REVIEW

The Role of Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 RA) in Diabetes-Related Neurodegenerative Diseases

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Abstract: Recent clinical guidelines have emphasized the importance of screening for cognitive impairment in older adults with diabetes, however, there is still a lack of understanding about the drug therapy. Glucagon-like peptide 1 receptor agonists (GLP-1 RAs) are widely used in the treatment of type 2 diabetes and potential applications may include the treatment of obesity as well as the adjunctive treatment of type 1 diabetes mellitus in combination with insulin. Growing evidence suggests that GLP-1 RA has the potential to treat neurodegenerative diseases, particularly in diabetes-related Alzheimer's disease (AD) and Parkinson's disease (PD). Here, we review the molecular mechanisms of the neuroprotective effects of GLP-1 RA in diabetes-related degenerative diseases, including AD and PD, and their potential effects.

Keywords: glucagon-like peptide-1, diabetes mellitus, Alzheimer's disease, Parkinson's disease, cognition

Introduction

Type 2 diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia caused by relatively insufficient insulin secretion. It is estimated that about 415 million people had diabetes in 2015, and this number may continue to rise to 642 million by 2040.[1] Diabetes-related neurodegenerative disease (ND) is of particular importance due to the cognitive impairment it causes in older patients with type 2 diabetes. The risk of incident mild cognitive impairment (up to 60%) and dementia (50–100%) is higher in patients with type 2 diabetes than in those without.[2] Recent clinical guidelines have emphasized the importance of screening for cognitive impairment in older adults with diabetes;[3] however, there is still a lack of understanding about drug therapy. Therefore, an urgent goal is to develop effective neuroprotective drugs that act on the common mechanisms of diabetes-related NDs, thereby slowing the disease progression.

Glucagon-like peptide 1 (GLP-1) is a 30-amino-acid peptide hormone produced in intestinal epithelial endocrine L-cells by the processing of proglucagon.[4] GLP-1 is widely used in the treatment of type 2 diabetes because it not only controls blood glucose but may also reduce body weight. Future uses of GLP-1 may also include the treatment of obesity, as well as the adjunctive treatment of type 1 diabetes mellitus in combination with insulin.[5] Natural GLP-1 degrades within 2–3 min in circulation, thus greatly limiting its effects. Various GLP-1 receptor agonists (GLP-1 RAs) have been developed to provide long-term effects. GLP-1 RA functions by activating the GLP-1 receptor (GLP-1R), and GLP-1R is widely located throughout the brain.[6,7] The ability of GLP-1 and its agonists to cross the blood–brain barrier[8–10] suggests its therapeutic potential for NDs. A large number of studies have demonstrated the neuroprotective ability of GLP-1 RA, resulting in the improvement of cognitive and non-cognitive dysfunction of the central nervous system (CNS).

The proposed mechanisms of diabetes-related NDs include cerebral insulin resistance (IR), vascular endothelial dysfunction, inflammation, blood–brain barrier injury, white matter disease of vascular origin, demyelination and axonal loss, and peroxidative membrane injury.[11] Among these mechanisms, brain IR may play a primary role, and it is worth noting that neurologic complications may already occur with prediabetes IR.[12] Oxidative stress,[13] mitochondrial

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dysfunction,[14] and endoplasmic reticulum (ER) stress[15] are all involved in NDs induced by brain IR. In this review, we discuss the accumulating evidence concerning the effects of GLP-1 RA in diabetes-related NDs.

The GLP-1 RA and Its Relationship with Brain Insulin Resistance

Brain IR can be defined as the failure of brain cells to respond to insulin, and the lack of response may be due to the downregulation of insulin receptors, an inability of insulin receptors to bind insulin, or faulty activation of the insulin signaling cascade.[16] Insulin receptors are distributed throughout the brain, but have the highest concentration in the olfactory bulb, cerebral cortex, hypothalamus, hippocampus, and cerebellum.[17] Insulin binds to the insulin receptor, phosphorylates the insulin receptor substrate (IRS), activates the phosphoinositide-3 kinase (PI3K) and mitogen-activated kinase (MAPK) pathways, and modifies the activity of several downstream effectors. PI3K activates protein kinase B (Akt), which inactivates several important substrate proteins, such as glycogen synthase kinase 3β (GSK-3β)[18] and forkhead box O,[19] and activates mammalian target of rapamycin (mTOR).[20] As a result, it modulates some cellular processes, such as cell survival, proliferation, apoptosis, protein synthesis, inflammation, ER stress, mitochondrial function, and autophagy in neurodegenerative disorders.[18–20] Akt also promotes B-cell lymphoma 2 and B-cell lymphoma extra-large transcription by activating cyclic adenosine monophosphate (cAMP) response element-binding protein (CREB).[21] Thereafter, it regulates learning, memory,[22] and neuron survival.[23] MAPK regulates various cellular activities including proliferation, differentiation, apoptosis or survival, inflammation, and innate immunity.[24] Impairment of insulin signaling is common in diabetes-related NDs.

GLP1-R is a class B G protein-coupled receptor,[25] and its expression has been reported in the cerebral cortex, especially the occipital and frontal lobes, hypothalamus, and thalamus, whereas lower levels are found in the caudate putamen, globus pallidus, and hippocampus.[21] GLP-1 and its RA cross the blood–brain barrier, with exendin-4 considered as one of the best based on the rate of brain influx, percentage of reaching the brain that accumulates in the brain parenchyma, and percentage of the systemic dose taken per gram of brain tissue.[8] Small amounts of GLP-1 may also be produced by preproglucagon neurons, located in the nucleus tractus solitarii of the brainstem[26,27] and projected to other brain regions, such as the nuclei of the hypothalamus, including the arcuate and paraventricular nuclei.[28] In the case of diabetes or obesity-related IR, GLP-1 secretion in the brain[29] and peripheries[30] may be impaired, which may contribute to the pathogenic change in neurodegeneration and cognitive decline; however, exogenous GLP-1 may help treat these diseases. When GLP-1 binds to the receptor, adenosine cyclase is activated and intracellular cAMP increases, thereby activating protein kinase A (PKA) and PI3K. The downstream pathways are mainly the PI3K and MAPK pathways; hence, the GLP-1 signaling and insulin signaling pathways are similar and partially overlapping (Figure 1).

