Degenerative Neurological and Neuromuscular Disease

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REVIEW

Potential Roles of Glucagon-Like Peptide-1 and Its Analogues in Dementia Targeting Impaired Insulin Secretion and Neurodegeneration

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Abstract: Dementia is a chronic, irreversible condition marked by memory loss, cognitive decline, and mental instability. It is clinically related to various progressive neurological diseases, including Parkinson's disease, Alzheimer's disease, and Huntington's. The primary cause of neurological disorders is insulin desensitization, demyelination, oxidative stress, and neuroinflammation accompanied by various aberrant proteins such as amyloid-β deposits, Lewy bodies accumulation, tau formation leading to neurofibrillary tangles. Impaired insulin signaling is directly associated with amyloid-β and α-synuclein deposition, as well as specific signaling cascades involved in neurodegenerative diseases. Insulin dysfunction may initiate various intracellular signaling cascades, including phosphoinositide 3-kinase (PI3K), c-Jun N-terminal kinases (JNK), and mitogen-activated protein kinase (MAPK). Neuronal death, inflammation, neuronal excitation, mitochondrial malfunction, and protein deposition are all influenced by insulin. Recent research has focused on GLP-1 receptor agonists as a potential therapeutic target. They increase glucose-dependent insulin secretion and are beneficial in neurodegenerative diseases by reducing oxidative stress and cytokine production. They reduce the deposition of abnormal proteins by crossing the blood-brain barrier. The purpose of this article is to discuss the role of insulin dysfunction in the pathogenesis of neurological diseases, specifically dementia. Additionally, we reviewed the therapeutic target (GLP-1) and its receptor activators as a possible treatment of dementia.

Keywords: dementia, insulin signaling, neurodegeneration, GLP-1 activators

Introduction

Dementia is an irreversible, slowly progressive syndrome characterized by cognitive decline and memory impairment due to anatomical changes in the brain.[1] It is primarily associated with Alzheimer's disease, vascular dementia, frontotemporal dementia, Creutzfeldt-Jakob disease, mixed dementia, Lewy body dementia, Parkinson-related dementia, and Huntington's disease.[2] More than 55 million people worldwide have dementia, with 10 million new cases diagnosed each year. Alzheimer's disease causes 60–70% of all dementia cases.[3] Most surveys conducted globally found annual incidence rates of 10–15 per 100,000 people, and its prevalence could reach 2% in people aged 65 and up.[4] Dementia is now the seventh leading cause of death worldwide and has become one of the most common causes of old age disability and dependency. Dementia is classified into three stages based on severity and progression: early, middle, and late stages. It typically begins with forgetfulness, but patients may develop difficulties with recognition and aggression as the disease progresses.[1] Dementia has significant physical, psychological, social, and economic consequences that affect dementia patients, caregivers, families, and society.[5] It affects memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgment does not affect consciousness. Changes in mood, emotional control, behaviour, or motivation are frequently associated with and occasionally precede cognitive function impairment.[1]

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Dementia, associated with several neurodegenerative diseases such as Huntington's disease (HD), causes genetic defects that decline a patient's memory, thinking, and emotional state.[6] Tau protein accumulation around brain cells causes the formation of neurofibrillary tangles via amyloid-β protein. Plaques may cause Alzheimer's disease, or they may be a byproduct of the disease process and related to dementia.[2] Additionally, when an abnormal infectious protein called a prion is expressed and accumulated in the brain at high levels, it causes irreversible damage to neuronal cells. This condition is known as Creutzfeldt-Jakob dementia, characterized by unusual anatomical changes in the brain, particularly in the frontal and temporal lobes.[7] Frontotemporal dementia is marked by atrophy in these brain areas and is associated with personality, behaviour, and language.[8] In Parkinson's disease, α-syn abnormal accumulation is found in substantia nigra neurons, leading to cognitive problems like memory loss and dementia. These are the Lewy bodies' deposits that lead to Lewy body dementia.[7] Neurocognitive complications caused by gradual vascular changes are estimated to have a global impact on mental abilities.[9]

According to the literature, the pancreas is primarily responsible for insulin production that reaches all body areas. Previously, the brain was thought to be an organ unaffected by insulin, but recent research has revealed the presence of insulin and insulin receptors in certain brain regions.[10] Insulin activity in neurons is dependent on its ability to cross the blood-brain barrier (BBB) via receptor-mediated transport and diffusion across the BBB.[10] According to post-mortem studies, the brain's hypothalamus region has the highest insulin concentration. The presence of insulin receptors in the brain suggests that insulin affects the CNS independent of glucose consumption.[11] Insulin regulates the brain-liver axis centrally by acting on specific brain stem nuclei containing pre-autonomic nuclei responsible for sympathetic and parasympathetic regulation of liver function. Furthermore, the neuronal insulin level is determined by the rate at which it crosses the blood-brain barrier (BBB) via a saturable (receptor-mediated) transport and diffusion mechanism located outside of the BBB.[10]

Insulin primarily affects peripheral tissues like muscle, adipose tissue, and liver. Furthermore, it has been discovered that peripheral insulin can reach the brain via a receptor-mediated transport pathway found in the blood-brain barrier.[12] When its receptor is activated, it causes phosphorylation and activation of the AKT and ERK pathways, resulting in the mobilization of the glucose transporter 4 (GLUT4) to the cell membrane and increased glucose uptake by these cells. However, it predominantly stimulates the insulin-insensitive glucose transporters GLUT1 (in astrocytes and blood-brain barrier endothelial cells) and GLUT3 (in glial cells and neurons).[13] Moreover, insulin and its receptors have also been implicated in neurite outgrowth and axon guidance via the P13K/AKT signaling pathway activation. It plays a critical role in learning and memory, reproduction, neuron development and maturation, and energy balance via controlling the brain's neuromodulator, neurotrophic, and neuroprotective activities.[14] It strongly influences the hypothalamus, inhibiting glucose release from the liver. Insulin binds to its receptors in many brain regions throughout the central nervous system, including the cortex, olfactory bulb, hypothalamus, cerebellum, and hippocampus (CNS).[15] Previously, it was considered that irregularities in the molecular signaling pathway of insulin played a crucial role in Alzheimer's disease etiology. As a result, intracellular pathways like PI3K, JNK, and MAPK are activated. Along with it, insulin interacts with its receptor, causing autophosphorylation of key tyrosine residues in the beta subunit, some of which are detected by the Src homology two domain of the PI3K regulatory subunit p85 (SH2 domain)[16] (Figure 1).

GLP-1 (glucagon-like peptide-1) is a gastrointestinal hormone secreted by intestinal L cells in response to food intake. GLP-1 regulates blood glucose levels by increasing glucose-dependent insulin secretion, reducing glucagon secretion, delaying gastric emptying, and decreasing food intake.[17] The GLP-1 receptor (GLP-1R) in type 2 diabetes is responsible for activating adenylyl cyclase (AC) to produce cAMP and protein kinase A (PKA) to phosphorylate and activate CREB.[18] It expresses a nuclear transcription factor (CREB) in a constitutively active state that regulates the expression of genes involved in neuronal survival and function. These drugs were designed, and FDA approved for diabetes treatment in 2005 and discoveries of their neurotrophic properties were made in the early 2000s.[19] In a previous study, GLP-1 agonists are beneficial in CNS diseases, including Parkinson's disease. Astrocyte cultured AGEs produce oxidative stress and cytokines. Astrocytes were considered because they produce GLP-1, GLP-1R and pro-inflammatory cytokines like TNF, which contribute to neuronal damage and the formation of Alzheimer's disease lesions.[17]

According to our findings, a GLP-1 receptor analogue (Liraglutide) inhibited AGE-mediated ROS generation, inflammatory cytokine secretion, caspase activation, and cell death by involving GLP-1R signaling via cAMP/PKA.[18]

