Review

Does Irisin Link Physical Exercise with Alzheimer’s Disease?

Dewan Md. Sumsuzzman 1,2, Yunho Jin 1,2, Yonggeun Hong 1,2,3,4,*

1 Department of Rehabilitation Science, Graduate School of Inje University, Gimhae, Korea; dewanpavelpharm@gmail.com (D.Md.S); jynh33@naver.com (Y.J.)
2 Biohealth Products Research Center (BPRC), Inje University, Gimhae, Korea
3 Ubiquitous Healthcare & Anti-aging Research Center (u-HARC), Inje University, Gimhae, Korea
4 Department of Physical Therapy, College of Healthcare Medical Science & Engineering, Gimhae, Korea

* Correspondence: Yonggeun Hong(DVM, PhD); Mailing address: Department of Rehabilitation Science, Graduate School of Inje University, Inje University, 197 Inje-ro, Gimhae, Gyeongnam 50834, Republic of Korea; Tel.: +82-55-320-3681; Fax: +82-55-329-1678; E-mail: yonghong@inje.ac.kr(yonguary12@gmail.com)

Abstract: The skeletal muscle-secreted myokine irisin, which is produced in response to physical exercise, has several protective functions both in the central and peripheral nervous systems, including regulation of brain-derived neurotrophic factor, modification of telomere length, inhibition of the endoplasmic reticulum stress response, and anti-inflammatory and anti-apoptotic effects that may be of benefit in neurodegenerative diseases such as Alzheimer’s disease (AD). The present review is based on the hypothesis that irisin connects physical exercise with AD progression. We herein describe current knowledge of the physiology of irisin and its potential role in AD. We conclude that, although current and ongoing research on irisin is very promising, further research is required to clarify its potential as a meaningful target for drugs to treat 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 is currently advocated as a behavioral intervention to ameliorate neurological impairments [7]; however, the precise cellular mechanism remains elusive. Many studies have highlighted the effects of exercise in various organs, such as the liver, brain, adipose tissue, and heart. Unlike other organs, skeletal muscle is directly affected by exercise [8]. Skeletal muscle has been identified as a secretory organ since it produces and releases cytokines and other peptides that function similarity to hormones [9]. These secretions may underlie the beneficial effects of exercise. The identification of several hundred components in the ‘secretome’ of skeletal muscle provides the basis for understanding how muscle communicates with other organs [8]. Irisin was recently identified as a muscle-derived myokine is released from skeletal muscle immediately after exercise. In this review, we discuss the plausible mechanism of the protective effects of irisin against AD.
2. Association between neuroinflammation and AD

Neuroinflammation in AD is characterized by glial activation and the release of inflammatory mediators, which provoke a ferocious cycle of neuroinflammatory attack [10]. As the first defensive response against brain injury, microglia shows their diverse phenotypes in response to specific signals from the microenvironment [11]. Two major phenotypes of activated microglia have been proposed: 1) a classically activated M1 pro-inflammatory phenotype that releases destructive pro-inflammatory mediators (e.g., interleukin [IL]-1β, IL-6, and tumor necrosis factor [TNF]-alpha, and 2) a selectively activated M2 repair/anti-inflammatory phenotype that secretes neuroprotective, anti-inflammatory factors (e.g., IL-4 and IL-10) [10, 11]. Interestingly, divergent roles for M1 and M2 polarized microglia have been reported in several neurodegenerative diseases, including AD, stroke, and spinal cord injury [11, 14–16], which raise the possibility that modulation of the microglial phenotype could yield translational benefits in these neurodegenerative disorders.

In addition to a role for neuroinflammation, there is adequate evidence that oxidative stress plays an important pathogenic role in AD [17–19]. It was previously demonstrated that oxidative stress leads to irreversible impairment of biological systems due to the oxidation of most of the major biomolecules in cells, including DNA, RNA, proteins, and lipids [20]. In fact, oxidation leading to a buildup of damaging oxidative byproducts has been consistently reported in AD progression, surprisingly at the preliminary stage before crucial senile plaques have formed [21–23]. Furthermore, the accumulation of reactive oxygen species in mitochondria causes subsequent destruction of the electron transfer chain leading to metabolic energy failure and mitochondrial dysfunction [24–26], which is crucial in AD pathology [27, 28].