Consequently, exogenous drugs that act on GLP-1Rs increase insulin sensitivity, possibly because GLP-1R stimulation compensates for some of the impaired insulin signaling. Among these drugs, liraglutide has been reported to have neuroprotective effects by ameliorating damage to the insulin pathway. In vitro experiments proved that it reversed the phosphorylation status of IRS1, Akt, and GSK-3β and reduced beta-amyloid formation and tau hyperphosphorylation in the human neuroblastoma cell line, SH-SY5Y.[31] In vivo experiments proved that liraglutide prevented the dysregulation of Akt and GSK-3β and Alzheimer-associated tau phosphorylation in the brains of diabetic mice.[32,33] Besides, it prevents the loss of brain insulin receptors in an Alzheimer's disease (AD) model.[34] Exenatide also has a similar effect on impaired insulin signaling pathways.[35,36]

The GLP-1 RA and Mitochondrial Dysfunction and/or Oxidative Stress

Mitochondria are the main energy production systems of most eukaryotic cells and are responsible for energy conversion, tricarboxylic acid cycle, oxidative phosphorylation, calcium storage, etc. Mitochondrial dysfunction has negative effects on the body and is believed to be an important factor in aging and disease. It has been found that insulin receptor knockout mice show reduced mitochondrial oxidative phosphorylation activity.[37] Abnormal mitochondrial calcium transport was observed in the myocardium and visceral adipose tissue of obese mice.[38,39] In the hippocampal tissue of type 2 diabetic mice, the expression of mitochondrial dynamin-related protein 1 (Drp1) increased, whereas inhibition of Drp1 restored neuronal function.[40] In diabetic models, peroxisome proliferator-activated receptor c coactivator 1a (PGC-1a), an important factor in diabetic mitochondrial biosynthesis, is often found to be abnormally expressed, whereas PGC-1a is critical for synaptic growth
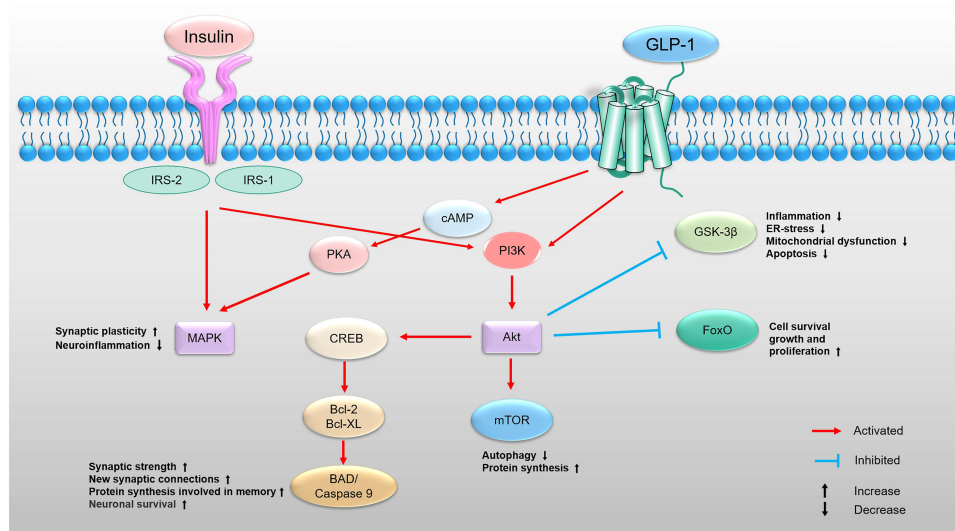
Figure 1 Insulin and GLP-1-dependent intracellular signal transduction pathways are similar. Insulin binds to the insulin receptor and further activates the PI3K/Akt and MAPK pathways signaling. PI3K/Akt pathway modulates some cellular processes, such as cell survival, proliferation, apoptosis, protein synthesis, inflammation, ER stress, mitochondrial function, autophagy, synaptic strength in neurodegenerative disorders. MAPK pathway regulates various cellular activities including synaptic plasticity and neuroinflammation. When GLP-1 binds to the GLP-1 receptor, adenosine cyclase is activated and intracellular cAMP increases, thereby activating PKA and PI3K. The downstream pathways are mainly the PI3K and MAPK pathways; hence, the GLP-1 signaling and insulin signaling pathways are similar and partially overlapping.

Abbreviations: IRS, insulin receptor substrate; PI3K, phosphoinositide-3 kinase; Akt, protein kinase B; ER, endoplasmic reticulum; GSK-3β, glycogen synthase kinase 3β; FoxO, forkhead box O; mTOR, mammalian target of rapamycin; CREB, cAMP-response element binding protein; Bcl-2, B-cell lymphoma 2; Bcl-XL, B-cell lymphoma extra-large; BAD, (Bcl-2) antagonist of death; cAMP, cyclic adenosine monophosphate; PKA, protein kinase A; MAPK, mitogen activated kinase.

and CNS function. Reduced levels of the mitochondrial autophagy-associated protein Parkin in the substantia nigra may contribute to the development of Parkinson's disease (PD) in db/db mice and high-fat diet-induced diabetic mice.[41] As discussed above, mitochondrial dysfunction (mitochondrial bioenergetics, calcium buffering) and mitochondrial quality control systems (mitochondrial dynamics, mitophagy, mitochondrial biogenesis) may be involved in the pathological mechanisms of diabetes-related NDs.

Oxidative stress refers to a state of imbalance between oxidation and antioxidant effects in the body, favoring oxidation, leading to inflammatory infiltration of neutrophils, increased protease secretion, and production of a large number of oxidative intermediates. Mitochondria are key sites for aerobic metabolism and reactive oxygen species (ROS) production in cells and are also one of the most important organelles related to oxidative stress. Some experts believe that cerebral IR is the result of ceramide accumulation in brain tissue, and ROS overproduction occurs due to metabolic abnormalities accompanying peripheral IR and impaired mitochondrial activity in the IR brain.[13] Studies have shown that ROS can cause age-related synaptic loss and ultimately cognitive impairment,[42] where ROS interactions with inflammation may play a role. Oxidative products, including lipid and protein oxidation, are promoters of brain inflammation.[43] Nuclear transcription factor-κB (NF-κB) Inflammatory pathway signaling plays a key role in regulating the amount of ROS in the cell.[44] Excessive ROS can inhibit IRS1 activation by activating inflammation-related protein kinase C, inhibitor kappa B kinase β (IKKβ), c-Jun N-terminal kinase (JNK), and p38 MAPK, thereby aggravating IR,[45] creating a vicious cycle.

