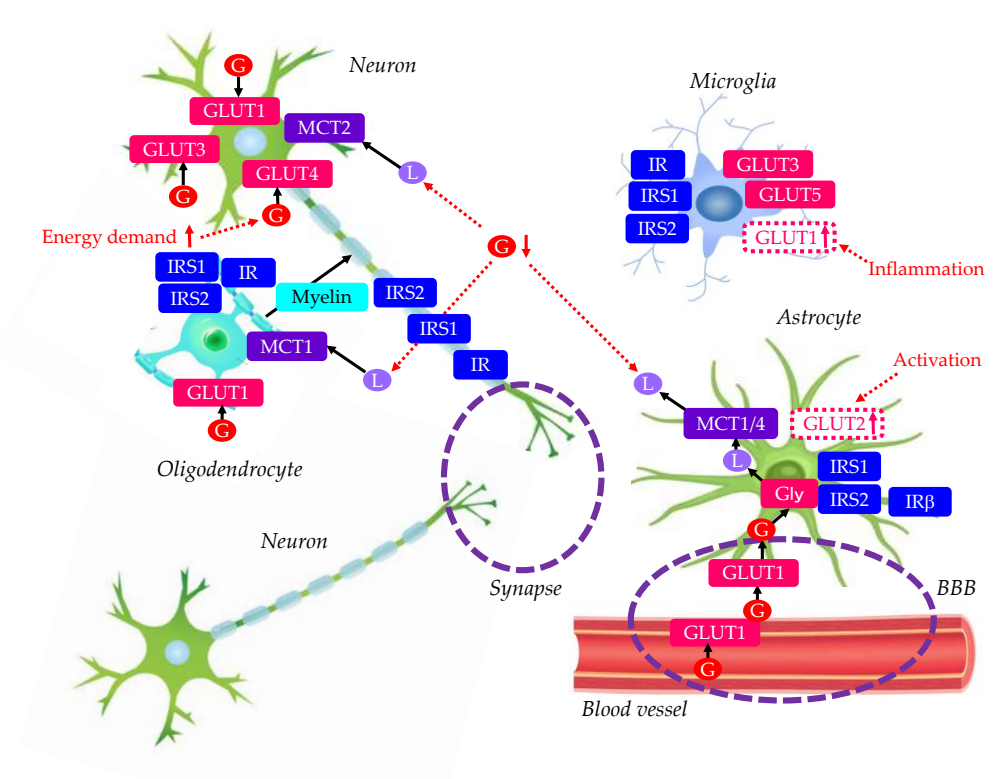

Figure 1. Glucose transporters, insulin receptor, insulin receptor substrate, and monocarboxylate transporters in normal brain. Red up and down arrows indicate increase in phenomenon, substances and expression of molecules. Black arrows indicate the flow of substances. BBB, blood brain barrier; G, glucose; GLUT, glucose transporter; Gly, glycogen; IR, insulin receptor; IRS, insulin receptor substrate; L, lactate; MCT, monocarboxylate transporter.

2.1. Neurons

The fundamental unit of the nervous system is the neuron, which forms complex circuits that receive and integrate information and generate adaptive responses [14]. Each neuron is composed of an input domain consisting of multiple dendrites along with the cell body, which is also responsible for the majority of macromolecule synthesis for the cell. The output domain is the axon which is a

singular extension from the cell body that propagates the action potential to the synapse, where signals pass from one neuron to another. The insulin-independent GLUT3 is the major glucose transporter in neurons. The density and distribution of GLUT3 in axons, dendrites and neuronal soma correlates with local cerebral energy demands [15]. Neurons also express GLUT1 [16]. Activation by insulin induces GLUT4 translocation to the neuron cell membrane via an AKT-dependent mechanism [17,18] and is thought to improve glucose flux into neurons during periods of high metabolic demand, such as during learning [19]. Neurons express IRS1 and IRS2, which are enriched in presynaptic and postsynaptic compartments [20]. Insulin has many roles in neurons, and these roles are mediated by signalling through its two major effector pathways: the insulin–IRS–AKT and Mitogen-activated protein kinase (MAPK) pathways [21,22]. Insulin receptors are highly enriched in synapses [23], and have important effects on neurosynaptic functioning [24–27]. Furthermore, insulin has a crucial role in the development and maintenance of excitatory synapses [28] and has been shown to promote dendritic spine formation and excitatory synapse development [29]. Insulin promotes neuronal survival by inhibiting apoptosis [30]. Facilitating functions of neurons are supported by astrocytes, oligodendrocytes and microglia.

2.2. Astrocytes

Astrocytes are a subtype of glial cells that make up the majority of cells in the human central nervous system (CNS). They perform metabolic, structural, homeostatic, and neuroprotective tasks such as clearing excess neurotransmitters, stabilizing and regulating the blood-brain barrier (BBB), and promoting synapse formation [31–34]. Glucose is transported across the BBB through GLUT1 expressed on endothelial cells. Astrocytes take up glucose via GLUT1 and can process glucose glycolytically and transport lactate to neurons as an alternative fuel source during hypoglycaemia in a process known as the astrocyte–neuron lactate shuttle [35,36]. Astrocyte-neuron lactate transport is required for long-term memory formation [37]. Like hepatocytes, astrocytes have been known for a long time to have a glucose-containing energy reserve in the form of glycogen [38]. It seems clear that it is mobilized during periods of high neuronal activity through the action of various neuroactive substances and that an energy substrate arising from glycogenolysis is released by astrocytes, most likely to be used by neurons. Unlike the situation in hepatocytes, however, this released energy substrate is not glucose but lactate. Astrocytes can export lactate through monocarboxylate transporter (MCT) 1/4 [39]. The lactate may be taken up by oligodendrocytes through MCT1, or by neurons through MCT2 [39]. Astrocytes bind insulin with high affinity and express IRS1, IRS2 and downstream signalling molecules AKT and MAPK [40]. Activation of such signalling is mediated by insulin or insulin-like growth factor 1 (IGF1) which also activates IR [41–43]. Glial IR are downregulated in response to chronically high levels of insulin whereas neuronal IR are not downregulated [44]. Astrocytes play a part in inflammatory responses in the brain, and insulin modulates astrocyte inflammatory cytokine secretion in response to inflammatory stimuli [41].

2.3. Oligodendrocytes

Oligodendrocytes form the myelin sheath which surrounds axons and enables rapid conduction of the nerve impulse [45]. They are the end product of a cell lineage which has to undergo a complex and precisely timed program of proliferation, migration, differentiation, and myelination to finally produce the insulating sheath of axons. Due to this complex differentiation program, and due to their unique metabolism/physiology, oligodendrocytes count among the most vulnerable cells of the CNS. GLUT1 exists in oligodendrocytes [46]. Glucose may also be taken up by oligodendrocytes through GLUT1 [39]. The lactate from astrocytes may be taken up by oligodendrocytes through MCT1 [39]. The lactate is converted to pyruvate, which can be used for ATP production in oligodendrocytes may be particularly important to produce lipids for myelination. Oligidendrocytes express IR, IRS1 and IRS2. AKT signalling is important for mediating oligodendrocyte proliferation, survival, differentiation and myelination. The activation of AKT signalling by IGF1 in oligodendrocytes is well established and is known to promote differentiation and axonal ensheathment [47,48].

