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Review

Does irisin link physical exercise with Alzheimer's disease?

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Abstract: Irisin, a skeletal muscle-secreted myokine, produced in response to physical exercise, has protective functions in both the central and the peripheral nervous systems, including the regulation of brain-derived neurotrophic factors and modification of telomere length. Such beneficial effects may inhibit or delay the emergence of neurodegenerative diseases, including Alzheimer's disease (AD). This review is based on the hypothesis that irisin produced by physical exercise helps control AD progression. Herein, we describe the physiology of irisin and its potential role in delaying or preventing AD. Although current and ongoing studies on irisin show promising results, further research is required to clarify its potential as a meaningful therapeutic target for treating human diseases.

Keywords: Physical Exercise, Irisin, Neurodegeneration, Aging, Alzheimer's disease

1. Introduction

Alzheimer's disease (AD) is a devastating age-associated neurodegenerative disorder characterized by progressive cognitive and functional decline. Extracellular amyloid-β (Aβ) aggregation and intracellular neurofibrillary tangles are considered the pathological hallmarks of AD. Notwithstanding several previous studies, the etiology of AD is largely unknown. However, a series of neurodegenerative events in the hippocampus, as well as microglial activation, neuroinflammation, oxidative stress, metabolic energy failure, and consequent neuronal apoptosis are believed to be closely correlated with the pathogenesis of AD [1–6]. Physical exercise ameliorates various neurodegenerative events and reduces the consequent production of harmful factors [7]. Indeed, aerobic exercise reverses hippocampal volume loss, causing a 2% increase followed by improved memory function [8]. Physical exercise slows the neurodegeneration-induced decline of executive functioning [9], and many studies have highlighted the effects of exercise in various organs, such as the liver, brain, adipose tissue, and heart. Unlike other organs, skeletal muscles are directly affected by exercise [10]. Skeletal muscle is a secretary organ that produces and releases cytokines and other peptides that function in manner similar to hormones [11]. These secretions may underlie the beneficial effects of exercise. Hundreds of secretome components of skeletal muscle are involved in muscle communication with other organs [10]. Among these components, irisin has attracted great attention, as it has recently been identified as a muscle-derived myokine released from skeletal

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muscle immediately after exercise. This review discusses the beneficial role of irisin and its potential protective effects against AD.

2. Irisin, the exercise-induced myokine, originated from the PGC-1α/FNDC5 pathway

The transcriptional coactivator, peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), regulates many biological processes involved in energy metabolism [12], and it modulates the factors secreted from skeletal muscle [12]. Fibronectin type III domain-containing protein 5 (FNDC5) is one of numerous muscle gene products affected by PGC-1α. FNDC5 proteolytically cleaved to form the hormone irisin [12]; after cleavage of its extracellular portion, irisin is secreted into the blood [12, 13]. Irisin is also synthesized in various tissues of different species [14]. Irisin upregulates UCP1 and transforms white adipose tissue (WAT) into brown adipose tissue (BAT), thereby increasing thermogenesis and the energy consumption of adipose tissue [15]. Additionally, it ameliorates insulin resistance, lowers blood glucose, and promotes weight loss. Furthermore, irisin further encourages cell proliferation and inhibits cell apoptosis. Previous studies have also indicated that irisin sustains the levels, and increases the proliferation, of human umbilical vein endothelial cells [16]. Irisin was also shown to increase the proliferation of H19-7 mouse hippocampal neurons [17]. Meanwhile, irisin suppresses the high-glucose-induced apoptosis of vascular endothelial cells and improves their function via the extracellular signal-regulated kinase (ERK) and the 5′-adenosine monophosphate-activated protein kinase (AMPK)-PI3K-protein kinase B (Akt)-eNOS signaling pathways [16, 18, 19]. Furthermore, by interfering with oxidative stress and inflammation, irisin protects against palmitic acid-induced apoptosis in liver cells [20].

