Clin Nutr Res. 2021 Oct;10(4):292-302
https://doi.org/10.7762/cnr.2021.10.4.292
pISSN 2287-3732·eISSN 2287-3740

cnr
CLINICAL NUTRITION RESEARCH

Review Article

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Irisin Acts via the PGC-1α and BDNF Pathway to Improve Depression-like Behavior

Danbi Jo [1,2] **Juhyun Song** [1,2]

[1]BioMedical Sciences Graduate Program (BMSGP), Chonnam National University, Hwasun 58128, Korea
[2]Department of Anatomy, Chonnam National University Medical School, Hwasun 58128, Korea

OPEN ACCESS

Received: Aug 15, 2021
Revised: Sep 9, 2021
Accepted: Sep 9, 2021

Correspondence to
Juhyun Song
Department of Anatomy, Chonnam National University Medical School, 264 Seoyang-ro, Hwasun-eup, Hwasun 58128, Korea.
E-mail: juhyunsong@chonnam.ac.kr

ORCID iDs
Danbi Jo
https://orcid.org/0000-0003-0013-9291
Juhyun Song
https://orcid.org/0000-0002-9165-8507

Funding
This study was financially supported by Chonnam National University (grant number: 2020-3836).

Conflict of Interest
The authors declare that they have no competing interests.

ABSTRACT

Depression is the most prevalent psychiatric disorder experienced by the world's population. Mechanisms associated with depression-like behavior have not been fully investigated. Among the therapeutic solution for depression, exercise is considered an important regulator attenuating depressive neuropathology. Exercise has been reported to boost the secretion of myokines such as irisin and myostatin in skeletal muscles. Myokines secreted during exercise are involved in various cellular responses including the endocrine and autocrine systems. Especially, irisin as a cleaved version of fibronectin domain-containing protein 5 has multiple functions such as white fat-browning, energy expenditure increase, anti-inflammatory effects, and mitochondrial function improvement in both systemic circulation and central nervous system. Furthermore, irisin activates energy metabolism-related signaling peroxisome proliferator-activated receptor-gamma coactivator-*1 alpha* and memory formation-related signaling brain-derived neurotrophic factor involved in depression. However, the role and mechanism of irisin in depression disorder is not obvious until now. Here, we review recent evidences regarding the therapeutic effect of irisin in depression disorder. We suggest that irisin is a key molecule that suppresses several neuropathological mechanisms involved in depression.

Keywords: Irisin; Depression; Energy metabolism; Brain-derived neurotrophic factor (BDNF); Peroxisome proliferator-activated receptor-gamma coactivator-1 alpha (PGC-1α)

INTRODUCTION

Depression is a common mental disorder with a lifetime prevalence of 20% in the global population [1,2]. Considering the global report, the number of patients with depression will increase to approximately 300 million by 2021, and depression is one of the main causes of mortality worldwide [3].

Depression is associated with damage in several regions of the brain such as the hippocampus, and linked to mood dysregulation, increased anxiety, fatigue, reduced attention, reduced self-esteem, disturbed sleep pattern, and hopeless behavior pattern [4,5].

Numerous studies have demonstrated that the risk factors of depression include dysregulation of energy metabolism [6,7], chronic neuroinflammation, and neurotransmitter

efficiency [8]. Studies have suggested that monoamine transmitters including serotonin (5-HT), norepinephrine, and dopamine are decreased in patients with depression [9].

For treating depressive neuropathology, many clinical approaches such as antidepressant medication, psychotherapy, light therapy, and herbal supplements have been suggested [10-12]. Among suggestions for attenuating depressive mood, physical exercise is the easiest and most effective, and acts by promoting the secretion of endorphin and myokines [13-15]. Physical exercise has been also reported to improve appetite [16], sleep disorder [17], learning and memory function [18,19], motor function [20], and mood [21]. Current study suggested that sarcopenia defined as decreased muscle mass is directly related with depressive behavior [22]. During exercise, skeletal muscle secretes various myokines, which exert endocrine and paracrine effects in numerous tissues and organs [23].

