Biomeditsinskaya Khimiya, 2025 vol. 71, issue 6, pp. 379–399.

REVIEWS

THE MYOKINE IRISIN: EFFECTS ON THE BRAIN AND THERAPEUTIC POTENTIAL IN THE TREATMENT OF DEPRESSION AND NEURODEGENERATIVE DISEASES

A.M. Gisina*, K.N. Yarygin

Institute of Biomedical Chemistry,
10 Pogodinskaya str., Moscow, 119121 Russia; *e-mail: alisa.gisina@ibmc.msk.ru

Epidemiological studies indicate a consistent global increase, including in the Russian Federation, in the number of patients with cognitive impairments associated with neurodegenerative diseases and various affective disorders. In this context there is a clear need in the development of more effective therapeutic approaches for their corrections. Good evidence exists that regular physical activity improves cognitive functions and alleviates depression. Working muscles secrete biologically active substances known as myokines, which regulate muscle recovery and functions of internal organs, endocrine glands, the immune system, and the brain. This results in a coordinated response of organs and systems aimed at restoring functional activity of the body after physical exercises and improves memory and learning ability. Patients with cognitive impairments or depression are often unable to engage in regular physical activity due to physical limitations or decreased motivation. Therefore, pharmaceuticals that mimic the effects of muscle activity are a promising therapeutic option. One potential direction in this field could be the development of drugs based on the myokine irisin, which is produced during physical exercise and exerts a range of beneficial effects on cognitive function and mood. This review summarizes existing data on the effects of physical exercise on cognitive function in health and disease; it describes the physiological effects of irisin, and presents the proposed mechanisms of irisin action on cognitive function and symptoms of depression.

Keywords: myokines; irisin; depression; neurodegenerative diseases

DOI: 10.18097/PBMCR1640

INTRODUCTION

Dementia and depression are the most common psychiatric conditions in aging. Dementia is characterized by acquired cognitive impairment, leading to a significant deterioration in the patient's ability to learn, work, and communicate, and ultimately to a loss of the ability to maintain a normal lifestyle [1]. Based on etiology and pathogenesis, two categories of dementia can be distinguished: 1) dementia observed in neurodegenerative diseases — Alzheimer's disease, dementia with Lewy bodies, Parkinson's disease and frontotemporal lobar degeneration; 2) dementia arising in other, non-neurodegenerative pathologies, such as hydrocephalus, traumatic brain injury (TBI), infections, immune disorders, tumors, poisoning and metabolic diseases [1]. In 2017, the global estimate of the number of patients diagnosed with dementia was approximately 50 million people, and their number was expected to double every 20 years [2]. Maintaining cognitive functions in the aging population is an important task, since dementia directly impacts the quality of life of older people and creates a significant burden on society, families and the healthcare system. Depression is an even more common serious mental illness, affecting nearly 300 million people worldwide [3] and is also a leading cause of temporary disability and sickness absenteeism [4].

Epidemiological studies have demonstrated that older adults with a history of depression are at higher risk of developing cognitive impairments. A link has also been found between previous cases of mental disorders and the onset of dementia [5]. Moreover, a survey of the elderly population has shown a high prevalence of depression, which often manifests as a complication of dementia [6]. Depression is accompanied by various physiological, biochemical, and morphological manifestations, such as vascular pathological changes, disruption of the molecular mechanisms of glucocorticoid regulation, hippocampal atrophy, neuroinflammation, deficiency of brain-derived neurotrophic factor (BDNF), and others [7]. Depression is associated with decreased hippocampal neurogenesis in adults [8]. Intravital brain imaging studies have shown decreased volume of cortical and limbic regions, particularly the prefrontal cortex and hippocampus, in patients with major depressive disorder, which is particularly pronounced in patients with multiple episodes, relapses, and longer illness duration [8]. Postmortem analysis of brain tissue from patients with major depressive disorder has shown decreased glial cell density and neuronal volume in the dorsolateral prefrontal cortex [9]. Reduced synaptic plasticity in patients with depression contributes to impaired mood regulation and cognitive function [10]. Reduced expression of genes related

to synaptic function and a decreased number of synapses have been found in the prefrontal cortex of patients with major depressive disorder [11].