3. Neuroprotective implications of irisin via the Akt/ERK signaling pathway

Irisin is expressed not only in the skeletal muscle and the heart but also in the brain [21]. It largely inhibits brain infarct volume and reduces neuroinflammation and post-ischemic oxidative stress. One group of scientists demonstrated that irisin activates the Akt and ERK1/2 signaling pathways in brain tissue [22]. Previous studies have also shown that irisin stimulates ERK1/2 signaling in adipocytes [23], endothelial cells [24], and bone marrow stromal cells [25], and activates Akt signaling in hepatocytes [26]. These results indicate that the activation of both Akt and ERK1/2 may be important for the neuroprotective effects of irisin because specific chemical inhibitors of the Akt and ERK1/2 pathways abolished the neuroprotection conferred by irisin. The same group also proved that mouse plasma irisin levels are negatively correlated with plasma tumor necrosis factor-alpha (TNF-α) and Interleukin-6 levels [22]. Finally, they demonstrated that the novel exercise-induced hormone irisin protects against neuronal injury via activation of the Akt and ERK1/2 signaling pathways [22]. These results suggest that irisin contributes to the neuroprotective effects of physical exercise in cerebral ischemia and is a promising agent for the prevention and treatment of ischemic stroke. Recent research has disclosed a role for chronic neuroinflammation in the pathophysiology of neurodegenerative diseases such as AD, and attention has focused the use of anti-TNF and TNF-modulating agents for prevention and treatment [27]. The brains of treated animals exhibited a significant reduction in pro-inflammatory TNF-α, and a diminished burden of neurofibrillary tangles, amyloid precursor protein, and Aβ plaques. The brief discussion above allows a clearer mechanistic understanding of the role of proinflammatory mediators such as TNF-α in AD, and suggests that irisin could be a novel target to reduce proinflammatory mediators for the prevention or treatment of AD.

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4. Irisin protects the nervous system

Physical activity has many positive effects, including lowering the risk of developing heart disease, stroke, and diabetes. Exercise, particularly endurance exercise, has salutary effects on brain health and cognitive functioning [28-30]. The improvement in cognitive functioning following exercise may be prominent in older adults [31]. Exercise ameliorates negative outcomes in neurological diseases, such as depression, epilepsy, stroke, AD, and Parkinson's disease [32–37]. The beneficial effects of exercise on the brain are most discernible in the hippocampus and its dentate gyrus, a region of the brain associated with learning and memory. Several studies have shown that exercise has markedly favorable effects on the brain including increased size, blood vessel growth of the human hippocampus, synaptic plasticity, and, importantly, de novo neurogenesis in the dentate gyrus in various animal models [28, 29]. These results are intriguing as the hippocampus is the region of the brain that is most affected by AD [38, 39]. As physical exercise has diverse benefits, the discovery of the exercise hormone irisin has attracted a great deal of attention [12]. Human studies have demonstrated that 10 weeks of physical training increases plasma levels of irisin [12]. Subsequent studies substantiated acute exercise-altered irisin levels [40, 41]. Irisin expression is induced by exercise, and this myokine converts WAT into BAT, leading to increased caloric expenditure [42]. Of the two types of adipose tissues, WAT stores energy as a form of fat, whereas BAT burns energy [43]. With the brown appearance derived from abundant mitochondria and small lipid droplets, BAT expresses UCP1, which is responsible for heat production via the uncoupling of respiration from ATP synthesis [43] (Figure 1). This type of adipose tissue is rich in metabolically active adults [44].