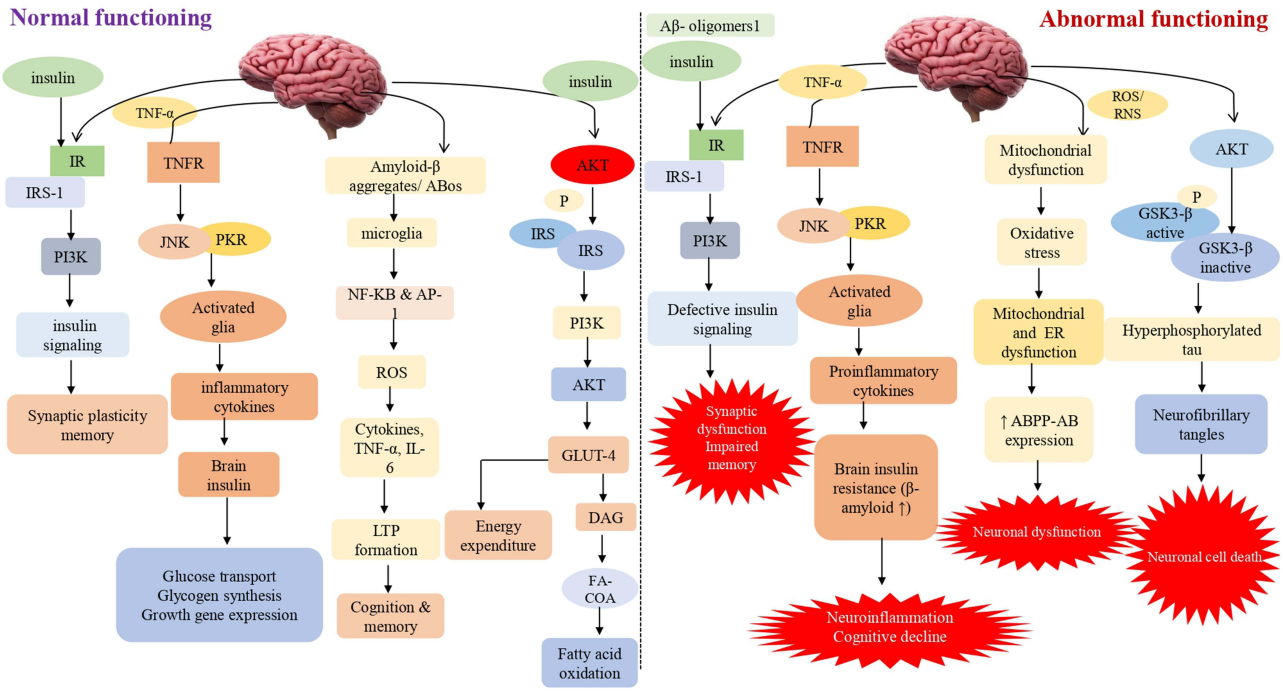

Figure 1 Impaired insulin signaling/ secretion involved in the progression of dementia This schematic diagram depicts both normal and abnormal insulin signaling in the brain. Insulin activates signaling pathways such as AKT, PI3K, JNK, NF-KB, GLUT4 and GSK3. Synaptic plasticity and memory are both linked to the PI3K pathway. The PI3K pathway is linked to synaptic plasticity and memory. As a result, aberrant insulin binding can cause neuroinflammation by activating proinflammatory cytokines and lowering cognitive capacities via JNK and NF-KB. Long-term memory loss is caused by oxidative stress, mitochondrial dysfunction, and inflammation caused by GSK3 and its hyperphosphorylation. It also elevates the expression of caspase-3 and 9, which ultimately leads to neuronal cell death.

The GLP-1 analogue cross the blood-brain barrier and exerts its anti-inflammatory and neuroprotective action. Research studies suggest these agents reduces amyloid plaque deposition in a mouse model of Alzheimer's disease and are currently being tested in clinical trials in Alzheimer's patients. Earlier, we investigated the effect of GLP-1 activators in diabetes, but recent studies suggest its therapeutic effect in treating neurodegenerative diseases.[20]

Throughout this article, we will explore the physiological and pathological effects of dementia and other neurodegenerative diseases on insulin signaling. Research into GLP-1 activators and their potential role in various neurodegenerative disorders has revealed some remarkable outcomes.

Impaired Insulin Signaling in the Progression of Dementia and Related Neurocomplications

Role of Amyloid-Beta Deposition

Dementia was first described in the second decade of the twentieth century but was not associated with high incidence or mortality rates. Most professionals are familiar with dementia symptoms and the functional decline that coincides with the restrictions placed on these patients' daily activities. According to various studies, Alzheimer's disease is the most prevalent type of dementia.[21] The most frequently discovered neuropathological entities are beta-amyloid plaques, extracellular complexes of the beta-amyloid (Aβ) peptide, and intracellular neurofibrillary tangles, composed of hyperphosphorylated tau protein.[22] Considering the symptoms, most healthcare professionals are unaware of the connection between dementia, Alzheimer's disease, insulin receptor function, and signaling pathway dysfunction. Dementia is classified as sporadic or familial. The most common type appears to be sporadic dementia, caused by environmental and genetic factors. The APO E gene is one of the most similar intrinsic risk factors. On the other hand, the rare and sporadic form of AD is caused by a mutation in the amyloid precursor protein (APP), presenilin 1 (PSEN1), or presenilin 2 (PSEN2) (PSEN2).[23] Alternate APP cleavage, which results in insoluble amyloid-beta (Aβ) fibrils, is one of the pathogenic processes underlying dementia. Synaptic signaling gets disrupted when Aβ fibrils infiltrate into synaptic

clefts. When oligo polymerizes and clumps, plaques are formed.[24,25] A40 and A42 are two types of Aβ polymers that play a significant role in the pathogenesis of dementia. Accumulation of A40/A42 disrupts ion channel function, alters calcium homeostasis, increases mitochondrial oxidative stress, impairs energy metabolism, and disrupts glucose homeostasis, all of which contribute to neuronal integrity degradation and cell death[26] (Figure 2).

Another pathogenic mechanism underlying dementia progression is hyperphosphorylation of Tau proteins. Tau protein aids in the organisation of microtubules, making them more stable. Hyperphosphorylated tau proteins form paired helical filaments, a critical component of neurofibrillary tangles.[27–29]

Memory loss is the primary symptom for the majority of people. Memory loss can occur either before or concurrently with the onset of cognitive impairment. Later in the disease's course, patients may develop executive dysfunction and visuospatial impairment. These flaws create covertly.[30] Dementia is a type of memory loss distinct from other types of memory loss. In most patients, semantic and episodic memory is impaired, particularly recollection of recent events, dependent on the hippocampus and other medial temporal lobe components. The subcortical system is involved in procedural memory and motor coordination and is not affected until late in the disease.[31–34]

Insulin receptors are abundant in astrocytes and neuronal synapses of the cerebral cortex, hippocampus, olfactory bulb, hypothalamus, septum, and amygdala. In this case, insulin signaling is involved in synaptogenesis and synaptic remodelling. In addition to its immediate effects on the specific receptor, insulin has additional neuromodulatory effects that affect intellectual ability.[35] Insulin, for instance, insulin may enhance the generation of long-term excitability, which is considered a necessary biological substrate for memory consolidation, by modulating the expression of the N-methyl-D-aspartate receptor on cell membranes. Insulin also regulates acetylcholine and norepinephrine, which is associated with memory.[36] Insulin may also enhance cortical cerebral glucose metabolism in areas of the brain associated with

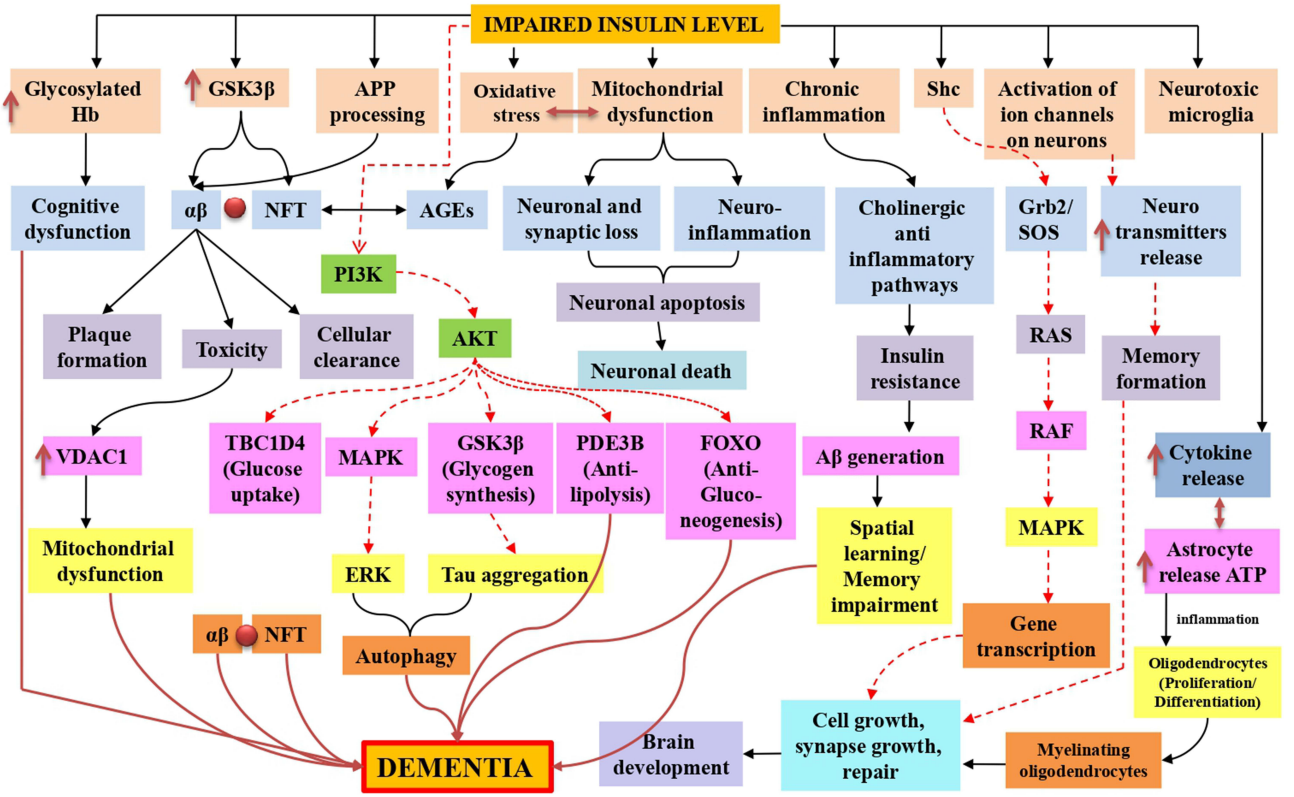

Figure 2 Insulin resistance in dementia is represented schematically by mitochondrial dysfunction, which leads to synaptic damage and neurodegeneration, glycosylated haemoglobin in intoxicated cognitive function due to failure in glucose transport for neurons, oxidative stress-induced amyloid beta and phosphorylated tau lineups via advanced glycation end products, inflammation caused by mitochondrial dysfunction and toxicities of amyloid-beta and glycation end products. Additionally, in both normal and impaired insulin signaling, Tau hyperphosphorylation was also observed, stimulates AKT, and inhibits tau hyperphosphorylation by inactivating GSK-3. Furthermore, the TOR pathway was also active for cellular growth and kept autophagy at a low level for cellular function. Black normal flow lines represent normal working mechanism; dotted red lines show inhibition of the pathway, and normal dark red flow lines show the overall cause of dementia.

cognition and memory. Given insulin's multiple effects on specific brain regions, including those in the medial temporal lobe associated with memory and learning, it's unsurprising that evidence linking insulin to cognitive performance is progressing.[37] Preclinical and clinical studies state that insulin treatment improves cognition.[37,38] By contrast, Aβ regulates insulin transmission in the brain. In preparations of mouse hippocampus slices, soluble Aβ adheres to the insulin receptor, impairing its signaling ability and inducing long-term potentiation.[38] These adverse effects were avoided by insulin pretreatment to the tissues before exposure to Aβ.