2.4. Microglia

Microglia are the resident immune cells, providing immune surveillance and remodeling of neuronal circuits during development and trauma. Microglia predominantly express GLUT3 and GLUT5, but under inflammatory conditions, GLUT1 expression is upregulated to increase glucose uptake and promote glycolysis [49–52]. Miicroglia express IR and IRS1, and insulin modulates microglial inflammatory responses in a complex manner [40]. Depending on its concentration in culture, insulin can enhance the secretion of certain inflammatory cytokines and inhibit the production of others.

3. Lipid Metabolism in Normal Brain

The brain is a highly energy-demanding organ. Brain utilizes about 20% of the total O_2 consumed by the resting body [53]. Lipids are components that make up over 50% of the brain, however, energy provision to the brain preferentially relies on a continuous circulatory supply of glucose to neural cells; the utilization of fatty acids (FAs) is less preferred [54]. About 20% of the total energy consumption of the adult brain originates from the oxidation of FAs [55,56], predominantly occurring in astrocytes and not neurons [55]. However, lipids play a crucial role in the maintenance of normal brain function as structural constituents of neuronal and neuroglial cell membranes and precursors of signaling molecules [57]. Lipid metabolism in normal brain was shown in Figure 2.
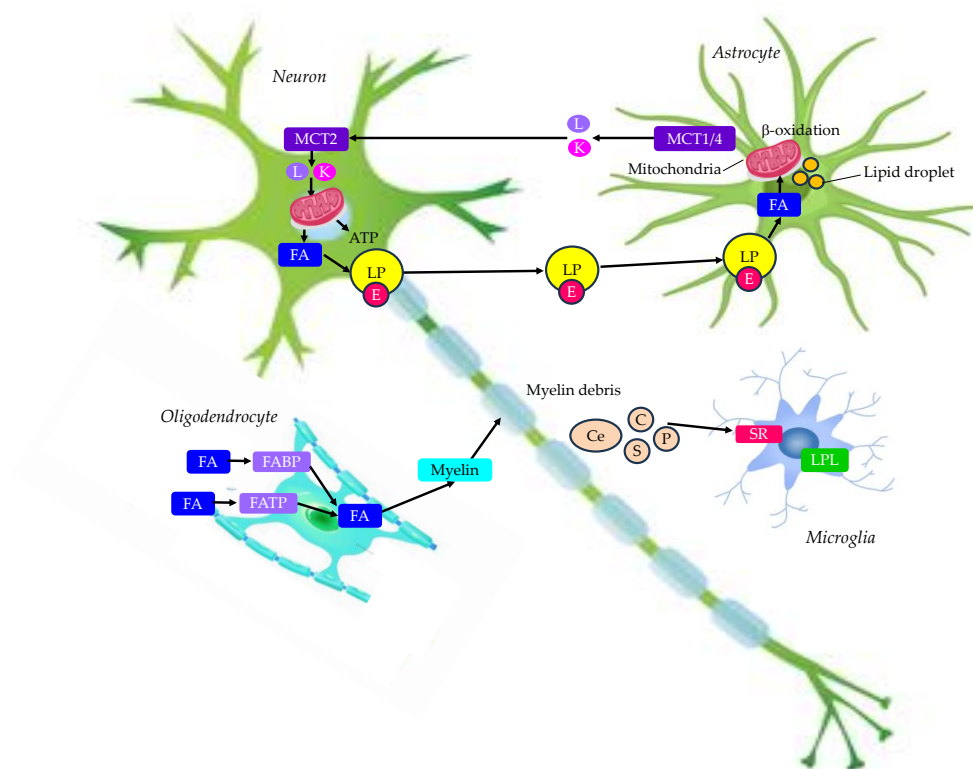

Figure 2. Lipid metabolism in normal brain. C, cholesterol; Ce, ceramides; E, apo E; FA, fatty acid; FABP, FA binding protein; FATP, FA transport proteins; GLUT, K, ketone bodies; L, lactate; LP, lipoprotein-like particles; LPL, lipoprotein lipase; MCT, monocarboxylate transporter; P, phospholipids; S, sphingolipids; SR, scavenger receptor.

3.1. Neurons and Astrocytes

Neurons and astrocytes operate as a tightly coupled unit for energy metabolism in the brain. Furthermore, neuron-astrocyte metabolic coupling protects against activity-induced FAs toxicity [58]. While neurons expend a considerable amount of ATP on neurotransmission, astrocytes provide neurons with metabolic substrates such as lactate and ketone bodies via MCTs, and antioxidants [59]. FAs are stored within cells as triacylglycerides (TG) in lipid droplets. FAs in lipid droplets removes excess free FAs (FFA) from the cytoplasm, which are toxic and disrupt mitochondrial membrane integrity [60,61]. Lipid droplets deliver FAs into mitochondria for an alternative energy source during periods of energy depletion [62]. Neurons do not make lipid droplets and have a low capacity for FAs consumption in mitochondria for energy production [63]. Neurons are especially susceptible to detrimental activities of reactive oxygen species (ROS) due to their poor antioxidative equipment [64]. Spurning the β-oxidation pathway in mitochondria of neurons and donation of metabolites to neurons for synthesis of antioxidants by astrocytes protect neurons against FFA-linked lipotoxicity [64]. Neuronal autophagy of ROS-emitting mitochondria combined with the transfer of degradation-committed FFA for their disposal in astrocytes, is a potent protective strategy against ROS and harmful activities of FFA [64].

During enhanced neuronal activity, lactate produced by astrocytes is transported to neurons via MCTs. In neurons, lactate is used in oxidative metabolism for ATP production and/or for FAs snthesis [65]. To avoid FFA toxicity, neurons release FAs in lipoprotein-like particles containing apo E, which can enter astrocytes by endocytosis. FAs are released from lipoprotein particles and are incorporated into lipid droplets [65]. FAs released from lipid droplets can be used as a fuel in mitochondrial β-oxidation in astrocytes. During energy deprivation, astrocytes metabolize FAs by β-oxidation to produce ketone bodies and transfer ketone bodies via MCTs to neuronal mitochondria for ATP synthesis [65].

3.2. Oligidendrocytes

Oligodendrocytes have much lower energetic demands than neurons, which require substantial energy to support the execution of action potentials [66,67]. Oligodendroglial energy demands are required for myelination and providing metabolic support to neurons. Oligodendrocytes support the energetic needs of neurons, being responsible for supplying neurons with glycolytic products, lactate and pyruvate, providing extra fuel to maintain their intense activity [68–70].

FAs can be taken up from the blood by endothelial cells and passed through the BBB by astrocytes to oligodendrocytes. Both oligodendrocytes and oligodendrocyte precursor cells express fatty acid transport proteins (FATP) and fatty acid binding proteins (FABPs) [71]. Ablation of these proteins impairs oligodendrocyte precursor cells proliferation and oligodendrocyte differentiation [72]. FAs derived from the circulation can support myelination, although they cannot fully substitute for specialized lipids that are internally synthetized by oligodendrocytes [73]. Interestingly, oligodendrocyte myelination also relies on lipids supplied by astrocytes, and when this synthesis is impaired, FAs derived by oligodendrocytes from the circulation may compensate [74]. FAs are stored as lipid droplets, mainly in astrocytes, but also in oligodendrocytes during development; however, these stored lipids are mainly used for myelin production [65].