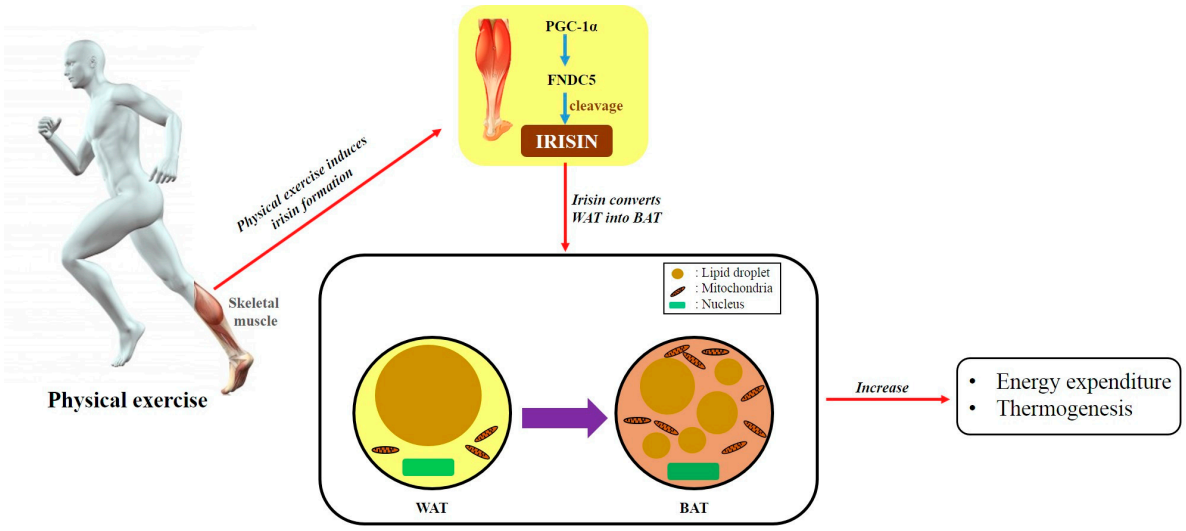

Figure 1. The general role of irisin. Physical exercise induces irisin. During exercise, the transcriptional coactivator PGC-1α modulates several factors secreted from skeletal muscle. Among the factors, FNDC5 is proteolytically cleaved to form irisin. This exercise-induced myokine converts WAT into BAT, thereby increasing thermogenesis and energy consumption. However, irisin has a range of functions beyond its role in adipose conversion.

The contribution of irisin is not confined to physical fitness and fat browning; the central nervous system may be another beneficiary. The beneficial roles of exercise described above are likely to be associated with irisin. Irisin administration increased the proliferation of hippocampal cells in vitro [45], and expression of FNDC5 resulted in elevated irisin concentrations and brain-derived neurotropic factor (BDNF) gene expression in culture [46]. These findings suggest that irisin could be a therapeutic target in neurodegenerative disorders [15, 47, 48]. PGC-1α, which functions upstream of the irisin precursor, FNDC5, has been reported to benefit tissues that have no primary metabolic functions, such as the brain [15]. PGC-1α-null mice show adverse neuropathological behaviors, such as stimulus-induced myoclonus, excessive startle responses, dystonic posture, and limb clasping [49].

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Additionally, it has been suggested that PGC-1α is a key controller of energy metabolism in the early stages of neurological disorders [50]. The irisin precursor, FNDC5, is increased by endurance exercise in the mouse hippocampus, and forced expression of FNDC5 in primary cortical neurons induces augmented BDNF expression [51]. Peripheral delivery of FNDC5 to the liver induces the expression of BDNF and other protective genes and elevates levels of blood irisin [51]. As BDNF is a critical regulator of neural plasticity, irisin may act as a key regulator of neuronal survival following neurodegenerative diseases, such as AD. BDNF is responsible for regulating neuron growth, function, and survival, as well as for synaptic stabilization and branching [52]. BDNF is believed to be involved in the pathophysiology of central nervous system diseases associated with neuroinflammation [52]. Evidence from human neuropathological studies has indicated that the levels of neurotrophins, such as nerve growth factor (NGF) and BDNF, are lower in patients with AD [53]. These studies demonstrated that BDNF mRNA levels are significantly reduced at very early stages of amyloid pathology in a transgenic rat model of AD. Furthermore, ileocecal valve Aβ-treated rats manifested a memory deficit and significantly decreased BDNF levels, with a concurrent increase in mitochondrial oxidative damage and inflammatory mediators in the hippocampus [54]. Several studies have suggested a link between irisin and BDNF. Irisin is formed primarily during contraction of the skeletal muscle, but it is also present in the brain [55]. Irisin enters the central nervous system and induces BDNF expression [55]. As described above, BDNF is responsible for neural plasticity. As irisin enhances the synthesis of BDNF [56], the neuroplasticity mediated by this neurotrophin may be strengthened by irisin. Yarrow et al. [57] showed that resistance exercise can induce ~77% transient elevation of circulating BDNF levels. Thus, physical exercise may increase irisin levels and BDNF synthesis. Additionally, irisin may enhance BDNF synthesis leading to the augmented neuroplasticity achieved by the collarboration of irisin and BDNF. This exercise-irisin-BDNF axis may magnify neuroplasticity including neuronal growth/survival and synaptic stabilization/branching (Figure 2).