Exercise upregulates the expression of peroxisome proliferator-activated receptor-gamma coactivator-1 alpha (PGC-1α) in skeletal muscle cells and subsequently promotes the generation of fibronectin domain-containing protein 5 (FNDC5); its cleavage results in the production of irisin as one of myokines [24]. Irisin is a peptide type myokine that is cleaved from FNDC5 [25]. Irisin is expressed in skeletal muscles [25], adipose tissue, pancreas, cardiac muscle [26] and several regions of the brain [27,28]. Several studies suggested that irisin and FNDC5 are observed in purkinje cells, neurons in cerebellum [28] and cerebrospinal fluid [29].

Numerous studies have mentioned that exercise increases the expression of *FNDC5* gene in skeletal muscle and levels of irisin in both circulating blood [30] and the hippocampus of the brain [31]. One cohort study demonstrated that FNDC5 and irisin levels are increased in skeletal muscle after exercise [32].

Therefore, we assume that irisin secreted by exercise may influence the improvement of depressive symptoms. Hence, understanding the mechanism of irisin in the regulation of depressive symptoms is crucial for a therapeutic solution for depression. Thus, we review emerging evidences regarding related mechanisms and the role of irisin in depressive symptoms.

IRISIN AND DEPRESSIVE BEHAVIOR

Irisin is a polypeptide hormone stimulated by exercise, and cleaved from FNDC5 [25,33]. It is found in various organs including the brain, heart, liver, and skeletal muscles [34], and has been reported to control glucose metabolism, lipid metabolism, and energy homeostasis in skeletal muscle and adipose tissues [35-37]. In addition, one recent study suggested that irisin has anti-inflammatory, anti-oxidative, and anti-apoptotic effects [38].

Since irisin plays a role in biological responses, it also contributes to the pathological process in chronic kidney disease [39], obesity [40], and type 2 diabetes mellitus [41]. Additionally, irisin prevents blood vessel dysfunction [42] and ameliorates metabolic imbalance [43] by controlling the expression of other myokines and adipokines [44]. Irisin is released into the circulatory system to induce browning of white fats, oxygen consumption, and thermogenesis in adipose tissues [45,46].

In the central nervous system (CNS), irisin crosses the blood brain barrier [47] and its expression is found in the hippocampus and ventral tegmental area involved in the reward

https://doi.org/10.7762/cnr.2021.10.4.292

system and learning process [48]. Few studies have reported that irisin promotes neuronal proliferation and differentiation, and cell protection against amyloid beta peptide 42 toxicity [49,50]. In addition, several studies suggested that irisin attenuates neuroinflammation, memory deficit [51], and ultimately improves neuropathogenesis in neurodegenerative diseases [52]. Irisin has been reported to positively influence memory-related brain regions such as the hippocampus and the dentate gyrus [53,54].

Recently, irisin is emerging as a therapeutic hormone for alleviating depressive behavior by affecting neuronal function in prefrontal cortex [55,56]. Some studies suggested that irisin secreted by exercise activates the PGC-1α-FNDC5/irisin pathway in hippocampus and, ultimately ameliorates depressive symptoms [57,58]. One study mentioned that irisin could help enhance mood by promoting the expression of brain-derived neurotrophic factor (BDNF) in various brain regions [59]. A current study suggested that irisin ameliorates depressive behavior by reducing the surface expression of epidermal growth factor receptor in mice [60]. Previous studies mentioned that irisin contributes to improvement in brain damage and depressive behavior after cerebral ischemic stroke [46,56,61].

Based on previous consequences on irisin levels in CNS, depressive symptoms would be improved by increasing irisin levels. The modulation of irisin levels may influence the suppression of depressive symptoms.