In the nervous system, the regulatory effect of GLP-1 RA on mitochondrial function and oxidative stress is involved in the remission of diabetes-related NDs. In diabetes-related AD, GLP-1 promotes mitochondrial biogenesis and the antioxidant system by regulating the PGC-1a signaling pathway in vivo to directly reverse tau hyperphosphorylation.[46] GLP-1(9-36) (amide) reduced elevated levels of mitochondrial-derived ROS in the hippocampus of AD model (APP/PS1) mice.[47] Exendin-4 significantly increased amyloid β protein (Aβ)-induced reduction in mitochondrial function, integrity, respiratory control rate, and mitochondrial P/O ratio in all brain regions and decreased Aβ-induced increase in the mitochondrial complex enzyme-I, IV, and V activities in all brain regions.[36] Exenatide also improved hippocampal mitochondrial morphology and dynamics and reduced oxidative stress in the hippocampus of AD model (5xFAD) mice.[48]

The mechanism by which GLP-1 RA regulates mitochondrial function and oxidative stress has not been well elucidated. GLP-1 signaling may improve mitochondrial biogenesis via PGC-1a/nuclear respiratory factor-1/mitochondrial transcription factor A signaling regulated by adiponectin/ adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK)[49] and elevates the expression of NAD-dependent protein deacetylase sirtuin 1 (SIRT1), which increases the expression of Parkin, leading to mitophagy activation.[50] Evidence strongly suggests that GLP-1 increases ER-mitochondria communication, resulting in higher mitochondrial activity.[51] Upregulating SIRT3 expression and activation of the extracellular signal-regulated kinase-Yes-associated protein (ERK-Yap) signaling pathway, as well as the CREB/adiponectin axis may also be involved in the protection of mitochondria by GLP-1.[52,53] The improvement of antioxidant stress through GLP-1 signaling seems to be related to the activation of the GLP-1 R/cAMP/PKA signaling pathway and nuclear factor erythroid 2-related factor 2/heme oxygenase 1 signaling pathway.[54,55]

The GLP-1 RA and Endoplasmic Reticulum (ER) Stress

The ER is the basic organelle for the synthesis of a series of important biological molecules, such as proteins, lipids (such as triglycerides), and carbohydrates. ER stress refers to the activation of ER responses, such as the unfolded protein response (UPR) and apoptosis signaling pathway, through the accumulation of misfolded and unfolded proteins and the disorder of calcium balance after various stress agents are applied to cells. The early role of UPR is to reduce translation to lessen the need for new protein folding, degrade unfolded proteins to minimize damage, and increase the expression of chaperone proteins to assist protein folding. The UPR is thought to promote cell homeostasis. However, if this mechanism persists, it may lead to different metabolic diseases[56] and NDs.[57] UPR is mainly involved in the activation of three transmembrane proteins, inositol-requiring enzyme 1 (IRE-1), activating transcription factor 6 (ATF6), and protein kinase R (PKR)-like ER kinase (PERK). Normally, these three proteins are associated with luminal binding immunoglobulin protein (BiP), also known as 78-kDa glucose-regulating protein (GRP78), and are inactive. Under stress conditions, BiP is released and thus activates the IRE-1, ATF6, and PERK signaling cascades.[58]

ER stress plays a role in the occurrence and development of diabetes and IR in peripheral tissues such as the pancreas, liver, adipose tissues, and skeletal muscle.[58–63] Although some of the effects of ER stress are tissue-specific, there are some commonalities in the damage to insulin signaling. Under the action of unhealthy metabolic factors (obesity, diabetes), ER stress is initiated, and IRE-1 is activated, which in turn leads to the phosphorylation of IRS1 at the serine 307 residue by activating JNK, thereby impairing insulin signaling.[64–66] A similar pattern was observed in the brain. Evidence indicates that ER stress was increased, thereby resulting in impaired insulin receptor signaling in the hippocampus and frontal cortex of obese rats, which is also caused by the activation of JNK.[67] Therefore, diabetes and ER stress are vicious cycles in the brain, and IR is the key link. ER stress is also involved in the degenerative brain changes caused by diabetes. Elevated expression of ER stress markers, including GRP78, ATF-6, X-box binding protein-1, C/EBP homologous protein (CHOP), and phospho-Jun N-terminal kinase (p-JNK), was evident in the hippocampal CA1 of diabetic rats,[68] which may ultimately affect synaptic plasticity.

ER stress has always been considered a result of NDs, but previous studies have shown that it is a more complex process by interfering with UPR to affect disease progression.[69] GLP-1 RA has been shown to interfere with UPR to protect against NDs. Liraglutide treatment reduced neuroinflammation and ameliorated ER stress in the inferior olive of the aged Wolfram syndrome rat model.[70] Moreover, it can prevent the disease before the appearance of metabolic symptoms.[71] Liraglutide may engage Akt and signal transducer and activator of transcription 3 signaling to favor adaptive responses and shift cell fate from apoptosis to survival under chronic ER stress conditions in nerve cells.[72] Our team used palmitic acid stimulation to induce neuronal IR, confirming that ER stress is involved in the functional damage of neurons induced by IR, and exendin significantly alleviates both ER stress and neuronal damage (data not shown).

However, it is not clear how GLP-1 RA regulates ER stress. Inhibiting the PI3K/Akt signaling pathway may eliminate the protective effect of GLP-1R by increasing ER stress, suggesting that this pathway may be involved in the effect of GLP-1 on ER stress.[73] Besides, the PKA pathway may also be involved in GLP-1, attenuating the ER stress signaling pathway and protecting cells from apoptosis.[74–76] Evidence suggests that PKA-dependent protection of GLP-1 is mediated through enhanced ATF4-CHOP-growth arrest and DNA damage inducible gene 34 (GADD34) signaling,

resulting in eukaryotic initiation factor 2 alpha dephosphorylation and translational recovery.[76] However, some researchers believe that exendin-4 protects β-cells against free fatty acids and salubrinal-induced ER stress and apoptosis, not through ATF4-CHOP- GADD34 feedback signaling but through enhancing cellular defense mechanisms (eg, BiP, Bcl-2, and JunB).[77] In addition, other studies have investigated the mechanism by which GLP-1 regulates ER stress. Exendin-4 enhances the binding of heat shock factor 1 to the promoter of heat shock protein (HSP) genes through SIRT1-mediated deacetylation, which then increased the expression of molecular chaperones HSP70 and HSP40 to alleviate lipid-induced hepatic ER stress.[78] ER oxidoreductase mediates the inhibitory effects of exendin-4 on ER stress, ameliorating hyperhomocysteinemia-induced endothelial dysfunction.[79] ER protein 46, a new member of the thioredoxin family, highly expressed in pancreatic β-cells, may mediate GLP-1 regulation of ER stress and thus increase the protection of pancreatic β cells.[80,81] These studies suggest the complexity of GLP-1 RA in regulating ER stress.