It has been suggested that a decrease in irisin levels may cause AD pathogenesis and cognitive deficits. These phenomena are strongly associated with neuroinflammation and apoptosis, mediated by a dramatic decrease of BDNF.

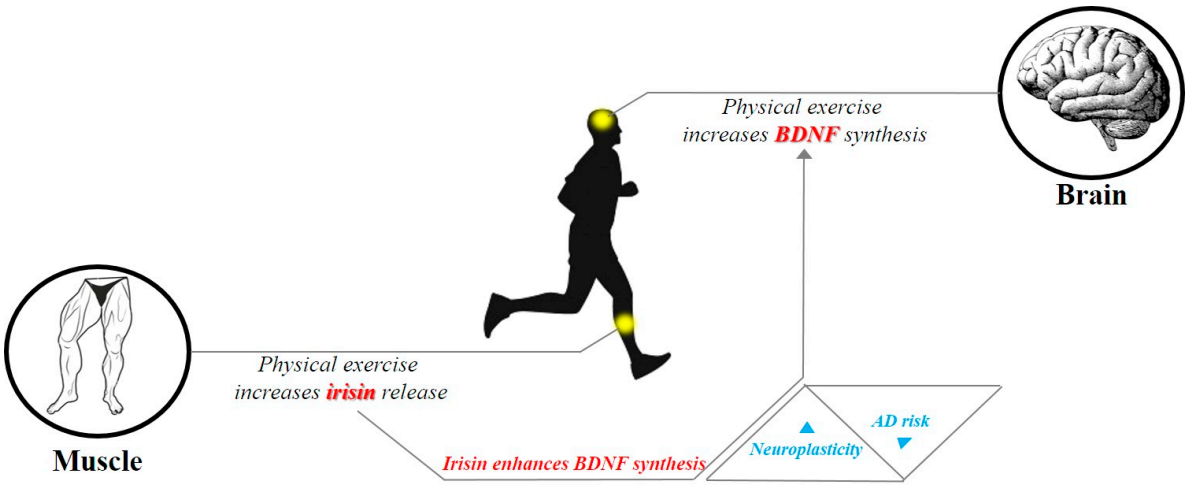

Figure 2. Physical exercise increases irisin levels and BDNF synthesis. In turn, irisin enhances BDNF synthesis and release, leading to augmented neuroplasticity achieved by the collaboration of irisin and BDNF. In this context, exercise and its sequelae, irisin and BDNF, may contribute to neuroplasticity and reduce the risk of AD.

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5. The underlying beneficial contribution of exercised-induced irisin in AD.