3.3. Microglia

Microglia are brain-resident macrophages that constitute the largest population of immune cells in the CNS. They can initiate, modulate, and resolve inflammation [75,76]. Microglial lipid metabolism is tightly regulated during development, damage, and disease [77]. Microglia facilitate primary myelination [78–80], by phagocytosis of apoptotic oligodendrocytes and myelin debris during early development [81]. Microglial clearance of myelin derived lipids is required for optimal remyelination following demyelination [82,83]. Demyelination causes release of myelin-derived lipids such as ceramides, cholesterol, phospholipids, and sphingolipids. Healthy microglia clear lipids via cell surface scavenger receptors [76].

Lipoprotein lipase (LPL) is predominantly expressed in the microglia [84,85]. Moreover, microglial LPL expression has been implicated in brain development, damage, and disease [86–88]. Patients with AD show reduced LPL abundance in the hippocampus, and reduced LPL enzymatic activity in their cerebrospinal fluid (CSF) [88]. LPL plays a key role in microglial metabolism and function [87,89–91]. LPL is a feature of phagocytic and "reparative" microglia, and that LPL may support remyelination by facilitating lipid uptake and promoting FAs oxidation while maintaining an anti-inflammatory microglial phenotype [89].

4. Risk Factors Related with Type 2 Diabetes for the Development of AD

Risk factors related with type 2 diabetes for the development of AD were shown in Figure 3.
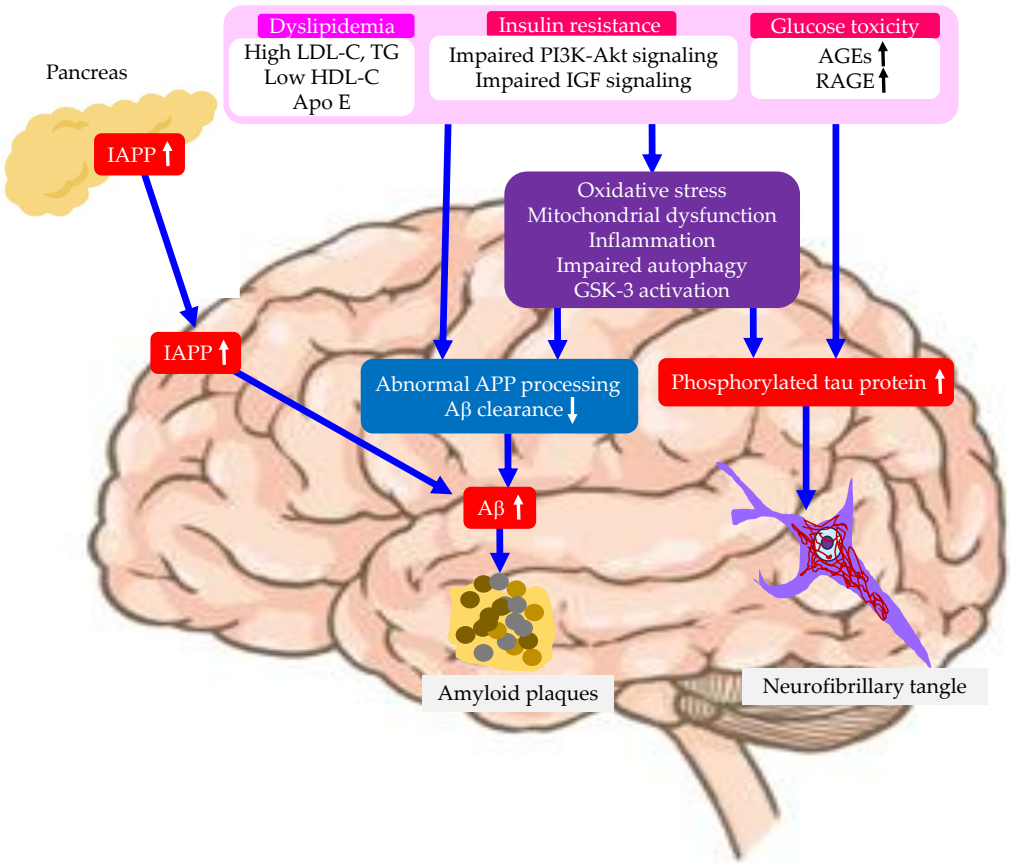

Figure 3. Risk factors related with type 2 diabetes for the development of AD. Aβ, amyloid beta; AGEs, advanced glycation end products; APP, amyloid precursor protein; GSK-3, glycogen synthase kinase-3; HDL-C, high-density lipoprotein-cholesterol; IAPP, islet amyloid polypeptide; IGF, insulin-like growth factor; LDL-C, low-density lipoprotein-cholesterol; PI3K, phosphatidyl-inositide 3-kinases; RAGE, receptor for AGEs; TG, triglyceride.

4.1. Insulin Resistance

A meta-analysis including 47 qualified articles with 2,981 patients showed that
fasting blood glucose levels ($p < 0.001$), fasting plasma insulin levels ($p < 0.001$), and homeostatic model assessment of insulin resistance (HOMA-IR) ($p < 0.001$) were higher in AD patients than in controls [92]. HOMA-IR was negatively correlated with Mini-Mental State Examination scale score (MMSE) ($p = 0.001$). This result suggests a significant association between insulin resistance and AD. Another meta-analysis showed a significant association between metabolic syndrome and AD,

mainly driven by large retrospective studies [93]. The pooled analysis revealed an increased risk of AD in metabolic syndrome (HR, 1.10; 95% CI, 1.05 to 1.15).

The reduction of expression of insulin, IGF-1 and IGF-2 as well as their receptors participates in the pathogenesis of AD. The expression of insulin and IGF-1/2 receptors were markedly reduced in AD brains, which is correlated with the pathological alterations, including increased glycogen synthase kinase-3 (GSK-3) activity and amyloid precursor protein (APP) mRNA level [94]. Insulin/IGF-1 signaling defects was associated with phosphatidyl-inositide 3-kinases (PI3K)/Akt pathway through producing harmful cascades in glucose metabolism [95]. Reduced expression and function of PI3K/Akt-mediated GLUTs in AD brain could lead to brain glucose hypometabolism and the subsequent decline in mitochondrial ATP production [96]. The comparison in the function of brain insulin-PI3K-Akt signaling pathway in the frontal cortices among subjects with AD, type 2 diabetes, type 2 diabetes and AD, and control subjects, showed that the deficiency of insulin-PI3K-Akt signaling was more significant in subjects with both type 2 diabetes and AD [95]. The levels and the activation of the insulin-PI3K-Akt signaling components were negatively correlated with the level of tau phosphorylation [95]. MAPK pathway has been shown to be significantly activated in AD patients, which is correlated with increased neuroinflammation, tau hyperphosphorylation, and Aβ trafficking [96]. The tau hyperphosphorylation is related to an excess activation of GSK-3β and MAPK, which are major tau kinases responsible for tau phosphorylation [97,98].