The GLP-1 RA and Central Nervous System (CNS) Inflammation

It is well known that CNS inflammation plays a major role in the pathophysiology of NDs.[82] In type 2 diabetes-associated cognitive impairment animal models and high-glucose in vitro studies, neuroinflammatory markers, such as IL-1 β, TNF-α, IL-6, and MCP-1, and inflammatory responses, such as toll-like receptor 4, cyclooxygenase 1 (COX1), COX2, NF-κB, leukocyte common antigen, and inducible nitric oxide synthase were increased in the brain.[83–88] Among participants with dementia and AD pathology, type 2 diabetes had a significantly positive relationship with JNK.[89] In vitro, high glucose increased the expression of inflammasome recombinant NLR Family, pyrin domain containing protein 3 (NLRP3) markers in hippocampal cells.[90] Besides, CNS inflammation is an immune response mediated by microglia and astrocytes. Evidence demonstrates that acute glucose fluctuation forms the stress that alters microglial activity (eg, inflammatory activation or self-degradation), which may be one of the mechanisms of cognitive deterioration in diabetic patients.[91] Diabetic mice also show astrocyte changes in the hippocampus.[92,93] Since astrocytes are important neuronal support cells, astrocyte changes may aggravate the dysfunction of neuronal function. Our team previously designed an IR model induced by palmitic acid in vitro and established a neuron-microglia-astrocyte co-culture system, confirming that IR induced microglial activation, and the secretion of cytokines were significantly increased. This study also confirmed that activated microglia can activate the NF-κB pathway in astrocytes, activate astrocytes, and reduce support for neurons (data not shown). However, the association between hyperglycemia and neuroinflammation is not clearly understood. Some researchers have suggested that oxidative stress-mediated mitochondrial dysfunction stimulates the upregulation of mitochondrial HSP60 and ultimately initiates diabetes-induced inflammatory pathways by activating pattern recognition receptors.[94]

GLP-1 RA has been shown to exert anti-inflammatory effects in the CNS. Under inflammatory conditions in vitro, GLP-1 suppressed the secretion of TNF-α-associated cytokines and chemokines in BV-2 microglia.[95] Liraglutide also decreased activated microglia and astrocyte load in the brain induced by chronic inflammation in mice.[96] Besides, liraglutide treatment prevented the neuroinflammatory process, promoting the production of anti-inflammatory molecules such as IL10, TGFβ, and arginase 1.[97] In a model of lipopolysaccharide (LPS)-induced inflammation, liraglutide inhibited the polarization of pro-inflammatory microglia and promoted the polarization of anti-inflammatory microglia, diminished inflammatory cytokine expression, and decreased NF-κB pathway activation.[98] Similarly, exendin-4 also decreased the mRNA levels of IL-1β and TNF-α in LPS-stimulated microglia, and significantly attenuated the activation of the NF-κB signaling pathway.[99] The anti-inflammatory effect of GLP-1 also occurs in diabetes-induced neuroinflammation. During exendin-4 treatment, IL- 1b was transiently increased in normoglycemic mice and decreased in hyperglycemic mice.[88] Liraglutide also protects astrocytes against advanced glycation end product (AGE)-induced TNF-α and IL-1β secretion.[100]

There are several possible mechanisms by which GLP-1 RA regulates neuroinflammation. First, GLP-1 RA inhibited LPS-induced IL-1β mRNA expression, whereas adenylate cyclase inhibitor preconditioning inhibited this effect, suggesting that cAMP mediated its anti-inflammatory effect.[101] The cAMP/ PKA pathway is also involved in the protection of astrocytes from AGE-induced inflammatory response.[100] Second, the anti-inflammatory effects of GLP-1 RA are partially mediated by its metabolite in a phosphorylated AMPK-dependent manner. Therapies that inhibit GLP-1 degradation may weaken the metabolite-mediated effects.[102]

The GLP-1 RA and Neurogenesis

Neurogenesis is a complete process in which neural stem cells (NSCs) proliferate, undergo balanced and imbalanced division to become directed progenitor cells and gradually migrate to functional areas, undergo plasticity changes, and establish synaptic connections with other neurons to generate neural function. Adult neurogenesis is generated mainly in two parts of the brain: the subventricular zone of the lateral ventricle and the subgranular zone of the dentate gyrus in the hippocampus. The integration of adult-born neurons into the circuitry of the adult hippocampus suggests an important role for adult hippocampal neurogenesis in learning and memory.[103] The insulin/insulin-like growth factor (IGF) pathway promotes NSCs proliferation, differentiation, and survival;[104] therefore, impaired insulin signaling may affect neurogenesis. The diabetes-induced reduction of neurogenesis in the hippocampal dentate implies a potential mechanism for diabetes-related cognitive decline.[105–110] A possible explanation is that pro-inflammatory factors in type 2 diabetes compromise endothelial caveolin-1, a major membrane intrinsic protein in the caveolae on the cell surface, leading to vascular dysfunction, affecting neurogenesis, and subsequently leading to AD.[111] IKKβ/NF-κB-mediated impairment[112] and γ-aminobutyric acid and glutamate transporter systems[113] may also be involved in diabetes-induced damage of neurogenesis.

Enhancing the GLP-1R signaling pathway leads to the proliferation of neuronal cells[114] and neuronal differentiation.[115] In severely obese and insulin-resistant mice, liraglutide elicits beneficial effects on metabolic control and synaptic plasticity and improves hippocampal neurogenesis.[116]

The mechanism by which GLP-1 RA influences neurogenesis remains unclear. One possible mechanism is, in part, through increased expression of mammalian achaete–scute homologue 1 (Mash1), which plays an important role in neuronal differentiation and is believed to improve hippocampal neurogenesis. Active Akt increased the protein levels and transactivation activity of Mash1,[117] suggesting the potential function of the GLP-1-activated PI3K-Akt pathway.