Aging-associated sarcopenia and learning disability are closely related. Gait speed and muscle strength are significantly inversely correlated with cognitive impairment. A meta-analysis of studies published over the past decade found a consistent two-fold increase in the odds of cognitive impairment among older adults with sarcopenia compared to individuals without significant age-related muscle loss [12]. A sedentary lifestyle and lack of physical activity are risk factors for sarcopenia in individuals with mild cognitive impairment and Alzheimer's disease [13]. Moreover, physical activity correlates with improved cognitive function and a reduced risk of neurodegenerative diseases [14]. Physical activity is an important factor in maintaining mental health and preventing episodes of anxiety and depression [15, 16]. Unfortunately, patients with cognitive impairment or depression are often unable to engage in regular physical activity due to physical limitations and lack of motivation. Therefore, myokine-based drugs that mimic the effects of exercise are a promising therapeutic option. A clear candidate for the active ingredient in such drugs is the myokine irisin, which has a range of beneficial effects on cognitive function and mood. This review summarizes existing information on the role of exercise in the treatment of cognitive impairment and depression; it describes the physiological effects of irisin, both endogenous and exogenous, produced during exercise, and discusses the putative mechanisms of beneficial effects of irisin on cognitive function and the reduction of depressive symptoms.

1. PHYSICAL ACTIVITY SUPPORTS MENTAL HEALTH

Regular physical exercises not only promote skeletal muscle growth and development but also improve physical and mental health in humans and enhance cognitive performance in healthy experimental animals [17, 18]. The effectiveness of physical exercise for depression is supported by the results of more than 40 meta-analyses and systematic reviews [19–22]. Epidemiological studies have shown that physical activity reduces the risk of Alzheimer's disease and dementia, with high levels of physical activity attenuating Alzheimer's-related cognitive decline [23]. These effects are partly explained by stimulation of neurogenesis, increased synaptic plasticity, and suppression of neuroinflammation in the hippocampal dentate gyrus [24]. Myokines, including irisin, interleukin-6 (IL-6), insulin-like growth factor-1 (IGF-1), brain-derived neurotrophic factor (BDNF), and leukemia cell inhibitory factor (LIF), are produced during exercises and are able to penetrate the blood-brain barrier (BBB). They coordinately participate in communication between skeletal muscle and the brain, mediating various neuroprotective effects, such as improved memory, neuroplasticity, appetite, and mood, as well as reduced neuroinflammation [25]. With age, due to limited physical activity, skeletal muscle mass decreases, and this, in turn, leads to a decrease in myokine secretion [26, 27].

Myokine secretion patterns are poorly understood. It is known that myokine production by muscles depends on individual characteristics, the type of physical activity, its intensity, and duration. Peak blood myokine levels are observed immediately after exercise and persist for approximately one hour, followed by a return to baseline levels 3–24 h after exercise completion [28]. Myokine production is dependent on age and a fitness level [29]. Resistance exercise increased blood levels of the proinflammatory myokine IL-6 in individuals with mild cognitive impairment to a greater extent than in the blood of controls [30]. A possible explanation for the increase in IL-6 levels in this situation may be that the resistance exercise was too intense for the elderly participants [31]. Low-intensity exercise is more beneficial for preserving cognitive function in individuals with Alzheimer's disease than more intense exercise [32]. Furthermore, some studies have shown that cardiovascular and strength training may have a more significant impact on cognitive function in people with mild cognitive impairments than multimodal exercises. This suggests that cardiovascular and strength training may serve as an effective strategy for slowing cognitive decline in this group of patients. Research is ongoing to identify optimal exercise combinations that promote effective interactions between various myokines and deliver maximum benefits.