Physical exercise reverses Aβ accumulation and delays the progression of AD-like neurobehaviors [58]. Treadmill exercise dampens the levels of amyloid peptides and induces BDNF [59]. As BDNF is a crucial regulator of brain plasticity, decreased circulating BDNF potentiates the risk of reduced memory and cognitive function that accompanies AD [60]. Similarly, the maturation of neurotrophin NGF from its pro-NGF premature form is dampened in AD [61]. The accumulation of Aβ in AD is thought to hinder the maturation of NGF [62]. However, exercise training contributes to a significant induction of NGF [63]. Exercise is thought to suppress the negative effects of AD by facilitating the normal secretion of neurotrophins. As previously mentioned, the myokine irisin is generated during exercise. Thus, exercise-induced irisin may be a novel therapeutic candidate. Indeed, low expression of PGC-1α, the upstream activator of the irisin precursor FNDC5, caused Aβ accumulation in the brains of patients with AD [64]. As PGC-1α regulates beta secretase 1 (BACE1), which drives Aβ formation, low levels of PGC-1α fail to block the formation of Aβ [65]. Likewise, BACE1-deficient mice showed decreased Aβ formation [66]. Accordingly, PGC-1α appears to inhibit the accumulation of Aβ, which is the prevalent characteristic of AD, by regulating BACE1 (Figure 3). In addition to PGC-1α, the downstream FNDC5 might also be involved in AD pathogenesis, as exercise-induced muscular expression of FNDC5 is regulated by PGC-1α (Figure 1) [64]. FNDC5 enhances the differentiation rates of embryonic stem cells, implying its role as a neurogenic factor [67]. Additionally, FNDC5 expression is increased in the hippocampus during exercise [46]. Both the irisin precursor, FNDC5, and its upstream factor, PGC-1α, are involved in the regulation of AD pathogenesis. Irisin, the cleaved form of FNDC5, encourages hippocampal neurogenesis, as evidenced by augmented proliferation of hippocampal neurons in the presence of irisin [45]. Thus, irisin, PGC-1α and FNDC5 might be linked to AD. These findings imply that PGC-1α, FNDC5, and irisin could have therapeutic potential to treat AD.

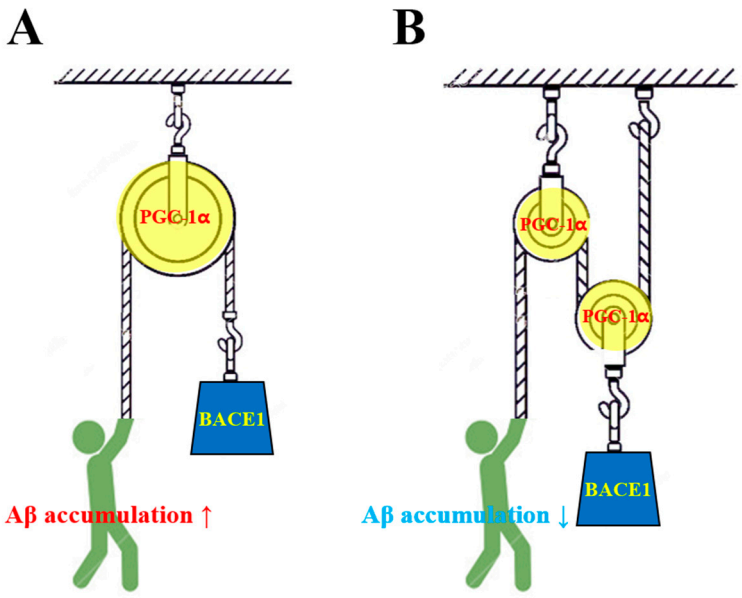

Figure 3. Aβ accumulation is regulated via reciprocal interactions between PGC-1α and beta secretase 1 (BACE1). Their interactions are depicted as a pulley system, with the wheel and load in the pulley system representing PGC-1α and BACE1, respectively, and the worker's stress representing Aβ accumulation. In a pulley system, greater numbers of wheels require less effort, whereas fewer wheels require greater effort, to lift a load. PGC-1α regulates BACE1, which is in charge of Aβ formation. A. In this example, the pulley system has only one wheel, and the worker cannot effectively lift the load. Similarly, low levels of PGC-1α cannot effectively hinder the activation of BACE1, leading to the accumulation of Aβ. B. The worker can lift the load with less effort, as two

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pulley wheels in the system ease the work. Likewise, PGC-1α may ameliorate BACE1 activation, resulting in a decrease in BACE1-induced Aβ accumulation.