GLP-1 RA and Synaptic Plasticity

Synaptic plasticity refers to the adjustable strength of connections between nerve cells, known as synapses. It is widely recognized that diabetes affects hippocampal synaptic plasticity, and this disruption in synaptic plasticity is related to cognition.[118] Reisi et al reported that both presynaptic and postsynaptic components are involved in diabetes-induced damage to synaptic plasticity.[119] In animal models of diabetes with cognitive impairment, synaptic plasticity was impaired in the two experimental forms of long-term enhancement (LTP)[120–124] and long-term depression (LTD).[125,126] Moreover, the ultrastructure of hippocampal synapses is destroyed,[127] thereby reducing the hippocampal dendritic spine density.[123] Besides, synaptic plasticity-related proteins, including CREB, pCREB, brain-derived neurotrophic factor (BDNF), and activity-regulated cytoskeleton (Arc) proteins, are significantly reduced.[128] Our previous data showed that central IR may significantly affect the expression of synaptic plasticity proteins, such as postsynaptic density protein-95 (PSD95), Arc, synapsin1, BDNF, resulting in the impaired synaptic plasticity of neurons and decreased learning and memory ability (data not shown). Sasaki-Hamada showed that disruption of synaptic plasticity occurs in the prediabetes stage, when glucose tolerance is impaired.[129] Further, the onset age[130] and duration of diabetes mellitus[131] may have some influence on synaptic plasticity. However, short-term acute changes in glucose concentrations may not directly contribute to the synaptic plasticity associated with diabetes, unless extremely severe.[132]

Glutamate receptors, including the amino-3-hydroxy-5-methyl-4-isoxazolepro-pionicacid (AMPA) and N-methyl-D-aspartate (NMDA) receptors, mediate excitatory synaptic transmission in the CNS, and its expression in the postsynaptic membrane is associated with LTP and LTD and is involved in the regulation of learning and memory activities. Abnormal regulation of glutamatergic receptors appears to participate in diabetes-induced impairment of synaptic plasticity.[120,122,125,133,134] In addition, insulin signaling is important for synaptic plasticity. IR β-subunit heterozygous mice[135] and complete disruption of IRS2 in mice[136] impaired the LTP of synaptic transmission in the hippocampus. Histone deacetylases (HDAC2), a member of the HDAC family, is correlated with insulin signaling components in postsynaptic glutamatergic neurons of the adult mouse hippocampus, and hyperactivity of the HDAC system (including HDAC2) may result in the suppression of the insulin signaling system and consequent disruption of synaptic plasticity in type 2 diabetes.[137]

GLP-1 RA has a definite effect on improving synaptic plasticity. Exendin-4 inhibits the reduction of LTP in the brain of a mouse fed a high-fat diet[138] and significantly increased the phosphorylation level of CREB and the expression level of BDNF. Furthermore, exendin-4 increased the membrane protein levels of the AMPA receptor GluR1 subunit and PSD-95.[139] Liraglutide also rescued the deleterious effects of a high-fat diet on hippocampal LTP of neurotransmission[140] and enhanced the number of hippocampal and cortical synapses in AD model mice.[141]

The effect of GLP-1 RA on synaptic plasticity is partly due to the GLP-1R. In a GLP-1R knockout mouse model, LTP in the CA1 area of the hippocampus was severely impaired.[142] In addition, GLP-1 RA upregulated neurotrophic tyrosine kinase receptor type 2 and mTOR genes in the hippocampus of high-fat-fed mice, which are involved in regulating synaptic plasticity and LTP.[143] By modulating calcium responses to glutamate and membrane depolarization,[144] and AMPA receptors,[139,145] GLP-1 RA may play important roles in regulating neuronal plasticity.

GLP-1 RA in Diabetes-Related AD and PD

AD is an insidiously progressive ND clinically characterized by memory impairment, aphasia, apraxia, agnosia, impaired executive function, personality and behavior changes, and other comprehensive dementia manifestations. PD is another common degenerative disease, and the main pathology is the degeneration and death of dopaminergic (DA) neurons in the substantia nigra of the midbrain, which leads to a significant decrease in DA content in the striatum. Both AD and PD are NDs associated with diabetes; however, the current treatment of these two diseases still focuses on the improvement of symptoms. It is necessary to better understand their mechanisms to obtain better medications on their pathogenesis.

Diabetes and Alzheimer's Disease

Diabetes is closely linked to AD, and a meta-analysis showed that patients with diabetes had a significantly higher incidence of AD than in those without diabetes (relative risk [RR], 1.53; 95% CI, 1.42–1.63),[146] suggesting that diabetes may promote the development of AD. Insulin acts on β-site amyloid precursor protein cleaving enzyme 1 and γ-secretase to regulate Aβ levels and degrades excess Aβ by modulating insulin-degrading enzyme.[147] Activation of insulin signaling pathway PI3k/Akt leads to Ser9 phosphorylation of GSK3β and its impaired kinase activity leads to phosphorylation of tau.[148] Hence, IR promotes the pathology of AD by reducing amyloid clearance and increasing tau hyperphosphorylation neurofibrillary tangles,[149] both of which are associated with cognitive impairment.[150,151]

It is widely accepted that changes in the mitochondria are involved in the development of AD. The manifestations of mitochondrial dysfunction in AD mainly include increased oxidative stress and ROS production,[152,153] mitochondrial DNA damage,[154] mitochondrial respiratory injury,[155] and calcium abnormalities.[156] Mitophagy,[157] mitochondrial dynamics,[158] and mitochondrial biogenesis[158] are also affected in patients with AD, ultimately resulting in the accumulation of dysfunctional mitochondria and mitochondrial fragmentation. Mitochondrial damage may not only be the common pathological mechanism of diabetes and AD, but also the key point of crosstalk between them. Two AD-related markers, Aβ-production and tau phosphorylation induced by IR, may be the upstream mechanisms of AD-related mitochondrial damage.[159–161] In addition, mitochondrial damage may be a contributing factor to the progression of diabetes to AD, as exposure to Aβ Increases the vulnerability of brain mitochondria in diabetic rats.[162]

ER stress plays a complex role in the control of neuronal survival, amyloid cascade, neurodegeneration, and synaptic function in AD.[163] In vitro, the abovementioned ER stress/JNK/IRS1 pathway was involved in Aβ$_{1-42}$ oligomer-induced tau hyperphosphorylation, which may indicate that IR promotes the role of ER stress in AD.[164] de la Monte et al suggested that in AD, a triangulated Mal-signaling network initiated by the brain's insulin/IGF resistance is transmitted through the ceramides and ER stress homeostasis disorder, which in turn promotes IR.[165]

Studies have established that inflammation contributes to the pathogenesis of AD. In AD, Aβ damages microglia, produces inflammatory cytokines and chemokines, and affects surrounding CNS resident cells (astrocytes, oligodendrocytes, and neurons), which may aggravate tau pathology and ultimately lead to neurodegeneration and neuron loss.[166] Inflammation may also be a potential link between diabetes and AD. Takeda et al crossed Alzheimer transgenic mice (APP23) with two types of diabetic mice (ob/ob and NSY mice) and found a significant increase in IL-6 in the brains of hybrid mice fed with a high-fat diet.[167] In addition, it has been shown that feeding AD model mice (triple transgenic AD

[3xTgAD]) a high-fat diet may increase the activation of microglia.[168] These studies suggest that diabetes mellitus and a high-fat diet may exacerbate AD inflammation.