Physical exercises represent an effective approach for treatment of mild-to-severe depression, with effects comparable to those achieved with antidepressants and cognitive behavioral therapy [33]. The combination of exercises with standard treatment produced a significantly higher antidepressant effect than the standard treatment alone [34]. Exercises also play a preventive role by reducing the risk of depression [35]. A recent systematic review and meta-analysis of 15 prospective studies have shown that the development of depression is associated with physical activity levels in a complex manner, with the greatest reduction in depression risk observed at relatively low levels of physical activity [36]. Another meta-analysis of 49 prospective studies has shown vigorous-intensity activity reduced probability of depression compared individuals who lead a sedentary lifestyle [34]. The protective effect of physical activity against depression was observed across age, gender, and geographic region. Exercises had a significant impact on the production of neurotransmitters such as dopamine, norepinephrine, and 5-hydroxytryptamine [37, 38]. In a randomized controlled trial, patients with depression who engaged in regular physical activity for 16 weeks had increased

plasma levels of the anti-inflammatory cytokine IL-10, decreased levels of pro-inflammatory cytokines and pro-inflammatory markers such as IL-6 and C-reactive protein, and decreased neutrophil and monocyte counts [39]. Animal studies have confirmed that exercises reduce depressive-like behavior, possibly due to the suppression of systemic inflammation by increasing IL-10 levels [40]. These findings suggest that regular physical activity may be a way to control inflammatory responses.

Endothelial damage caused by oxidative stress is linked to the onset and progression of a number of central nervous system disorders, including vascular depression and late-life depression [41]. Voluntary running wheel exercise increased endogenous glutathione levels and ameliorated depressive-like behavior in male rats with significantly elevated ethanol-induced lipid peroxidation and protein oxidation in the hippocampus and cerebellum [42]. In adult humans, the antidepressant effect of exercises is accompanied by, and may be associated with, improved synaptic plasticity, neuronal growth, and neurogenesis in the hippocampus [43–46]. In a mouse model of depression induced by chronic unpredictable stress, physical exercises increased the number of mature neurons and dendritic spines in the dentate gyrus and other hippocampal regions and they were more effective than fluoxetine in promoting neuronal maturation and modulating synaptic plasticity [43].

Increasing evidence suggests that BDNF is involved in the antidepressant effect of exercises. Clinical studies have shown that physical exercises increased BDNF levels differentially depending on its intensity, and changes in BDNF were closely associated with improvements in depressed mood after exercise [47]. In rats, 28 consecutive days of physical activity increased BDNF mRNA and protein expression in hippocampal neurons, primarily in their dendrites [48].

2. MYOKINE IRISIN

In 2002, Teufel et al. identified the transmembrane protein FNDC5, containing a fibronectin type III domain and playing a role in myoblast determination and differentiation [49]. In 2012, Boström et al. discovered that an unknown enzyme could cleave the extracellular portion of membrane-embedded FNDC5, resulting in the release of a 112-amino acid residue polypeptide, subsequently named as irisin, into the peripheral circulation [50]. FNDC5 transcription is regulated by peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), a transcription cofactor involved in energy metabolism (Fig. 1). FDNC5 consists of a signal peptide and the structural domain of fibronectin III, which contains irisin, as well as transmembrane and cytoplasmic domains [50–52]. Irisin has a highly conserved structure and is 100% homologous in mice and humans [50]. Specific antibodies or tandem mass spectrometry can be used to identify and quantify circulating irisin in the human body.

The spatial structure of irisin was determined using X-ray diffraction [52]. Irisin contains the typical fibronectin III arrangement with a four-stranded β-sheet that packs tightly against a three-stranded β-sheet [52] (Fig. 2).