Synthetic soluble Aβ oligomers cause synaptic spine atrophy in primary hippocampal cultured neurons by inhibiting plasma membrane insulin receptors. Additionally, pretreatment with insulin was effective in reversing this.[39] Synaptotoxic effects are another mechanism by which insulin and Aβ may work together to modify disease. The absence of synapses is the first structural flaw that becomes apparent. Insulin inhibits the attachment of Aβ to synapses, thereby preserving synaptic stability. Soluble oligomeric forms of Aβ are synaptotoxic. Insulin also inhibits oligomer formation, which appears to have significant protective effects; one operational consequence seems to be protection against Aβ-induced loss of long term potentiation stability.[40] A process of synaptic remodelling suspected to be involved in memory consolidation.[40,41]

Tau Hyperphosphorylation in Dementia

Intraneuronal neurofibrillary tangles (NFTs) are composed of helical strands of hyperphosphorylated tau protein-coupled together. Hyperphosphorylation of tau results in aggregation, which results in the production of NFTs and neurodegeneration.[42] The primary risk factor for dementia is increasing age.[43] Other common disorders associated with ageing include diabetes mellitus, impaired glucose tolerance, insulin resistance, and a decline in pancreatic endocrine activity and insulin secretion. Insulin signaling may also play a role in regulating longevity and brain ageing. Compared to age-matched controls, patients with memory impairment had lower CSF insulin, impaired insulin-like signal transduction, insufficient brain insulin and insulin-like growth factor I expression and function,[44] and impaired glucose metabolism. Insulin may also act as a neurotrophic and regulatory peptide in the human brain by regulating tau phosphorylation in neuronal cells.[45] (Figure 2). Returning the mice to normothermia partially alleviated this massive hyperphosphorylation, indicating that it is primarily caused by hypothermia and not just associated with it. On the other hand, insulin treatment of diabetic rats completely restored tau phosphorylation to normal levels, demonstrating that a lack of insulin resulted in moderate hyperphosphorylation.[46] It has been postulated that tau hyperphosphorylation occurred via kinase and/or phosphatase dysregulation, which causes aggregation and hinders attachment to microtubules, disrupting the microtubule network in dementia.[47] In vitro, hyperphosphorylation of human tau causes microtubule disruption and tau aggregation leading to dementia-like symptoms.[48,49]

Genetic Alteration in Dementia

Insulin resistance and insulin disintegrating enzymes are increasingly implicated in the pathogenesis of dementia, associated neuronal cytoskeletal abnormalities and Aβ deposits in the brain. Reports demonstrating reduced brain growth and increased tau phosphorylation in animals lacking either the insulin receptor substrate-2 or the neuronal insulin receptor gene have driven this fresh wave of curiosity.[50,54] Insulin, IGF-I, and IGF-II peptides and receptors are all highly expressed in the brain. Dementia is associated with significant decreases in insulin and IGF-I mRNA expression and downregulation of related receptors.[51, 52] Furthermore, it was discovered that genes encoding oxidative phosphorylation system subunits were differentially expressed in dementia patients, implying that mtDNA abnormalities may be responsible for the phenotypic variability.[53] The correlation established between mtDNA mutations and the degree of nucleic acid injury in the cytoplasm,[54] implying a possible link between neuronal oxidative damage and chromosomal defects, supports the idea that aberrant insulin contributes to genetic abnormalities.[55] Dementia has also been linked to several hereditary factors. The APO E e4 allele expression has been shown to increase the risk of developing the disease. APO E is a polymorphic protein encoded by three alleles on chromosome 19. It exists in three isoforms (apo e2, e3, and e4) that appears to increase the risk of sporadic or familial late-onset diabetes.

Moreover, mutations in the APP and presenilin (PS1 and PS2) genes have been linked with a small percentage of dementia cases.[56] In the recent decade, extensive cell biology research has suggested that mutations in these genes cause

dementia-like illness via a shared biological mechanism, culminating in aberrant Amyloid precursor protein (APP) metabolism.[56] Recently, transgenic mice were used to assess the effects of the mutations listed above in vivo. Excessive expression of mutant dementia-related proteins in animals exhibits many neuropathological and behavioural characteristics as in humans. Transgenic animals with mutations in APP, PS1, and PS2 genes have been developed. These mutations are associated with the stimulation of astrocytes and microglial cells in the hippocampus and cerebral cortex.[57] Additionally, animal models of Alzheimer's disease-related dementia have been used to develop and test drugs that decrease Ab 42 peptide[57] concentrations in the brain, thereby advancing the development of novel therapeutic techniques.[58]

Cholinergic Dysfunction in Dementia

Dementia is strongly intertwined with degenerative and functional diseases of the central nervous system, resulting in various neurochemical, neurophysiological, and anatomical abnormalities.[59] Dementia patients were found to have lower test scores for memory, cognitive flexibility, fast data processing, and psychomotor efficacy.[60] The link between poor insulin and the CNS greatly increases the risk of memory loss.[59] Impaired glucose and energy metabolism[61] hyperglycemia,[62] reduced insulin sensitivity,[44] insulin resistance and insulin/insulin receptor dysfunction,[63] changes in hippocampal synaptic plasticity and transmission,[64] increased advanced glycation end products (AGE) that cause memory dysfunction in dementia-like conditions,[65] Poor insulin caused memory loss in rats, which was linked to increased cholinergic activity and oxidative stress, leading to dementia.[66] Insulin resistance causes cognitive impairment in type 2 diabetes. A PPAR-c agonist has recently been linked to memory loss. Glucotoxicity is reported to be exerted by increased intracellular glucose oxidation in neurons.[67] Insulin resistance causes cognitive issues in type 2 diabetes.

A PPAR-γ agonist has recently been linked to memory loss. It was also observed that glucotoxicity is caused by increased intracellular glucose oxidation in neurons.[67] Oxidative damage to the rat hippocampus synapse has been linked to cognitive deficits.[68] Cholinergic neurotransmission is the central process governing mental performance. In the nucleus basalis magnocellularis, cholinergic basal forebrain neurons innervate the cerebral cortex, amygdaloid complex, and hippocampus, required for cognitive and memory consolidation.[70] The enzyme ChE is involved in one of the most critical pathways necessary for proper cholinergic function. Also, the hippocampus and cortex are innervated by cholinergic projections.[68] Cholinergic abnormalities result in insufficient processing in the hippocampus area.

Furthermore, it has been discovered that cholinergic transmission is linked to recollection and cue perception.[69] Due to the critical role of acetylcholinesterase in inhibiting acetylcholine-induced responses, using an acetylcholinesterase inhibitor may aid in memory.[70] Numerous studies have linked increased ChE activity in the brain to cognitive deficits.[69]

Cognitive stimulation requires cholinergic stimulation from the nucleus basalis of Meynert (NBM).[69,70] The deterioration of the NBM in dementia contributes to the cognitive impairment observed in dementia patients. The activity of choline acetyltransferase (ChAT) is significantly decreased in patients with the same severity of dementia, primarily in the neocortex. In other parts of the brain, there is less atrophy and neuronal dysfunction but more cholinergic loss.[71,72] These findings are critical for elucidating the etiology of dementia and developing the most effective pharmacologic treatment strategy.

Neurotransmitters Dysfunction in Dementia

Alzheimer's disease and senile dementia are associated with abnormal neurotransmitter levels in the brain.[73] Because neurotransmitters have both excitatory and inhibitory effects in the brain, the proper balance of messenger types may be as critical as the total number of transmitters. Alzheimer's disease and senile dementia are associated with abnormal neurotransmitter levels in the brain.[73] Since neurotransmitters have both excitatory and inhibitory effects in the brain, the proper balance of messenger types may be as critical as the total number of transmitters. With increasing age, people naturally experience reduced transmitter generation and discharge, contributing to the mild forgetfulness associated with old age. Pathologies linked to inadequate insulin have been proposed as a probable cause of cognitive impairment due to neuron loss and long-term brain damage caused.[74,75] Glucose synthesises neurotransmitters and serves as the brain's primary energy source.[76] Glucose is required for the amino-acid cycle, cortical neurons, and synaptosomes to function correctly.

In the brain, mitochondrial function is associated with synthesising and eliminating neurotransmitters. Because glutamate is the primary excitatory neurotransmitter in the brain[77] and a direct precursor of the inhibitory neurotransmitter g-aminobutyric acid, mitochondria are connected to glutamate regulation (GABA).[78] Glutamate is required for synaptic communication, but it must be cleared from the extracellular space as soon as active synapses release it to avoid unnecessary stimulation of its receptors, which could result in excitotoxicity.[77] Recent evidence suggests that glutamate may contribute to the pathogenesis of various neurodegenerative diseases, including dementia and Alzheimer's disease.[79] Aspartate, like glutamate, is a major excitatory neurotransmitter in the brain that plays a critical role in converting brain energy.[80] Insulin-induced hypoglycemia increases extracellular aspartate levels while decreasing glutamate and glutamine levels throughout the brain and in specific brain regions such as the hippocampus and striatum. Others discovered a significant increase in aspartate's extracellular level in the hippocampus and striatum, as well as a minor increase in glutamate and GABA. Due to their excitotoxic properties at higher extracellular concentrations, glutamate and aspartate have been implicated in the neuronal injury that occurs in the brain following a hypoglycemic episode. Numerous studies on neurotransmitter abnormalities in dementia have been conducted over the last twenty years, resulting in a better understanding of the relationship between neurotransmitter irregularities and dementia.[81–83] According to studies, decreased neurotransmitter activity does not always correlate with the severity of Lewy body pathology.[84] Neurotransmitter synthesis modifications occur early in the disease process in several brain areas affected by dementia, implying that axonal transport fidelity is compromised before the apparent neuronal loss.