IRISIN AND ENERGY METABOLISM THROUGH PGC-1α PATHWAY

Recently, energy metabolism is emerging as a key phenomenon in depressive symptoms [62,63]. Current studies suggested that impaired brain energy metabolism led to severe pathogenesis in patients with depressive symptoms [64-66].

Glycogen is the main energy supply of the brain, and it regulates neuronal activity. Its accumulation is observed in the brain of depressive patients [67,68]. Patients with depression commonly showed abnormal glucose metabolism [69]. Tricarboxylic acid cycle which provides adenosine triphosphate (ATP) was significantly altered in patients with mild depressive disorder [70]. Some studies reported that glucose levels in blood is elevated in patients with depression than in normal subjects [71,72] and high glucose levels in blood leads to fatigue symptoms in patients with mild depressive disorder [73].

One study indicated that administration of irisin in the third ventricle of the brain boosts energy metabolism such as heat production and oxygen consumption [74]. Regarding depressive symptoms, energy metabolism is directly linked to progression of depression by decreasing astrocytic ATP production [75]. Astrocytes provide metabolic nutrients to neurons and produce cellular energy ATP [76]. Furthermore, abnormal mitochondrial dysfunction has been reported to trigger energy metabolism impairment in the brain of depressed individuals [77].

One study mentioned that exercise could modulate metabolic ability, leading to improvement in depressive behaviors in the prefrontal cortex by promoting irisin secretion [78]. Exercise activates *PGC-1α* gene in the skeletal muscle, and subsequently increases the expression of FNDC5 [79-81].

https://doi.org/10.7762/cnr.2021.10.4.292

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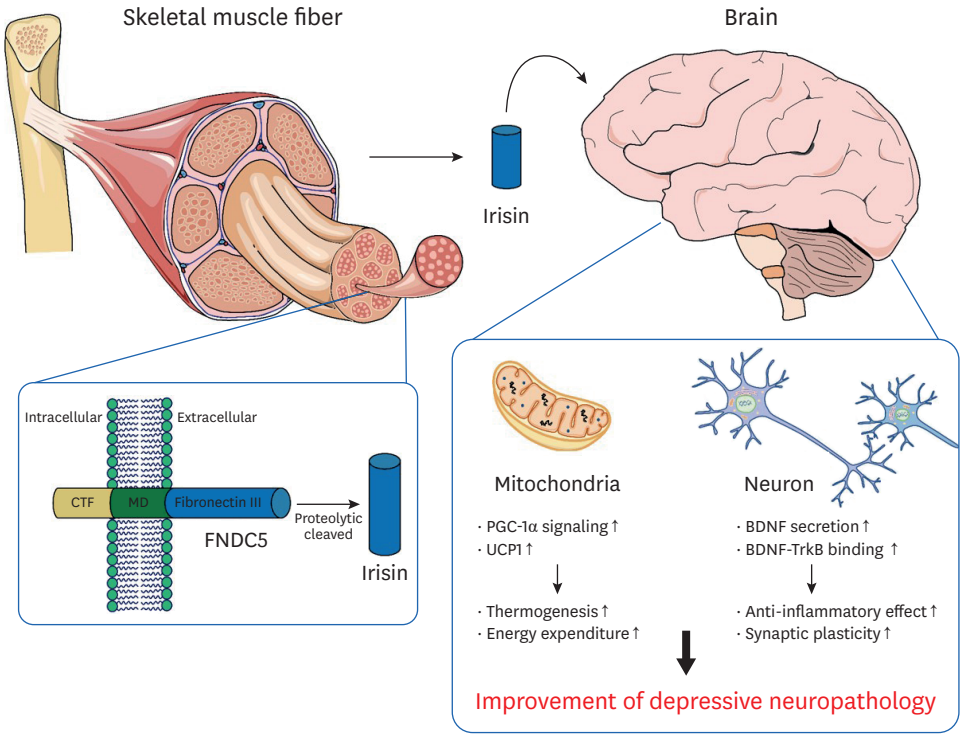

Figure 1. Schematic images showing the effects of irisin on PGC-1α and BDNF pathways. In central nervous system, irisin plays multiple roles to improve mitochondria function through PGC-1α signaling and to enhance synaptic plasticity through BDNF signaling in neurons, leading to the improvement of depressive neuropathology. CTF, C-terminal fragment; MD, membrane domain; FNDC5, fibronectin domain-containing protein 5; PGC-1α, proliferator-activated receptor-gamma coactivator-1 alpha; UCP1, uncoupling protein one; BDNF, brain-derived neurotrophic factor; TrkB, tropomyosin receptor kinase B.