4.2. Dyslipidemia

A dose-response meta-analysis of prospective cohort studies showed that every 3-mmol/L increase in serum total cholesterol (TC) or triglyceride (TG) is linearly associated with a 9% or 12% increase in RR of AD [99]. The longitudinal cohort study showed that LDL-C was associated with all measures of AD neuropathology (neurofibrillary tangles, beta-amyloid, Braak stage, modified Consortium to Establish a Registry for AD [CERAD] score and global AD pathology) and cerebral amyloid angiopathy independent of Apo E after adjusting for age, sex, cholesterol-lowering medication use, body mass index, smoking and education [100]. A systematic search of meta-analyses using 100 primary studies and five meta-analyses demonstrated that LDL-C levels increased risk for AD [101]. A meta-analysis of a case-control study indicated that increased TC levels were associated with an elevated risk of AD and decreased HDL-C levels and increased LDL-C levels may be related with an elevated risk of AD in subjects aged 60-70 [102]. In the meta-analysis, serum LDL-C and TC levels were associated with the risk of AD in Asian individuals [103]. A wealth of experimental and epidemiological evidence has suggested that apolipoprotein A-I (apoA-I), the main protein constituent of HDL, may protect against AD. In the meta-analysis, compared to healthy controls, AD subjects had a lower serum apo A-I level. The pooled weighted mean difference from a random-effects model was -0.31 g/L (p < 0.0001) (95% CI, -0.62 to 0.01) [104].

The human Apo E gene is encoded on chromosome 19, and it has three allelic variants: ε2, ε3, and ε4 [105]. The individuals carrying the Apo E ε4 allele exhibit a high risk of sporadic AD [106]. Individuals with a single Apo E ε4 allele have a 3.2 times higher risk of developing AD, whereas, in those with two Apo E ε4 alleles, the risk of developing AD is increased by 8 to 10 folds [107]. This can be attributed to the influence of the Apo E ε4 allele on Aβ, either by reducing its clearance or by increasing its production in the brain [108]. The study aimed to investigate whether Apo E alleles have a distinct impact on serum lipids in AD was performed [109]. Higher TC and LDL-C levels were found in Apo E ε4 allele carriers compared with non-carriers, and the difference was more significant in patients with AD than in healthy controls.

4.3. Advanced Glycation End Products (AGEs) and the Receptor for AGEs (RAGE)

AGEs accumulation in the brain leads to AD. AGEs are a crucial contributing factor to the onset and development of AD [110]. The need for focused treatment strategies is emphasized by the harmful consequences of AGEs on the brain, which include oxidative stress, inflammation, the development of amyloid plaques, and the creation of neurofibrillary tangles. RAGE, a multiligand receptor found in both neurons and cerebral microvascular endothelia that bind Aβ, is also a

substrate for A disintegrin and metalloproteinase 10 (ADAM10) [111,112]. The interaction of RAGE with Aβ has been implicated in the amplification of oxidative stress, mitochondrial dysfunction and inflammation, resulting in RAGE-induced Alzheimer-like pathophysiological changes that contribute to the development of AD [113]. Ectodomain shedding of RAGE by ADAM10 generates a soluble counterpart of RAGE, sRAGE, which lacks the cytosolic and transmembrane domains, and sRAGE acts as a decoy receptor that antagonizes RAGE-mediated adverse effects [111,114]. The circulating sRAGE levels decreased in the plasma of AD patients [115]. The ADAM10 polymorphism was associated with the risk and development of AD by decreasing the expression of ADAM10 and reducing the plasma levels of sRAGE, which may be correlated with the clinical progression of AD [116].

4.4. Oxidative Stress

Abnormal oxidative stress is an established feature of AD. A meta-analysis of in vivo magnetic resonance spectroscopy studies showed that neuroinflammation and oxidative stress may occur in the early stages of AD, and may likely precede neuron loss in its progression [117]. Isoprostanes are biomarkers of oxidative stress. They are produced in membranes by ROS-induced lipid peroxidation of polyunsaturated fatty acids (PUFAs) like arachidonic acid. A systematic review of observational studies on the associations of F2-isoprostanes and the specific biomarker 8-iso-prostaglandin F2α which is the most abundantly produced F2-isoprostane with AD were conducted [118]. F2-isoprostane levels were significantly associated with AD [118]. F2-isoprostane and 8-iso-prostaglandin F2α levels were significantly elevated in tissue samples of the frontal lobe of AD patients. Moreover, F2-isoprostane levels in CSF and 8-iso-prostaglandin F2α levels in blood samples of AD patients were significantly increased.

The markers of lipid peroxidation are elevated in blood in AD, and total antioxidant capacity is decreased [119]. Non-enzymatic antioxidants in blood (uric acid, vitamins A, E and C, α- and β-carotene) were significantly decreased [119]. There is significant oxidative damage in peripheral blood early in the process of neurodegeneration. Selenium is an essential trace element well recognized for its antioxidant role in humans. Random-effects meta-analysis indicated a decrease (standard mean difference [SMD], - 0.42) in brain tissue selenium levels in AD as compared to non-AD controls [120]. The selenium levels were decreased in the temporal, hippocampal, and cortex regions in AD.

4.5. Inflammtion

The Neutrophil-to-Lymphocyte Ratio (NLR) is a clinical indicator of peripheral inflammation that has been extensively studied and is easily accessible. It is a straightforward calculation that indicates the equilibrium between the innate (neutrophils) and adaptive (lymphocytes) immune responses in different diseases and situations [121,122]. The mean NLR was 0.59 higher in AD patients compared to healthy participants (95% CI, 0.38 to 0.80) [123]. Similarly, the mean NLR was higher in AD than mild cognitive impairment (MCI) patients (MD, 0.23; 95% CI, 0.13 to 0.33). The mean NLR was higher in individuals with MCI compared to healthy participants (MD, 0.37; 95% CI, 0.22 to 0.52).

The 18-kDa translocator protein (TSPO) is increasingly recognized as a molecular target for positron emission tomography (PET) imaging of inflammatory responses in various CNS disorders [124,125]. Regions known to be vulnerable in AD, such as posterior cingulate cortex and hippocampus, are consistently shown to display increased TSPO PET signal [126]. In fact, volume changes assessed on MRI in these two regions, designated as epicentres of the pathology, are considered the best predictors of AD progression [127].

4.6. Mitochondrial Dysfunction

Mitochondrial dysfunction has also been observed prior to amyloid plaque deposition [128]. Mitochondrial dysfunction induces overproduction of ROS [129,130]. In AD, mitochondrial

abnormalities are considered the main source of oxidative stress [131]. The PET studies also indicated that mitochondrial dysfunction has shown in the early stage of AD, and the mitochondrial-related energy failure may precede glycolysis-related hypometabolism in regions with pathologically confirmed early neurodegeneration in AD [132]. Proteomics studies showed that mitochondrial dysfunction is an early biochemical event that might play a central role in driving AD pathogenesis [133].

4.7. Impaired Autophagy

Autophagy, also known as self-cleaning and self-eating, is a conserved biological process in eukaryotes [134]. Autophagy can provide nutrients to maintain cellular function by breaking down macromolecules, organelles, proteins, and end products, under starvation conditions. Moreover, it also helps in maintaining cellular homeostasis by eliminating damaged organelles, misfolded proteins, and lipid droplets [135]. Autophagy is intricately linked to glycolipid levels within the body, and it exerts a protective effect on pancreatic β-cells [136]. Studies have shown that a prolonged high-glucose-high-fat diet can hinder autophagy while fasting and restricting calorie intake can activate it [137].

