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Insulin Signaling Abnormality and Insulin Resistance: A Common Pathogenic Mechanism Between Type 2 Diabetes Mellitus and Alzheimer's Disease

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ABSTRACT

Alzheimer's disease (AD) is one of the major neurodegenerative disorders, accounting for 60%–80% of dementia cases. Its pathogenesis is complex, and there is a lack of effective intervention strategies. Type 2 diabetes mellitus (T2DM) is an independent risk factor for AD, and the two diseases share common pathogenic mechanisms. Abnormal insulin signaling and insulin resistance are key convergence points in the pathogenesis of both T2DM and AD. Meanwhile, factors such as inflammation, oxidative stress, and mitochondrial dysfunction further exacerbate AD-related pathology. This review summarizes the shared pathogenic mechanisms of abnormal insulin signaling and insulin resistance in T2DM and AD, as well as other common pathogenic mechanisms. The aim is to identify potential therapeutic targets for T2DM-associated AD, provide a basis for early intervention by regulating metabolic pathways, and thereby achieve the research goal of preventing the occurrence and progression of AD.

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Type 2 diabetes mellitus (T2DM) is a metabolic disorder characterized by insulin resistance (IR) and impaired pancreatic β cell function. According to the International Diabetes Atlas 2025, the number of adults aged 20–79 years living with T2DM worldwide has exceeded 589 million, and this figure is projected to reach 853 million by 2050 [1]. Its core pathophysiology involves reduced insulin sensitivity in peripheral tissues, including skeletal muscle, adipose tissue, and liver, leading to defective insulin signaling. This is manifested as inhibition of the phosphatidylinositol 3 kinase (PI3K)/protein kinase B (Akt) pathway, decreased membrane translocation of glucose transporter 4 (GLUT4), and abnormal glucose metabolism. Persistent hyperglycemia further induces oxidative stress, chronic inflammation, and vascular injury, increasing the risk of multisystem complications [2]. Alzheimer's disease (AD) is the predominant form of neurodegenerative disease, accounting for 60–80% of all dementia cases, The deposition of β amyloid (Aβ) and hyperphosphorylation of tau protein represent the core pathological hallmarks of AD [3]. Studies have demonstrated marked impairment of insulin signaling in the brains of AD patients, characterized by aberrant phosphorylation of insulin receptor substrate (IRS), reduced Akt activity, and disturbed cerebral glucose metabolism. Accordingly, some scholars have designated AD as "type 3 diabetes" [4]. Dysregulation of the insulin signaling pathway, closely linked to insulin resistance, serves as a shared pathogenic mechanism underlying T2DM and AD [5].

Source and Biological Functions of Insulin in the Alzheimer's Disease Brain

As a pivotal pleiotropic hormone, insulin exerts core effects including promoting glucose uptake, suppressing hepatic glucose output and regulating lipid metabolism, in addition, insulin facilitates protein synthesis and cell growth and participates in the integration of energy homeostasis, such as inhibiting lipolysis and modulating mitochondrial function [6-8]. Insulin in the brain is predominantly derived from the periphery. Under normal physiological conditions, insulin readily crosses the blood-brain barrier (BBB) via receptor-mediated transport to exert central effects, and its transport rate can be modulated by multiple factors including receptor expression, metabolic status, inflammation, and hormonal milieu, some investigators have also reported that insulin can access brain regions not protected by the BBB. Moreover, accumulating evidence supports a central source of insulin. A rodent study demonstrated the presence of insulin mRNA in

the brain, and that γ aminobutyric acid (GABA) ergic interneurons and choroid plexus epithelial cells secrete insulin [9-10]. STEEN E et al. detected insulin mRNA transcripts in the hippocampus and hypothalamus in human postmortem brain tissues, further confirming that brain insulin is not exclusively of peripheral origin [11].

Within the brain, insulin exerts its biological effects by activating insulin receptors (IR) located on the neuronal surface. IR is expressed in neurons, astrocytes, microglia, and the cerebrovascular system. Portuguese researchers summarized insulin receptor density across distinct brain regions and found the highest densities in the olfactory bulb, hypothalamus, hippocampus, cerebral cortex, striatum, and cerebellum, among these regions, the hippocampus and cerebral cortex are the primary sites of Alzheimer's disease pathology and also represent core regions responsible for learning and memory, suggesting that insulin may play a critical role in memory processing [12].

