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Review

Exercise Suppresses Insulin Resistance: A Potential Mechanism for Improving the Interaction Between Type 2 Diabetes and Alzheimer's Disease

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Abstract

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by hyperglycemia, hyperinsulinemia, and impaired insulin sensitivity. Although classified as a metabolic disorder, T2DM also contributes to cognitive decline. Alzheimer's disease (AD) is a progressive and irreversible neurodegenerative disorder. T2DM is strongly associated with AD and is considered a major risk factor for its development. AD is therefore recognized as a metabolic disorder mediated by cerebral insulin resistance, often termed "type 3 diabetes". T2DM and AD exhibit crosstalk, sharing overlapping molecular mechanisms including insulin resistance, mitochondrial dysfunction, oxidative stress, chronic inflammation, autophagy dysregulation, tau hyperphosphorylation, and β-amyloid deposition. Among these, insulin resistance may play a potential role in this interplay. As a non-pharmacological intervention, exercise demonstrates distinct advantages in preventing and managing metabolic and neurological disorders. Exercise maintains glucose homeostasis by mitigating insulin resistance, enhances insulin sensitivity, and concurrently reduces tau hyperphosphorylation and β-amyloid aggregation, thereby improving cognitive function. Building on current literature, this review explores how exercise mitigates insulin resistance to prevent and manage both T2DM and AD. It further proposes that insulin resistance may serve as a potential mechanistic link through which exercise modulates the pathological crosstalk between the two disorders.

Keywords: Alzheimer's disease; exercise; insulin resistance; type 2 diabetes mellitus

1. Introduction

Type 2 diabetes mellitus (T2DM) and Alzheimer's disease (AD) are two prevalent chronic disorders that affect middle-aged and elderly individuals. T2DM is primarily characterized by pancreatic β-cell dysfunction and insulin resistance (IR) [1]. The global prevalence of T2DM is projected to reach 10.9% by 2045 [2]. Although T2DM is a metabolic disorder, it is also associated with cognitive decline [3]. Individuals with T2DM exhibit a significantly elevated risk of developing AD [4], nearly doubling the likelihood of dementia [5]. Consequently, T2DM is recognized as a pivotal risk factor for AD [6]. AD is a progressive neurodegenerative disorder marked by hallmark pathologies, including extracellular accumulation of insoluble β-amyloid (Aβ) peptides forming senile plaques, hyperphosphorylation of tau protein resulting in neurofibrillary tangles (NFTs), and widespread neuronal degeneration [7]. The global population affected by AD and other forms of dementia are estimated to increase from 57 million in 2019 to 153 million by 2050 [8]. Studies have indicated that individuals with T2DM have a 60% higher risk of developing dementia than do those without diabetes [9]. Moreover, patients with AD also exhibit a markedly increased risk of developing T2DM [10]. This bidirectional association may be attributed to shared etiological factors [11] and overlapping pathogenic mechanisms, including IR, mitochondrial dysfunction, oxidative stress, and chronic inflammation [12].

IR plays a pivotal role in T2DM pathogenesis. Primarily, it promotes hyperinsulinemia and chronic hyperglycemia [13]. Notably, elevated levels of IR biomarkers have been detected in the hippocampal tissue of non-diabetic individuals with AD, suggesting that IR may be a critical etiological factor in AD pathogenesis [14]. Consequently, AD has been referred to as "type 3 diabetes" [15]. Brain insulin resistance precedes peripheral insulin signaling impairment and is regarded as a potential initiator of T2DM [16]. Current therapeutic strategies for addressing IR in both T2DM and AD involve dietary modifications, weight management, and pharmacological interventions such as metformin, which effectively reduces peripheral IR and may slow the progression of AD [17]. However, most pharmacotherapies target peripheral IR, and the effectiveness of dietary modifications and weight management in mitigating AD remains controversial [18,19]. There is a notable lack of effective interventions that directly target brain insulin resistance. Exercise, as a non-pharmacological intervention, has been shown to enhance both peripheral and central insulin sensitivity, thereby miti-

gating IR [20,21] and holding significant clinical relevance in modulating the pathological crosstalk between T2DM and AD. In summary, exercise holds promise as an effective strategy for mitigating IR and preventing both T2DM and AD. This review discusses the pivotal role of IR in the pathogenesis of both conditions and systematically examines the mechanistic links through which IR contributes to their crosstalk, exploring the therapeutic potential of exercise in mitigating IR to prevent and manage both T2DM and AD. Finally, the review explores the underlying mechanisms by which exercise may alleviate IR, aiming to provide a theoretical foundation for future clinical research and intervention.

2. Insulin and the Central Nervous System

Insulin, a 51-amino acid peptide hormone secreted primarily by pancreatic β-cells, plays a central role in glycemic regulation [22,23]. Upon binding to the extracellular α-subunit of the insulin receptor, insulin induces a shift in the receptor's tetrameric conformation, triggering autophosphorylation of intracellular β-subunits on tyrosine residues. This event facilitates the recruitment and phosphorylation of insulin receptor substrates (IRS), subsequently activating a pivotal downstream signaling cascade involving phosphoinositide 3-kinase (PI3K) and protein kinase B (Akt). The activated PI3K/Akt pathway promotes glucose uptake via glucose transporters (GLUTs) [24,25]. In addition, insulin activates the mitogen-activated protein kinase (MAPK) signaling pathway to modulate cellular growth and proliferation [26]. Insulin also crosses the blood-brain barrier (BBB) via receptor-mediated transport to exert essential functions in the central nervous system [27–29]. The brain was once considered an insulin-insensitive organ. However, subsequent studies revealed markedly elevated expression of *GLUT1* and *GLUT3* genes in the hippocampus [30], thereby demonstrating that the brain is a key site of insulin responsiveness. Moreover, insulin can be synthesized by neuronal subpopulations in the cerebral cortex and by hippocampal neurons, complementing the slower influx from pancreatic β-cells and thereby enabling precise regulation of synaptic transmission and the energy homeostasis of neural circuits on demand [31]. This dual source of insulin implies that the central nervous system is governed by both peripheral and neuronally derived signals, integrating direct and indirect modes of regulation.

2.1 The Direct Relationship Between Insulin and the Central Nervous System

The relative contributions of peripheral versus brain-derived insulin in modulating central nervous system (CNS) functions remain a topic of debate. Nonetheless, mounting evidence underscores the direct actions of insulin within the CNS, including the regulation of appetite, neuronal glucose uptake, growth hormone secretion, and neuroprotection. For instance, insulin administration into the central amygdala has been shown to reduce food intake and body weight, likely by modulating neuropeptide Y signaling and activity in other neuronal subpopulations involved in feeding regulation (Fig. 1A) [32]. In another study, intranasal insulin significantly enhanced the suppression of endogenous glucose production compared to placebo, suggesting that increased insulin signaling in the hypothalamus and striatum contributes to glucose homeostasis by simultaneously inhibiting hepatic glucose output and promoting peripheral glucose uptake (Fig. 1B) [33]. In addition, neurons in the hypothalamic paraventricular nucleus have been shown to transport newly synthesized insulin via their axon terminals to the anterior pituitary, where it stimulates growth hormone gene expression and secretion, thereby promoting somatic growth (Fig. 1C) [34]. In terms of neuroprotection, cultured-cell studies have demonstrated that insulin promotes neurite distribution and axonal growth in rat fetal neurons through MAPK-dependent phosphorylation [35]. Consistently, the first trial of intranasal insulin administration in healthy subjects reported improvements in attention and memory performance [36], highlighting the essential role of insulin signaling in preserving neuronal integrity and survival (Fig. 1D) [37]. Collectively, these findings highlight the multifaceted and direct roles of insulin in the CNS, which are closely linked to central nervous system homeostasis.

2.2 The Indirect Relationship Between Insulin and the CNS

The CNS plays a pivotal role in regulating insulin secretion and maintaining glucose homeostasis, primarily through glucose-sensing neurons located in the hypothalamus [38]. For instance, high-fat diet (HFD)-induced obesity has been shown to impair hypothalamic glucose sensing mechanisms, including alterations in AMPK activity [39], thereby disrupting energy and glucose homeostasis. Moreover, recurrent hypoglycemic episodes can desensitize hypothalamic glucose-sensing neurons, impairing the ability of diabetic individuals to suppress insulin secretion and augment glucagon release during hypoglycemia, ultimately leading to a blunted sympathoadrenal response [39]. Insulin interacts with the CNS not only through direct actions but also, seemingly, through indirect pathways.