3. Irisin as a mediator of the beneficial effects of exercise on the brain

Exercise, particularly endurance exercise, has salutary effects on brain health and cognitive function [29–31]. The improvement in cognitive function following exercise may be beneficial to older adults [32]. Exercise has also been reported to ameliorate negative outcomes in neurological diseases, such as depression, epilepsy, stroke, AD, and Parkinson’s disease (PD) [33–38]. The beneficial effects of exercise on the brain are most discernable in the hippocampus and its dentate gyrus, a region of the brain associated with learning and memory. The markedly favorable effects of exercise on the brain include increases in the size of, and blood flow to, the hippocampus in humans, morphological variations in dendrites and dendritic spines, increased synaptic plasticity and, importantly, de novo neurogenesis in the dentate gyrus in various animal models [29, 30]. De novo neurogenesis in the mature brain is believed to occur in only two areas, one of which is the dentate gyrus of the hippocampus; exercise is one of the few known stimuli of this de novo neurogenesis [39].

The discovery of the “exercise hormone” irisin has attracted a great deal of attention [40]. Irisin was identified as a communicator between skeletal muscle and adipocytes; thus, it acts as a potent messenger of the positive effects of physical exercise on target organs other than muscle [41] (Figure 1). Human studies have demonstrated that 10 weeks of physical training resulted in increased plasma levels of irisin [40]. Subsequent studies substantiated acute exercise-altered irisin levels [42, 43]. The results were, however, more equivocal with respect to physical training interventions delivered over several weeks [44–47]. The observations that irisin administration increased the proliferation of hippocampal cells in vitro [48], and that the expression of fibronectin type III domain-containing 5 (FNDC5) resulted in elevated irisin concentrations and brain-derived neurotropic factor (BDNF) gene expression in culture [49], suggest that irisin could be a therapeutic target in neurodegenerative disorders [50–52].
Figure 1. Mechanisms of irisin biogenesis in the human body. 5'-adenosine monophosphate-activated protein kinase (AMPK) leads to the creation of proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α). In turn, fibronectin type III domain-containing 5 (FNDC5) is expressed during prolonged exercise. FNDC5 is cleaved by an unknown peptidase and secreted as irisin.

4. Irisin

Irisin, a newly discovered skeletal muscle-derived myokine secreted during exercise, is also synthesized in various tissues of different species [53]. It is secreted from FNDC5 after cleavage of its extracellular portion [54]. The production of irisin occurs similarly to the shedding and release of other hormones and hormone-like polypeptides, such as epidermal growth factor and transforming growth factor α, from transmembrane precursors. After the N-terminal signal peptide is withdrawn, the peptide is proteolytically cleaved from the C-terminal moiety, glycosylated, and released as a hormone of 112 amino acids. This molecule upregulates uncoupling protein 1 (UCP1) and transforms white adipose tissue (WAT) into brown adipose tissue (BAT), thereby increasing thermogenesis and the energy consumption of adipose tissue [51]. In addition, it ameliorates insulin resistance, lowers blood glucose, and promotes weight loss. Studies have shown that 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 [55]. Irisin was also shown to increase the proliferation of H19-7 mouse hippocampal neurons [56]. 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 [55, 57, 58]. Furthermore, by interfering with oxidative stress and inflammation, irisin protects against palmitic acid-induced apoptosis in liver cells [59].
5. AMPK/FNDC5/IRISIN/BDNF signaling

There are many good reasons to be physically active, including to reduce the odds of developing heart disease, stroke, and diabetes. The activation of various signaling pathways, such as AMPK pathway, contributes to the beneficial effects of exercise [60, 61]. As irisin is an exercise-induced hormone, the intriguing question of whether it links physical activity with brain function has been raised. Wrann et al. reported that irisin is elevated in the hippocampal tissue of mice by endurance exercise [62]. Moreover, they showed that forced expression of FNDC5 in primary cortical neurons increased BDNF expression, and peripheral delivery of FNDC5 to the liver induced BDNF expression in the hippocampus [62]. Because BDNF is a critical regulator of neural plasticity, irisin may act as a key regulator of neuronal survival following neurodegenerative diseases such as AD (Figure 2).

As one of the well-known neurotrophins, BDNF is responsible for regulating the growth, function, and survival of neurons, as well as synaptic stabilization and branching [63]. BDNF is believed to be involved in the pathophysiology of central nervous system diseases associated with neuroinflammation [63]. Neuroinflammation refers to the inflammation of nervous tissue and can lead to neurodegenerative disorders, including AD. Evidence from human neuropathological studies has indicated that the levels of neurotrophins-nerve growth factor and BDNF are lower in AD [64]. These studies demonstrated that BDNF mRNA levels were 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 [65].

In summary, it is hypothesized that a decrease in irisin levels may cause AD pathogenesis and cognitive deficits. These phenomena are highly associated with neuroinflammation and apoptosis, mediated by a dramatic decrease of BDNF.