By initiating the canonical phosphatidylinositol 3 kinase (PI3K)/ protein kinase B (AKT/PKB) pathway, as well as the mitogen activated protein kinase (MAPK)/extracellular signal regulated kinase (ERK) signaling cascade, insulin regulates glucose uptake (e.g., promoting membrane localization of neuronal GLUT1/3) and energy metabolism, thereby maintaining ATP supply essential for synaptic function. Meanwhile, insulin reduces tau hyperphosphorylation through Akt mediated inhibition of glycogen synthase kinase 3β (GSK3β), and promotes synaptogenesis and long term potentiation (LTP) via mammalian target of rapamycin complex 1 (mTORC) dependent protein synthesis, thereby enhancing learning and memory.

Furthermore, insulin counteracts neuroinflammation, for instance by inhibiting nuclear factor KB (NF KB) activation in microglia. It also suppresses oxidative stress via Forkhead box protein O1 (Fox O) mediated regulation of antioxidant genes, thereby mitigating amyloid β (Aβ) toxicity and exerting potential protective effects against neurodegenerative disorders including AD [13].

Specific Mechanisms of Abnormal Insulin Signaling Transduction in Alzheimer's Disease

Normal insulin signaling is essential for maintaining the function of brain regions relevant to AD pathology. In the AD brain, however, impairments in this pathway exhibit distinct specificity that differs from the signaling defects observed in peripheral tissues during type 2 diabetes mellitus (T2DM). In AD, aberrant insulin signaling directly targets pathways governing Aβ metabolism, tau phosphorylation, and neuronal survival. Moreover, these central abnormalities interact with peripheral pathophysiology in T2DM in a mutually amplifying manner, collectively accelerating disease progression in AD.

Process of Insulin Signaling Transduction

Under physiological conditions (Figure 1 Process of insulin signaling transduction, Created with BioGDP.com[1]), Insulin first binds to and activates insulin receptors (IR) on the cell membrane, triggering its intrinsic tyrosine kinase activity and inducing tyrosine phosphorylation of the receptor itself as well as insulin receptor substrate (IRS) proteins. Phosphorylated IRS proteins recruit and activate phosphatidylinositol 3 kinase (PI3K), which catalyzes the production of the second messenger phosphatidylinositol (3,4,5)-trisphosphate (PIP_3). PIP_3 then recruits 3 phosphoinositide dependent protein kinase 1 (PDK1) and mammalian target of rapamycin complex 2 (mTORC2), which phosphorylate Akt at Thr308 (within the kinase T loop) and Ser473 (within the hydrophobic motif), respectively, leading to its full activation.

Activated Akt modulates AD related pathogenesis via three key downstream targets: first, it inhibits glycogen synthase kinase 3β (GSK3β), thereby reducing tau phosphorylation; second, it promotes phosphorylation of Forkhead box protein O1 (FoxO1), preventing its nuclear translocation and alleviating neuroinflammation and oxidative stress; third, it regulates the activity of insulin degrading enzyme (IDE), thereby accelerating Aβ clearance.

Meanwhile, activation of the MAPK/ERK pathway upregulates the expression of neuronal survival factors such as brain derived neurotrophic factor (BDNF), preserves synaptic plasticity, and complements the neuroprotective effects of the PI3K/Akt pathway.

Collectively, the insulin signaling pathway can be divided into three stages: receptor activation, downstream signal transmission, and effector activation followed by biological responses. Therefore, insulin signaling transduction can be impaired by abnormalities at multiple levels, including dysfunctional insulin receptors, impaired insulin receptor substrate activity, decreased PI3K activity, defective Akt activation, or dysfunction of downstream effector molecules.