In AD, defects in endocytosis and autophagy have emerged as key drivers of accumulation of cellular waste products, progressive neuronal dysfunction, and neurodegeneration [138]. A systematic review and meta-analysis suggested that dsregulation of proteins in the endosomal-lysosomal and autophagy pathway may play an important role in AD pathogenesis [139].

4.8. Overactivity of GSK-3

A reduced ability of insulin to activate glucose transport in skeletal muscle, termed insulin resistance, is a primary defect leading to the development of impaired glucose tolerance and type 2 diabetes. GSK-3 is a serine/threonine kinase with important roles in the regulation of glycogen synthesis, protein synthesis, gene transcription, and cell differentiation in various cell types [140]. Overexpression and overactivity of GSK-3 in skeletal muscle of rodent models of obesity and obese type 2 diabetic humans are associated with an impaired ability of insulin to activate glucose disposal and glycogen synthase [140]. Selective inhibition of GSK-3 in insulin-resistant skeletal muscle causes improvements in insulin-stimulated glucose transport activity that are likely caused by enhanced post-insulin receptor insulin signaling and GLUT4 translocation [140]. Inhibiting GSK-3 activity by pharmacological intervention has become an important strategy for the management of type 2 diabetes [141]. The inhibition of GSK-3 improves insulin signaling through IRS-1, PI3K and protein kinase B (PKB/Akt) pathways [141]. GSK-3 overactivation disrupts neural growth, development, and function. It directly promotes tau phosphorylation, regulates APP cleavage, leading to Aβ formation, and directly or indirectly triggers neuroinflammation and oxidative damage [142].

4.9. Islet Amyloid Polypeptide (IAPP, or Amylin)

The IAPP plays a role in glucose homeostasis but aggregates to form islet amyloid in type 2 diabetes [143]. Islet amyloid formation contributes to β-cell dysfunction and death. IAPP is asscoaited with cctivation of the inflammasome, defects in autophagy, endoplasmic reticulum (ER) stress, generation of ROS, membrane disruption in AD brain. AD and type 2 diabetes are considered protein misfolding disorders associated with the accumulation of protein aggregates; Aβ and tau in the brain during AD, and IAPP in pancreatic islets in type 2 diabetes. Misfolded IAPP produced in type 2 diabetes may potentiate AD pathology by cross-seeding Aβ, providing a molecular explanation for the link between these diseases [144]. Transgenic animals expressing both IAPP and APP exhibited exacerbated AD-like pathology compared with AD transgenic mice or AD transgenic animals with type 1 diabetes [144]. IAPP was colocalized with amyloid plaques in brain parenchymal deposits, which suggested that IAPP and APP may directly interact and aggravate AD [144]. Inoculation of pancreatic IAPP aggregates into the brains of AD transgenic mice resulted in more severe AD

pathology and significantly greater memory impairments than untreated animals. IAPP and Aβ co-aggregation and cross-seeding might contribute to the cross-talk between two diseases.

Furthemore, the ion-mobility mass spectrometry study showed the direct molecular interaction between tau and IAPP [145]. The effect of IAPP on tau aggregation and the IAPP-tau fibrils were tested in vitro [146]. IAPP interacts with tau and accelerates the formation of a more toxic strain with enhanced seeding activity and neurotoxicity. Intrahippocampal injection of the IAPP-tau strain into the tau P301S transgenic mice substantially promoted the spreading of tau pathology and induced more severe synapse loss and cognitive deficits compared with tau fibrils.

5. Changes in Energy Metabolism by Type 2 Diabetes and AD

Changes in expression of GLUTs by type 2 diabetes and AD were shown in Table 1.

Table 1. Changes in expression of glucose transporters by type 2 diabetes and AD.

Glucose transporters	Type 2 diabetes	AD
GLUT1	↓	↓ (↑ in microglia)
GLUT2	Unknown	↑ (in astrocytes)
GLUT3	↓	↓
GLUT4	↓	Translocation ↓

5.1. Changes in GLUTs by Type 2 Diabetes

GLUT1 is expressed in all brain cells including the endothelial cells and with very low neuronal expression, while GLUT3 is almost restricted to neurons [147]. Levels of the main BBB carrier GLUT1 were found reduced in the hippocampus of insulin resistant rats [148]. Lower levels of both GLUT1 and GLUT3 were found in the brain of mice under a diet rich in fat and sugar for 3 months [149]. Mice fed an high fat diet for 3 months also showed reduced density of the neuronal GLUT3, and of the insulin-dependent GLUT4 that is key for synaptic fueling, when compared to controls [150]. Hippocampal neurons of obese type 2 diabetic subjects displayed reduced GLUT4 expression and neuronal soma area, associated with an increased expression of NF-κB. [151]. Insulin resistance and type diabetes reduce GLUT3 and GLUT4 which are crucial GLUTs for neuron.

5.2. Changes in GLUTs by AD

AD is characterized by cerebral glucose hypometabolism. Post-mortem studies showed consistent reductions in GLUT1 and GLUT3 in the hippocampus and cortex of AD brains, areas of the brain closely associated with AD pathology [152]. Longitudinal rodent studies clearly indicate that changes in GLUT1 and GLUT3 only occur after Aβ pathology is present, and several studies indicate Aβ itself may be responsible for changes in GLUTs expression [152]. Uncontrolled microglial activation has been implicated in AD [153], glucose uptake in microglia is facilitated predominately by GLUT1, particularly under inflammatory conditions [154]. 2-Deoxy-2-[^{18}F]fluoro-d-glucose PET (FDG-PET) is widely used to study cerebral glucose metabolism. AD patients exhibited a positive association between glucose uptake and microglial activity [155]. Increased glucose uptake by activated microglia may deprive glucose availability in neruon, astrocytes and oligodendrocytes. Oligomeric Aβ causes impaired hippocampal insulin signaling and reduced GLUT4 translocation, accompanied by cognitive impairment and hippocampal hypometabolism [156]. GLUT4 immunoreactivity colocalises with cholinergic markers [157], suggesting a role for GLUT4 dysregulation in AD which is characterised by damage to cholinergic neurons [158,159]. GLUT2 was significantly increased in the AD brain and brains of subjects with both AD and type 2 diabetes, possibly due to astrocyte overactivation [160]. Thus, the increase of GLUT2 level in AD brain homogenates is most likely due simply to astrocyte over-activation, which is a well known phenomenon in AD brain [161].

5.3. Changes in MCTs by Type 2 Diabetes

Astrocytes mainly express MCT1 and MCT4, whereas neurons mainly express MCT2 [162,163]. The activity of the astrocyte-neuron lactate shuttle is involved in brain energetic support, and the process of lactate transport from astrocytes to neurons, which are important in neuronal energy support, depends on the activity of MCTs [164,165]. MCT2 protein levels in type 2 diabetes model rats decreased significantly in the hippocampus and hypothalamus compared to their controls [166], suggesting that type 2 diabetes reduces lactate or ketone bodies availability of neuron.

5.4. Changes in MCTs by AD

Alterations of cerebral lactate metabolism in the double-transgenic APP/presenilin 1 (APP/PS1) mouse model of AD was studied [167]. Lactate content and expressions of cerebral MCT1, MCT2, and MCT4 were decreased in APP/PS1 mice, suggesting that the decreases of cerebral lactate content and lactate transporters may lead to the blockage of lactate and ketone bodies transport from glia to neurons, resulting in neuronal enegy substrate deficit in neurons.