2.2.1 Metabolic Regulation

A recent study using retrograde viral tracing in Ins1-Cre mice demonstrated direct CNS-to-pancreas connectivity: 72 hours after viral injection into the pancreatic duct, fluorescent signals were observed specifically in the paraventricular nucleus of the hypothalamus, but not in other regions such as the arcuate nucleus, central amygdala, periaqueductal gray, parabrachial nucleus, or dorsal motor nucleus of the vagus [40]. These findings indicated a discrete neurocircuit linking a subset of hypothalamic paraventricular nucleus neurons to pancreatic β-cells, implicating a sympathetic pathway through which hypothalamic neu-

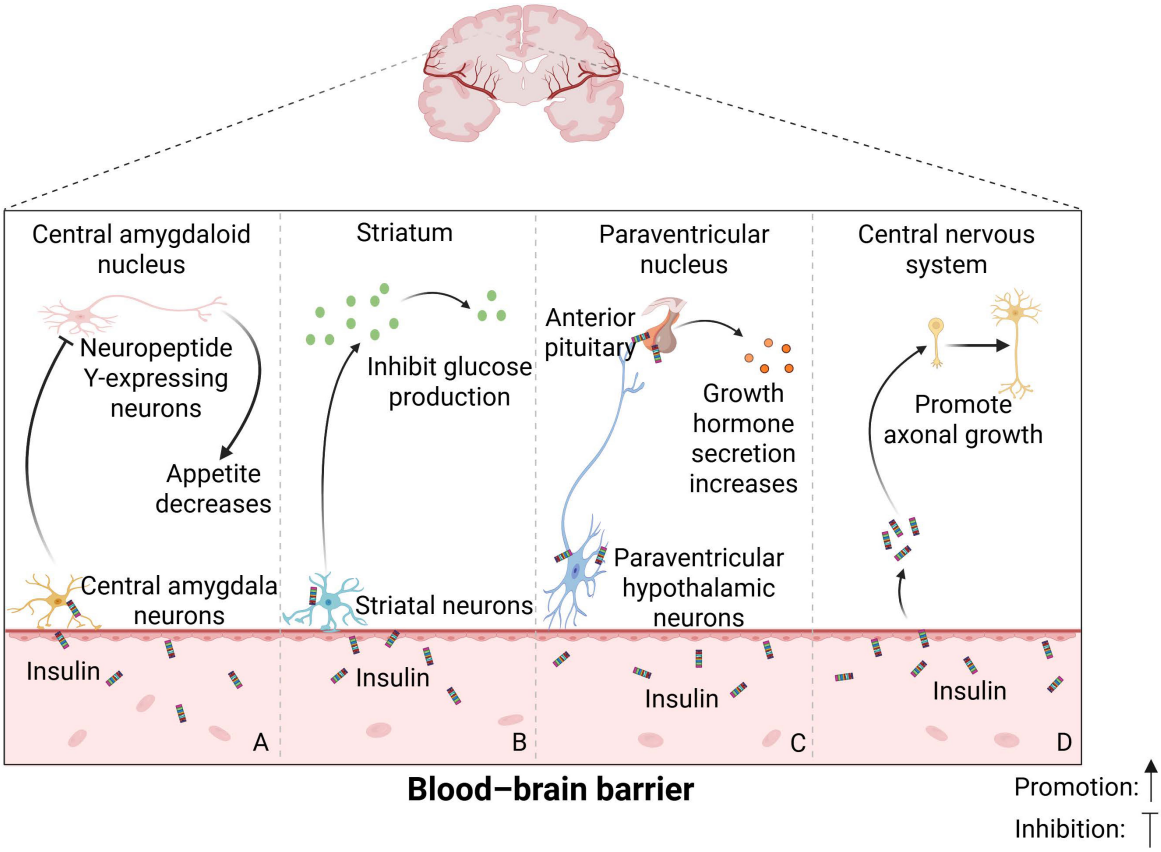

Fig. 1. The role of insulin in the central nervous system. Insulin performs a range of critical functions within the central nervous system, including (A) the regulation of appetite, (B) modulation of neuronal glucose uptake, (C) control of growth hormone secretion, and (D) neuroprotection. Figure created with BioRender (https://www.biorender.com).

rons communicate with peripheral insulin-secreting cells. Of particular note, insulin plays a pivotal role in energy metabolism [41], with the CNS also serving as a critical target of its actions [42]. Compared with basal metabolic conditions, neuronal stimulation markedly enhances glycolytic flux under the influence of insulin, thereby sustaining the energy homeostasis required for normal neuronal function [43]. When insulin signaling is impaired, the resulting loss of metabolic control in the brain may compromise synaptic transmission and plasticity, ultimately leading to memory deficits [44]. These results further underscore the existence of a bidirectional and mechanistically critical information flow between the CNS and peripheral metabolic systems.

2.2.2 Inflammatory Response

The initial (cephalic) phase of insulin secretion is mediated by vagal stimulation and occurs independently of direct glucose sensing by pancreatic β-cells. Recent studies have revealed that this phase is impaired in both obese humans and animal models, primarily due to dysregulated interleukin (IL)-1β signaling. Specifically, microglia-derived IL-1β appears to integrate sensory cues related to nutrient intake and, via central nicotinic acetylcholine receptor signaling, orchestrates the neuronally mediated release of insulin during the cephalic phase. This mechanism is thought to underlie the autonomic dysfunction in cephalic insulin release observed in individuals with obesity [45]. It is interesting to note that insulin is regarded as an anti-inflammatory factor [46], capable of suppressing IL-1β secretion by preventing the assembly of apoptosis-associated speck-like proteins in macrophages [47]. This interaction appears to establish a negative feedback loop, linking energy metabolism with immune regulation. Moreover, insulin can activate the PI3K/Akt signaling pathway and, in combination with antioxidants, markedly reduce serum tumor necrosis factor (TNF)-α levels, thereby attenuating inflammation [48]. Peripheral inflammation has been shown to compromise the blood-brain barrier, allowing peripheral immune cells and inflammatory mediators to infiltrate the CNS. Pro-inflammatory cytokines such as TNF-α and IL-1β promote microglial activation toward the M1 phenotype, leading to elevated reactive oxygen species (ROS) levels, oxidative stress, synaptic dysfunction, and neuronal apoptosis [49]. These findings suggest that insulin may exert an indirect role in maintaining CNS homeostasis by mitigating inflammatory responses.

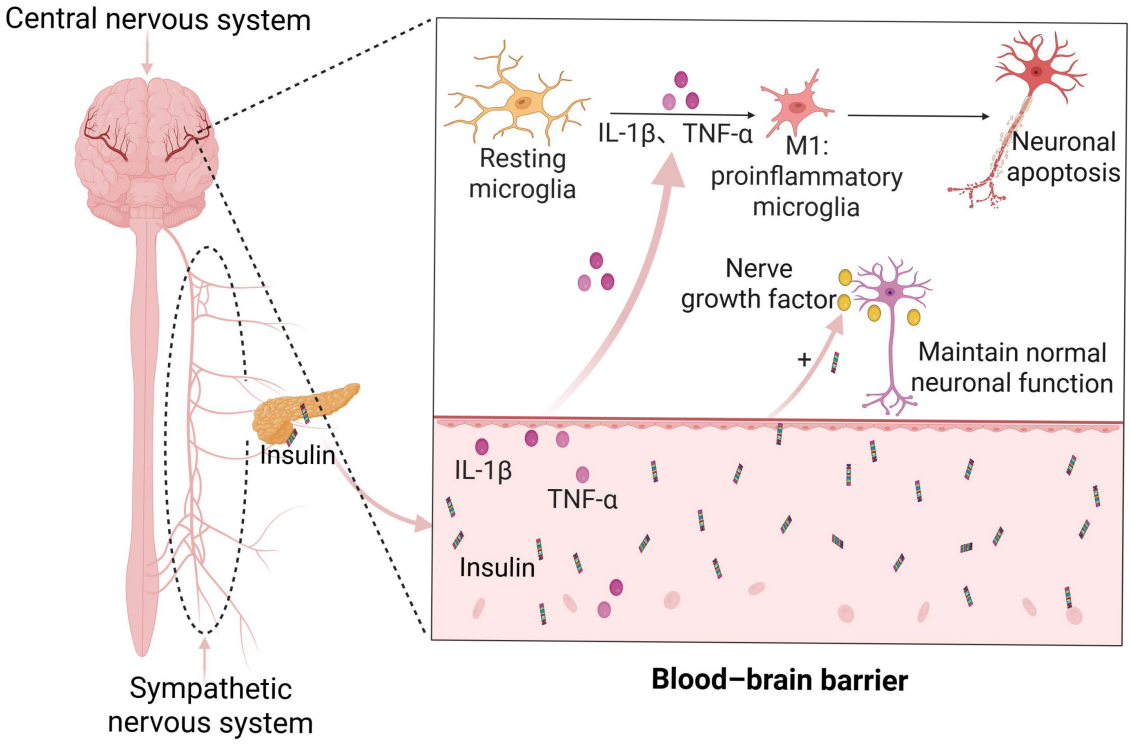

Fig. 2. The indirect relationship between insulin and the central nervous system. The central nervous system communicates bidirectionally with the periphery via sympathetic neuronal projections to pancreatic β-cells. pro-inflammatory cytokines such as TNF-α and IL-1β drive the activation of microglia toward a pro-inflammatory m1 phenotype. insulin mitigates neuronal apoptosis by suppressing IL-1β and TNF-α expression, while synergistically augmenting the actions of nerve growth factor to preserve neuronal integrity and sustain normal neurophysiological function. TNF, tumor necrosis factor; IL, interleukin. Figure created with BioRender (https://www.biorender.com).

2.2.3 Neuronal Integrity

Notably, insulin functions not only as a regulator of glucose homeostasis but also as a neurotrophic factor, exerting significant effects in both the central and peripheral nervous systems [50]. For instance, elevated insulin secretion can enhance levels of nerve growth factor (NGF), which binds with high affinity to calmodulin-dependent protein kinase A, promoting the growth and development of central and peripheral neurons, accelerating repair after neural injury, and sustaining normal neural function [51]. A number of studies have indicated considerable overlap between insulin and NGF signaling pathways [52], with insulin synergistically enhancing NGF-induced neurite outgrowth [53]. Conversely, NGF can increase Na^+ current density in pancreatic β-cells, thereby stimulating insulin secretion [54]. Through this reciprocal relationship, insulin can be regarded as a complementary mechanism to NGF, indirectly contributing to the maintenance of neuronal integrity.