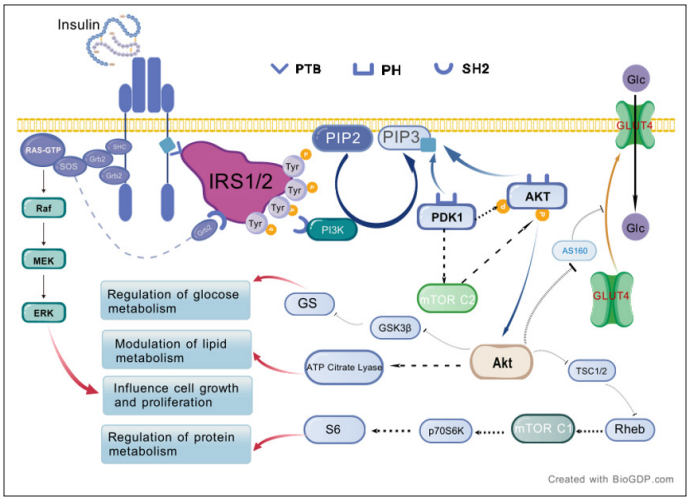

Figure 1: Process of Insulin Signaling Transduction

Tips: RAS-GTP: Rat Sarcoma Protein-Guanosine Triphos phate;SOS:SonofSevenless;Grb2:Growth Factor Receptor-Bound Protein2; Shc: Shc Adaptor Protein; Raf: Rapidly Accelerated Fibrosarcoma; MEK: Mitogen-Activated Protein Kinase Kinase; ERK: extracellular signal-regulated kinase;IRS1/2:Insulin Receptor Substrate1/2;PI3K:Phosphatidy linositol3-Kinase;PIP2:Phosphatidy linositol 4,5-bisphosph ate;PIP3:Phosphatidy linositol3,4,5-trisphosphate;PDK1:3-Phosphoinositide-Dependent Protein Kinase1;AKT:Protein KinaseB; GS: Glycogen Synthase;GSK3β:Glycogen Synthase Kinase3β;mTORC1/C2:Mammalian Target of Rapamycin Complex1/2;AS160: AKT Substrateof 160kDa; GLUT4:Glucose Transporter4;TSC1/2:Tuberous Sclerosis Complex1/2;Rheb:Ras Homolog Enrichedin Brain; p70S6K:70kDa Ribosomal S6Kinase;S6:Ribosomal ProteinS6;

PTB: Phosphotyrosine -BindingDomain, Proteins such as IRS contain a PTB domain and can specifically recognize and bind to phosphorylated tyrosine residues on the insulin receptor, thereby mediating signal transduction. PH: Pleckstrin Homology Domain, many signaling proteins contain this domain, which can bind to phosphatidylinositol lipids (such as PIP_2 and PIP_3), assist in targeting proteins to specific locations such as the cell membrane, and also participate in protein-protein interactions.

[1]Figure 1 Process of insulin signaling transduction, Created with BioGDP.com [14].

SH2:SrcHomology2Domain, this domain can recognize and bind to short peptide sequences containing phosphorylated tyrosine residues. During signal transduction, it recruits downstream signaling molecules by binding to phosphorylated substrate proteins, thereby promoting the activation and transmission of signaling pathways.

Abnormal Insulin Signaling in AD

Insulin signaling transduction in the AD brain is characterized by multi-node blockade and occurs in parallel with the progression of AD pathology. Amyloid β (Aβ) aggregation is a hallmark of AD, and Aβ clearance largely depends on insulin degrading enzyme (IDE). Insulin and Aβ compete for binding to IDE. Dysregulated insulin signaling in the brain (such as elevated insulin levels or impaired signaling) inhibits IDE activity, resulting in reduced Aβ clearance and accelerated plaque formation. Disturbances in the insulin signaling pathway also increase Aβ production and promote aberrant tau phosphorylation, thereby driving neurodegeneration in AD [15].

Abnormalities in receptors and substrates represent the initiating events of signaling blockade. In the AD brain, insulin receptor substrate 1 (IRS 1) undergoes specific hyperphosphorylation at serine residues, primarily Ser616 and Ser636. This serine phosphorylation competitively inhibits tyrosine phosphorylation of IRS 1, preventing its normal recruitment of PI3K and directly blocking downstream signal transmission. Notably, the level of IRS 1 serine phosphorylation is positively correlated with the severity of cognitive impairment in AD patients and is detectable at an early stage of AD (i.e., mild cognitive impairment), suggesting its potential as a molecular biomarker for early AD diagnosis [15].

Accumulating evidence has confirmed that insulin signaling is modulated by multiple pathways, including inflammatory signaling, endoplasmic reticulum stress (ERS), the Wnt pathway, hypoxia inducible factor (HIF) signaling, and the Hippo/YAP pathway, conferring a highly interconnected regulatory network [2]. To further validate that impaired insulin signaling represents a shared pathogenic mechanism between AD and T2DM, numerous studies have been conducted at the genetic, molecular, and cellular levels, with findings from different levels mutually supporting and progressively reinforcing this concept.