![Figure 2. Cross-talk between irisin and neurohormones in the brain. Exercise improves cognitive function and the outcomes of neurodegenerative diseases, such as AD. This effect has been linked to the increased expression of brain-derived neurotropic factor (BDNF). Particularly, in the brain, BDNF is activated by binding with the TrkB receptor, resulting in synaptic plasticity, learning, memory, and neural development. Importantly, irisin is a key player that increases the expression of BDNF and acts as a mediator between exercise and brain development.](image)
6. IRISIN/AKT/ERK signaling pathway

Irisin was previously reported to be expressed in the brain, as well as skeletal muscle and the heart [66]. This hormone 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 [67]. Previous studies have also shown that irisin stimulates ERK1/2 signaling in adipocytes [68], endothelial cells [69], and bone marrow stromal cells [70], and activates Akt signaling in hepatocytes [71]. 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 TNF-α and IL-6 levels [67]. Finally, they demonstrated that the novel exercise-induced hormone irisin protects against neuronal injury via activation of the Akt and ERK1/2 signaling pathways [67]. 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 [72]. 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 β-amyloid 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.

7. Irisin, as a biomarker of age-dependent telomere shortening, is associated with AD pathogenesis

Telomeres are the caps at the end of each DNA strand that preserve our chromosomes, similar to the plastic tips at the ends of shoelaces [73]. Without this coating, shoelaces become frayed until they can no longer do their job; in the same manner, without telomeres DNA strands become damaged so that our cells cannot perform their job. Telomere shortening is associated with all aspects of the aging process on a cellular level. Telomere length (TL) describes our biological age as opposed to our chronological age. Numerous empirical studies have uncovered a strong connection between short telomeres and cellular aging [74]. For example, the immune system, which normally atrophies as we age, is highly sensitive to telomere shortening [75]. Telomere shortening has been confirmed to play a causative role in age-related neurodegenerative diseases, including AD. Telomere 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 [76]. 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 [77]. It seems that long-term chronic inflammation and/or oxidative stress accelerate telomere shortening in monocytes [78]. 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 [79]. Monocytes migrate through the blood-brain barrier in AD and convert into microglial cells in the brain, and microglial activation has been reported to be associated with amyloid-plaques in the AD brain [80]. Additionally, increased expression of chemokine receptors and cytokines in the peripheral blood mononuclear cells of AD patients has been reported [81]. Previous studies have reported that lifestyle factors, including exercise, can have a notable impact on the accumulation of DNA damage and TL [82]. The discovery of irisin, which prompts a peroxisome proliferator-activated receptor gamma coactivator 1-alpha...
(PGC-1-α)-dependent ‘browning’ of WAT to a BAT-like phenotype, and upregulates thermogenesis and energy expenditure, may represent a novel mechanism by which modest exercise attenuates age-related decline. Recently, Karan et al. [83] 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 [84-86]. 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 [87], which regulates cellular proliferation and the expression of human telomere reverse transcriptase [88]. In summary, it is hypothesized the age-related decrease of irisin may be a cause of AD pathogenesis and cognitive impairments. This association is highly linked to telomere shortening induced by oxidative stress and inflammation.

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

The ER is associated with several crucial cellular functions (e.g., protein folding, quality control, maintenance of Ca2+ 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 a number of studies have reported that ER stress is linked with several neurodegenerative diseases [89-91]. The unfolded protein response (UPR) induced by ER stress involves both immediate protein kinase responses and subsequent changes in the expression of hundreds of target genes [92, 93]. Evidence of activated UPR signaling has been revealed in AD, PD, and Huntington’s disease, as well as in amyotrophic lateral sclerosis [94, 89-91]. Furthermore, cerebral ischemia can trigger the UPR, although this is clearly reduced by the concomitant dramatic decline in protein synthesis [95]. Recent studies have shown that ER stress can generate signals that warn neighboring cells and elicit inflammatory responses to prevent extensive tissue damage [96, 97]. 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 [98, 99-102]. 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 believed to improve physical fitness and prevent chronic diseases and age-related disorders. 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 [103]. Recent studies have revealed that irisin dramatically suppresses the expression of phosphorylated PERK (protein kinase R-like endoplasmic reticulum kinase) and eIF2α induces by oxidized low-density lipoprotein (ox-LDL) and tunicamycin, indicating that irisin alleviates ox-LDL-induced apoptosis via PERK/eIF2α/CHOP/Bcl-2 CHOPERS signaling pathways [104]. It was previously reported that, among the four eIF2α kinases, PERK is emerging as a key regulator of the memory impairments and neurodegeneration that characterize AD [105]. In summary, it is hypothesized that a sedentary lifestyle and aging are fundamental to irisin deficiency, which is directly followed by the development of AD. This is correlated with ER stress-induced disruption of the protective effects of the UPR and subsequent inflammation, apoptosis and, ultimately, AD (Figure 3).
Figure 3. Interrelationship between irisin and endoplasmic reticulum (ER) stress responses in degenerative brain diseases. Brain ER stress is caused by several disease-associated stressors, including amyloid-β (Aβ) in Alzheimer’s disease (AD). In such disorders, abnormal ER stress leads to activation of the protein kinase R-like endoplasmic reticulum kinase (PERK)/eIF2α signaling pathway. ATF4 is a transcription factor that is activated translationally by eIF2α phosphorylation and plays a role in the transcriptional activation of CHOP in the integrated stress response. Abnormally high eIF2α-P levels increase ATF4 production and impair translation. Excessive eIF2α-P signaling and its downstream effectors impair cell function and may result in brain dysfunction and neurodegeneration. Since irisin strongly inhibits PERK/eIF2α signaling, it may serve as become a novel therapeutic agent [104].