Neurogenesis is defective in the AD model, which is characterized by decreased proliferation and differentiation, diminished neuronal maturity, and reduced survival, before processes that may secondarily affect neurogenesis, such as neuronal loss, amyloid deposition, and inflammation.[169] Chronic hyperglycemia decreases the complexity and differentiation of 3xTg-AD newborn neurons and depressed synaptic facilitation, accompanied by defective hippocampal-dependent memory,[109] suggesting that diabetes promotes changes in AD neurogenesis that ultimately exacerbates cognitive impairment.

Diabetes and Parkinson's Disease

A systematic review and meta-analysis suggested that diabetes was a risk factor for PD (RR = 1.37, 95% CI, 1.21–1.55; P < 0.0001).[170] Diabetes may exacerbate the progression of PD, including cognitive impairment and axial motor symptoms.[171] IR is still the key link between diabetes and PD and may impair nigrostriatal dopamine function,[172] exacerbate nigrostriatal DA depletion,[173] and enhance cognitive impairment[174] and behavioral abnormalities.[175]

Mitochondrial dysfunction is a defect in the early stage of PD and mainly includes impairment of the mitochondrial electron transport chain, alterations in mitochondrial morphology and dynamics, mutations in mitochondrial DNA, and anomalies in calcium homeostasis,[176] which are closely related to the PD phenotype. Mitochondrial damage may also be the reason why diabetes-related IR promotes the development of PD. In vitro, in differentiated human DA neurons, IR was associated with increased α-synuclein and ROS levels, as well as mitochondrial depolarization, which may be mediated by polo-like kinase-2.[177] In vivo, mitochondrial dynamics-related factor Parkin was significantly reduced in the substantia nigra of a mice fed a high-fat diet and a diabetic mice, leading to the accumulation of Parkin-interacting substrate and the reduction of PGC-1α.[41] Also, high glucose levels may modulate Parkin/PINK1-mediated mitochondrial autophagy in DA cells through the thioredoxin-interacting protein.[178] All the above mechanisms suggest that diabetes-related metabolic factors may promote PD by regulating the mitochondria.

All branches of the UPR in ER stress are likely implicated in PD etiology.[179] At present, studies on whether diabetes and IR aggravate ER stress in PD are few. However, given the ubiquity of ER stress-related pathways and IR crosstalk mentioned above, diabetes-related IR is likely to be involved in the generation of ER stress in PD.

Similar to AD, neuroinflammation is involved in the degeneration of DA neurons, which is mainly mediated by activated glial cells and surrounding immune cells. This cellular response may eventually lead to the death of DA cells, leading to disease progression.[180] A study that used 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) to mimic PD-like neural injury found that neuroinflammation is aggravated in the midbrain of type 2 diabetes mice, who are more susceptible to the neurotoxicity induced by MPTP.[181] This may indicate that diabetes exacerbates DA neuronal degeneration during the progression of PD, which may be mediated by neuroinflammation.

Adult neurogenesis is severely affected in PD, although the exact mechanisms and effects of these changes are not fully understood, there may be a dynamic interaction between them and PD-related pathology.[182] Although it is not clear whether there is crosstalk between diabetes and PD in neurogenesis, similar pathophysiological changes may indicate a close association between the two diseases.

GLP-1 RA Show Effects

Some similar or overlapping mechanisms certainly exist between diabetes and AD or PD, such as mitochondrial dysfunction, oxidative stress, and inflammation, that may strengthen their correlation. Furthermore, these mechanisms may underlie the use of the diabetes drug GLP-1 RA to treat AD and PD. In some AD and PD models, a considerable number of studies have clarified the role of GLP-1 RA in these cellular processes. However, GLP-1 RA also has some disease-specific effects in AD and PD, such as reduced Aβ levels, tau hyperphosphorylation in AD, and reduced α-synuclein pathology and DA neuronal loss in PD, suggesting that GLP-1 RA has a strong neuroprotective function (Tables 1 and 2).

The mechanism of GLP-1 RA on Aβ is not clear. One possibility is that amyloid precursor protein (βAPP) binds to GLP-1 as a G-protein-coupled receptor, resulting in reduced βAPP synthesis.[183] GLP-1 RA reduces tau

Table 1 Effects of GLP-1 Receptor Agonists in Models of AD: Data from Animal Experimental Models