At the omics level, researchers have developed novel statistical methods for constructing multilevel causal omics networks. Using gene expression, DNA methylation, environmental factors, and multiple phenotypes, these approaches delineated cascades underlying shared causal pathways between AD and type 2 diabetes. This work identified common pathways shared by AD and T2DM, including the CREB binding protein (CREBBP) axis, MAPK and PI3K AKT signaling, tetratricopeptide repeat protein 3 (TTC3) and FoxxO transcription factor networks [16]. These findings may explain why therapies targeting only a limited number of signaling nodes often fail, as they cannot cover the full spectrum of causal pathways driving disease pathogenesis.

At the molecular mechanistic level, Chinese researchers experimentally demonstrated that exendin 4 (Ex 4), an insulin-like receptor agonist, activates the insulin signaling pathway by stimulating the hippocampal Wnt/β catenin pathway and upregulating its downstream factor neurogenic differentiation 1 (NeuroD1). This in turn reduces GSK3β activity and ultimately attenuates tau hyperphosphorylation [17]. These findings further confirm that the Wnt pathway is critically implicated in both T2DM and AD.

At the level of transcriptional regulation and non coding RNAs, studies have further expanded the regulatory landscape of shared mechanisms between AD and T2DM. On one hand, with respect to transcription factors, existing studies have shown that the expression of anaplastic lymphoma kinase (ALK) and receptor like tyrosine kinase (RYK) is significantly and consistently downregulated in postmortem tissues from patients with AD and T2DM. Paired box 4 (PAX4) regulates the expression of growth factor receptor bound protein 2 (Grb2) and NADPH oxidase 4 (NOX4). MiR 1271 downregulates ALK and RYK, thereby reducing the expression of aristaless related homeobox gene (ARX), a suppressor of PAX4, and consequently elevating PAX4 levels via the Wnt/β catenin signaling pathway. Upregulation of PAX4 contributes to alleviating pathological features in both AD and T2DM [18]. This cascade links non coding RNAs, transcription factors, and canonical signaling pathways, refining the regulatory network underlying shared pathogenic mechanisms. On the other hand, Kiana summarized the involvement of non coding RNAs (ncRNAs, including miRNAs and lncRNAs) in the pathogenesis of AD. These ncRNAs participate in AD progression by modulating insulin signaling pathways such as the PI3K/Akt, MAPK, and GSK3β axes. For instance, miR 26b and miR 98 promote Aβ aggregation by inhibiting insulin like growth factor 1 (IGF 1), while metastasis associated lung adenocarcinoma transcript 1 (MALAT1) acts as a competing endogenous RNA (ceRNA) to regulate the PI3K/Akt pathway [19]. These studies provide theoretical support for lncRNA targeted therapy and gene editing strategies, although further investigations are warranted to validate these findings and facilitate clinical translation.

Central and Peripheral Insulin Resistance

Insulin resistance in T2DM refers to reduced responsiveness of peripheral tissues to insulin, which is associated with downregulation of insulin receptors, impaired insulin–receptor binding, or defective activation of the insulin signaling cascade. Researchers measured insulin, glucose, and albumin concentrations in 160 paired human serum and cerebrospinal fluid (CSF) samples and found that adults with Alzheimer's disease exhibited reduced peripheral insulin sensitivity and hyperinsulinemia, Peripheral insulin resistance impairs glucose uptake and glycogen synthesis in skeletal muscle, disturbs lipoprotein lipase activity and apolipoprotein B degradation in adipocytes, and consequently elevates peripheral levels of glucose, lipids, and insulin [20]. Chronic hyperglycemia and hyperlipidemia trigger sustained inflammation and oxidative stress, and exert detrimental effects on brain function through multiple mechanisms, including glucotoxicity, vascular damage, and accumulation of advanced glycation end products [21]. Prolonged hyperinsulinemia also downregulates insulin receptors at the blood–brain barrier and impairs BBB integrity, thereby reducing insulin transport into the brain - a process proposed to be a major contributor to the development of central insulin resistance. Insulin resistance in the central nervous system is not merely a simple extension of peripheral insulin resistance; it is mechanistically distinct and can also occur independently of T2DM [22]. Some investigators have proposed the concept of brain insulin resistance (BIR), a complex condition characterized by one or more defects that lead to insufficient insulin responsiveness in the brain and cerebral vasculature. BIR is associated with the availability of insulin within the CNS, the expression of insulin receptors (INSR) and their isoforms, and/or aberrant downstream signaling events of INSR in the brain [23].