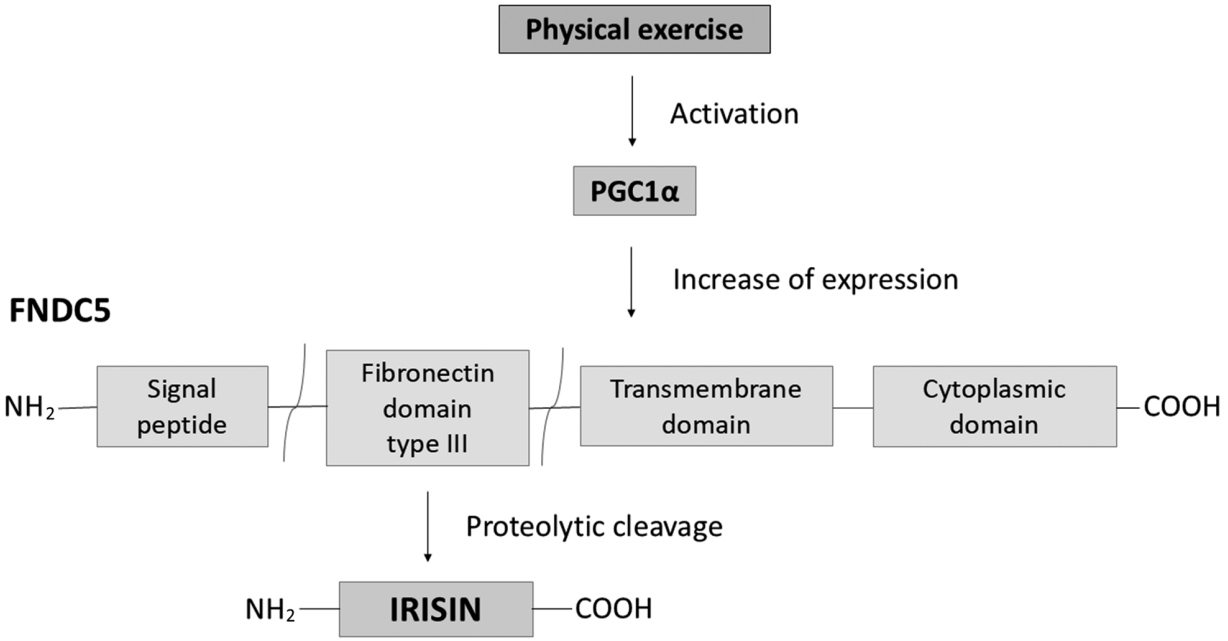

Figure 1. Physical exercise induces activation of the transcriptional coactivator PGC-1α in skeletal muscle, leading to increased expression of FNDC5, which is cleaved by an unidentified enzyme to produce irisin. Abbreviations: PGC-1α – peroxisome proliferator-activated receptor gamma coactivator-1 alpha; FNDC5 – fibronectin type III domain-containing protein 5.