Numerous muscarinic receptors regulate the excitation and suppression of acetylcholine (ACh) discharge by the presynaptic neuron. Notably, the presence of multiple muscarinic receptor subtypes on the post-synaptic cell can result in a complicated reflex in the post-synaptic neuron in response to the presynaptic cell's release of Ach. Nicotine has a long history of being associated with memory and learning, as well as having a beneficial effect on attentiveness and alertness.[84–87] When nicotinic receptors on presynaptic cells are stimulated, ACh and other neurotransmitters involved in cognition and behaviour are released.[88] The 4ß2 receptors are the most abundant high-affinity receptors in the central nervous system (CNS), whereas the homomeric seven receptors have a low affinity. Based on high-affinity nicotine binding in the brain, individuals with dementia were compared.[84,89] Nicotine adherence is significantly reduced in the substantia nigra. Dementia patients demonstrated significant neuronal loss. This indicates that, as is the case in other brain areas, the loss of cholinergic activity in the substantia nigra precedes the degradation and loss of neurons in dementia. Interestingly, the parahippocampal gyrus region with the highest LB density did not correspond to the region with tremendous loss of nicotinic receptor in dementia. Individuals with significant receptor loss in the edentulous granular area may experience cognitive impairment.[85,90]

Neuronal Apoptosis in Dementia

Apoptosis occurs in the absence of insulin and as a long-term consequence of diabetes. It has been linked to type 1 diabetes,[91] diabetic retinopathy,[92] and nephropathy.[93] On the other hand, apoptosis has been associated with various neurological disorders, including dementia, Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis (ALS).[94] (Figure 2). Numerous studies have discovered neuronal death in the hippocampus of type 1 diabetic rats, which is associated with cognitive deficits and previous IGF system disturbances. Only in 8-month diabetic rats was the unique ladder configuration of genomic DNA discovered. It was associated with an increased Bax/Bcl-x ratio, L caspase-3 activity, and hippocampal neuronal death. These defects were not observed in 2-month diabetic rats, indicating that neuronal death occurs only following an extended period of insulin deficiency. Ischemia with intracytoplasmic calcium deposition and mitochondrial dysfunction,[95] receptor-mediated or non-receptor-mediated processes, or decreased IGF activity are all examples of biological mechanisms that could result in neural cell apoptosis.[96] Purkinje cell death in pcd mice is associated with decreased IGF-I expression.[97] Reduced IGF activity may contribute to CNS disorders in streptozotocin-induced diabetic rats.[98] According to a recent study, dementia patients' vulnerable hippocampus areas have decreased IGF-I, IGF-IR, and IR activity.[100] In addition, studies demonstrate that insulin resistance occurs before the onset of apoptosis.[99]

Cerebral blood vessel dysfunction compromises the function of capillaries, arterioles, and venules, as well as myelinated axons. Disruption of myelin and axons results in abnormalities in the white matter, which contributes to the pathophysiology

of vascular dementia.[100] Arterial blockade and lesions in the cortex, basal ganglia, pons, lacunar infarctions in the white matter, disrupted tight endothelial junctions, and BBB degradation appears to be significant pathologic features that impair normal cerebroarterial blood flow.[101] Ependymal leaking, disturbed interstitial fluid flow, vasogenic perivenular white matter enlargement and abscesses, and A dispersion and accumulation along perivascular gaps contribute to increased apoptosis and vascularisation resistance in dementia. Ischemic infarction and vascular dementia are caused by a lack of oxygen in specific brain areas, resulting in axonal damage, apoptotic neuronal cell death, and ultimately neurodegeneration.[102] Indeed, cortical neuronal apoptosis is known to occur following white matter axonal loss caused by the breakdown of afferent nerve cell synapses or regressive neuronal degradation.[103] There is a strong correlation between neuronal apoptosis and pyramidal neuron death, as evidenced by the increased caspase-3 expression upon stimulation. It results in discrete subcortical protuberances in the layers III–IV of the cerebral cortex and proximal white matter metastases and neuropathies in subcortical fibres.[104] Cortical apoptosis has also been associated with vascular injury, as evidenced by vacuolar atrophy, dark pyknotic nuclei, and micro-infarcts. It damaged the white matter, which eventually manifested as memory loss and dementia.[105] Neurodegeneration is caused by two processes: neural apoptosis and vascular injury. They are defined by program rather than incremental cell death. Anti-apoptotic drugs were critical in masking the functionalities or progression of neuronal apoptosis and vascular damage in vascular dementia, particularly in subcortical ischemic vascular disorders, where anti-apoptotic drugs were essential in masking the functionalities or progression of neuronal apoptosis and endothelial damage.[103,106]

Neuronal Excitation Dysfunction

In response to an increase in extracellular glucose, a subset of neurons in the brain known as "glucose-excited" neurons depolarize and increase their activation level, potentially leading to poor insulin signaling.[107] Glucose has been shown to activate POMC neurons in the hypothalamic arcuate nucleus.[110] Stimulation is thought to cause cognitive deficits such as dementia and Alzheimer's disease by ATP-induced shutdown of KATP channels in the plasma membrane.[107–109] Various studies have established a critical role for neurovascular dysfunction in vascular cognitive decline and other types of dementia, including Alzheimer's disease.[111] Ischemia and neurodegenerative disease co-occurring have been shown to alter the development of clinical symptoms of dementia, implying reciprocal interactions between them.[112] Cerebrovascular diseases, dementia, and Alzheimer's disease all share common risk factors, suggesting that vascular factors may play a role in the pathogenesis of the disease.[113,114] The neurovascular unit comprises endothelial cells, myocytes, neurons and their processes, astrocytes, and perivascular cells. This unit modulates cerebral blood flow, blood-brain barrier (BBB) exchange, immunological monitoring, trophic assistance, and hemostatic balance. The morphological and physiological interrelationships of the neurovascular unit are critical for brain homeostasis, as evidenced by the neurovascular unit's severe impairment in dementia.[113,115]

Alterations in insulin-associated inflammation, aberrant endoplasmic reticulum-stress modulation, excitotoxicity, and lipotoxicity have all been identified as possible biochemical mechanisms of insulin resistance. The direct consequences of insulin resistance in peripheral tissues such as the brain, liver, skeletal muscle, and adipose tissue have received considerable attention.[116] Numerous extra-hypothalamic nuclei, such as sensory and cognitive units in the hindbrain[117,118] and autonomic, parasympathetic, and sympathetic preganglionic brainstem neurons, are also included in the control centres of the brain.[119,120]

Severe distortions of hormonal and nutritional signaling in pro-opiomelanocortin, neuropeptide Y, and agouti-related peptide neurons (ARPN) influence insulin metabolic activity in peripheral tissues directly through their ability to incorporate ancillary signals and adjust their electrical activity in response to resource consumption.[121,122] After abruptly increasing insulin levels in the circulation using cell-specific excitatory methods, it was discovered that acute stimulation of ARPN neurons impairs systemic glucose tolerance and insulin intolerance. Following ARPN neuron excitation, transient stimulation decreased sympathetic nerve function supporting brown adipose tissues, and decreased -adrenergic activity resulted in systemic insulin resistance, which may be associated with dementia-like symptoms.[123]

Failure of Mitochondria Leading to Impaired Energy in Dementia

Numerous abnormalities associated with insulin resistance have been proposed to contribute to the detrimental effects of severe diabetes-related dementia.[124,125] Additionally, increased renin-angiotensin system activity is associated with the

development of insulin resistance, a fundamental characteristic of the cardiometabolic syndrome that is increasingly believed to be a nexus linking the syndrome.[126,127] Numerous abnormalities associated with insulin resistance have been proposed to contribute to the detrimental effects of severe diabetes-related dementia.[124,125] Additionally, increased renin-angiotensin system activity is associated with the development of insulin resistance, a fundamental characteristic of the cardiometabolic syndrome that is increasingly believed to be a nexus linking the syndrome.[126,127] Metabolic stability predominately depends on mitochondria, which metabolises nutrients and generates ATP and heat to maintain energy balance. Mitochondrial dysfunction is defined by a decreased energy production ratio (ATP synthesis) to respiration due to an energy intake-expenditure imbalance.[128,129] Exercise, food, ageing, and anxiety affect mitochondrial performance and insulin sensitivity.[130,131] Significantly, mitochondrial dysfunction has been associated with insulin resistance in skeletal muscle,[132–134] and other tissues such as the liver, fat, heart, blood vessels, and pancreas.[135–137] Insulin resistance, caused partly by mitochondrial dysfunction, may thus contribute to the pathophysiology of a wide variety of chronic diseases. Mitochondrial function can be influenced by genetic factors, oxidative stress, mitochondrial biogenesis, and ageing, contributing to insulin resistance and other pathological conditions (Figure 2).