5.5. Changes in Lipid Metabolism by AD

The utilization of FAs is less preferred in neuron [54], however, neurons in AD patients cannot glucose, lactate and ketone bodies due to reduced expression of GLUTs and MCTs. Therefore, neurons in AD patients must use FAs. Brain-type FABP levels were elevated in serum of 29% of the patients with AD, and in 2% of the healthy donors [168], suggesting an increased FA use in brain in AD patients. CSF levels of FABP3 were elevated in AD patients compared with control subjects (p < 0.01) [169]. Another work showed that CSF FABP3 concentration distinguished between healthy controls and patients with AD with a sensitivity and specificity of 76% and 84%, respectively. Both patients with AD and MCI due to AD had higher FABP3 levels in CSF when compared with cognitively healthy controls [170]. An increased FA use in brain may be a crucial determinant of the development of AD.

FFAs accumulated in non-adipose tissues are metabolized through the de novo synthesis pathway into lipid derivatives, such as ceramides and other sphingolipids [171]. Excessive accumulation of ceramides triggers a series of cellular stress responses, leading to apoptosis in different tissues and contributing to the pathogenesis of type 2 diabetes and AD [172–174]. Ceramide accumulation is involved in the pathogenesis of AD. Ceramide accumulation in the brain could be directly due to the increase in FFAs levels or indirectly promoted by FFAs-induced neuroinflammation under lipotoxic conditions [175]. High levels of FFAs can enter and be metabolized in the brain, resulting in increased ceramide synthesis [176]. An increase in ceramide levels has been observed in the brains of patients with early stages of AD [177]. Healthy microglia clear ceramide via cell surface scavenger receptors [76], however, activated microglia cannot clear ceramide which may increase ceramide accumulation.

Astrocytes provide key neuronal support, and their phenotypic transformation is implicated in neurodegenerative diseases. Brain critically depends on astrocytic mitochondrial oxidative phosphorylation to degrade FAs. Astrocytic mitochondria dysfunction is observed in patients with type 2 diabetes [178]. Aberrant astrocytic mitochondrial oxidative phosphorylation induces lipid droplet accumulation followed by neurodegeneration that recapitulates key features of AD [179]. When FA load overwhelms astrocytic mitochondrial oxidative phosphorylation capacity, elevated acetyl-CoA levels induce astrocyte reactivity by enhancing signal transducer and activator of transcription 3 (STAT3) acetylation and activation [179]. Intercellularly, lipid-laden reactive astrocytes stimulate neuronal FA oxidation and oxidative stress, activate microglia through interluekin-3 signaling, and inhibit the biosynthesis of FAs and phospholipids required for myelin replenishment [179].

Microglia become increasingly dysfunctional with aging and contribute to the onset of AD through defective phagocytosis, attenuated cholesterol efflux, and excessive secretion of pro-inflammatory cytokines. High blood glucose drives microglial activation and M1 polarization, and

M1 microglia release pro-inflammatory cytokines, causing neuronal damage [180]. Dysfunctional microglia also accumulate lipid droplets. Microglia lacking LPL showed excessive accumulation of lipid droplet-like structures, and displayed a pro-inflammatory lipidomic profile, increased cholesterol ester content, and reduced cholesterol efflux [181]. Peroxisome proliferator-activated receptor (PPAR) agonists rescued the lipid droplet-associated phenotype in microglia lacking LPL [181].

5.6. Effects of Changes in Energy Metabolim in Brain Due to Type 2 Diabetes on the Development of AD

Effects of changes in energy metabolism in brain due to type 2 diabetes on the development of AD were shown in Figure 4.
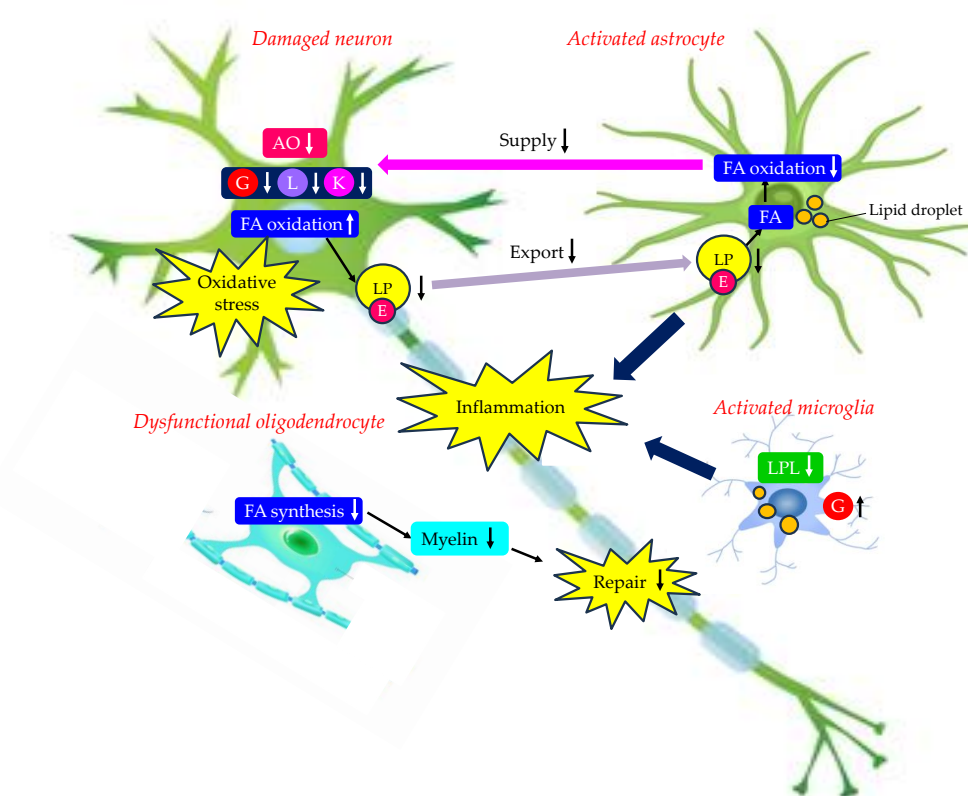

Figure 4. Effects of changes in energy metabolism in brain due to type 2 diabetes on the development of AD. AO, antioxidants; E, apo E; FA, fatty acid; G, glucose; K, ketone bodies; L, lactate; LP, lipoprotein-like particles; LPL, lipoprotein lipase.

Neurons are provided with energy substrates by astrocytes. Insulin resistance and type 2 diabetes reduce expressions of GLUTs in neuron and astrocytes. Increased glucose uptake by activated microglia further deprives glucose availability in neuron and astrocytes. Dysfunctional astrocytes cannot supply glucose, lactate and antioxidants to neuron. Astrocytic dysfunctional mitochondria cannot oxidize FAs, resulting in reduced supply of ketone bodies to neuron. Neurons critically depends on astrocytic mitochondrial oxidation to degrade FAs. Dysfunctional activated astrocytes stimulate neuronal FA oxidation and increase neuronal oxidative stress, activate microglia, and inhibit the biosynthesis of FAs required for myelin replenishment in oligodendrocytes. Furthermore, activated astrocytes and microglia induce inflammation. Such phenotypic changes in neurons, astrocytes, microglia and oligodendrocytes due to changes in energy metabolism due to type 2 diabetes may be associated with the development of AD.