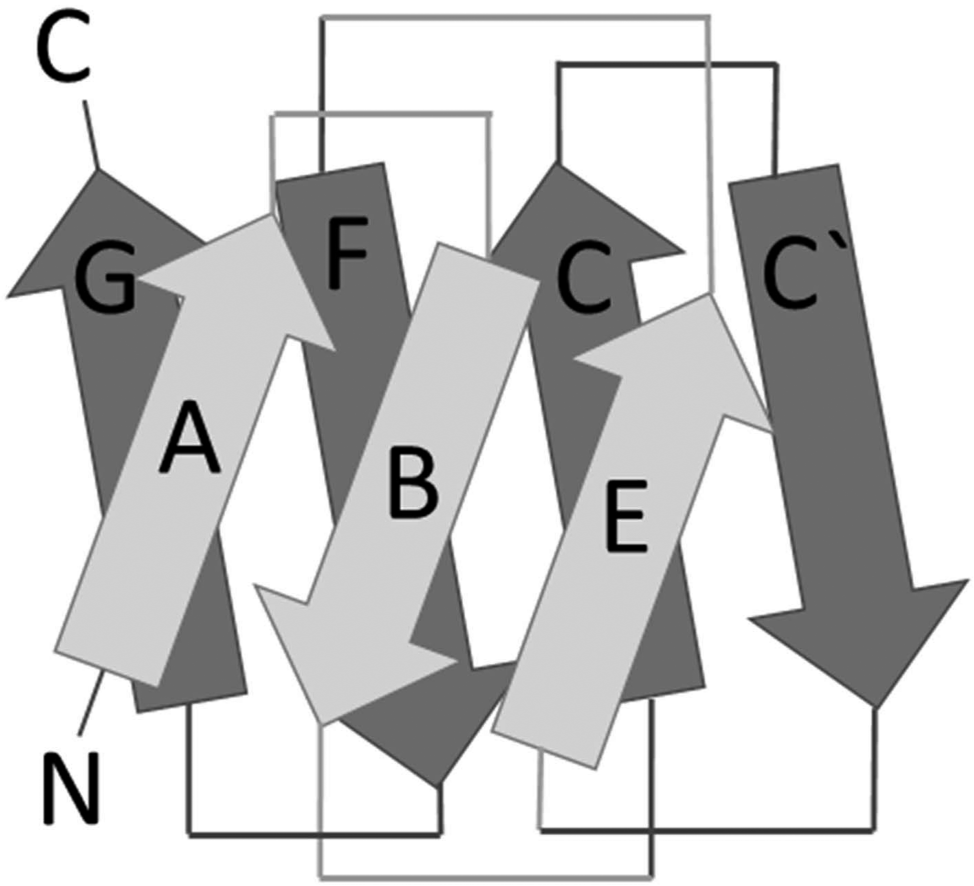

Figure 2. Schematic representation of the irisin crystal structure determined by X-ray crystallography (adapted from [52]).

Irisin is mainly produced by skeletal muscle and cardiomyocytes (cardiomyocytes produce it even more actively per mass unit) [50, 53]. Skeletal muscles can be considered as endocrine organs, as they secrete irisin into the bloodstream, where its concentration is maintained in the range of 3–5 ng/ml characteristic of peptide hormones. The molecular mechanism activating irisin production during physical exercise is as follows. Hypoxia occurring in muscles during exercise leads to a decrease in ATP levels and an increase in AMP. High AMP levels, as well as reactive oxygen species (ROS), accumulate during hypoxia, activate AMP-dependent protein kinase (AMPK), which stimulates PGC-1α production [54, 55]. Accumulation of Ca^{2+} in the cytoplasm of working muscles leads to phosphorylation also contributing to AMPK activation and PGC-1α stimulation, which alters gene expression, including *FNDC5*. Among the genes activated by PGC-1α there are many genes involved in energy metabolism genes.

The described pathway activating FNDC5 expression and irisin production is characteristic of muscles. In other tissues, FNDC5 expression may be regulated differently. In addition to muscle, PGC-1α expression has also been detected in the brain and kidneys, at lower levels in the liver; minimal levels were detected in white adipose tissue [56].

FNDC5/irisin has been shown to be expressed not only in muscle tissue but also in adipose tissue. FNDC5/irisin is also detected in serum and cerebrospinal fluid (CSF) [53, 57–60]. Details of the quantitative and qualitative detection of FNDC5/irisin at the protein and mRNA levels are presented in Table 1.

Results of recent studies show that irisin is also detected in the brain, particularly in cerebellar Purkinje cells, as well as in the cerebral cortex, hippocampus, basal ganglia, and hypothalamus. It is unclear whether CSF irisin is of central or peripheral origin. It is hypothesized that irisin can cross the BBB via a saturable transport system [59]. This is supported by increased muscle expression of the FNDC5 protein, which influenced hippocampal gene expression and ameliorated memory impairments [64, 65]. Irisin receptors are a family of αV integrins, in particular the αV/β5 integrin complex. Certain evidence exists that irisin can reduce neuroinflammation after cerebral hemorrhage by binding to integrin αVβ5 expressed in microglia [66]. Irisin has been found to stimulate energy metabolism, reduce insulin resistance, regulate glucose and lipid metabolism disorders, and participate in the formation of brown adipose tissue involved in thermogenesis [50, 67]. Thus, irisin may alleviate metabolic disorders, including obesity, diabetes, and cardiovascular diseases [50, 68].