6. Implications of irisin for age-related telomere length (TL) shortening and AD pathogenesis

Telomeres, which resemble the plastic tips at the ends of shoelaces, are the caps at the end of each DNA strand and function to preserve chromosomes [68]. TL becomes progressively shorter with mitosis, and this TL shortening eventually provokes cellular senescence [69, 70]. TL shortening has been confirmed to play a causative role in age-related neurodegenerative diseases, including AD. TL shortening has also been associated with cognitive impairment, amyloid pathology, and hyper-phosphorylation of Tau in AD, and plays a significant role in the pathogenesis of AD via the mechanisms of oxidative stress and inflammation [71]. A shorter TL in leukocytes has been connected to age-related diabetes, and cardiovascular and heart diseases, as well as an elevated risk of neurodegenerative diseases, including dementia [72]. It seems that long-term chronic inflammation and/or oxidative stress accelerate TL shortening in monocytes [73]. In addition, since TL is shortened by aging, elderly populations are more susceptible to AD. Interestingly, microglia also exhibit shorter telomeres in the brains of AD subjects, suggesting that these cells undergo early replicative senescence, which could be due to the intense amyloid plaque profusion seen in AD [74]. Monocytes migrate through the blood-brain barrier in AD and they are converted into microglial cells in the brain, and microglial activation has been reported to be associated with amyloid-plaques in the AD brain [75]. Additionally, increased expression of chemokine receptors and cytokines in the peripheral blood mononuclear cells of AD patients has been reported [76]. Previous studies have reported that lifestyle factors, including exercise, can have a notable impact on the accumulation of DNA damage and TL [77]. Recently, Karan et al. [78] demonstrated that plasma irisin levels showed a significant correlation with TL. The shortening of TL with aging is well-understood and, as expected, shows an inverse relationship with age. Since plasma irisin is likely associated with TL, irisin may exhibit anti-aging properties. Previous research has reported that exercise, which increases plasma irisin, can modulate TL [79-81]. The data presented herein describe a potential mechanism by which exercise is associated with an increased TL. Previously published data have uncovered that irisin activates signaling pathways connected to the regulation of cellular proliferation, including p38 MAPK [82], which regulates cellular proliferation and the expression of human telomere reverse transcriptase [83]. In summary, it is hypothesized that the age-related decrease of irisin may be a cause of AD pathogenesis and cognitive impairments. This association is highly linked to TL shortening induced by oxidative stress and inflammation.

7. Reduction of endoplasmic reticulum (ER) stress responses by irisin in AD

The ER is associated with several crucial cellular functions, such as protein folding, quality control, maintenance of Ca^{2+} balance, and cholesterol synthesis. Many genetic and environmental insults can disrupt the function of the ER, resulting in ER stress. Therefore, it is not surprising that ER stress is linked to several neurodegenerative diseases [84-86]. The ER stress response, an important defense mechanism for cell survival, has three major signaling branches: protein kinase RNA-like endoplasmic reticulum kinase (PERK), inositol-requiring enzyme 1α (IRE1α), and activating transcription factor 6 (ATF6) [87]. Upon ER stress, PERK phosphorylates eukaryotic translation initiation factor 2α (eIF2α), inhibiting protein translation [88]. Then, eIF2α phosphorylation specifically activates translation of activating transcription factor (ATF) 4 [88], which upregulates various foldases to prevent the accumulation of unwanted proteins [88, 89]. Under prolonged ER stress, ATF4 stimulates C/EBP homologous protein (CHOP) to activate apoptotic cell death [88, 89]. IRE1α induces splicing of the X-box-binding protein 1 (XBP1s) mRNA to produce spliced version of XBP1 (XBP1s), which is an active transcription factor [90]. XBP1s controls the expression of several genes responsible for protein folding, secretion, protein entry into the ER, and