Taken together, insulin orchestrates a complex network of signaling mechanisms between peripheral and central compartments, regulating metabolism, inflammatory responses, and neuronal integrity to maintain physiological homeostasis (Fig. 2).

3. IR as a Potential Mechanism in the Pathogenesis of T2DM and AD

IR refers to a diminished biological response of insulin-targeted tissues to physiological levels of insulin, and is also termed reduced insulin sensitivity [55]. IR represents a central pathological feature of T2DM, affecting multiple tissues including the liver, skeletal muscle, myocardium, and pancreatic β-cells [56]. In the liver, IR manifests as altered lipid metabolism, resulting in increased hepatic fat accumulation [57]. Prolonged compensatory hyperinsulinemia may lead to progressive β-cell failure; studies have demonstrated that β-cell volume reduction precedes the onset of T2DM [58]. In IR, impaired glucose uptake in muscle is primarily attributed to abnormalities in insulin signaling pathways, rather than to defects of the glucose transport machinery itself [59] (Fig. 3A). In patients with T2DM, the expression of insulin receptors and IRS-1 in peripheral tissues is markedly downregulated [60]. IR impairs IRS autophosphorylation, thereby attenuating the PI3K/Akt signaling cascade, which ultimately results in hyperactivation of glycogen synthase kinase (GSK)-3β [61]. GSK-3β, a subtype of GSK-3, exerts detrimental effects when overactivated, impairing glucose transport and reducing insulin sensitivity [62]. Inhibition of GSK-3β activity has been

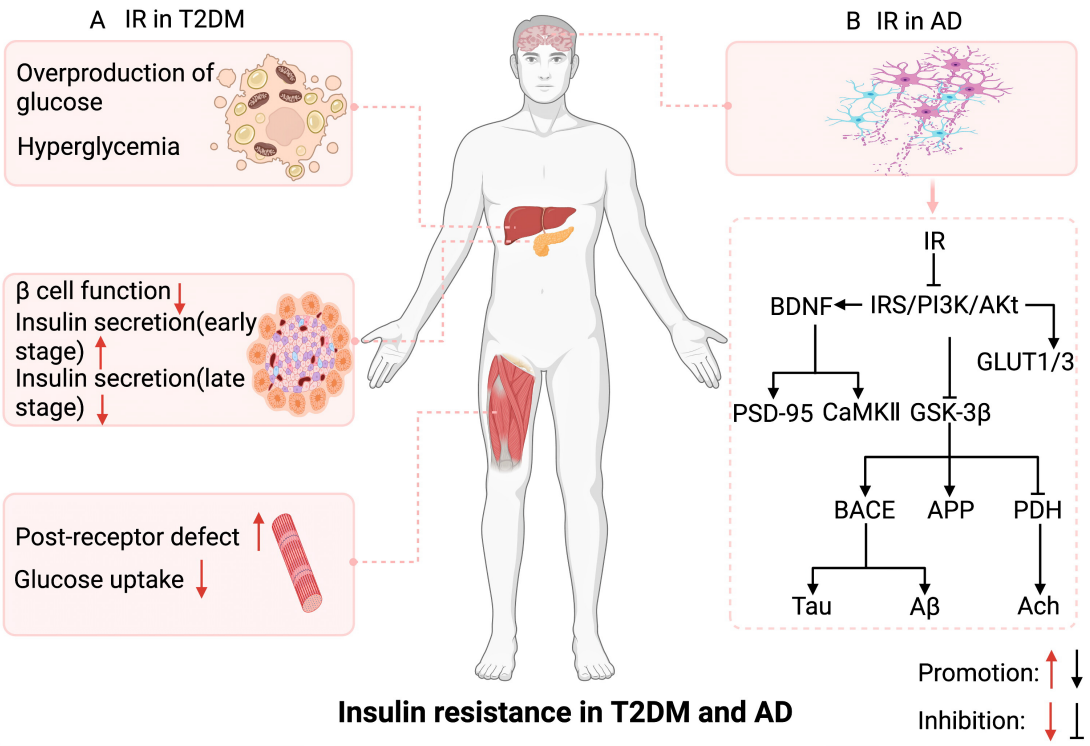

Fig. 3. The potential mechanism of insulin resistance in the pathogenesis of T2DM and AD. (A) Insulin resistance in T2DM involves multiple tissues, including the liver, skeletal muscle, and β-cells. (B) Insulin resistance in AD is associated with pathological alterations in brain tissue. T2DM, Type 2 diabetes mellitus; AD, Alzheimer's disease; IR, insulin receptor; BDNF, brain-derived neurotrophic factor; IRS, insulin receptor substrate; PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; GLUT, glucose transporter; PSD-95, postsynaptic density protein 95; CaMKII, Ca^{2+}/calmodulin-dependent protein kinase II; GSK-3β, glycogen synthase kinase-3 beta; BACE, β-site amyloid precursor protein-cleaving enzyme; APP, amyloid precursor protein; PDH, pyruvate dehydrogenase; Tau, microtubule-associated protein tau; Aβ, amyloid-beta; Ach, acetylcholine. Figure created with BioRender (https://www.biorender.com).

shown to improve IR, positioning it as a potential therapeutic target for T2DM [63,64]. Moreover, excessive activation of GSK-3β also induces neuropathological damage, including synaptic injury and hyperphosphorylation of tau protein [65]. Specifically, overactivation of GSK-3β stimulates the expression of amyloid precursor protein (APP) mRNA in AD, enhancing the activity of β-site APP cleaving enzyme 1 (BACE1), and promotes tau phosphorylation and the formation of NFTs. This cascade exacerbates Aβ aggregation, memory impairment, and inflammatory responses induced by microglial activation [66,67]. Furthermore, GSK-3β can phosphorylate and inactivate pyruvate dehydrogenase in the brain, leading to a reduction in acetylcholine, a key neurotransmitter in cholinergic neurons, thereby accelerating AD progression [68]. In other words, IR can affect AD through multiple pathways, including energy metabolism and the preservation of neuronal integrity.

3.1. IR and Brain Energy Metabolism

Despite representing approximately 2% of total body weight, the human brain consumes nearly 25% of the body's resting glucose supply [69]. IR impairs cerebral energy metabolism in AD patients, resulting in neuronal energy deficiency [70]. Compelling evidence has indicated a strong association between AD and metabolic dysfunction, with impaired glucose metabolism emerging more than a decade prior to clinical-symptom onset [71]. As glucose cannot freely cross cell membranes, its cellular uptake relies on facilitative GLUTs. In the brain, GLUT1 and GLUT3 serve as the primary transporters mediating glucose entry into neurons [72]. IR compromises the function of GLUT1 and GLUT3, reducing neuronal glucose uptake and subsequently lowering levels of uridine diphosphate N-acetylglucosamine (UDP-GlcNAc), a key glucose-derived metabolite [73]. UDP-GlcNAc is a direct donor substrate for O-linked N-acetylglucosaminylation (O-GlcNAcylation). Reduced tau O-GlcNAcylation has been implicated in tau hyperphosphorylation and neurofibrillary degeneration [74], suggesting that diminished cerebral glucose uptake may actively contribute to AD progression [75]. Moreover, decreased brain energy metabolism is associated with enhanced BACE1 activity, promoting the generation and accumulation of Aβ [76].

3.2 IR and Neurons

Notably, brain-derived neurotrophic factor (BDNF) plays a pivotal role in neuronal growth and the maintenance of synaptic plasticity. Elevated BDNF levels are critical for mitigating the progression of AD [77]. In the brain, insulin promotes synaptogenesis by upregulating BDNF expression via activation of the IRS/PI3K/Akt signaling cascade [78]. BDNF binds to its receptor TrkB and modulates both postsynaptic density protein 95 and calmodulin-dependent protein kinase II, thereby enhancing synaptic plasticity. Inhibition of IR elevates endogenous BDNF levels [79,80] (Fig. 3B). IR-driven chronic inflammation exacerbates AD progression, potentially mediated by the release of proinflammatory cytokines from activated microglia [81,82]. Furthermore, mitochondrial dysfunction and endoplasmic reticulum (ER) stress, induced by IR, contribute to the progression of AD pathology [83]. Specifically, mitochondrial impairment reduces cellular energy production and elevates reactive ROS, impairing neuronal function and structure [84]. Concurrently, ER stress exacerbates the accumulation of misfolded proteins, disrupting intracellular homeostasis and diminishing neuronal efficiency [85]. Additionally, IR has been shown to suppress neuronal autophagy, promoting the aggregation of Aβ plaques and hyperphosphorylated tau, ultimately driving the formation of hallmark amyloid plaques and NFTs characteristic of AD [86,87]. Emerging evidence has focused on a significant epigenetic association between IR and AD at the *CPT1A* gene locus [88]. A separate study reached a similar conclusion, further substantiating a potential causal link between IR and AD from a genetic perspective [89]. Collectively, these findings suggest that targeting IR may represent a promising therapeutic strategy for the intervention of both T2DM and AD.