Table 1. Tissues in which FNDC5/irisin expression has been detected

Tissue	Research objects	Detected substance	Method of detection	Result	Reference
Plasma	Humans	Protein	Mass spectrometry	Detected; concentration at rest: ~3.6 ng/ml; after exercises: ~4,3–4,4 ng/ml	[61]
Cerebrospinal fluid	Humans	Protein	Mass spectrometry	Detected; concentration: 0.26–1.86 ng/ml	[62]
Adipose tissue	Rats	Protein, mRNA	Immunoblotting, QRT-PCR, secretome study	Detected; concentrations are not shown	[63]

QRT-PCR – quantitative real-time PCR.

Animal and human studies have shown that exercises increased irisin levels in circulation and hippocampus and increased FNDC5 mRNA and protein expression in muscle tissue [50, 69–72]. In humans, irisin levels at rest are about 3.6 ng/ml, and after aerobic interval training, they increase to 4.3 ng/ml [61]. Other factors, such as temperature, diet, and certain medications such as fenofibrate and metformin, also affect irisin levels [73]. In general, individuals with sarcopenia have lower irisin levels [74]. Although irisin production decreases with age, it can be partially restored by resistance training [75]. Resistance, aerobic, or combined exercise appears to play a beneficial role, with irisin production levels corresponding to increases in exercise intensity [76]. However, in several studies, physical exercises did not change serum irisin levels [77, 78]. These results can likely be explained by the fact that serum irisin concentrations are influenced by a number of factors, such as age, gender, weight, and physical fitness level of the subjects. The most important factors are the time of sample collection and the type of exercise regimen used. Failure to account for these factors may lead to the conclusion that there is no relationship between physical exercise and irisin secretion [79–81]. Since the half-life of irisin in the body is less than 1 h, attention should be paid to the timing of blood collection after a single bout of physical exercise [61].

3. IRISIN EFFECTS IN NEURODEGENERATIVE DISEASES AND DEPRESSION

A positive correlation has been shown between irisin levels and cognitive dysfunction. In an experimental study on rats, intrahippocampal administration of beta-amyloid, mimicking some symptoms of Alzheimer's disease and inducing impairments in spatial learning and memory, was accompanied by a decrease in FNDC5 expression in the hippocampus. However, 4 weeks of physical exercise in the form of moderate-intensity running led to an increase in FNDC5 mRNA levels in the hippocampus and improved spatial learning and memory in experimental animals [82]. Irisin also has an antidepressant effect [82, 83]. Several clinical trials have examined the relationship between depression and the ability to produce irisin during exercise. A randomized trial showed that aerobic exercise increased serum irisin levels and reduced depression and fatigue in patients with relapsing-remitting multiple sclerosis [84]. A 6-month study of patients with acute ischemic stroke showed that serum irisin levels were lower in patients with post-stroke depression compared to non-depressed patients. In this context, irisin is a more effective biomarker in predicting post-stroke depression than age and serotonin [85]. Studies performed using animal models of depressive disorder have shown that irisin released during exercise has a beneficial effect on behavior by increasing dopamine and norepinephrine levels [86]. Thus, irisin produced during exercise may have an antidepressant effect [82].

Pattern separation strongly depends on *de novo* neuron formation in the hippocampus [87]. Certain evidence exists that the dorsal hippocampus controls cognitive functions, while the ventral hippocampus controls emotional behavior [88]. Hippocampal neurogenesis is reduced in mice and humans during aging and Alzheimer's disease [89, 90], while exercises promote neurogenesis in the adult hippocampus and improve learning and memory [91]. FNDC5 knockout affects the development of hippocampal neurons and alters their morphology, transcriptome, and function. Under the same exercise conditions, wild-type mice exhibited improved spatial learning and memory compared to FDNC5 knockout mice (F5KO mice), with aged (21–24 months) F5KO mice exhibiting a greater decline in cognitive performance than wild-type mice [64]. Abnormal activation patterns were found in the hippocampus of adult F5KO mice. During running exercise, the total length of dendrites increased to a greater extent in wild-type mice than in F5KO mice. In the hippocampal ventral dentate gyrus of sedentary F5KO mice there was a more complex dendritic structure compared to wild-type mice, suggesting that the absence of irisin could lead to excessive growth or defective