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protein quality control [91, 92]. ATF6 is an ER transmembrane transcription factor [93], and ER stress induces the translocation of inactivated ATF6 from the ER to the Golgi apparatus [93, 94]. The translocated ATF6 is proteolytically cleaved by site-1 (SIP) and site-2 (S2P) proteases to release the cytoplasmic domains of ATF6 [94, 95]. Next, cleaved ATF6 translocate into the nucleus and acts directly as a transcription factor, activating transcription of the endogenous GRP78/BiP gene, which plays a role in protein folding [94, 96]. Evidence of activated UPR signaling has been revealed in AD, PD, and Huntington's disease, as well as in amyotrophic lateral sclerosis [84-86, 97]. Furthermore, cerebral ischemia can trigger the UPR, although this is clearly reduced by the concomitant dramatic decline in protein synthesis [98]. Recent studies have shown that ER stress can generate signals that warn neighboring cells and elicit inflammatory responses to prevent extensive tissue damage [99, 100]. In fact, moderate ER stress improves cellular protection by a series of changes called the 'hormetic response', which is characterized by alteration of the transcriptome and proteome of the cell, thus elevating the adaptive capacity of the ER [101-105]. However, the prolonged ER stress manifested in neurodegenerative diseases is believed to disrupt the protective effects of the UPR, leading to the activation of inflammatory and apoptotic programs that promote neurotoxicity. Therefore, prolonged ER stress disrupts the protective mechanism of the UPR, leading to inflammation and apoptosis, which promote AD pathogenesis. Exercise is believed to improve physical fitness and prevent chronic diseases and age-related disorders [106]. Exercise promotes the expression of several myokines such as irisin, which is linked to the transcription factor PGC-1α and is not related to ER-stress, whereas typical ER-stress-induced cytokines, such as fibroblast growth factor 21 and growth/differentiation factor 15 are not exercise-induced myokines under normal physiological conditions [107]. The unfolded protein response (UPR), a stress response to abnormalities in protein folding in ER, has been found in the brains of patients with AD [108]. The molecular chaperone GRP78/BiP, which improves the protein-folding function of the ER, is upregulated in the AD temporal cortex and hippocampus of patients with AD, implying an increased role of UPR [108]. Additionally, phosphorylated PERK has been found in the neurons of patients with AD [109]. Exercise suppresses AD-induced UPR, as treadmill exercise decreased the activation of PERK, eIF2α, and ATF6 in an experimental AD mouse model [110]. This diminished UPR was followed by a decrease in apoptosis and inflammatory responses [110]. The connection between irisin and ER stress might involve the role of irisin in alleviating tunicamycin-induced apoptosis, presumably by inhibiting PERK/eIF2α/ATF/CHOP signaling pathways [110]. In this context, one somewhat controversial view argues that exercise may regulate UPR in patients with AD. Considering the fact that irisin is formed during exercise, this myokine is thought to be involved in UPR regulation.

8. Conclusions

The roles of the recently discovered myokine, irisin are not confined to fat browning and thermogenesis; this myokine seems to be involved in diverse actions. Exercise and irisin have been implicated in increased BDNF levels and decreased Aβ accumulation, which is the prevalent trait of AD. Additionally, irisin might encourage BDNF release, leading to augmentation in neural plasticity. TL shortening, which is commonly found during aging and pathological conditions, appears to be delayed by irisin. In short, exercise-induced irisin may discourage the emergence of AD by promoting neural plasticity and suppressing TL shortening. Whether exercise increases ER stress-induced UPR has not been clearly defined; however, the connection between ER stress and exercise-induced irisin clearly plays a role in AD. Extensive studies are required to clarify the interrelationship of these factors in AD pathology.

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Conflicts of Interest: The authors declare no conflict of interest.

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