Cellular Processes	Drug	Animal Model	Results and/or Effects	Reference
Mitochondrial dysfunction and/or Oxidative Stress	Exendin-4	Aβ (1–42)-induced cognitive deficit rats	Increased amyloid β protein (Aβ)-induced decrease in mitochondrial function, integrity, respiratory control rate, and ADP/O in all brain regions. Decreased Aβ-induced increase in the mitochondrial complex enzyme-I, IV, and V activities in all brain regions	[36]
	Exenatide	5xFAD transgenic mice	Improved mitochondrial morphology, alleviated oxidative stress and energy crisis, normalized mitochondrial dynamics	[48]
	Liraglutide	3xTg-AD female mice	Rescued brain oxidative/nitrosative stress markers, and attenuated the altered mitochondrial fission/fusion proteins	[204]
CNS inflammation	Liraglutide	APP/PS1 mice	Reduced cortical astrocytosis	[205]
	Liraglutide	APP/PS1 mice	Reduced activated microglia	[206]
	Liraglutide	APP/PS1 mice	Halved activated glia	[207]
	Exenatide	3xTg-AD^{HFD}	Decreased NF-κB Inflammatory pathway levels	[35]
	Lixisenatide	3xTg-AD female mice	Decreased activation of microglia in the hippocampi	[208]
Neurogenesis	Liraglutide	APP/PS1 mice	Increased the number of young neurons in the dentate gyrus was increased, and normalized cell proliferation	[206]
	Liraglutide	APP/PS1 mice	Increased in neurogenesis	[207]
	Liraglutide	APP/PS1 mice	Improves cell proliferation in subgranular zone, and increased differentiation of progenitor cells to neurons	[209]
Synaptic Plasticity	Liraglutide	APP/PS1 mice	Enhanced long-term enhancement (LTP), and increased synaptophysin levels	[206]
	Exenatide	3xTg-AD^{CD}	Positively affected brain-derived neurotrophic factor signaling	[35]
	Lixisenatide	Aβ-induced impairments in rats	Prevented suppression of hippocampal LTP	[210]
Aβ levels	Liraglutide	5xFAD mice and streptozotocin-Induced sporadic AD mice	Reduced the amount of Aβ Levels in the cortical and the hippocampal of the 5xFAD Mice, but not in sporadic AD mice	[211]
	Exendin-4	Aβ (1–42)-induced cognitive deficit rats	Decreased Aβ-induced increase in the level of Aβ	[36]
	Liraglutide	3xTg-AD female mice	Reduced brain Aβ1–42 levels	[204]
	Liraglutide	APP/PS1xdb/db mice	Reduced Aβ aggregates levels	[212]
	Exenatide	5xFAD transgenic mice	Reduced Aβ1-42 deposition in the hippocampal CA1 region	[48]
	Exendin-4	STZ 3xTg-AD mice	Reduced Aβ protein precursor and Aβ	[213]
	Liraglutide	APP/ PS1 mice	Reduction in the number of amyloid plaques in the cortex and hippocampus	[207]
	Lixisenatide	3xTg-AD female mice	Reduced amyloid plaques	[208]
Tau levels	Liraglutide	Aβ1-42 induced AD in mice	Reduces tau hyperphosphorylation	[186]
	Liraglutide	APP/PS1xdb/db mice	Reduced tau hyperphosphorylation	[212]
	Liraglutide	hTauP301L mouse	Reduced neuronal phospho-tau load	[214]
	Liraglutide	3xTg-AD mice	Decreased levels of hyperphosphorylated tau	[190]

phosphorylation not only in the AD model, but also in diabetes.[32,33,184,185] However, the mechanism by which GLP-1 RA reduces tau hyperphosphorylation may be complex. It has been reported that GLP-1 RA reduces tau phosphorylation through Akt and GSK-3β, a pathway related to insulin signaling, which also confirmed that insulin resistance is the key to tau phosphorylation.[186–188] It has also been reported that the effects of liraglutide on decreasing the hyperphosphorylation of tau by enhancing O-glycosylation of neuronal cytoskeleton protein, improving the JNK and ERK signaling pathway.[189,190] In addition, the mitochondrial PGC-1α signaling pathway is also the mechanism of GLP-1 RA to protect neurons from tau hyperphosphorylation, indicating that mitochondrial dysregulation has cross-talk with tau pathology.[46] The common mechanism of GLP-1 RA reduction in Aβ overproduction and tau

Table 2 Effects of GLP-1 Receptor Agonists in Models of PD: Data from Animal Experimental Models

Cellular Processes	Drug	Animal Model	Results and/or Effects	Reference
Mitochondrial dysfunction and/or Oxidative Stress	Semaglutide and liraglutide	MPTP mouse model	Inhibited the mitochondrial mitophagy signaling pathway	[215]
	Liraglutide	Acute MPTP mouse model	Normalized mitochondria dynamic Imbalance, enhanced impaired autophagy flux, and relieved oxidative stress	[216]
	Exenatide	Rotenone-Induced Rat Model	Decreased malondialdehyde	[217]
	Exenatide	MPTPx STZ rats	Reduced striatal oxidative stress markers	[218]
CNS inflammation	Semaglutide and Liraglutide	MPTP mouse model	Alleviated astrocyte and microglia activation in the striatum	[215]
	Exendin-4	MPTP mouse model	Prevented microglial activation	[219]
	Exenatide	Rotenone-Induced Rat Model	Decreased tumor necrosis factor alpha levels	[217]
	Exenatide	MPTPx STZ model rats	Reduced striatal inflammatory markers	[218]
Neurogenesis	Exendin-4	6-OHDA model rats	Stimulated subventricular zone neurogenesis	[220]
Synaptic Plasticity	Liraglutide	MPTP mouse model	Increased synaptophysin and neuroprotective growth factor glial-derived neurotrophic factor expression	[221]
α-synuclein pathology	Liraglutide	Acute MPTP mouse model	Decreases α-synuclein aggregation in substantia nigra	[216]
	Exendin-4	AAV-A53T-α-syn-injected rats	Mitigated pathologic α- synuclein aggregation	[192]
	Semaglutide and liraglutide	MPTP mouse model	Reduced the levels of α- synuclein	[215]
Dopaminergic neuronal loss	Liraglutide	Acute MPTP mouse model	Protected dopaminergic neurons	[216]
	Semaglutide and Liraglutide	MPTP mouse model	Attenuated dopaminergic neuronal loss	[215]
	Exendin-4	MPTP mouse model	Reduced nigrostriatal dopaminergic loss	[219]
	Exenatide	Rotenone-Induced Rat Model	Reduced the loss of dopaminergic neurons in the striatum	[217]

hyperphosphorylation may be the restoration of protein phosphatase 2A activity and inhibition of β- and γ-secretase.[191] The mechanism of GLP-1 RA to improve dopaminergic degeneration and pathological α -synuclein aggregation in the PD model may involve inhibiting the PI3K/Akt/mTOR pathway[192] and enhancing AMPK/PGC-1a signaling pathway.[193]

Although some results have been achieved in animal models, clinical studies on GLP-1 RA remain limited. This review summarizes some of the clinical data on GLP-1 RA (Table 3), with some exciting results. But some studies failed to find efficacy due to early termination[194] or some studies may fail to find drug effects due to short follow-up time or low statistical thresholds.[195] Several systematic reviews or meta-analyses have attempted to comprehensively summarize the clinical data of GLP-1 RA in the treatment of AD or PD, but the results are still inconclusive,[196–200] possibly because some clinical studies are still ongoing and require ongoing attention.[201,202] Due to the limitations of clinical studies, the