Mitochondrial dysfunction is frequently observed in patients suffering from dementia.[138,139] Deficiencies in mitochondrial oxidative phosphorylation, specifically complex IV, have been found in brain tissue, platelets, and cell lines (cytochrome c oxidase or COX).[140] Moreover, the AAβ peptide has been shown to enter the mitochondria and inhibit COX and L-3-hydroxy acyl-coenzyme Q dehydrogenase. The inhibition of these enzymes accelerates the formation of reactive oxygen species (ROS) in mitochondria.[141,142] Similarly, it has been discovered that a neuron-specific protease cleaves the ApoE 4 protein, with the resulting peptides entering the mitochondrion, inhibiting oxidative phosphorylation and thus increasing ROS generation, resulting in dementia-like symptoms.[143,144]

Progressive Dementia Due to Microglial Overactivation

Insulin resistance is a significant risk factor for cognitive impairment and dementia in the periphery.[145] Insulin affects the performance and lifespan of neurons.[146] As a result, it is critical for learning and memory and regulating mechanisms associated with ageing.[146] Physiological insulin contributes to the removal of beta-amyloid (A) protein, the primary cause of neurodegeneration and memory loss.[147] Microglia cells, immune cells in the central nervous system, are activated by AAβ protein and cluster around or penetrate neuritic plaques, releasing neurotoxins and aggravating the neuronal injury. In particular, elevated brain insulin levels result in the formation of Aβ plaque, which stimulates microglia, produces numerous inflammatory mediators, and eventually results in memory loss and dementia.[147] As a result, medications that inhibit activated microglia and Aβ protein synthesis may be potential treatments options for individuals with cognitive impairment associated with insulin resistance (Figure 2).

When advanced glycated end products (AGEs) bind to their receptors, reactive oxygen species (ROS) are generated, resulting in cell death.[148] Yang et al discovered that diabetic mice with cognitive impairment had increased activation of AGEs receptors in neurons and glia.[149] It has been suggested that GLP-1 analogues inhibit the expression of the AGE receptor, which could be used to mitigate the effect of AGEs on neuronal cell death.[150] This study examined microglia, a critical regulator of the Aβ protein in the cell. Pioglitazone and exenatide treatment inhibited microglia activity in the hippocampus. Others validated microglia's protective role in Alzheimer's disease, claiming that Aβ protein stimulates microglia, causing them to release pro-inflammatory cytokines and reactive oxygen species, thereby inducing apoptosis and neuronal injury.[151,152] Astrogliosis and microglial stimulation demonstrate that neuroinflammation is a pathogenic feature associated with plaque and tangle formation.[153,154] In ICV-STZ-treated rats, astrocytes and microglia are activated as well.[155] As a result, targeting the brain insulin signaling pathway as a potential therapeutic option for dementia treatment has emerged.[156,157] Insulin intranasal administration for six weeks restored spatial memory in ICV-STZ mice, decreased tau pathology and microglial activation, and increased hippocampus neurogenesis. These findings establish a molecular basis for treating dementia with intranasal insulin. Additionally, as evidenced by astrogliosis and microglia, dementia is associated with neuroinflammation. Prolonged stimulation of these glial cells results in the production of inflammatory mediators, which contribute to the development of dementia.[158] Due to impaired insulin signaling, activated microglia and astrocytes are visible in post-mortem brains, both preclinically and medically.[159]

Inflammation of Neural Cells in Dementia

Inflammation in the brain can result in an insulin-resistant state linked to the etiology and pathogenesis of dementia.[160,161] Other common dementia symptoms include protein complexes,[162] mitochondrial dysregulation,[163] oxidative stress,[164] neuroinflammation,[165] brain cholinergic impairments,[166] and adult neurogenesis disorder.[167] The subventricular zone of the lateral ventricles and the subgranular zone of the hippocampus's dentate gyrus are two neurogenic regions in the central nervous system where the resident neural stem and progenitor cells proliferate. Numerous endogenous and environmental factors can affect the adult neurogenesis process. Growth factors and neurotrophins, such as brain-derived neurotrophic factor (BDNF), stimulate neurogenesis by enhancing the differentiation, development, and lifespan of replicating NSC/NPC.

On the other hand, it has been demonstrated that microglial stimulation and the production of proinflammatory cytokines (eg, interleukin-1, IL-6, and tumour necrosis factor) inhibit neurogenesis by inhibiting NSC/NPC development. Prohibition results in cognitive deficits, as evidenced by difficulties with spatial and recognition memory and learning[168] (Figure 2).

STZ dementia type models have shown an increase in neuroinflammation characterised by reactive gliosis and an increase in proinflammatory markers linked to cognitive impairment.[155,169–171] In other studies, neurogenesis has been associated with oxidative stress[172] and amyloid pathology.[173] Acute and chronic neuroinflammation can impair several stages of adult neurogenesis in the mammalian brain, including proliferation, differentiation, and survival of newborn neurons. Adult neurogenesis is damaged in various neurodegenerative diseases, with neuroinflammation as a characteristic symptom.[174] STZ dementia type models have shown an increase in neuroinflammation characterised by reactive gliosis and an increase in proinflammatory markers linked to cognitive impairment.[155,169–171] In other studies, neurogenesis has been associated with oxidative stress[172] and amyloid pathology.[173] Acute and chronic neuroinflammation can impair several stages of adult neurogenesis in the mammalian brain, including proliferation, differentiation, and survival of newborn neurons. Adult neurogenesis is damaged in various neurodegenerative diseases, with neuroinflammation as a characteristic symptom.[174] An investigation found a significant inflammatory response in the periventricular regions and the hippocampus of STZ-ICV rats, evidenced by increased immunoreactivity for Iba-1 (microglial marker) and GFAP (astrocytes markers). An extreme inflammatory response was found to be triggered by STZ, which is thought to be involved in inhibiting neuron growth and differentiation.[175]

After conducting a systematic review of the literature, another research identified 28 studies that used in vivo neuroimaging to assess one or more indicators of neuroinflammation in dementia patients. Most research used PET imaging to detect increased neuroinflammation in at least one neuroanatomical location in dementia patients, most frequently AD.[176] For summary object recognition, another study employed oral extended curcumin therapy. The examined curcumin doses resulted in a slight improvement in neuroinflammation, resulting in a modest restoration of hippocampal and subventricular neurogenesis. These findings suggest that curcumin may improve object recognition recall in dementia patients. Additional research is needed to determine the efficacy of neuroinflammation treatment in dementia, particularly in models of the disease's early stages.[175]

Role of Oxidative Stress in Dysregulated Insulin Linked Dementia

Dementia has been linked to insulin receptors in the brain, which are found in abundance in the hippocampus and other parts of the cerebral cortex and are crucial for memory.[63] The degeneration of brain insulin receptors have been linked to the aetiology of degenerative brain diseases such as dementia. Desensitization of the insulin receptor has resulted in decreased energy metabolism and acetyl CoA production, resulting in cholinergic insufficiency.[62] Increased generation of free radicals may result from neurons' insufficient energy consumption.[177,178] Reduced glucose metabolism in the brain reduces the release of acetylcholine from the cortex, which may cause cognitive decline.[179] STZ treatment in the rat brain results in severe abnormalities in metabolic pathways regulated by the IR signaling cascade.[180] Studies have shown that STZ injection causes low cerebral energy metabolism, which results in memory impairment, as evidenced by decreased choline acetyltransferase (ChAT) activity in the hippocampus and enhanced acetyl-CoA synthesis in the rat brain, which results in a cholinergic deficiency.[181] To improve cholinergic function and thus alleviate symptoms of dementia, it is essential to inhibit the AChE enzyme. Increasing evidence has shown that free radicals can cause neuronal degeneration,

emphasising the need for antioxidants to treat neurodegenerative illnesses. Poor insulin signaling has been linked to increased oxidative stress[182] and mitochondrial dysfunction in brain cells, which have been linked to dementia (Figure 2).[183–185]

IRs have been shown to play a role in cognition and interact with the cholinergic system and oxidative stress. In a rat dementia model, the researchers used ICV STZ to estimate IR protein levels, AChE action as a marker of cholinergic activity, and oxidative stress markers (MDA and GSH) in various parts of the rat brain. Acyl CoA, glutamate, and ATP are essential for proper neuron construction and performance when brain insulin regulates glycogen breakdown via IR. Acetyl CoA is a critical component of acetylcholine synthesis and plays a role in memory and learning. The alkylating activities of STZ metabolites produce reactive oxygen species (ROS), which cause oxidative stress and DNA damage.[179]

Oxidative stress markers, oxidised lipids and proteins, and ROS production all contribute to neurodegenerative diseases such as dementia and Alzheimer's disease. In the AD brain and patients with cognitive decline, enzymes involved in metabolic pathways such as glycolysis and the Krebs cycle are oxidised, implying that these changes occur early in dementia.[186–188] Cerebral glucose metabolism is disrupted due to these changes, resulting in decreased ATP synthesis, which contributes to neuronal dysfunction, synaptic loss, and general neurotoxicity.[186,190]

The early stages of the disease have been linked to decreased mitochondrial enzymatic activity and oxidative stress.[189] This could imply that the oxidative mechanisms resulting in ROS production occur before any significant accumulation of Aβ. However, in vitro studies show that the more neurotoxic Aβ oligomers can reduce cytochrome-oxidase function by increasing ROS production.[190] However, in dementia, Aβ-mediated mitochondrial dysfunction and ROS generation may initiate a vicious cycle, resulting in increased insulin signaling problems. Finally, numerous evidence and studies have established that altered insulin signaling may play a role in the malfunction and progression of dementia and related neurological problems (Table 1).