formation of new hippocampal neurons [64]. Furthermore, the neuronal density in the dorsal hippocampus of F5KO mice was significantly reduced and dendritic spine heads were smaller compared to wild-type mice [64]. These results suggest that irisin specifically affects the growth and maturation of new neurons in the hippocampus and, consequently, cognitive abilities. Irisin maintains normal gene expression in hippocampal neurons. Regardless of the type of physical activity, the transcriptome profile of newborn neurons in F5KO mice was abnormal. Nuclear RNA sequencing identified a total of 459 genes that were differentially expressed between neurons in F5KO and wild-type mice. Gene enrichment analysis suggests that irisin knockdown in newborn hippocampal neurons may lead to a number of serious neurological diseases, including Alzheimer's disease [64]. RNA sequencing data from another study, including a total of 2114 samples from 1234 individuals, showed a significant decrease in irisin expression in the parahippocampal gyrus of individuals diagnosed with Alzheimer's disease compared to controls [64]. In APP/PS1 mice, a well-known transgenic model of Alzheimer's disease, *FNDC5* gene expression in the hippocampus was markedly reduced compared to wild-type mice [92]. At the age of 6 months, amyloid plaque formation, gliosis, and cognitive decline were observed. Cognitive function of APP/PS1-F5KO mice (created by hybridizing F5KO mice with APP/PS1 mice) was reduced after exercise compared to APP/PS1-wild-type hybrids. Furthermore, APP/PS1-F5KO mice had significantly elevated levels of cortical soluble beta-amyloid, contributing to beta-amyloid plaque formation. Despite lack of elevated hippocampal irisin expression, male APP/PS1 mice with elevated liver irisin expression and elevated circulating irisin levels, demonstrated significant gains in spatial learning and memory tasks. After irisin treatment 5xFAD mice (another type of transgenic Alzheimer's disease mouse model) showed improved spatial learning and memory performance in the Morris water maze test [92]. These results suggest that peripheral administration of irisin improves cognitive performance in animal models of Alzheimer's disease.

Irisin may play a role in neuronal differentiation [93–95]. Irisin expression increased in mouse embryonic stem cells during retinoic acid-induced neural differentiation [93]. Subsequent experiments demonstrated that suppression of irisin expression in neuronal progenitor cells blocks the differentiation of mouse embryonic stem cells into neurons and the maturation of astrocytes [93]. The mRNA and protein levels of BDNF and its receptors, tyrosine kinase and p75, were reduced after FDNC5 knockout. FNDC5 knockout suppressed neuronal differentiation by affecting the expression of BDNF and its receptors at the transcriptional and translational levels [95]. In contrast, increased FNDC5/irisin expression promoted the expression of neuronal progenitor markers Sox1 and Pax6, mature neuronal markers such as Neurocan, and the astrocytic marker GFAP, likely through the induction of increased BDNF expression [94]. This highlights the importance of FNDC5 in neuronal differentiation.

Irisin induces BNDF expression and improves synaptic plasticity in an Alzheimer's disease model [96, 97]. It enhances maturation of hippocampal neurons and alters their morphology, transcriptome, and function. Studies have shown that irisin administration effectively mitigates cognitive decline even when significant pathological changes already occurred in the mouse brain [98]. Patients with late-stage Alzheimer's disease had significantly reduced irisin levels in the hippocampus compared to patients with early-stage Alzheimer's disease or individuals with normal cognitive function [65]. Furthermore, patients with Alzheimer's disease had lower CSF irisin levels compared to patients with mild cognitive impairments or with normal cognitive function. A positive correlation was also found between CSF irisin levels in patients with Alzheimer's disease and their Mini-Mental State Examination scores, as well as CSF levels of beta-amyloid and BNDF [99]. In C57BL/6 mice, decreased irisin activity resulted in impaired long-term potentiation in the hippocampus, suggesting that irisin could influence hippocampal synaptic plasticity, memory, and novel object recognition (NOR). Direct intrahippocampal administration of recombinant irisin may protect against impairment in memory and NOR. Intraventricular administration of the irisin-containing adenoviral vector AdFNDC5 to C57BL/6 mice for 6 days resulted in increased irisin mRNA and protein levels in the cortex and hippocampus and effectively protected against beta-amyloid infusion-induced impairment in various memory types [65].