Table 3 Clinical Trials of GLP-1 Receptor Agonists in AD and PD

Disease	Drug	Treatment	Duration	Results and/or Effects	Reference
AD	Liraglutide	Increased from 0.6 mg/day to 1.8 mg/day.	26 weeks	Prevented the expected decline of cerebral Glucose Metabolism (CMRglc); No differences with respect to amyloid deposition or cognition	[222]
	Liraglutide	Increased from 0.6 mg/day to 1.8 mg/day	26 weeks	Restored blood-brain glucose transfer capacity (T max)	[223]
	Exenatide	Increased from 10 mcg/day to 20 mcg/day	18-month	No differences or trends compared to placebo for clinical and cognitive measures, MRI cortical thickness and volume, or biomarkers in cerebrospinal fluid, plasma, and plasma neuronal extracellular vesicles (EV) except for a reduction of Aβ42 in EVs	[194]
	Liraglutide	Increased from 0.6 mg/day to 1.8 mg/day	12 weeks	There were no cognitive differences	[195]
PD	Exenatide	5–10 μg twice daily	12 months	Mean improvement at 12 months on the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) of 2.7 points	[224]
	Exenatide	5–10 μg twice daily	Exenatide treatment for 12 months followed by 12 months of cessation (24 months)	Had an advantage of 5.6 points (95% CI, 2.2–9.0; p = 0.002) using blinded video rating of the MDS-UPDRS part 3 motor subscale, and an advantage of 5.3 points (95% CI, 9.3–1.4; p = 0.006) on the Mattis Dementia Rating scale	[225]
	Exenatide	2 mg once weekly	48 weeks followed by a 12-week washout period	Off-medication scores on part 3 of the MDS-UPDRS had improved by 1.0 points (95% CI −2.6 to 0.7)	[226]
	Exenatide	2mg once-weekly	48 weeks followed by a 12-week washout period	Have benefits in individual non-motor symptoms subdomains assessing mood dysfunction/depression	[227]
	Exenatide	2 mg once weekly	48 weeks followed by a 12-week washout period	Augmented tyrosine phosphorylation of insulin receptor substrate 1 at 48 weeks and 60 weeks; Elevated expression of downstream substrates, including total protein kinase B and phosphorylated mechanistic target of rapamycin (mTOR). Improvements in MDS-UPDRS part 3 off-medication scores were associated with levels of total mTOR and phosphorylated mTOR	[228]
	Exenatide	2 mg once weekly	48 weeks followed by a 12-week washout period	Tremor-dominant phenotype and lower MDS-UPDRS Part-2 scores predicted greatest motor response to exenatide. Patients with older age of onset and disease duration over 10 years responded less well	[229]

evaluation of drugs needs to rely on some new examination methods, such as imaging.[203] There is reason to believe that with the continuous improvement of technology, the judgment of drug efficacy will be easier and more diversified.

Conclusion

In recent years, clinical guidelines have begun to emphasize the importance of diabetes-related NDs and their risk of cognitive impairment, despite widespread concerns. Diabetes and related NDs share common mechanisms, such as central IR, oxidative stress, and inflammation, which underlie their crosstalk, which has also inspired the investigation of hypoglycemic agents, particularly GLP-1 RA, as potential treatments for diabetes and related NDs.

This review describes in detail the beneficial effects of GLP-1 RA on the central pathological mechanisms of diabetes and related degenerative diseases. However, the role of GLP-1 RA in the body is complex. First, GLP-1 RA has been shown to have powerful hypoglycemic effects, and the influence of blood glucose on these mechanisms cannot be ruled out. Second, IR exists in the brains of patients with diabetes mellitus, AD, and PD and is also a factor affecting these mechanisms. Therefore, it is not clear whether GLP-1 RA directly improves mitochondrial function, reduces ER stress, and reduces neuroinflammation, or indirectly improves these mechanisms by lowering blood glucose and improving IR. Further studies are needed to confirm the central protective effect of GLP-1 RA, and further clinical trials should be actively conducted.

Abbreviations

Aβ, amyloid β protein; AD, Alzheimer's disease; AGE, advanced glycation end product; Akt, protein kinase B; AMPA, amino-3-hydroxy-5-methyl-4-isoxazolepro-pionicacid; AMP, adenosine 5'-monophosphate; AMPK, AMP-activated protein kinase; Arc, activity-regulated cytoskeleton; ATF6, activating transcription factor 6; βAPP, amyloid precursor protein; BDNF, brain-derived neurotrophic factor; BiP, binding immunoglobulin protein; CHOP, C/EBP homologous protein; CNS, central nervous system; cAMP, cyclic adenosine monophosphate; COX, cyclooxygenase; CREB, cAMP response element-binding protein; DA, dopaminergic; Drp1, dynamin-related protein 1; ER, endoplasmic reticulum; ERK-Yap, extracellular signal-regulated kinase-Yes-associated protein; GADD34, growth arrest and DNA damage inducible gene 34; GLP-1, glucagon-like peptide 1; GLP-1 RA, GLP-1 receptor agonists; GLP-1R, GLP-1 receptor; GRP78, 78-kDa glucose-regulating protein; GSK-3β, glycogen synthase kinase 3β; HDAC, histone deacetylase; HSP, heat shock protein; IGF, insulin-like growth factor; IKKβ, inhibitor kappa B kinase β; IR, insulin resistance; IRE-1, inositol-requiring enzyme 1; IRS, insulin receptor substrate; JNK, c-Jun N-terminal kinase; LPS, lipopolysaccharide; LTD, long-term depression; LTP, long-term enhancement; MAPK, mitogen-activated kinase; Mash1, mammalian achaete–scute homologue 1; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; mTOR, mammalian target of rapamycin; ND, neurodegenerative disease; NLRP3, recombinant NLR Family, pyrin domain containing protein 3; NMDA, N-methyl-D-aspartate; NSCs, neural stem cells; NF-κB, nuclear transcription factor-κB; PD, Parkinson's disease; PERK, PKR-like ER kinase; PGC1a, peroxisome proliferator-activated receptor c coactivator 1a; PI3K, phosphoinositide-3 kinase; p-JNK, phospho-Jun N-terminal kinase; PKA, protein kinase A; PSD95, postsynaptic density protein-95; PKR, protein kinase R; ROS, reactive oxygen species; RR, relative risk; SIRT1, NAD-dependent protein deacetylase sirtuin 1; UPR, unfolded protein response; 3xTgAD, triple transgenic AD.

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Disclosure

The authors report no conflicts of interest in this work.

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