4. Mechanistic Impact of IR in T2DM and AD

T2DM and AD exhibit bidirectional crosstalk, sharing numerous overlapping molecular mechanisms—including IR, mitochondrial dysfunction, oxidative stress, chronic inflammation, impaired autophagy, tau hyperphosphorylation, and Aβ deposition—with IR emerging as a potential contributor. Beyond impairing insulin signaling, IR also induces neuroinflammation, disrupts neuronal autophagy, and alters energy metabolism, thereby facilitating the accumulation of Aβ and hyperphosphorylated tau. Furthermore, IR may interact synergistically with mitochondrial dysfunction, oxidative stress, inflammation, and autophagic dysregulation, to form a vicious cycle that accelerates pathological progression in both diseases.

4.1 IR and Mitochondrial Dysfunction

Mitochondria, as essential organelles, play a central role in energy metabolism, apoptosis, and the modulation of ROS [90,91]. Mitochondrial dysfunction can be characterized by aberrant alterations in biogenesis, fusion-fission dynamics, mitophagy, and overall mitochondrial function [92]. Mitochondrial biogenesis is primarily regulated by peroxisome-proliferator-activated receptor-gamma coactivator 1-alpha (PGC-1α). A marked downregulation of PGC-1α expression has been observed in the skeletal muscle of T2DM patients and in AD mouse models [93,94]. This impairment in mitochondrial biogenesis may contribute to the progression of both T2DM and AD by compromising mitochondrial renewal capacity [95–97]. Under physiological conditions, mitochondrial fission and fusion are maintained in dynamic equilibrium. However, in AD, this balance is disrupted, with increased fission and reduced fusion. Aberrant interactions among Aβ, phosphorylated tau, and the fission protein dynamin-related protein 1 contribute to decreased expression of mitophagy regulators, including PTEN-induced putative kinase 1 and Parkin RBR E3 ubiquitin protein ligase, ultimately resulting in impaired clearance of damaged mitochondria [98]. Modulating mitochondrial dynamics—namely fission, fusion, and mitophagy—may thus alleviate AD-related cognitive deficits [99]. Moreover, dysregulated mitochondrial fusion and fission have also been implicated in hepatic IR [100], and therapeutic manipulation of these processes has shown potential in the prevention and treatment of T2DM [101]. In addition, prolonged high-glucose dietary exposure in an AD mouse model induced mitochondrial abnormalities that exacerbate cerebral Aβ aggregation, suggesting that hyperglycemia may accelerate AD pathological progression [102]. These findings underscore mitochondrial dysfunction as a shared pathological hallmark of both T2DM and AD [103].

Mitochondrial dysfunction can induce IR and is closely associated with the development of T2DM [104, 105]. It may also represent a key factor contributing to cognitive impairment [106]. In states of IR, mitochondrial dysfunction in the brain is accompanied by impaired cognitive function [107] (Fig. 4A). Intranasal insulin administration, which ameliorates IR, has been shown to restore methamphetamine-induced cognitive impairment, likely due to the activation of the insulin signaling pathway (PI3K/Akt/GSK-3β) and enhanced mitochondrial biogenesis in the brain [108]. In T2DM animal models, peripheral IR develops prior to the onset of cerebral mitochondrial dysfunction, impaired brain insulin sensitivity, and cognitive deficits [109]. Further studies have confirmed that IR may induce mitochondrial dysfunction by modulating the IRS/PI3K/FOXO signaling pathway [110,111]. FOXO1 regulation of peroxisome-proliferator-activated receptor δ may serve as a key link between IR and mitochondrial function [112]. In T2DM patients with IR, increased IRS-1 serine phosphorylation and reduced Akt activation correlate with diminished skeletal muscle mitochondrial function [113]. Collectively, these findings highlight that IR and mitochondrial dysfunction mutually reinforce one another,

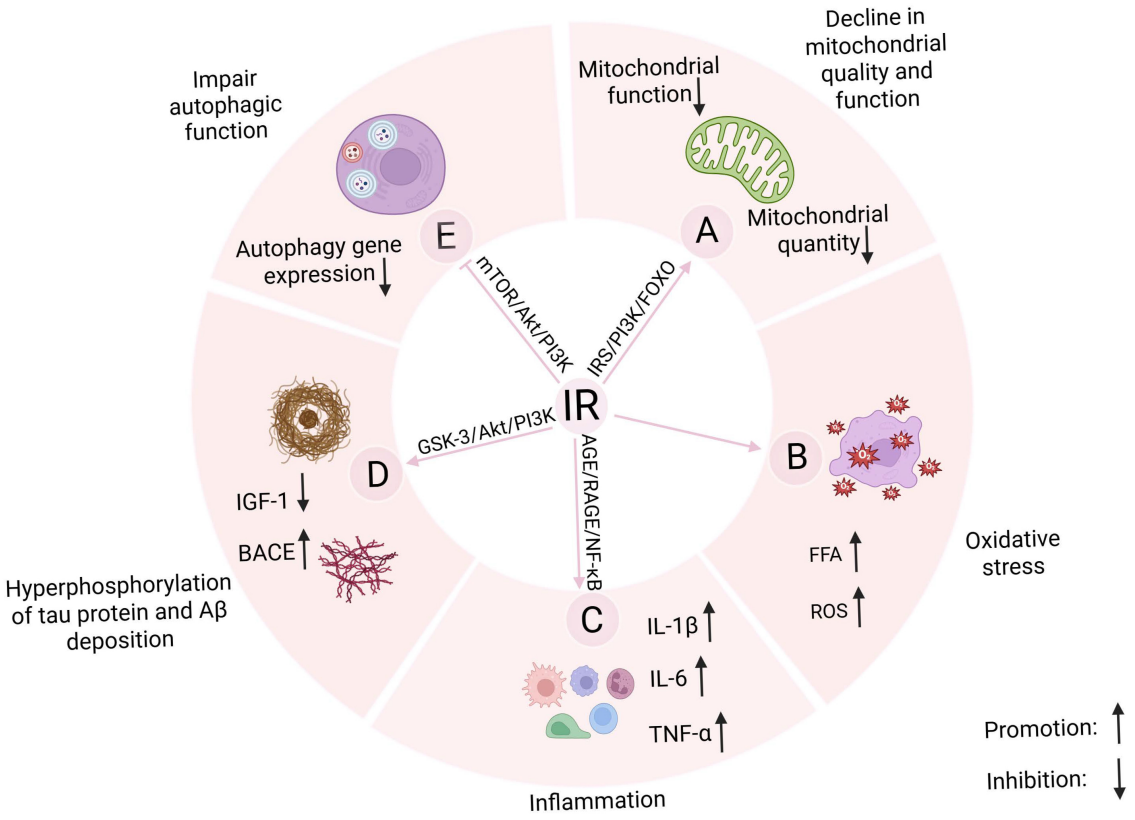

Fig. 4. Effect of insulin resistance on the mechanism of crosstalk between T2DM and AD. Insulin resistance may engage in a vicious cycle with (A) mitochondrial dysfunction, (B) oxidative stress, (C) chronic inflammation, and (E) autophagy dysregulation, mutually exacerbating these processes while (D) contributing to Aβ accumulation and phosphorylated Tau aggregation. FFA, free fatty acids; ROS, reactive oxygen species; IGF, insulin-like growth factor; AGE, advanced glycation end products; RAGE, receptor for advanced glycation end products; IRS, insulin receptor substrate; FOXO, forkhead box O; mTOR, mechanistic target of rapamycin. Figure created with BioRender (https://www.biorender.com).

playing a critical role in both the onset and progression of T2DM and AD.

4.2 IR and Oxidative Stress

Disruption of redox homeostasis leads to the accumulation of ROS or reactive nitrogen species, which interferes with normal cellular signaling, induces damage to biomolecules—including proteins, lipids, and DNA—and alters the expression of stress-responsive genes, compromising cellular integrity and potentially triggering cell death [114]. The central mechanism of oxidative stress lies in the imbalance between ROS production and clearance [115,116]. Excessive ROS generation compromises antioxidant defenses and induces oxidative damage, which serves as a critical contributor to the pathogenesis of both T2DM and AD [117]. In streptozotocin-induced diabetic mice, levels of superoxide, protein oxidation products, and lipid peroxidation products are markedly elevated in the brain, accompanied by a significant reduction in the activities of antioxidant enzymes such as superoxide dismutase (SOD) and catalase (CAT) [118]. In AD patients, the enzymatic activities of key antioxidants—including glutathione peroxidase (GPX), CAT, and peroxiredoxins—are also diminished in the superior temporal gyrus [119]. Moreover, oxidative stress exacerbates T2DM progression [120], thereby promoting the accumulation of advanced glycation end products (AGEs). The specific binding of AGEs to their receptor (RAGE) suppresses antioxidant enzyme activity and reduces glutathione (GSH) levels, thereby amplifying ROS generation [121]. Notably, persistently elevated levels of AGEs in T2DM patients may exacerbate amyloid pathology by inhibiting α-secretase activity and enhancing the expression and activation of β- and γ-secretases [122,123], ultimately increasing Aβ production, aggregation [124], and oligomerization, which in turn impairs memory function.

Studies have shown that oxidative stress contributes to IR, mainly manifested as an increase in oxidative stress markers and a significant reduction in insulin-receptor activation [125,126]. Conversely, IR also exacerbates oxidative stress [127]. Under IR conditions, increased oxidative stress is primarily reflected by enhanced NADPH oxidase activity, alongside reduced activities of antioxidant enzymes such as CAT, GPX, and SOD, as well as decreased GSH synthesis [128]. The degree of oxidative

damage in the brain is positively correlated with the IR index, suggesting that IR contributes to the development of neuronal oxidative stress [129]. Under IR conditions, excessive fatty acids crossing the blood-brain barrier may elevate ROS production in neurons, inducing ER stress and neuronal toxicity, thereby exacerbating AD pathology [130,131] (Fig. 4B). In T2DM, IR impairs β-cell function and vitality, leading to increased lipotoxicity and ROS production [132], while also activating c-Jun N-terminal kinase (JNK) and IκB kinase (IKK) inhibitors, thereby exacerbating the pathological progression of T2DM [133]. Collectively, the elevated oxidative stress induced by IR may contribute to the onset and progression of both T2DM and AD.