AD and Diabetic Encephalopathy (DE)

In AD, brain insulin resistance is characterized by elevated basal serine phosphorylation of insulin receptor substrate 1 (IRS-1) in the hippocampus and cerebral cortex [22]. Diabetic encephalopathy (DE) is a severe microvascular complication of diabetes mellitus, mainly manifested by alterations in neurochemistry, brain structure, and cognitive function, and is particularly detrimental in elderly diabetic patients. Its pathogenesis involves multiple pathological processes, including oxidative stress induced by chronic hyperglycemia, neuroinflammation, insulin resistance, accumulation of advanced glycation end products (AGEs), activation of the polyol pathway, and abnormal free fatty acid metabolism [24]. The pathological alterations in DE are dominated by AD-like lesions, some of which are associated with vascular damage [25]. Insulin resistance plays a pivotal role in DE by disrupting insulin signaling pathways, particularly the PI3K/Akt and MAPK axes, leading to neuronal dysfunction, impaired synaptic plasticity, and reduced levels of neuroprotective factors such as brain-derived neurotrophic factor (BDNF), thereby exacerbating cognitive impairment. Hyperglycemia and insulin resistance promote Aβ production and tau hyperphosphorylation. Meanwhile, the interaction between AGEs and their receptors activates inflammatory cascades, further aggravating neuroinflammation and oxidative injury. Furthermore, dysregulated insulin signaling suppresses Aβ clearance and facilitates tau pathology, resulting in neurodegenerative changes similar to those observed in AD [15]. Collectively, these mechanisms induce neuronal damage in the hippocampus and cerebral cortex, manifesting as memory decline and cognitive impairment, highlighting the close molecular and pathological links between diabetic encephalopathy and AD. In one study, brains from patients with AD exhibited reduced, mislocalized insulin receptors and decreased receptor-ligand affinity compared with controls [11]. Other studies have demonstrated that impaired insulin signaling in the central nervous system leads to increased Aβ oligomers (AβOs), which in turn further attenuate insulin signaling, forming a vicious cycle: "BIR → increased AβOs → aggravated BIR".

Downregulation of insulin receptors is accompanied by elevated GSK3β activity. As a major tau kinase, increased GSK3β is likely responsible for the elevated levels of phosphorylated tau (p-Tau) [26]. Nevertheless, the precise causes and detailed mechanisms underlying brain insulin resistance remain to be fully elucidated, including its functional roles and clinical consequences.

Therapeutic Potential of Targeting Insulin Resistance for AD Intervention

Insulin resistance represents a shared pathogenic mechanism between AD and T2DM, and cytokines serve as critical mediators exacerbating both insulin resistance and AD pathology. In a mouse model of AD comorbid with T2DM, Sankar et al. highlighted the promoting roles of IL 1 family cytokines and tumor necrosis factor in the progression of both diseases [27]. β site amyloid precursor protein cleaving enzyme 1 (BACE1) plays a central role in AD pathogenesis by catalyzing the cleavage of amyloid precursor protein (APP), ultimately leading to Aβ generation and deposition. A cohort study by Hong Bao et al. verified a novel function of BACE1 in T2DM: it mediates increased cleavage of the insulin receptor, thereby accelerating T2DM progression and elevating the risk of cognitive impairment via insulin resistance [28]. Intracellular non GPI anchored CD59 isoforms IRIS 1 and IRIS 2 are essential for insulin secretion in pancreatic β cells. A study by Ewelina Golec et al. further expanded their neuroprotective roles by demonstrating reduced neuronal expression of IRIS 1 and IRIS 2 in patients with AD and non demented individuals with T2DM. Knockout of all CD59 isoforms (including IRIS 1 and IRIS 2) in the SH SY5Y neuroblastoma cell line not only elevated phosphorylated tau levels but also increased the expression of CDK5, a key driver of tau hyperphosphorylation. These findings indicate that loss of IRIS 1 and IRIS 2 may exacerbate peripheral insulin resistance by impairing insulin secretion and promote tau pathology via CDK5 upregulation, underscoring their essential functions in neurotransmitter secretion and involvement in the pathogenesis of both AD and T2DM [29].