Potential Role of GLP-1 Signaling Activators in the Protection of Various Neurodegenerative Dysfunctions Associated with Dementia

A study discovered that liraglutide, a GLP-1 analogue, protected rats' brains from amyloid protein-induced impairments in spatial learning and memory, as well as a deficiency of late-phase long-term potentiation, and activated the cAMP signaling pathway.[218] After eight weeks of systemic liraglutide treatment, a consistent study demonstrated repair of cerebral and systemic microvascular architecture in seven-month-old APP/PS1 transgenic mice.[219] The clinical trial was conducted to determine whether long-acting intranasal insulin detemir, given for 21 days, improves cognition or daily functioning in individuals with amnestic mild cognitive impairment (MCI) or early-stage Alzheimer's dementia. Daily treatment with 40 IU intranasal detemir was associated with improved verbal memory in people with MCI and AD (APOE-£4 allele carriers) and with improved visuospatial and verbal working memory in all trial participants.[220]

A randomised, placebo-controlled, double-blind clinical study discovered that six months of treatment with liraglutide (a GLP-1 analogue) significantly reduces the formation of amyloid β plaques and the deterioration of the brain glucose metabolism in patients with Alzheimer's disease.[221]

Additionally, another study examined the effect of sitagliptin (a DPP-4 inhibitor that inhibits glucagon secretion and the degradation of GLP-1) on cognitive functions in elderly diabetic patients with and without cognitive impairment. The authors concluded that six months of sitagliptin treatment might improve cognitive function in elderly diabetic patients with or without Alzheimer's disease.[222]

A case-control study conducted in Germany discovered a link between antihyperglycemic medications and the incidence of dementia in type 2 diabetes patients. The study discovered that treatment with glitazone (a PPAR-agonist that activates the GLP-1 receptor) was associated with a decreased risk of dementia (odds ratio = 0.80). Additionally, metformin monotherapy (odds ratio = 0.71) or combination treatment with sulfonylurea derivatives (odds ratio = 0.90) was associated with a decreased risk of developing dementia later.[223]

A subsequent population-based cohort study in Korea examined the incidence of dementia in geriatric type 2 diabetes patients treated with dipeptidyl peptidase 4 (DPP-4) inhibitors and sulfonylurea. The study found that taking a DPP-4

Table 1 Impaired Insulin Signaling Dysfunction in the Progression of Dementia and Related Neurological Complications

S.No	Disease Model/ Condition	Study Type	Brain Area Affected	Factors Involved	Duration of Study	Key Findings	References
1.	Central and peripheral insulin resistance	Preclinical study Tg2576, 3xTg-AD mice, WT mice Age: 10- and 16-months-old	Brain homogenates, Cerebral cortex, Hippocampal tissue	↓IRS-1 expression, ↑Inhibitory Ser612 phosphorylation, ↓Phosphorylation of AKT at Thr308, ↑AKT phosphorylation at Ser473	16 months	↑Cognitive deficits, ↑Extracellular plaques deposition	[191]
2.	Hypoglycaemia	Clinical study Population-based cohort study Propensity-Score Matched Analysis Senior South Korean cohort 7752 T2DM patients who had ever experienced hypoglycaemia, matched cohort	Cerebral cortex	↑Risk for all-cause dementia (HR 1.254), ↑Risk for AD dementia (HR 1.264), ↑ Risk for VD (HR 1.286)	14 years	Patients with a history of hypoglycaemia have an↑risk for dementia, AD dementia and VD	[192]
3.	Insulin dysregulation and diabetes	Clinical study 233 subjects Ethnicity: older Catholic clergy Mean age: 86 years, 45% male participants	Cerebral region, Cortical region, Subcortical region	↑ Cortical infarction, ↑ Subcortical infarction, ↑Risk of dementia	6 years	Diabetes morbidity ↑ the probability to develop cerebral infarctions, compared to those without diabetes	[193]
4.	T2DM	Clinical study Population-based cohort 2574 Japanese-American men, Number of diabetic subjects=900,	Cortex, Hippocampus	↑Risk for total dementia (IRR=1.6), ↑VD risk (IRR=2.0)	2.9 years	T2DM↑risk factor for AD and VD	[194]
5.	Diabetes mellitus	Clinical study Longitudinal cohort study 824 Catholic participants Age:≥55 years	Pre-frontal cortex, Frontal lobe	↓Cognitive ability, ↑Rate of decline in perceptual speed	9 years	Diabetes mellitus may be associated with an ↑ risk of developing AD and may affect cognitive systems differentially	[195]

(*Continued*)

Table 1 (Continued).

S.No	Disease Model/ Condition	Study Type	Brain Area Affected	Factors Involved	Duration of Study	Key Findings	References
6.	Diabetes mellitus	Clinical study Prospective population-based cohort study 6370 elderly subjects, with diabetes mellitus	Pre-frontal area	↑Risk of dementia (HR 1.3 to 2.8), ↑Risk of AD (HR 1.2 to 3.1)	2.1 years	Diabetes may ↑ the pathogenesis of dementia	[196]
7.	Hyperinsulinemia	Clinical study Longitudinal, cohort analyses 683 elderly subjects, without prevalent dementia Age: ≥65 years	Cerebral cortex, Hippocampus, Amygdala	↑Risk of AD (HR = 2.1; 95% CI: 1.5, 2.9), ↑Decline in memory-related cognitive scores in neuropsychiatric tests	5.4 years	Hyperinsulinemia is associated with an↑ risk of AD and ↓ in memory	[197]
8.	Diabetes	Clinical study Longitudinal cohort study in older Canadians, 5574 subjects without cognitive impairment at baseline	Cerebrum	↑Incident VCI (RR: 1.62; 95% CI: 1.12–2.33) and its subtypes, ↑ Risk of VD (RR: 2.03; 95% CI: 1.15–3.57), ↑ Risk of VCI (RR: 1.68; 95% CI: 1.01–2.78)	5 years	Diabetes was associated with ↑incidence of VCI	[198]
9.	Abnormal insulin level	Clinical study 25 patients with AD (6 apolipoprotein E homozygotes, 19 non-homozygotes), 14 healthy age-matched adults	Blood plasma, Cerebrospinal fluid	↓CSF insulin concentrations, ↑ Plasma insulin levels, ↓Ratio of CSF insulin levels to true plasma insulin levels	2 years	↓CSF insulin concentration led to more advanced dementia ↑ Plasma insulin levels signified more advanced dementia	[199]
10.	Diabetes mellitus	Clinical study Longitudinal, cohort study Dementia-free cohort, 1301 Stockholm, Sweden community dwellers Age: ≥75 years	Cerebellum, Hippocampus	↑Risk of dementia (HR=1.5), ↑Risk of AD (HR=1.3), ↑Risk of VD (HR=2.6)	6 years	Diabetes mellitus ↑risk of dementia, and VD The risk for dementia and VD↑ when diabetes mellitus occurs together with severe systolic hypertension/heart diseases	[200]

(*Continued*)

Table 1 (Continued).

S.No	Disease Model/ Condition	Study Type	Brain Area Affected	Factors Involved	Duration of Study	Key Findings	References
11.	Diabetes	Clinical study Epidemiological study 1892 Jewish male civil servant cohort, Mean age: 82 years	Cerebral cortex, Hippocampus, Amygdala	↑Risk of dementia (HR=2.83, 95% CI= 1.40 to 5.71)	5 years	Diabetes in midlife ↑risk factor for dementia	[201]
12.	Severe hypoglycaemia	Clinical study Prospective study 302 diabetic patients, with a history of severe hypoglycaemia, Age: ≥70 years	Cerebellum, Hippocampus	↑Risk of dementia (HR= 3.00, 95% CI 1.06–8.48)	5 years	Hypoglycaemia ↑ risk factor for dementia and vice-versa	[202]
13.	Diabetes with impaired insulin secretion and impaired glucose tolerance	Clinical study Population-based Uppsala Longitudinal cohort study, 2322 adult male participants, Mean age: 50 years old	Hippocampus	↑Cumulative risk of AD (HR= 1.31; 95% CI, 1.10–1.56), ↑ Risk of VD (HR= 1.45; 95% CI, 1.05–2.00), ↑ Risk of any-dementia or cognitive impairment	32 years	Impaired acute insulin response at midlife was associated with an ↑ risk of AD dementia	[203]
14.	Hypoglycaemic episodes	Clinical study Longitudinal cohort study 16,667 patients, Mean age: 65 years Morbidity: T2DM, without prior diagnoses of dementia or MCI	Cerebral cortex	↑ Risk of dementia (HR: 1.72–3.01%)	4.8 years	A history of severe hypoglycaemic episodes was associated with an ↑risk of dementia	[204]
15.	Diabetes mellitus with hypoglycaemic episodes	Clinical study 15,404 diabetic subjects, without prior dementia Mean age: 64.2 years	CNS	↑ Incidence rate of dementia	7 years	Adult diabetic patients with prior hypoglycaemia had a significantly ↑risk of dementia.	[205]

(*Continued*)

Table 1 (Continued).