9. Conclusions

Several studies suggest that neuroinflammation in the brain may play a role in neurodegeneration during aging. Reduced irisin levels in elderly populations may be a factor increasing the risk of AD. During aging, chronic irisin deficiency may disrupt BDNF signaling, increase proinflammatory mediators, shorten the TL, and upregulate the ER stress response. These age-related changes accompany Aβ production, causing neuroinflammation and neurodegeneration. Regarding its neuroprotective roles, including the regulation of BDNF signaling, age-dependent telomere shortening, and anti-inflammatory and anti-apoptotic effects, irisin can be regarded as a therapeutic candidate to prevent and treat AD (Figure 4).
Figure 4. A hypothetical model demonstrating the role of irisin in AD. A schematic diagram depicting the potential molecular mechanisms underlying irisin-conferred protection against AD, i.e., by inhibiting telomere shortening, reducing endoplasmic reticulum (ER) stress, increasing BDNF and decreasing inflammation.

Acknowledgments: This work was supported by the grants from the National Research Foundation (NRF-2013R1A2A2A01067169 to Y.H., NRF-2017R1A2A2A01067169 to Y.H.), and by the KRIIBB Research Initiative Program (KGM4611714 to Y.H.). This work was also supported by the 2017 Creative Research Program of Inje University, Republic of Korea.

Author Contributions: This review was conceptualized and designed by Yonggeun Hong; Dewan Md. Sumsuzzman, Yunho Jin and Yonggeun Hong wrote the manuscript; Dewan Md. Sumsuzzman and Yunho Jin collected the references and created the figures appearing in the manuscript under supervision by Yonggeun Hong. All authors commented on the manuscript and approved the final form of manuscript.

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

References


Neuromolecular. Med. PGC1alpha/FNDC5/BDNF elicit the beneficial effects of exercise on neurodegenerative disorders? Metab.


chronic exercise on PGC-1alpha, irisin and browni ng of subcutaneous adipose tissue in humans. Metab.

increased irisin may directly modulate muscle metabolism through AMPK activation. Cell Metabolism.

α  Long, J.Z.; et al. A PGC1-

neurotrophic stimulus in environmental enrichment. Cell. Metabolism.

ischemia in rats. Neuroscience.

Jodeiri, F.M.; Ghaedi, K.; Megraw, T.L.; Curtiss, J.; Shirani, F.M.; Vaziri, P.; Nasr-Esfahani, M.H. Does


48. Moon, H.S.; Dincer, F.; Mantzoros, C.S. Pharmacological concentrations of irisin increase cell proliferation without influencing markers of neurite outgrowth and synaptogenesis in mouse H19-7 hippocampal cell lines. Metabolism. 2013, 62, 1131–1136.


56. Moon, H.S.; Dincer, F.; Mantzoros, C.S. Pharmacological concentrations of irisin increase cell proliferation without influencing markers of neurite outgrowth and synaptogenesis in mouse H19-7 hippocampal cell lines. *Metabolism.* 2013, 62, 1131-1136.


67. Li, D.J.; Li, Y.H.; Yuan, H.B.; Qu, L.F.; Wang, P. The novel exercise-induced hormone irisin protects against neuronal injury via activation of the Akt and ERK1/2 signaling pathways and contributes to the neuroprotection of physical exercise in cerebral ischemia. *Metabolism.* 2017, 68, 31-42.


Pathol. unfolded protein response is activated in pretangle neurons in Alzheimer’s disease hippocampus opportunities.


13, 85-392.


MAP kinase and ERK MAP kinase signaling.

Tang, D. Irisin stimulates browning of white adipocytes through mitogen-activated protein kinase p38 length.

Spector, T.D.; Aviv, A. The association between physical activity in leisure time and leukocyte telomere gain in adulthood and telomere length.


of DNA damage and telomere dysfunction in human blood.