Considering recent studies, irisin could effectively improve depressive symptoms [55,56] by activating PGC-1α-FNDC5/irisin pathway [57] in brain areas, involved in learning, mood, attention, and reward system (**Figure 1**) [82]. Irisin increases the activation of PGC-1α, and subsequently increases the expression of uncoupling protein one (UCP1) mRNA in skeletal muscle cells and adipocytes [25]. The increase in UCP1 expression means an increase in thermogenesis and energy processes in cells [83]. Previous studies demonstrated that irisin administration could activate neuroplasticity-related genes and improve depressive symptoms through improvement in energy expenditure in the prefrontal cortex and hippocampus of the brain of depressed individuals through the activation of PGC-1α [84].

Given emerging findings, irisin could modulate energy metabolism in brain through the activation of PGC-1α, and subsequently could exert therapeutic effect in depressive like behavior.

IRISIN AND SYNAPTIC PLASTICITY THROUGH BDNF PATHWAY

BDNF is known to have anti-inflammatory effect by regulating microglia activation and polarization with binding its receptor tropomyosin receptor kinase B (TrkB) [85]. In the brain, BDNF and TrkB are also expressed in various brain regions such as the hippocampal formation and brain stem [31,86].

https://doi.org/10.7762/cnr.2021.10.4.292

BDNF controls inflammation signaling such as extracellular-signal-regulated kinase, nuclear factor-kappa light chain enhancer of activated B cells, p38 and c-Jun N-terminal kinase [87-89] and boosts memory function-related signaling including glycogen synthase kinase 3 and cAMP-response element binding protein [90].

Some studies indicated that BDNF is a critical marker in major depressive disorders [91], and the BDNF levels in serum shows negative correlation with the depression score [92,93]. BDNF is secreted during exercise and protects neurons and glia against brain damage [31].

Moreover, BDNF secretion is related with FNDC5/irisin expression in the hippocampus of the brain [28,31]. Furthermore, elevation of FNDC5/irisin expression in brain hippocampus boosts activation of BDNF, and subsequent neuroprotective effects (**Figure 1**) [31]. One study demonstrated that FNDC5/irisin expressed in the wide brain region is modulated by BDNF levels and promotes hippocampal neurogenesis and memory function (**Figure 1**) [31]. Another study indicated that activation of irisin-BDNF signaling could effectively reduce stress-induced depression [94].

Recent studies suggested that irisin could induce BDNF secretion in the ventral tegmental area, hippocampal area, and limbic circuit, involved in reward system, learning system, mood, and motivation [48,82,95,96]. The ventral tegmental area, ventral-striatum axis, dentate gyrus, and hippocampus are important target areas in major depressive disorder and anxiety [97-99]. Regarding that irisin promotes the expression of BDNF in various brain regions such as the hippocampus, irisin may play a key role in modulating depression-like symptoms by promoting the secretion of BDNF (**Figure 1**).

CONCLUSION

Irisin is helpful in enhancing depressive neuropathology. Impairment of energy metabolism and synaptic impairment caused by a deficit of neurotrophic factors are important features in the brain of patients with depressive disorders. Irisin secreted during exercise could control energy expenditure through PGC-1α and moreover, improves the production of BDNF in depressive brain. Finally, irisin may enhance the depressive mood problem in patients with depression through the activation of PGC-1α and BDNF pathways.

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