S.No	Disease Model/ Condition	Study Type	Brain Area Affected	Factors Involved	Duration of Study	Key Findings	References
16.	Hypoglycaemia	Clinical study Prospective population-based study 783 old adults with diabetes, Mean age: 74.0 years; Ethnicity: Black race, 47.6% females	Hippocampus	↓Cognitive performance, ↑Risk for developing dementia in hypoglycaemic event (34.4% multivariate-adjusted HR= 2.1; 95% CI)	12 years	A bidirectional association occurs between hypoglycaemia and dementia in older adults with diabetes mellitus	[206]
17.	Hypoglycaemia	Clinical study Prospective observational Koreanstudy National Diabetes Program cohort, 4540 participants, Age: ≥60 years, without any history of hypoglycaemia or cognitive dysfunction	Hippocampus	↑Incidence of dementia (HR= 2.689; 95% CI, 1.080–6.694)	3.4 years	Hypoglycaemia significantly ↑the risk of dementia in Korean elderly patients	[207]
18.	Diabetes with hypoglycaemia	Clinical study Retrospective longitudinal cohort study, Age >65 years, diagnosed with T2DM, with no prior diagnosis of dementia	Cerebral cortex	↑Risk with the number of hypoglycemia episodes: one episode (HR = 1.26; 95% CI = 1.03–1.54)	3 years	Hypoglycaemia is associated with ↑ risk of dementia and may be responsible for the ↑ risk of dementia in patients with diabetes	[208]
19.	Diabetes	Clinical study Quantitative meta-analysis of longitudinal studies 6184 subjects with diabetes and 38,530 subjects without diabetes, subjects were without dementia or MCI at baseline	Hippocampus	↑Risk for AD (RR:1.46, 95% CI: 1.20–1.77), ↑Risk of VD (RR: 2.48, 95% CI: 2.08–2.96), ↑Risk of any dementia (RR: 1.51, 95% CI: 1.31–1.74) and ↑Risk of MCI (RR: 1.21, 95% CI: 1.02–1.45)	>3 years	Diabetes ↑risk factor for incident dementia (including AD, VD and any dementia) and MCI	[209]

(*Continued*)

Table 1 (Continued).

S.No	Disease Model/ Condition	Study Type	Brain Area Affected	Factors Involved	Duration of Study	Key Findings	References
20.	Severe hypoglycaemia in T2DM	Clinical study Prospective study 1066 men and women with T2DM Age: 60–75 years	Cerebral cortex, Hippocampus	↓Cognitive ability at baseline, ↑Cognitive decline during follow-up	4 years	Severe hypoglycaemia is associated with ↓initial cognitive ability and ↑cognitive decline	[210]
21.	T2DM and T1DM	Clinical study Retrospective national record linkage cohort study 3,43,062 people with T1DM; 18,55,141 people with T2DM; and a reference cohort Age: ≥30 years Ethnicity: English cohort	Pre-frontal cortex, Hippocampus	↑Risk for developing dementia in T1DM people (RR= 1.65; 95% CI 1.61, 1.68), ↑Risk for developing dementia in T2DM people (RR= 1.37), ↑Risk for VD by Two-folds	13 years	T1DM and T2DM significantly↑risk of dementia	[211]
22.	Lifetime history of severe hypoglycaemia (Self-reported)	Clinical study Cross-sectional, population-based study 1066 men and women Age: 60–75 years, with T2DM	Hippocampus	↓Late-life cognitive ability, ↑Age-related cognitive decline and dementia	5 years	Severe hypoglycaemia is associated with ↓late-life cognitive ability	[212]
23.	Diabetes-related factors (Insulin resistance, Hyperinsulinemia, Hyperglycaemia)	Clinical study Long-term prospective cohort study 135 autopsies of residents of Hisayama town (74 men and 61 women)	Middle frontal gyrus, Superior and middle temporal gyri, Inferior parietal lobule, Anterior cingulated gyrus, Amygdala, Hippocampus with entorhinal and trans entorhinal cortex Calcarine cortex, Basal ganglia	↑Risk for neuritic plaques, ↑Risk of AD pathology	5 years	Hyperinsulinemia and hyperglycaemia caused by insulin resistance ↑ neuritic plaque formation	[213]

(*Continued*)

Table 1 (Continued).

S.No	Disease Model/ Condition	Study Type	Brain Area Affected	Factors Involved	Duration of Study	Key Findings	References
24.	Diabetes mellitus	Clinical study Prospective observational Meta-analysis study 1,148,041study participants, 89,708 diabetic subjects, 1,058,333 non-diabetics subjects	Pre-frontal cortex, Amygdala, Hippocampus	3% ↑Risk of all type dementia, 56% ↑Risk of AD dementia, 127% ↑Risk of VD	13 years	↑Risk of all type dementia, AD and VD	[214,216]
25.	Diabetes	Clinical study Systematic observational study Cohort of individuals reported on; cognitive function at baseline and at follow-up; and glucose status	Cerebral cortex	↑Rate of decline in cognitive function (1.2–1.7-fold, 95% CI), ↑Odds of future dementia (1.6 folds,95% CI 1.4–1.8)	20 years	People with diabetes have a ↑rate of cognitive dysfunction as compared to non-diabetics	[215,217]

Notes: Symbols: (↑) Increases, (↓) Decreases, (%) Percent, (≥) Greater than or equal to.
Abbreviations: AD, Alzheimer's disease; VD, Vascular dementia; CI, Confidence interval; HR, Hazard ratio; RR, Relative risk; IRS, Insulin receptor substrate; CNS, Central nervous system; IRR, Incident rate ratio; WT, Wild type; AKT, Protein kinase B; T2DM, Type 2 diabetes mellitus; T1DM, Type 1 diabetes mellitus; MCI, Mild cognitive impairment; CSF, Cerebrospinal fluid; VCI, Vascular cognitive impairment.

inhibitor reduces the risk of dementia in the elderly (hazard ratio = 0.66) compared to taking sulphonylurea. Additionally, when compared to sulphonylurea use (hazard ratio = 0.66), DPP-4 inhibitor use was associated with a significantly lower risk of Alzheimer's disease (hazard ratio = 0.64) and a lower risk of vascular dementia (hazard ratio = 0.66).[216]

Moreover, a population-based longitudinal study found that pioglitazone, when used as a second-line glucose-lowering medication after metformin, may have a protective effect on the risk of dementia in type 2 diabetic study participants.[224]

A comparable retrospective cohort study examined the effect of metformin (a direct AMPK-dependent GLP-1 activator) use on the risk of dementia in type 2 diabetes patients using the Taiwanese National Health Insurance reimbursement database. Overall hazard ratios indicated a significantly lower risk of dementia in type 2 diabetes patients who had used metformin (especially for more than two years) in either the unmatched or matched group.[225]

Exendin-4 (a long-acting GLP-1 agonist) was investigated to improve cerebrovascular integrity and vascular-induced cognitive impairment and dementia (VCID) in diabetic mice when given at a dose of 30ng/kg/day for four weeks.[226]

All these shreds of evidence point to GLP-1 activators/analogues as a promising strategy for dementia treatment. Additionally, mechanistic research on the safety and efficacy of GLP-1 target activators may be used to develop a preventative therapy for dementia and related neurodegenerative dysfunctions. Thus, we encourage readers to understand better the cellular and molecular pathways underlying neurodegenerative diseases to establish a novel disease-modifying therapeutic intervention. GLP-1 signaling activators/analogues/agonists are neuroprotective in preventing a variety of dementia-related neurodegenerative abnormalities, as summarised in Table 2.

Table 2 Neuroprotective Role of GLP-1 Signaling Analogs in the Protection of Various Dementia Related Neurodegenerative Abnormalities

S. No	GLP-1 Signaling Activators	Brain Areas Affected	Neuro-Complications Prevented	Study Type	Dose and Route	Duration of Study	References
1.	Exendin-4 (GLP-1 agonist)	Cerebrum, Brain pericytes	↓Cerebral pathological neovascularization indices, ↑Learning and memory functions, ↓Diabetes-induced inflammation, ↓Oxidative stress, ↓Vascular-induced cognitive impairment and dementia	Pre-clinical study Control and diabetic mice, Human brain microvascular pericytes	Exendin-4: 30ng/kg per day	28 days	[226]
2.	Metformin (Direct, AMPK-dependent, GLP-1 activator)	CNS	↓Dementia risk in unmatched cohort (HR= 0.550; 95% CI), ↓Dementia risk in matched cohort (HR= 0.707; 95% CI)	Clinical study Retrospective, unmatched and matched-pair cohort study Mean age: 63 years, Morbidity: T2DM, no dementia at baseline	Prescribed doses	> 58.1 months	[225]
3.	Glitazone, Metformin (↑ GLP-1 in the plasma)	CNS	Glitazones ↓dementia risk (OR: 0.80), Metformin, prescribed as monotherapy (OR = 0.71) or as dual therapy with sulfonylureas (OR = 0.90), was associated with ↓dementia risk	Clinical study Retrospective, case-control study 8276 diabetes patients with dementia and 8276 diabetes patients without dementia, Mean age: 79.7 years, 56.2% women candidates	Prescribed doses	5 years	[223]
4.	Dipeptidyl-Peptidase 4 Inhibitors (↑ level of incretins like GLP-1)	CNS	↓Risk of dementia compared to sulphonyl urea use (HR= 0.66), ↓Risk of AD dementia (HR=0.64), ↓Risk of VD non-significantly (HR= 0.66)	Clinical study Population-based, retrospective observational cohort study, 7552 users of sulfonylureas and 7552 users of DPP-4 inhibitors, Age >60 years, with T2DM, dementia-free at baseline	Prescribed doses	1362 days	[216]

(*Continued*)

Table 2 (Continued).