4.3 IR and Chronic Inflammation

Inflammation is primarily regulated by two categories of cytokines: pro-inflammatory cytokines such as IL-1β, IL-6, IL-18, TNF-α, and interferon (IFN)-γ, and anti-inflammatory cytokines such as IL-4, IL-10, IL-13, and transforming growth factor (TGF)-β [134]. Extensive research has established chronic inflammation as a pivotal shared pathogenic factor in both T2DM and AD [135,136]. Hyperglycemic conditions impair leukocyte activity, inducing immune dysfunction, promoting the production and release of pro-inflammatory cytokines such as IL-6, IL-1β, and TNF-α. This, in turn, disrupts peripheral insulin signaling pathways and β-cell function in T2DM patients [137,138]. In AD patients, levels of pro-inflammatory cytokines such as TNF-α and IL-1β are significantly elevated [139]. Inflammation is considered a crucial precursor to Aβ deposition and the abnormal phosphorylation of tau protein [140]. Specifically, cytokines released upon microglial activation can promote the pathological processes of AD [141]. For instance, IL-18 exacerbates Aβ deposition by activating the GSK-3β pathway [142]. TNF-α enhances the production of β-secretase, thereby increasing Aβ generation [143].

A vicious cycle exists between IR and the inflammatory response, with each exacerbating the other [144]. Under physiological conditions, insulin is the only hypoglycemic hormone in the human body exerting anti-inflammatory effects [145]. For example, insulin in combination with antioxidants markedly suppressed TNF-α levels in diabetic mice [146], and local administration of insulin in mice with colitis similarly attenuated inflammatory responses [147]. Further studies have confirmed that insulin inhibits IL-1β secretion by modulating the NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome, thereby reducing inflammation [47]. Conversely, IR promotes the local accumulation of macrophages, triggering inflammatory processes [148]. Macrophages activate inflammatory signaling pathways such as JNK, IKK/NF-κB, and JAK/STAT by secreting pro-inflammatory cytokines (e.g., TNF-α, IL-6, and IL-1β), which contribute to IR in adipose tissue, liver, and muscle [149,150]. In IR, insulin fails to exert its normal function, resulting in compensatory hyperinsulinemia and disruption of the insulin signaling pathway [151]. IR induces hyperglycemia, leading to the excessive formation of AGEs, which bind to RAGE and subsequently activate the AGE-RAGE-NF-κB axis [152]. NF-κB activation further influences JNK and IKKα/β, exacerbating inflammation [153] (Fig. 4C). In brain tissue, activation of microglial cells mediates the inflammatory response, identified as a key mechanism driving IR [154]. Chronic inflammation driven by IR may accelerate AD progression by sustaining a damaging cycle of inflammation and neuronal damage [83]. Therefore, chronic inflammation induced by IR may both initiate and exacerbate the development of T2DM and AD.

4.4 IR and Aβ Deposition, Abnormal Phosphorylation of Tau Proteins

Two pathological hallmarks of AD are the aberrant accumulation of insoluble Aβ peptides, generated through sequential cleavage of APP by β- and γ-secretases, and tau hyperphosphorylation [155,156]. Notably, similar pathological alterations occur in peripheral organs and are closely linked to T2DM [157]. Aβ antagonizes the binding of insulin and insulin-like growth factor 1 (IGF-1) to their receptors, promoting the release of pro-inflammatory cytokines and contributing to IR [158]. In T2DM, dysregulated insulin signaling, chronic inflammation, and oxidative stress disrupt APP metabolism, thereby promoting Aβ accumulation and aggravating AD-related neurodegeneration [159]. Tau, a microtubule-associated protein, plays a pivotal role in maintaining microtubule stability and modulating intracellular signaling under physiological conditions [160]. Tau levels are elevated in pancreatic β cells of individuals with T2DM, and tau deficiency enhances insulin secretion and disrupts glucose homeostasis [161]. The aberrant accumulation of Aβ and hyperphosphorylated tau may exacerbate pancreatic β-cell dysfunction and impair insulin sensitivity in peripheral tissues such as the liver. These alterations may represent key molecular links mediating the bidirectional crosstalk between AD and T2DM [161,162].

Insulin has been shown to inhibit Aβ aggregation by reducing the GM1 ganglioside–rich microdomains in neuronal membranes [163] and decreasing the amount of cell-surface-bound Aβ peptides [164]. In AD mice treated with insulin, cerebral Aβ deposition exhibited a trend toward reduction [165,166]. Conversely, insulin deficiency impaired cerebral insulin signaling in AD mice, promoting hyperphosphorylation of tau protein [167]. Both peripheral and intranasal insulin administration can effectively reverse this process [168–170], leading to improvements in cognitive function [171]. Under conditions of IR, the PI3K/Akt signaling pathway is inhibited, reducing the dephosphorylation of APP by IGF-1 and promoting amyloid plaque formation and tau phosphorylation [172,173]. Furthermore, IR can induce excessive tau phosphorylation via the JNK

Table 1. Exercise improves insulin resistance in type 2 diabetes and Alzheimer's disease.

Disease model	Type of exercise	Exercise dose	Related functional and molecular changes	Source and tests	Reference
T2DM patients	Aerobic exercise	60 min/time, 75% VO_2 peak, 4–5 times/week, 12–16 weeks	Fasting blood glucose↓; Insulin sensitivity↑	Plasma	[200]
	Short-term interval training	2 × 30 s bouts, 15 min/time, 2 weeks	Insulin sensitivity and Brain glucose metabolism↑	Brain and plasma	[211]
	Short-term exercise training (treadmill walking and stationary cycling)	50–60 min/time, 80–85% HRmax, 7 days	Insulin sensitivity↑	Plasma	[212]
	Structured exercise programs (aerobic, resistance, and combined)	15–45 min/time, 3–5 times/week, 12 weeks	Fasting blood glucose, HbA1c↓; Insulin resistance↓	Plasma	[204]
T2DM mice	Treadmill running	10 m/min, 60 min/d, 5 times/week, 4 weeks	Insulin sensitivity and GLUT4↑; Insulin resistance↓	Plasma	[198]
	Aerobic exercise	45 min/time, 5 times/week, 8 weeks	IRS-1 and Akt↑	Liver	[199]
	High-intensity interval training	16–26 m/min, 4 min/time, 5 times/week, 8 weeks	Fasting blood glucose↓; Glucose tolerance, GLUT4, and PGC-1α↑	Plasma	[202]
		16–26 m/min, 4 min/time, 5 times/week, 8 weeks	IRS1/PI3K/Akt↑; Insulin sensitivity and Glucose tolerance↑	Liver and Plasma	[203]
T2DM rat	Chronic resistance exercise	3 sets/4 reps daily, 3 times/week, 8 weeks	Muscle musclin protein and fasting blood glucose↓; Akt/GLUT4↑	Muscle and Plasma	[201]
AD patients	Treadmill running	4 km/h, 80% HRmax	IGF-1↑	Plasma	[208]
	Aerobic exercise	45–60 min/time, 4 times/week, 24 weeks	Insulin sensitivity↑	Plasma	[213]
AD rat	Treadmill running	8–14 m/min, 30 min/times, 5 times/week, 6 weeks	IRS/PI3K/Akt/GSK3α and cognitive function↑	Brain	[206]
		10–15 m/min, 30–60 min/times, 4 weeks	IGF-1, BDNF, and GLUT4↑	Hypothalamus	[207]
AD mice	Treadmill running	3–13 m/min, 30–50 min/times, 1/d, 6 times/week, 12 weeks	IRS/PI3K and Cognitive function↑	Hippocampus	[205]
		22 m/min, 60 min/times, 5 times/week, 16 weeks	GLUT1 and Cognitive function↑	Plasma	[209]
AD-like model	Aerobic exercise and resistance exercise	60 min/time, 3 times/week, 6 weeks	IGF-1 and Cognitive function↑	Brain and plasma	[210]

IGF-1, insulin-like growth factor 1; BDNF, Brain-Derived Neurotrophic Factor; PGC-1α, Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-Alpha; IRS, Insulin Receptor Substrate; GLUT1/4, glucose transporter type 1/4; ↑, upregulation; ↓, downregulation.

pathway [174]. In T2DM, IR is associated with the overactivation of GSK-3, which impairs glucose transport [175]. GSK-3 enhances Aβ synthesis by downregulating α-secretase activity and upregulating β-secretase activity, while also disrupting acetylcholine activity. This accelerates axonal degeneration and failure of axonal transport, contributing to cognitive impairments in AD patients [176]. Additionally, GSK-3 is critically involved in tau protein regulation. Inhibition of GSK-3 can prevent tau hyperphosphorylation and Aβ aggregation [177] (Fig. 4D). Taken together, Aβ deposition and tau hyperphosphorylation serve as crucial links between T2DM and AD, with IR potentially playing a pivotal role in exacerbating these pathological processes, thereby facilitating the progression of both diseases.