6. Possible Therapeutic Intervention for AD Considering AD Risk Factors

Possible therapeutic intervention for AD based on considering AD risk factors were shown in Table 2.

Table 2. Possible therapeutic interventions for AD considering AD risk factors.

Risk factors	Possible therapeutic interventions
High LDL-C	Diet, Exercise, Statin
High TG	Diet, Exercise, PPAR-a agonists, n3-PUFA
Low HDL-C	Diet, Exercise, Stain, PPAR-a agonists
Apo E abnormality	PPAR-a agonists
Insulin resistance	Diet, Exercise, Metformin, Pioglitazone, SGLT2is, GLP-1RAs
Oxidative stress	Antioxidants (Vitamin C and E, Polyphenols)
Mitochondrial dysfunction	Imeglimin

AD, Alzheimer's disease; GLP-1RAs, glucagon-like peptide 1 receptor agonists; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; PPAR, peroxisome proliferator-activated receptor; SGLT2is, sodium glucose co-transporter-2 inhibitors; TG, triglyceride.

6.1. Exercise

The meta-analysis including 29 prospective cohort studies showed a favorable effect of physical activity on AD risk decline (HR, 0.72; 95% CI, 0.65 to 0.80). Subgroup analysis of physical activity intensity demonstrated an inverse dose-response relationship between physical activity and AD, effect sizes of which were significant in moderate (HR, 0.85; 95% CI, 0.80 to 0.93) and high physical activity (HR, 0.56; 95% CI, 0.45 to 0.68), but not in low physical activity (HR, 0.94; 95% CI, 0.77 to 1.15) [182].

The meta-analysis including 27 randomized controlled trials (RCTs) showed a nonlinear dose-response relationship between exercise and cognitive improvement in AD, with the optimal aerobic exercise dose identified at 660 METs-min/week for enhancing cognitive function in AD [183].

6.2. Diet

In the meta-analysis comprising 35 studies, individuals reporting the highest vs. the lowest fish consumption were associated with a lower likelihood of AD (RR [relative risk], 0.80; 95% CI, 0.67 to 0.96) [184]. The Mediterranean diet was reported to reduce the risk of development of AD (OR, 0.73; 95% CI, 0.62 to 0.85) [185].

6.3. Antioxidants

6.3.1. Vitamin E

Individuals with AD had lower circulatory concentrations of α-tocophenol compared with healthy controls [186]. However, levels of β-, γ- and δ-tocophenols did not significantly differ between groups of AD and age-related cognitive deficits compared to controls. Another meta-analysis also showed that AD patients had a lower concentration of serum vitamin E compared with healthy controls among older people (WMD [weighed mean difference], -6.811 μmol/L; 95% CI, -8.998 to -4.625; p < 0.001) [187]. High vitamin E intake from diet and supplements significantly reduces the risk of AD (OR, 0.78; 95% CI, 0.64 to 0.94) [188].

6.3.2. Vitamin C

A Mendelian randomization study to investigate the causality of vitamin C on the risk of AD found suggestive evidence that genetic liability to higher vitamin C levels was associated with a lower risk of AD (OR, 0.968; 95% CI; 0.946 to 0.991; p = 0.007) using the fixed-effects inverse-variance-weighted method [189]. The meta-analysis including 73 eligible cohort studies totaling > 28,257

participants showed that the pooled RR of AD was 0.70 (95% CI, 0.51 to 0.95) for the dietary plus supplemental intake of vitamin C. Moreover, pooled RRs of AD and vitamin C intake per 20 mg/day increase were 0.98 (95% CI, 0.97 to 0.99) via dietary plus supplemental intake, 0.98 (95% CI, 0.96 to 1.00) in the dietary only intake [190].

6.3.3. Resveratrol

Resveratrol is a potent Sirtuin1 (SIRT1) enhancer that facilitates neuroprotection and promotes neurogenesis in the hippocampus of the adult brain [191]. In the meta-analysis comprised five trials involving 271 AD patients, compared with placebo therapy, resveratrol treatment resulted in a significant improvement in AD Cooperative Study- Activities of Daily Living (ADAS-ADL) scores, CSF Aβ40 and plasma Aβ40 levels (SMD, 0.43; 95% CI, 0.07 to 0.79) [192].

6.4. Statins

3-hydroxyl 3-methylglutaryl CoA reductase (HMGCR)-based anti-AD drugs can provide lipid-lowering-targeted and anti-inflammatory effects and have thus been receiving extensive attention in recent years [193]. As a highly functional gene of AD, HMGCR provides multi-target effects while inducing lipid accumulation, oxidative stress, Aβ deposition, and microgliosis, which further aggravate damage to the CNS. In the pooled analyses of the meta-analysis, statins were associated with a decreased risk of AD [21 studies, OR 0.68 (CI 0.56-0.81)] [194].

6.5. PPARα Agonists

PPAR-α is expressed in the brain and plays a significant role in oxidative stress, energy homeostasis, mitochondrial FA metabolism and inflammation. PPAR-α takes part in regulation of genes coding proteins that are involved in glutamate homeostasis and cholinergic/dopaminergic signaling in the brain [195]. PPAR-α regulates expression of genes coding enzymes engaged in APP metabolism, and activates gene coding of α secretase, which is responsible for APP degradation. It also down regulates β secretase (BACE-1), the main enzyme responsible for Aβ peptide release in AD. In AD brain expression of genes of PPAR-α and PPAR-γ coactivator-1 alpha (PGC-1α) is significantly decreased [195]. Specific activators of PPAR-α may be important for improvement of brain cells metabolism and cognitive function in AD.

Bezafibrate treatment led to significant improvement of cognitive/memory function in AD mice accompanied by alleviation of amyloid pathology and neuronal loss as well as reduced oxidative stress and neuroinflammation [196]. Fenofibrate increased the expression of PPAR-α, and decreased BACE-1 mRNA and protein levels, and also reduced soluble APP and Aβ releases in APP/PS1 transgenic mice [197].

6.6. n-3-PUFA

Omega-3 fatty acids (n-3-PUFA) such as eicosatetraenoic acid (EPA) and docosahexaenoic acid (DHA) are essential to normal neural development and function. Comparing the highest to lowest category of fish intake, a higher intake of fish was associated with a 36% (95% CI, 8 to 56%) lower risk of AD [198]. Dose-response meta-analysis showed that an increment of 100g per week of fish intake was associated with an 11% lower risk of AD (RR, 0.89; 95% CI, 0.79 to 0.99). In the meta-analysis, the Clinical Dementia Scale showed reduced progression of cognitive decline among AD patients with n-3-PUFA supplemental interventions, with no differences between different n-3-PUFA supplements [199].

6.7. Anti-Diabetic Drugs

A systematic umbrella review and meta-analysis including 100 reviews and 27 cohort/case-control studies (n = 3046661) showed that metformin, pioglitazone, glucagon-like peptide 1 receptor agonists (GLP-1RAs) and sodium glucose co-transporter-2 inhibitors (SGLT2is) were associated with significant reduction in risk of dementia [200].