For AD treatment, anti diabetic agents such as glucagon like peptide 1 (GLP 1) receptor agonists have shown promising translational potential in preclinical and early clinical studies. GLP 1 receptor agonists are glucose dependent insulinotropic agents that uniquely improve both peripheral insulin resistance and central nervous system function. In T2DM, these drugs activate GLP 1 receptors on pancreatic β cells to promote insulin secretion in a glucose dependent manner and alleviate insulin resistance in peripheral tissues. In AD, the GLP 1 receptor agonist liraglutide has been shown to enhance cerebral glucose metabolism and functional connectivity in small scale pilot trials [30]. This dual "peripheral glucose lowering and central neuroprotective" profile establishes GLP 1 receptor agonists as one of the most clinically promising drug classes for intervening in AD by modulating insulin resistance.

Other Shared Synergistic Pathogenic Mechanisms between AD and T2DM

The insulin signaling pathway serves as the molecular basis of insulin resistance. By disrupting insulin signaling pathways (PI3K/Akt and GSK-3β), insulin resistance induces abnormal glucose metabolism in neurons and glial cells, leading to mitochondrial dysfunction, which is characterized by reduced ATP production and excessive generation of reactive oxygen species (ROS). Excessive ROS not only directly damages neuronal structures, such as lipid peroxidation, protein glycosylation, and DNA damage, but also promotes the release of pro-inflammatory cytokines (TNF-α, IL-6, and IL-1β) by activating inflammasomes including nuclear factor KB (NF-KB) and NOD-like receptor pyrin domain-containing protein 3 (NLRP3), thereby triggering chronic neuroinflammation. Inflammatory mediators such as TNF-α further inhibit insulin receptor signaling through the c-Jun N-terminal kinase (JNK)/inhibitor of KB kinase β (IKKβ) pathway, exacerbating insulin resistance and forming a vicious cycle [31,32]. Therefore, inflammation, oxidative stress, and mitochondrial dysfunction, as shared pathological features of AD and T2DM, do not exist independently. Instead, they interact with insulin-related pathology to form a "synergistic amplification effect", accelerating the progression of core AD pathology.

Inflammation

Impaired insulin signaling in both AD and T2DM may result from increased inflammatory responses. Various pro-inflammatory cytokines inhibit insulin receptor substrate 1 (IRS-1) by chronically upregulating its phosphorylation at serine residues (including Ser616 or Ser636). This mechanism attenuates insulin signaling in a feed-forward manner by reducing tyrosine phosphorylation of IRS-1 [33]. Secreted Phosphoprotein 1 (SPP1) is a highly phosphorylated secreted glycoprotein that is upregulated during inflammation and also plays a role in AD and metabolism-related cognitive impairment [34]. Researchers including Sarah found that mice fed a high-fat diet (HFD) for 6 weeks exhibited persistent metabolic and cognitive impairments, along with alterations in peripheral and central inflammatory responses, including changes in plasma SPP1 levels and morphological changes of microglia in

the hippocampus. Through spatial transcriptomic analysis, they demonstrated that HFD induced changes in the expression of genes related to neurodegeneration, metabolism, and inflammation in the mouse brain. They also analyzed postmortem hippocampal samples from three humans diagnosed with AD comorbid with T2DM and obtained consistent results with animal experiments, indicating a close relationship between neurodegenerative and inflammatory mechanisms, and reaffirming SPP1 as a potential inflammatory marker for predicting neurodegeneration [34]. This study is of great significance for the treatment of metabolism-driven cognitive impairment; however, the small sample size and the lack of further cell type-specific SPP1 knockout or pharmacological intervention experiments limit the confirmation of the causal relationship between SPP1 and cognitive impairment.

Researchers such as Sankar also identified the roles of other pro-inflammatory factors in the diseases. Using multiple animal models, they found that the interaction between T2DM pathology and AD pathology significantly increased the expression of pro-inflammatory cytokines such as MCP-1, IL-1α, IL-3, and IL-17 in the brain. These cytokines not only participate in inflammatory responses but also may promote the development of Aβ and tau pathology, as well as the disruption of the blood-brain barrier [35]. Therefore, intervention strategies targeting neuroinflammatory signaling pathways, combined with metabolic control, may be therapeutic approaches for preventing the development of diabetes and AD.