4.5 IR and Autophagy

Autophagy is a lysosome-dependent degradation mechanism responsible for clearing damaged organelles and aberrantly aggregated proteins within cells [178]. During brain aging, defects in the autophagy-lysosomal pathway increase neuronal vulnerability, and genetic mutations affecting autophagic or lysosomal function are causally linked to the development of neurodegenerative disorders, including AD [179]. Similarly, dysregulated autophagy in pancreatic β cells is closely associated with the pathogenesis of T2DM [180]. Autophagy has been identified as a critical and commonly dysregulated pathway in both AD and T2DM [181]. In AD, impaired autophagy disrupts the extracellular clearance of Aβ, thereby altering its secretion dynamics [182]. Activation of autophagy suppresses tau aggregation and reduces its cytotoxicity [183]. Under physiological conditions, autophagy confers resistance to oxidative stress and preserves the functional integrity of pancreatic β cells and insulin-responsive tissues. Conversely, autophagy deficiency contributes to β-cell dysfunction and promotes IR, thereby accelerating the progression of T2DM [184,185].

Studies have demonstrated that activation of autophagy alleviated IR in both T2DM and AD [186,187], further underscoring the bidirectional interplay between autophagy and IR [86]. Under physiological conditions, insulin exerts anabolic effects by activating the PI3K/Akt/mTORC1 (mechanistic target of rapamycin complex 1) pathway, thereby suppressing autophagic flux [188]. Moreover, insulin has the potential to suppress autophagy in various diseases [189,190], including diabetes [191]. In addition, insulin can effectively inhibit astrocytic autophagy via transcriptional regulation, thereby improving neural function [192]. It is intriguing that although IR triggers autophagy upregulation in adipose tissue [193], paradoxical suppression of both autophagic activity and expression of key autophagy-related genes occurs under conditions of IR and hyperinsulinemia [194] (Fig. 4E). Transcriptomic analyses of skeletal muscle from individuals with longstanding and severe IR in the context of T2DM have revealed the downregulation of autophagy-related genes, suggesting that IR may contribute to the suppression of autophagy in muscle tissue [195]. In addition, IR impairs neuronal autophagy, promoting the accumulation of Aβ and tau phosphorylation. Notably, decreased expression of the autophagy-related protein beclin1 has been observed in the early stages of AD, accompanied by intraneuronal Aβ accumulation [87]. These findings point to a complex bidirectional relationship between IR and autophagy, wherein IR suppresses autophagic activity, leading to cellular dysfunction and exacerbation of metabolic dysregulation, whereas impaired autophagy may further intensify IR, perpetuating a vicious cycle.

5. The Preventive and Therapeutic Role of Exercise-Induced Suppression of IR in T2DM and AD

IR is a potential pathogenic mechanism in both T2DM and AD, and its inhibition can effectively delay progression in both conditions. Exercise, a non-pharmacological intervention, offers significant advantages in preventing and treating neurological and metabolic disorders. By ameliorating IR, physical exercise helps maintain glucose homeostasis and stabilize blood glucose levels, enhancing insulin sensitivity. Moreover, it alleviates the excessive phosphorylation of tau protein and the aggregation of β-amyloid, ultimately improving cognitive function.

5.1 Exercise-Induced Reduction of IR in the Improvement of T2DM and AD

As chronic conditions, T2DM and AD profoundly impair patients' quality of life. Among various therapeutic strategies, exercise emerges as a non-pharmacological intervention that mitigates both conditions by effectively attenuating IR [196]. Studies have confirmed that in patients with T2DM [197], aerobic exercise can significantly improve glycemic control, enhance insulin sensitivity [198], and even upregulate genes critical for maintaining glucose homeostasis and reducing IR [199]. For example, T2DM patients who performed aerobic exercise 4–5 days per week, 60 minutes per day at 75% of VO_2 peak for 12–16 weeks, exhibited marked reductions in fasting blood glucose levels and improvements in insulin sensitivity (Table 1, Ref. [198–213]) [200].

In the context of exercise-mediated suppression of IR, myokines have garnered increasing attention. Evidence from both animal and human studies suggests that myokines may contribute to IR in T2DM by impairing glucose metabolism [214,215]. Resistance training may attenuate IR and hyperglycemia in T2DM rats by downregulating myokine expression and activating the Akt/GLUT4 signaling pathway [201]. In HFD mouse models, eight weeks of high-intensity interval training (HIIT) or moderate-intensity continuous training (MICT) signifi-

cantly enhanced hepatic PI3K/Akt/GSK3β signaling. Notably, both exercise modalities also promoted the formation of mitochondria-associated membranes (MAMs) in the liver. These findings suggest that exercise may alleviate hepatic IR by facilitating the formation of MAMs [216]. Recent evidence has indicated that HIIT significantly improves glycemic parameters in T2DM murine models, including fasting blood glucose, fasting insulin levels, and HOMA-IR index, while enhancing glucose homeostasis, mitochondrial dynamics, and skeletal muscle function [202,203,217]. Furthermore, a 12-week structured exercise intervention showed that aerobic, endurance, and combined exercise modalities effectively suppress IR and improve glycemic control in T2DM patients [204]. Notably, exercise may also exert synergistic effects when combined with other interventions. For instance, co-treatment with exercise and Bifidobacterium longum OLP-01 significantly reduced glycemic and lipid profiles—such as fasting glucose and HbA1c—and enhanced insulin sensitivity in *db/db* mice [218].

Studies in AD mice have shown that physical exercise may mitigate IR and cognitive deficits by enhancing hippocampal insulin signaling, particularly through IRS-1, Akt, and GSK-3β pathways [205,219]. Aerobic running improves insulin signaling in AD rats, thereby enhancing glycemic control and cognitive function [206]. As a prototypical aerobic intervention, swimming markedly elevated BDNF levels in the hippocampal and cortical regions of AD models [220]. Furthermore, acute aerobic training in AD patients increased circulating IGF-1, suggesting that aerobic exercise may potentiate the efficacy of insulin therapy by augmenting IGF-1 signaling, thereby attenuating the decline of BDNF and GLUT4 protein levels [207,208] (Table 1). Another study demonstrated that 16 weeks of treadmill exercise restored insulin and glucose homeostasis in AD mice while conferring neuroprotection through the upregulation of GLUT-1, BDNF, and antioxidant genes such as SOD-1, catalase, and Bcl-2 [209]. In D-galactose-induced AD animal models, aerobic exercise, endurance training, and combined aerobic-endurance training elevated serum IGF-1 levels and improved cognitive function [210]. Notably, baseline cerebral glutamate levels exhibit a positive correlation with fasting insulin concentrations and an inverse association with systemic insulin sensitivity. Sprint interval training (SIT) has been shown to significantly reduce insulin-stimulated cerebral glutamate levels in individuals with IR [211], suggesting that SIT may attenuate fasting hyperglycemia and enhance insulin sensitivity. Collectively, these findings demonstrate that exercise suppresses IR, thereby playing a critical role in preventing and managing both T2DM and AD.

5.2 Potential Mechanisms of Exercise-Induced Inhibition of IR

IR is a hallmark of T2DM and has been strongly implicated in AD [221]. Insulin plays a pivotal role in systemic metabolism by activating the PI3K/Akt signaling pathway. This cascade critically regulates glucose metabolism, neuronal homeostasis, and mitochondrial function. After IR onset, the PI3K/Akt pathway is inhibited, exerting detrimental effects on downstream targets, including GSK-3β, PGC-1α, and SIRT1. This disruption leads to the onset of oxidative stress, mitochondrial dysfunction, excessive accumulation of Aβ, and abnormal phosphorylation of tau [222]. Exercise, as a non-pharmacological intervention, significantly alleviates symptoms in both T2DM and AD patients [223–225]. Given that IR represents a potential pathogenic mechanism shared by both disorders, targeted exercise interventions may offer novel therapeutic strategies for T2DM and AD prevention. Although the beneficial effects of exercise in reducing IR are established, the precise underlying mechanisms remain unclear, prompting us to explore several potential pathways.

5.2.1 Mitochondrial Function

Exercise alleviates IR through multiple, convergent mechanisms, with mitochondrial enhancement and redox regulation as central nodes. By stimulating mitochondrial biogenesis and boosting respiratory activity, exercise delays aging and attenuates the progression of metabolic disorders [226,227]. In T2DM models, it not only suppresses IR via PI3K/Akt activation [228] but also acts in concert with the mitochondrial-derived peptide MOTS-c to enhance glucose metabolism through the AMPK–PGC-1α axis [229] (Fig. 5A). Comparable benefits are observed across modalities, for example, resistance training restores mitochondrial function and reduces IR in high-fat diet-fed mice [230].

Exercise also counteracts oxidative stress through complementary pathways. It inhibits ROS accumulation and augments Akt signaling to lower skeletal muscle IR [231], while simultaneously downregulating the ROS/GRK4 cascade, thereby restoring D1 receptor function and improving insulin sensitivity [198]. In parallel, exercise strengthens endogenous antioxidant defenses (SOD, CAT, GPX, GR) [232] and upregulates the stress-responsive protein SESN3, which via the SESN3/mTORC2/Akt pathway enhances GLUT4 expression and prevents obesity-associated hepatic steatosis and IR [233] (Fig. 5B).

Collectively, these findings indicate that exercise may mitigate IR by reinforcing mitochondrial function and antioxidant capacity, offering a promising strategy for the prevention and treatment of T2DM and AD.