S. No	GLP-1 Signaling Activators	Brain Areas Affected	Neuro-Complications Prevented	Study Type	Dose and Route	Duration of Study	References
5.	Pioglitazone and Metformin	CNS	↓ Risk of dementia compared with those on metformin +sulfonylurea (HR 0.56; 95% CI 0.34, 0.93)	Clinical study Retrospective cohort study, 2,04,323 individuals with T2DM, receiving metformin-based dual therapy, Age: ≥18 years and ≥65 years, Dementia-free at baseline	At prescribed doses	3 months	[227]
6.	Pioglitazone (GLP-1activator)	CNS	↓ Dementia risk, Greater ↓ in dementia risk on prolonged use	Clinical study Retrospective cohort study 11,011 pioglitazone users, 11,011 never-users of pioglitazone Mean age: 59 years, No dementia at baseline	Prescribed doses	>20 months	[225]
7.	Exenatide (Long-acting, GLP-1 receptor agonist)	Caudate, Putamen	↑Neuronal survival pathways, ↑Mitochondrial function, ↓Neuro-inflammation	Clinical study Randomized, double-blind, placebo-controlled trial Age: 25–75 years	Exenatide- 2 mg, once weekly, subcutaneous injections	48 weeks exposure period, 2 weeks washout period	[228]
8.	Sitagliptin (DPP-4 inhibitor, ↓GLP-1 degradation and ↓glucagon secretion)	CNS	↑Glycemiccontrol, ↓Insulin requirement, ↑Cognitive function in elderly diabetic patients,	Clinical study Prospective, observational study 253 elderly patients with T2DM, with and without AD	Regular prescribed doses	6 months	[222]
9.	Pioglitazone (PPAR-γ agonist, activates GLP-1 receptor)	Substantia nigra, Striatum	↓Dementia incidence	Clinical study Prospective cohort study 1,45,928 subjects Age: ≥60 years	Prescribed doses, oral route	2 years	[229]

(*Continued*)

Table 2 (Continued).

S. No	GLP-1 Signaling Activators	Brain Areas Affected	Neuro-Complications Prevented	Study Type	Dose and Route	Duration of Study	References
10.	Liraglutide (a novel GLP-1 analog)	Frontal cortex	↓ Insulin receptor aberrations, ↓Amyloid-β plaque load, ↓ IRS-1 pS^{616} levels, ↓Glial activation, ↓Astrocytosis	Pre-clinical study APP_{SWE}/PS1dE9 mouse model of AD Age: 7 months	25 nmol/kg body weight, *i.p.*, once daily	8 weeks	[230]
11.	Liraglutide (GLP-1 analog)	Hippocampus	↓Memory impairment, ↓Neuronal loss, ↑Synaptic plasticity, ↓Amyloid plaque deposition by 40–50%, ↓Inflammatory response, ↓Activated microglial cell numbers	Pre-clinical study AD transgenic mice APP/PS1 and WT littermate controls Age: 7-months-old	Systemic administration 25 nmol/kg body weight, *i.p.*, once daily	8 weeks	[231]
12.	Liraglutide, Exenatide (GLP-1 receptor agonists)	Cerebral cortex, Hippocampus	↑ Axonal transport ↓Hippocampal IRS-1pSer, ↑Behavioral measures of cognition	Pre-clinical study Model: APP/PS1 Tg mice and WT controls Age: 13 to 14 months old	25 nmol/kg body weight, *i.p.* route	3 weeks	[232]
13.	GLP-1, Exendin-4 (a stable analog of GLP-1)	Hippocampus	↓Endogenous levels of amyloid peptide, ↓Dementia like-effect of amyloid β oligomers, ↓Neuronal death induced by amyloid β	Pre-clinical study In vitro: PC12 cell culture, In vivo: db+/db +mice	PC12 cells: GLP-1 (3.3, 33, and 330 ng/mL), exendin-4 (0.1, 1.0, and 10 μg/mL) Mice: GLP-1 (3.3 ng, 6.6 ng), exendin-4 (0.2 ng), via bilateral infusion	18 days	[233]
14.	Liraglutide (GLP-1 agonist)	Cerebral cortex	↑ Cerebral microvasculature, ↓Cerebral microaneurysms and leakage	Pre-clinical study Transgenic mice APP/PS1 and WT mice Age: 7-months old	Liraglutide - 25 nmol/kg body weight, saline (0.9% w/v), via *i.p.*injection, once daily	8 weeks	[219]
15.	Liraglutide (Novel GLP-1 analog, pre-treatment)	Hippocampal CA1 region	↓Aβ25–35-induced impairment of spatial learning and memory, ↑Late-phase long-term potentiation, ↑Intracellular cAMP level	Pre-clinical study Adult, male, Sprague Dawley rats Weight:230–250 grams	Liraglutide:2 μL, injected at a rate of 0.2 L/min, and 25 nmol/kg body weight by *i.p.* injection	2 weeks	[218]

(*Continued*)

Table 2 (Continued).

S. No	GLP-1 Signaling Activators	Brain Areas Affected	Neuro-Complications Prevented	Study Type	Dose and Route	Duration of Study	References
16.	GLP-1	Hippocampus	↑Intracellular calcium levels, ↓ Calcium responses to glutamate, ↓Membrane depolarization, ↓Neuronal death induced by glutamate, ↑ Neuronal plasticity, ↑ Cell survival	Pre-clinical study In-vitro study Dissociated hippocampal cell cultures, Density: 80–100 cells/mm^2	10 nM GLP-1 treatment	10 days	[234]
17.	GLP-1 receptor agonists	Substantia nigra, Striatum	↓Inflammatory response ↑ Insulin receptor signaling ↓Proinflammatory cytokine levels	Clinical study Meta-analysis of randomized controlled trials Adult participants, Body mass index: 25 or higher; with or without T2DM	Exenatide: twice daily and once weekly, Liraglutide: once daily at clinically relevant doses	20 weeks	[235]
18.	GLP-1 analog (Liraglutide)	Temporal lobe, Occipital lobe, Parietal lobe, Cerebellum	↑Glucose metabolism, ↓Decline of brain glucose consumption	Clinical study Randomized, placebo-controlled, double-blinded study, 38 AD patients	Liraglutide-0.6 mg subcutaneously daily for 1 week, then 2 mg daily for 1 week, and then 1.8 mg daily	26 weeks	[221]
19.	Intra-nasal insulin detemir	Hippocampus, Amygdala, Pre-frontal cortex	↑Verbal memoryin APOE-€4 positive carriers, ↑Working memory in the 40 IU group, ↑Visuospatial working memory	Clinical study Total: 60 old subjects, 39 participants with amnestic MCI and 21 participants with probable AD with Mini-Mental State Examination scores >15	20 IU and 40IU, daily treatment for 3 weeks, via nasal drug delivery device	2 years	[220]
20.	Geniposide (a novel agonist for GLP-1)	Pheochromocytoma	↑Anti-apoptotic Bcl-2 protein level, ↑ Heme oxygenase-1, ↑Phosphorylation of c-Raf, MEK ↑Phosphorylation of MAPK, and p90RSK ↓Oxidative damage	Pre-clinical study In-vitro study Rat PC12 cell line, cultured in Dulbecco's modified Eagle's medium, at 37°Celsius with 5% CO_2	GLP-1: 33 mg/l, Geniposide: 50 mg/l,	4 hours	[227,236]

Notes: Symbols: (↑) Increases, (↓) Decreases, (>) Greater than, (≥) Greater than or equal to, (<) Less than, (%) Percent.

Abbreviations: IU, International unit; OR, Odds ratio; HR, Hazard ratio; CI, Confidence interval; APP/PS1, Amyloid precursor protein/presenilin 1mutant form of Alzheimer's disease; GLP-1, Glucagon like peptide-1; CA1, Cornu ammonis1; CNS, Central nervous system; cAMP, Cyclic AMP; i.p., Intra-peritoneal; AD, Alzheimer's disease; VD, Vascular dementia; DPP-4, Dipeptidyl peptidase-4; IRS, Insulin receptor substrate; WT, Wild type; PC12, Pheochromocytoma cell 12; Bcl-2, B cell lymphoma-2; c-Raf, c-Rapidly accelerated fibrosarcoma; MEK, Mitogen-activated protein kinase kinase; MAPK, Mitogen-activated protein kinase; CO_2, Carbon dioxide; T2DM, Type 2 diabetes mellitus; APOE-€4, *Apolipoprotein E*, type epsilon *4* allele; MCI, Mild cognitive impairment; AMPK, AMP-activated protein kinase; PPAR-γ, Peroxisome proliferator-activated receptor gamma.

Conclusion and Future Perspectives

This review focuses on the therapeutic potential of insulin in a variety of neurodegenerative disorders, as well as the cellular effects of insulin resistance on multiple brain cells. It summarises recent research on the roles of hypothalamic inflammation induced by obesity in neurodegeneration, impaired adult neurogenesis, and impaired neural stem cell regeneration and their relevance to obesity and related diseases. Additionally, similarities in neuroinflammation between neurodegenerative diseases and metabolic diseases caused by malnutrition are discussed. These neuro complications have been identified as promising research targets in obesity and other conditions associated with excessive food consumption. Despite strong indicators, insulin signaling and pharmacological modulators may have adverse effects, especially long-term treatments. In a nutshell, abnormalities and dysfunction of the insulin signaling pathway and its molecules may contribute to the neurodegenerative process. Numerous studies have demonstrated that altering molecules downstream in the insulin signaling pathway increases insulin sensitivity. Recently, the therapeutic effect of insulin and the detrimental impact of insulin resistance on neuronal and glial cells in neurodegenerative diseases were reviewed.

Neuroinflammation, neurodegeneration, and insulin resistance all have a strong correlation. It appears as though the outcomes vary according to the duration of the stimulus. Non-pharmacological interventions such as physical exercise and intermittent fasting may provide new information about the onset and progression of neurodegenerative diseases. Along with the impaired insulin signaling, we discussed the various agents in this class of drugs (GLP-1 receptor agonists, dual/triple receptor agonists, and DPP-4 inhibitors) and the evidence supporting their potential role in the treatment of neurodegenerative diseases.

Additional research is needed to determine the optimal insulin dose, tolerability, long-term safety, and schedule for patients with neurological disease and trauma and gain a better understanding of the role of insulin resistance in the development and progression of brain disorders.

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