Oxidative Stress

Oxidative stress can directly oxidize and damage key proteins in the insulin signaling pathway, such as insulin receptor (IR), IRS, and Akt, thereby promoting the development of brain insulin resistance, which is closely associated with cognitive impairment. As an energy-sensing enzyme, AMP-activated protein kinase (AMPK) plays a central role in regulating energy metabolism and stress responses. Its activity is inhibited in both T2DM and AD, which may exacerbate insulin resistance and neurodegeneration. The accumulation of Aβ and tau proteins is associated with oxidative stress. Studies have shown that activation of AMPK can reduce Aβ production, but its effect on tau phosphorylation remains controversial [36]. Both Aβ and islet amyloid polypeptide (IAPP) can increase ROS levels by inhibiting antioxidant enzymes, inducing lipid peroxidation and protein carbonylation. Overexpression of the p66Shc protein exacerbates mitochondrial ROS generation, and its knockout can improve cognitive impairment in AD/T2DM models. Therefore, controlling oxidative stress may be of great significance for the prevention and treatment of T2DM and AD.

Mitochondrial Dysfunction

Mitochondrial dysfunction is characterized by changes in the number of mitochondria in tissues, ultrastructural abnormalities in organelle depth, impaired mitochondrial biogenesis, reduced activity of mitochondrial multienzyme complexes, impaired ATP synthesis, disrupted calcium homeostasis, decreased opening threshold of mitochondrial permeability transition pore (mPTP), and excessive formation of ROS. Mitochondrial dysfunction is closely related to insulin resistance and abnormal insulin signal transduction, and is one of the important mechanisms for their occurrence and development. As the "energy factory" of cells, abnormalities in mitochondrial functions such as energy metabolism, ROS generation, and metabolite homeostasis can interfere with insulin signal transmission through multiple pathways and induce insulin resistance. Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1 (PGC-1α) is a transcriptional coactivator that interacts with various transcription factors and regulates the expression of key genes involved in mitochondrial biogenesis, adaptive thermogenesis, and metabolism. Dysregulation of the PGC-1α/PPAR pathway exists in both AD and T2DM.Studies have found that mitochondrial proteins reflecting neuronal mitochondrial damage are present in the peripheral blood of patients with T2DM and AD. For example, the levels of NADH-ubiquinone oxidoreductase core subunit S3 (NDUFS3) and succinate dehydrogenase complex subunit B (SDHB) in neural exosomes are significantly reduced [35]. Aging is a common risk factor for T2DM and AD. Aging can lead to the accumulation of mitochondrial DNA (mtDNA) mutations, causing dysfunction of respiratory chain complexes (such as complex IV) and increased ROS generation. In turn, ROS can further damage mtDNA, forming a vicious cycle of "mitochondrial oxidative stress" and accelerating the progression of AD and T2DM.Meanwhile, the pathologies of AD and T2DM, such as Aβ aggregation and islet amyloid polypeptide (IAPP) aggregation in pancreatic β-cells, can activate microglia and release neuroinflammatory factors such as IL-1β and TNF-α. Inflammatory factors of T2DM (such as IL-6) can cross the blood-brain barrier, exacerbate neuroinflammation, and damage mitochondrial function, forming a vicious cycle of "mitochondrial inflammation" that bidirectionally affects and jointly promotes disease progression [37].

Conclusion

Abnormal insulin signal transduction and insulin resistance (IR) are important intersections in the pathogenesis of T2DM and AD. IR occurs not only in peripheral tissues but also in the central nervous system. By disrupting key signaling pathways such as PI3K/Akt and MAPK/ERK, IR can lead to abnormal neuronal glucose metabolism, tau hyperphosphorylation, and Aβ deposition, thereby linking metabolic disorders to cognitive decline. Chronic low-grade inflammation, mitochondrial dysfunction, and oxidative stress are interconnected with IR and abnormal insulin signaling pathways, further exacerbating disease pathology. A large number of studies have identified various potential therapeutic targets based on the shared pathogenic mechanisms, including anti-inflammatory agents, insulin sensitizers, and mitochondrial biogenesis modulators. Non-coding RNAs and epigenetic regulation also provide new ideas for disease treatment by affecting insulin signaling and neuroprotective effects. However, due to the heterogeneity of disease progression and the protection of the blood-brain barrier, the clinical translation of these potential therapeutic targets still faces challenges, requiring more in-depth research for further exploration.

Conflict of Interest

All authors declare no conflicts of interest.

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