5.2.2 Inflammation

IR and inflammatory responses mutually reinforce each other, creating a vicious cycle [234]. Exercise effectively mitigates IR by suppressing microglial activation and reducing inflammation [235,236]. Correlative analyses indicate that IR is positively associated with NLRP3 inflammasome activity, suggesting that exercise may alleviate IR through modulation of this pathway [237]. In skeletal muscle, exercise reduces inflammation and muscle IR by inhibiting the TNF-α/NF-κB pathway while activating the IRS-1/PI3K/Akt/GLUT4 signaling cascade [238]. Aerobic training further enhances synaptic plasticity and decreases Tau phosphorylation by suppressing the FOXO1/NF-κB/NLRP3 inflammatory axis [239]. Notably, swimming interventions lower neuroinflammation, upregulate JNK/IRS-1/PI3K/Akt pathway components (Fig. 5C), and increase hippocampal BDNF and PSD95 expression, thereby improving cognitive function and reducing hippocampal IR [240]. These findings suggest that exercise may serve as an effective strategy for counteracting inflammation-associated IR, with beneficial implications for both T2DM and AD.

5.2.3 Gut Microbiota

The gut microbiota plays a pivotal role in maintaining physiological homeostasis and has been closely implicated in the pathogenesis of both AD and T2DM through its regulation of inflammation and oxidative stress [241–244]. IR serves as a potential pathogenic mechanism in both T2DM and AD, engaging in bidirectional crosstalk with the gut microbiota. IR induces dysbiosis of gut microbial composition, whereas its suppression can restore microbial community structure and function, thereby attenuating inflammation [245–247]. Conversely, modulating the gut microbiota effectively mitigates IR and associated inflammatory responses [248]. For instance, conjugated linoleic acid reduces IR by regulating host-microbe metabolic and immunological interactions [249]. Moderate exercise promotes the proliferation of beneficial bacteria and enhances gut microbiota diversity. These beneficial microbes regulate mucosal immunity, strengthen the gut barrier, and produce metabolites such as short-chain fatty acids (SCFAs), which help prevent gastrointestinal diseases [250]. Studies have shown that SCFAs enhance glucose homeostasis, with elevated levels improving insulin sensitivity [251,252]. Moreover, the gut microbiota may play a pivotal role in mediating the effects of exercise on the regulation of the NLRP3 inflammasome [253] (Fig. 5D). Animal studies have indicated that exercise can counteract the negative impact of altered gut microbiota on brain function, mitigating the reduction in hippocampal neurogenesis and related behaviors in adult rats [254]. This suggests that exercise may delay the progression of AD and T2DM by modulating the gut microbiota and its metabolic products [255–257]. Although direct studies on the role of exercise in modulating the gut microbiota to reduce IR are limited, a bidirectional interaction exists between the gut microbiota, exercise, and IR. In summary, exercise may reduce IR through the regulation of gut microbiota, providing a potential therapeutic pathway for the treatment of T2DM and AD.

5.2.4 Autophagy

As a shared mechanism in both T2DM and AD, autophagy is closely linked to IR. In IR states, autophagic flux and the expression levels of autophagy markers are significantly increased [258]. Suppression of miR-188, a regulator of the autophagy-related gene *Atg12*, exacerbated IR severity [259], indicating that autophagic dysfunction may initiate the development of IR [260]. Another study confirmed that induction of aberrant autophagy in granulosa cells increased the LC3-II/LC3-I ratio, elevated *Atg7* levels, and decreased p62, thereby promoting IR development [261]. Conversely, activating autophagy within physiological limits helped reduce IR. Studies have shown that autophagy exerts a protective effect against hyperuricemia-induced hepatic IR [262]. Additionally, administration of Kun-Dan decoction alleviated IR in high-fat-diet rats by activating autophagy through the AMPK/mTOR pathway, whereas dihydromyricetin treatment enhanced autophagy via the AMPK/PGC-1α and PPARα pathways, thereby reducing IR [263,264]. Overall, enhanced autophagic activity, achieved by activating the AMPK and SIRT1 signaling pathways or inhibiting the mTORC1 pathway, effectively reduces the degree of IR [265]. It is noteworthy that exercise is one of the key pathways for activating autophagy and can lower IR by modulating autophagic processes [235]. Exercise training activates the AMPK/PGC1-α pathway, thereby promoting protective autophagy in high-fat-diet mice and regulating endoplasmic reticulum stress to alleviate IR [266]. HIIT-induced lactate accumulation inhibits the mTOR/ribosomal protein S6 kinase beta-1 (p70S6K) signaling pathway, promoting autophagy in male rats with T2DM, thereby reducing IR and lowering blood glucose [267] (Fig. 5E). Therefore, promoting protective autophagy through exercise, to mitigate IR, presents a promising strategy for the intervention of T2DM and AD.

5.2.5 Alternative Mechanisms

In addition to the aforementioned mechanisms, several other factors, including molecular and epigenetic regulation, are believed to contribute to the link between exercise and IR. Irisin, a myokine produced during exercise, displays pleiotropic functions, such as metabolic modulation and neuroprotection, and may play a crucial role in treating metabolic and neurodegenerative diseases. Pilates and resistance training, as effective exercise interventions, can significantly reduce IR in overweight women by stimulating irisin secretion [268]. Adiponectin, a protein hormone secreted by adipocytes, stimulates mitochondrial biogenesis by activating PGC-1α. Exercise has been

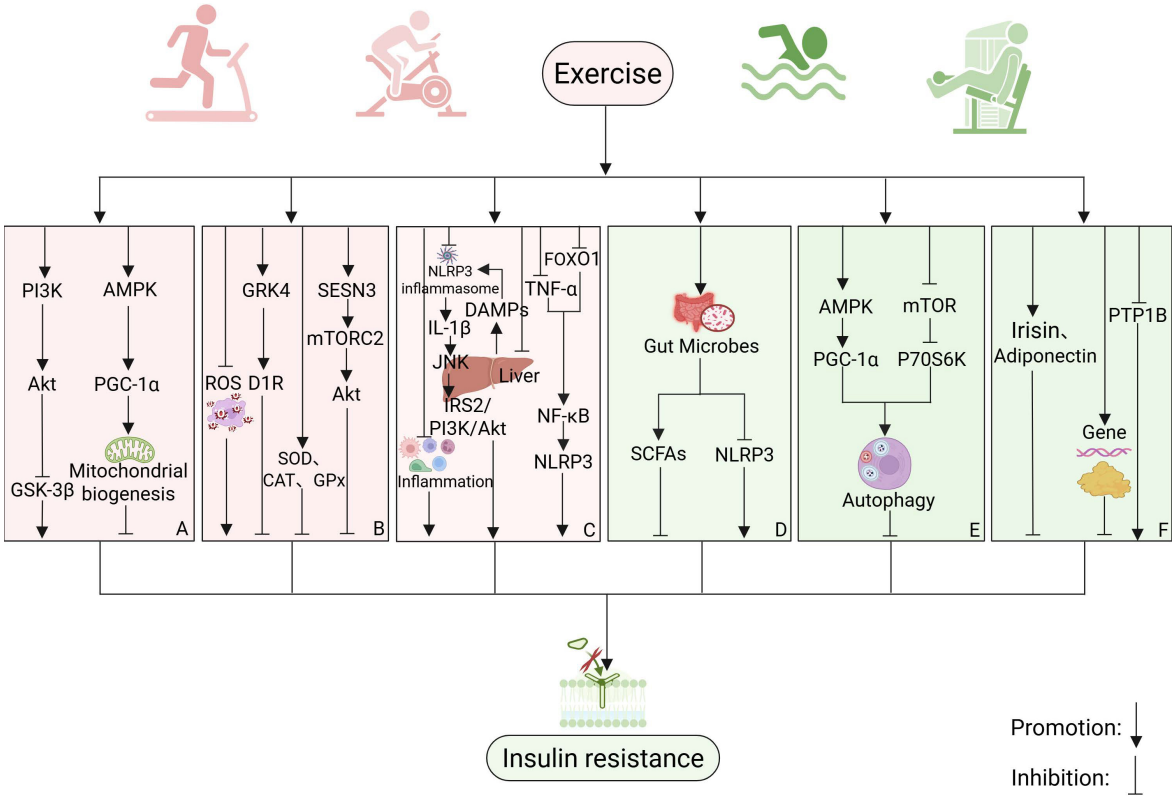

Fig. 5. The potential mechanisms by which exercise alleviates insulin resistance. (A) Exercise attenuates insulin resistance by targeting the PI3K/Akt/GSK-3β signaling pathway and modulating PGC-1α expression via AMPK signaling. (B) Exercise reduces ROS accumulation and mitigates insulin resistance by regulating ROS/GRK4-mediated D1R expression. Additionally, it enhances the levels of SOD, CAT, and GPX while alleviating insulin resistance through the SESN3/mTORC2/Akt pathway. (C) Exercise alleviates insulin resistance by inhibiting microglial overactivation and NLRP3 inflammasome hyperactivation. Furthermore, it suppresses TNF-α/NF-κB signaling activation and enhances the IRS-1/PI3K/Akt/GLUT4 pathway. (D) Exercise promotes the proliferation of beneficial gut microbiota and the production of metabolites such as short-chain fatty acids (SCFAs), thereby improving glucose homeostasis and enhancing insulin sensitivity. (E) Exercise activates the AMPK/PGC-1α pathway and induces lactate accumulation, which inhibits the mTOR/P70S6K signaling pathway and promotes protective autophagy to mitigate insulin resistance. (F) Exercise reduces insulin resistance by inducing the release of irisin, adiponectin, and PTP1B while modulating DNA methylation enzymes. AMPK, AMP-activated protein kinase; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1 alpha; GRK4, G protein-coupled receptor kinase 4; D1R, dopamine D1 receptor; SOD, superoxide dismutase; CAT, catalase; GPx, glutathione peroxidase; SESN3, sestrin 3; mTORC2, mechanistic target of rapamycin complex 2; NLRP3, NOD-like receptor family pyrin domain containing 3; JNK, c-Jun N-terminal kinase; FOX, forkhead box; NF-κB, nuclear factor kappa B; SCFA, short-chain fatty acids; PTP1B, protein tyrosine phosphatase 1B. Figure created with BioRender (https://www.biorender.com).