6.7.1. Pioglitazone

Pioglitazone have shown promising effects on neuroinflammation and homeostasis of amyloid plaques, but there is a lack of research papers providing conclusive evidence. In the meta-analysis, the Wechsler Memory Scale-Revised logical memory I scores had a significant improvement in the pioglitazone group (MD, 2.02; 95% CI, 0.09 to 3.95), suggesting that pioglitazone is a safe medication that has a promising effect in slowing the advancement of AD [201].

6.7.2. Metformin

The study was performed to comprehensively investigate the risk of AD associated with various antidiabetic classes. A total of 1,565,245 patients from 16 studies were included. AD risks were significantly lower with metformin and SGLT2is than other antidiabetic drugs [202]. However, two meta-analyses failed to show that metformin reduces risk of AD [203,204].

6.7.3. SGLT2is

Acetylcholine is one of the important neurotransmitters in the human brain, and participates in the electrophysiological activity between neurons, ensuring signal transmission between neurons [205]. The cholinergic hypothesis revealed the important role of acetylcholine in AD, emphasizing that synaptic loss and atrophy in AD impair neurotransmitter conduction [206]. Reduced binding of acetylcholine and cholinergic receptors is one of the important reasons for the emergence of psychiatric symptoms in AD patients. Therefore, acetylcholinesterase (AChE) inhibitors (such as donepezil and galantamine) are used to improve cognitive function in AD patients. SGLT2 inhibition significantly reduced AChE activity and increased monoamine levels, leading to an improvement in memory dysfunction in mice [207]. There is emerging data from murine studies that SGLT2is can cross the BBB and may have neuroprotective effects, such as increasing the brain-derived neurotrophic factor (BDNF), reducing the amyloid burden, inhibiting AChE [208]. Furthermore, SGLT2is have the multifaceted mechanisms of action for the treatments of AD, such as encompassing antioxidative stress, anti-neuroinflammation, upregulation of autophagy, anti-apoptosis, and protection of endothelial cells [209].

A very recent database containing information on medications prescribed to 233183 patients aged 50 years or older between 2018 and 2020 showed that GLP-1RAs and SGLT2is might be associated with lower odds of anti-AD drugs usage, while insulins might be linked to higher odds of using anti-AD drugs [210]. A retrospective examination of data from a cohort of 1,348,362 participants with type 2 diabetes ($\geq$ 40 years) showed that SGLT2is use was associated with reduced risks of AD (aHR, 0.81; 95% CI, 0.76 to 0.87) [211].

6.7.4. GLP-1RAs

GLP-1 has been shown to have neuroprotective properties in vitro and in vivo. In AD mouse model, APP/PS1 mice, liraglutide prevented memory impairments in object recognition and water maze tasks, and prevented synapse loss and deterioration of synaptic plasticity in the hippocampus [212]. In liraglutide-treated APP/PS1 mice, overall β-amyloid plaque count in the cortex and dense-core plaque numbers were reduced by 40-50%, while levels of soluble amyloid oligomers were reduced by 25%. Activated microglia was significantly reduced by liraglutide. Liraglutide increased young neurons in the dentate gyrus in APP/PS1 mice.

A systematic review and meta-analysis of preclinical studies showed that GLP-1 RAs could improve the learning and memory abilities of AD rodents; in terms of pathology, GLP-1 RAs could reduce Aβ deposition and phosphorylated tau levels in the brains of AD rodents [213].

In a placebo-controlled double-blind phase II clinical trial testing liraglutide in 200 patients with AD (NCT01843075), liraglutide significantly slowed down the deterioration in cognitive impairments, and found that brain temporal lobe volumes and parietal lobe volumes shrank less, and the total grey matter cortical volume shrank less in the liraglutide group compared to the placebo group as shown in MRI brain scans [214].

SIRT1 was found to be closely related to expression of GLP-1R in hippocampus of AD model mice [214]. Semaglutide increased the expression levels of SIRT1 and GLUT4 in the hippocampus of AD model mice, accompanied by an improvement in learning and memory, decreased in Aβ plaques and neurofibrillary tangles [215]. Further, semaglutide improved glucose metabolism by promoting glycolysis, improving glycolytic disorders, and increasing the membrane translocation of GLUT4, in the brain of AD model mice. These effects were blocked by the SIRT1 inhibitor, suggesting that SIRT1/GLUT4 signaling pathway may be an important mechanism for GLP-1RAs to promote glucose metabolism in the brain. Two phase III clinical trial testing semaglutide (Wegovy, Ozempic, Rybelsus) in AD patients are underway (NCT04777396 and NCT04777409) [216].

6.7.5. Dual GLP-1 and Glucose Dependent Insulinotropic Polypeptide (GIP) Receptor Agonist (Dual GLP-1/GIP RA)

GIP is a peptide hormone of the incretin family. In AD, energy utilization is much reduced, and GIP has the potential to reverse this [217]. Furthermore, GIP can reduce the inflammation response in the brain and reduce levels of pro-inflammatory cytokines. In GIP-treated AD models, memory is rescued, synapse numbers and synaptic plasticity in the hippocampus is normalized, amyloid plaque load and the chronic inflammation is reduced [217]. Recently, dual GLP-1/GIP receptor agonists have been developed.

Dual GLP-1/GIP RA administration significantly prevented spatial learning deficits, and decreased phosphorylated tau levels in the rat cerebral cortex and hippocampus in streptozotocin-induced AD model rat [218]. Dual GLP-1/GIP RA reduced chronic inflammation and apoptosis, by reactivating insulin signaling pathways. Dual GLP-1/GIP RA improved cognitive impairment in a range of tests and relieved pathological features of APP/PS1/tau mice, enhanced long-term potentiation in the hippocampus, increased numbers of synapses and dendritic spines, normalized volume and numbers of mitochondria, while downregulating amyloid, phosphorylated tau protein [219]. Dual GLP-1/GIP RA was more effective in reversing memory loss, enhancing synaptic plasticity in the hippocampus, reducing amyloid plaques and lowering pro-inflammatory cytokine levels in the brain than liraglutide in the APP/PS1 mouse model of AD [220].

6.7.6. Imeglimin

Mitochondrial dysfunction is a prominent pathological feature of type 2 diabetes and AD. Apoptotic cell death has been shown to constitute the terminal process in AD. A decrease in mitochondrial membrane potential causing opening of the permeability transition pore (PTP) in mitochondrial membranes has been implicated as a critical effector of apoptosis [221]. Opening of the PTP leads to the release of so-called apoptosis initiation factors that induce the degradative events of apoptosis [221].

Imeglimin improves mitochondrial dysfunction and reduces ROS [222]. The effects of imeglimin on ischemia-induced brain damage, induced in rats by the occlusion of the cerebral artery, was investigated [223]. Imeglimin significantly reduced the size of cerebral infarction, cerebral edema, and the neurological defects of ischemia. Imeglimin protected against ischemia-induced neuronal loss, microglial proliferation and activation, and increased astrocytes and cells that produce anti-inflammatory cytokines. Further, imeglimin acutely prevented the opening of PTP in cultured neurons and astrocytes. Such properties of imeglimin can be promising treatment for AD.

7. Conclusions

The functions of neurons, astrocytes, oligodendrocytes and microglia are highly regulated by glucose and insulin signaling in normal brain. Changes in brain energy metabolism due to type 2 diabetes are significantly associated with the development of AD. We showed possible therapeutic interventions based on considering risk factors and altered brain energy metabolism due to type 2 diabetes for the development of AD.

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