shown to increase adiponectin levels, thereby alleviating IR [269]. Moreover, protein tyrosine phosphatase 1B (PTP1B), a non-receptor protein tyrosine phosphatase, inhibits insulin signaling by dephosphorylating the insulin receptor and its substrates, thereby impairing glucose uptake and metabolism. Studies have shown that short-term resistance exercise reduces PTP1B expression in the liver of obese mice, emerging as a significant strategy to enhance hepatic insulin sensitivity and suppress hepatic gluconeogenesis [270]. In T2DM, the expression of miRNA-299-5p is reduced; however, aerobic exercise can restore its expression by modulating DNA methylation enzymes, enhancing insulin signaling through the inhibition of resistin, thereby reducing IR [271]. It is interesting that study results suggest that exercise-induced improvements in sleep quality may contribute to the alleviation of IR, although the specific molecular mechanisms remain to be fully elucidated [272] (Fig. 5F).

6. Limitations and Future Directions

Numerous studies have demonstrated that exercise plays a critical role in preventing and managing both T2DM and AD by reducing IR. However, the optimal exercise modality, intensity, duration, and frequency for different diseases and disease stages remain to be precisely defined.

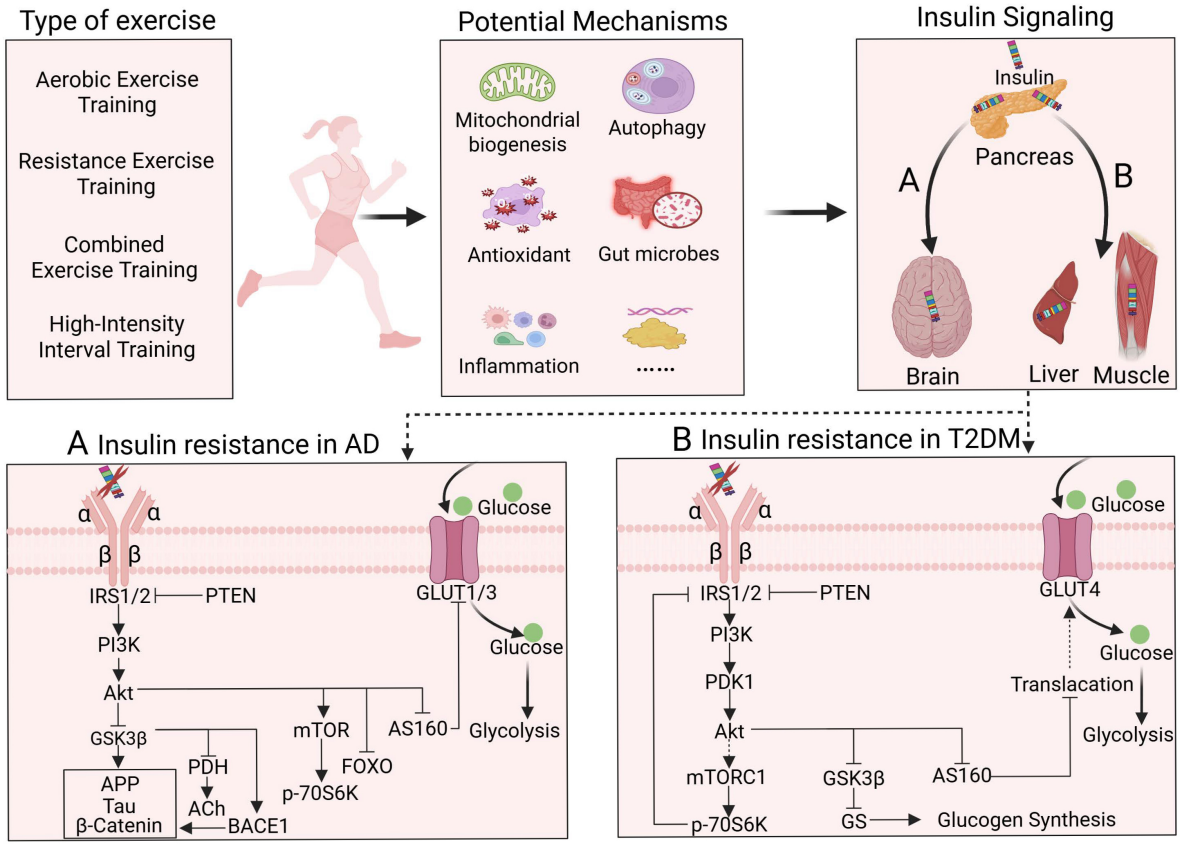

Fig. 6. The potential molecular pathways of exercise to alleviate insulin resistance and the pathways of insulin resistance in T2DM and AD. (A) The induction pathway of insulin resistance in AD. (B) The induction pathway of insulin resistance in T2DM. Standard arrows indicate activation, bar-headed lines indicate inhibition, and dotted arrows indicate indirect or potential links. Figure created with BioRender (https://www.biorender.com).

Some studies indicate that aerobic training alone may not improve systemic IR [273], whereas similar exercise regimens, when matched for intensity and duration, appear to exert differential effects on IR [274]. These discrepancies may stem from variations in sample size, the uncontrollability of human interventions, and differences between human and animal models. Consequently, translating data from animal studies into precise exercise prescriptions for humans remains a major challenge.

Furthermore, critical questions regarding IR as a potential mechanistic link between T2DM and AD remain unresolved. For instance, the temporal sequence through which peripheral and central IR are initiated, and whether a causal relationship exists between them, is still unclear. In addition, given the unique characteristics of the human brain, reliable methods to assess the stage of cerebral IR are lacking, and it is uncertain whether biomarkers could facilitate monitoring of brain IR and disease progression. Notably, much of the current understanding of AD derives from animal models, with limited support from human studies.

Collectively, these limitations point to key avenues for future research, including the investigation of exercise as a modulator of IR in the context of T2DM and AD, and underscore the need for further studies to validate and expand upon the perspectives presented in this review.

7. Conclusions

A substantial body of animal and clinical studies suggests a bidirectional interplay between T2DM and AD, with numerous overlapping molecular mechanisms, including IR, mitochondrial dysfunction, oxidative stress, chronic inflammation, and cellular autophagy. Among these, IR appears to play a central role. IR impedes insulin signaling, energy metabolism, and cellular autophagy, and simultaneously exacerbates oxidative stress and inflammation, thereby increasing the risk of both T2DM and AD (Fig. 6). Exercise, as a non-pharmacological intervention, has significant potential to mitigate both T2DM and AD by restraining IR. However, the relationship between brain IR and peripheral IR remains controversial, and validation requires further investigation. Additionally, the precise mechanisms by which exercise reduces IR are not yet fully understood, and further evidence is needed in order to elu-

cidate the exact pathways involved. IR may represent the potential mechanism through which exercise attenuates the interplay between T2DM and AD, potentially serving as a critical target for prevention and treatment strategies.

Abbreviations

T2DM, Type 2 diabetes mellitus; AD, Alzheimer's disease; IR, insulin resistance; NFTs, neurofibrillary tangles; IRS, insulin receptor substrates; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; GLUTs, glucose transporters; MAPK, mitogen-activated protein kinase; BBB, blood–brain barrier; CNS, central nervous system; HFD, high-fat diet; IL, Interleukin; TNF, Tumor Necrosis Factor; ROS, reactive oxygen species; NGF, nerve growth factor; GSK-3, glycogen synthase kinase-3; BACE1, β-site APP cleaving enzyme 1; UDP-GlcNAc, uridine diphosphate N-acetylglucosamine; O-GlcNAcylation, O-linked N-acetylglucosaminylation; BDNF, brain-derived neurotrophic factor; ER, endoplasmic reticulum; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; SOD, superoxide dismutase; CAT, catalase; GPX, glutathione peroxidase; AGEs, advanced glycation end products; GSH, glutathione; JNK, c-Jun N-terminal kinase; IKK, IκB kinase; IFN, Interferon; TGF, transforming growth factor; NLRP3, NOD-like receptor family pyrin domain containing 3; IGF-1, insulin-like growth factor 1; FoxO1, forkhead box protein O1; GRK4, G protein-coupled receptor kinase 4; HIIT, high-intensity interval training; MICT, moderate-intensity continuous training; MAMs, mitochondria-associated membranes; SIT, Sprint interval training; SESN3, Sestrin3; NLRP3, NOD-like receptor family pyrin domain containing 3; SCFAs, short-chain fatty acids; PTP1B, Protein Tyrosine Phosphatase 1B; STSE, short-term resistance exercise.

Author Contributions

BW contributed to the study conception and design, collected and sorted references, designed and drew the figures and tables, and wrote the manuscript. YPS and RXL contributed to the study conception, design, and critical revision of the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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