In a study, involving 63 elderly subjects (38 with cognitive impairment and 25 without cognitive impairment), 41 elderly subjects were diagnosed with depression, which was associated with decreased CSF irisin and BDNF levels, comparable to those seen in patients with dementia [100]. Major depressive disorder is both a predisposition factor for Alzheimer's disease and a comorbidity [101]. Regular exercises caused a reduction in the incidence and severity of major depressive disorder and Alzheimer's disease [102]. Another study showed that subcutaneous injection of irisin (100 μg/kg per day for 5 days) caused marked antidepressant and antianxiety effects in young mice [103]. One form of depression seen in patient and experimental animals (mice), is depression induced by propofol, a pharmacological agent used in surgical practice, which induces postoperative depression in humans. Irisin blocks propofol-induced depressive behavior in mice [93]. Furthermore, irisin mitigated neuronal death induced by high concentrations of propofol *in vitro* and suppressed propofol-induced increases in cytokine

levels in astrocyte cultures [104]. In a rat model of depression induced by chronic unpredictable stress, irisin (100 ng/ml or higher concentrations) exerted an antidepressant effect in rats, modulating energy metabolism, including in the prefrontal cortex [105].

4. MECHANISMS OF IRISIN ACTION ON COGNITIVE FUNCTION AND MOOD

Irisin is a key mediator between physical activity and metabolic homeostasis in the brain. The proposed mechanisms by which irisin improves cognitive function and exerts antidepressant effects include: 1) regulation of glucose and lipid metabolism; 2) increased BDNF expression in the hippocampus; 3) activation of the AKT and ERK1/2 signaling pathways; 4) attenuation of neuroinflammatory responses in the brain; 5) suppression of oxidative stress; 6) reduction of neuronal apoptosis; 7) protection of the integrity of the blood-brain barrier; 8) reduction of the accumulation of pathological α-synuclein (α-syn) in the brain (Fig. 3).

4.1. Regulation of Glucose and Lipid Metabolism

Impaired brain energy metabolism is a significant factor in the pathogenesis of depression [106, 107]. Combined proteomic and metabolomic analysis demonstrated that patients with mood disorders had impairments in energy metabolism [108–110]. Disturbances in glucose, lipid, and amino acid metabolism are common in patients with major depressive disorder. Irisin plays a role in the regulation of lipid and glucose metabolism in skeletal muscle and adipose tissue [50, 111–113]. In obese mice, irisin reduced insulin resistance, corrected disturbances in glucose and lipid metabolism, and increased lipolysis via the cAMP/PKA/perilipin pathway [112]. Furthermore, irisin injection at a the range of doses from 1.5 μg/kg to 2.5 μg/kg increased oxygen consumption and carbon dioxide and heat production in rats [114].

Impaired glucose metabolism in the brain is a key pathological feature of depression and contributes to its onset and progression [106, 115]. According to results of some studies, patients with depression have higher than normal blood glucose levels, and elevated glucose levels are associated with fatigue symptoms in patients with mild depression [116]. Patients with monophasic depression have lower glucose metabolism in the dorsal prefrontal and anterior cingulate cortex compared to healthy controls. Numerous studies have demonstrated the beneficial effects of irisin on glucose metabolism and insulin sensitivity [113]. Irisin levels were reduced in patients with type 2 diabetes mellitus and obesity, and circulating plasma irisin levels were inversely related to the level of insulin resistance [113]. Irisin increased fatty acid oxidation and glucose uptake in type 2 diabetes mellitus by modulating the AMPK signaling pathway and reducing the expression of the gluconeogenic enzymes phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase) in the liver [117]. Furthermore, irisin activated p38 MAPK in an AMPK-dependent manner, and inhibition of p38 MAPK blocked irisin-induced glucose uptake [118]. Irisin also increased the expression of β-trophin, a hormone stimulating pancreatic β-cell

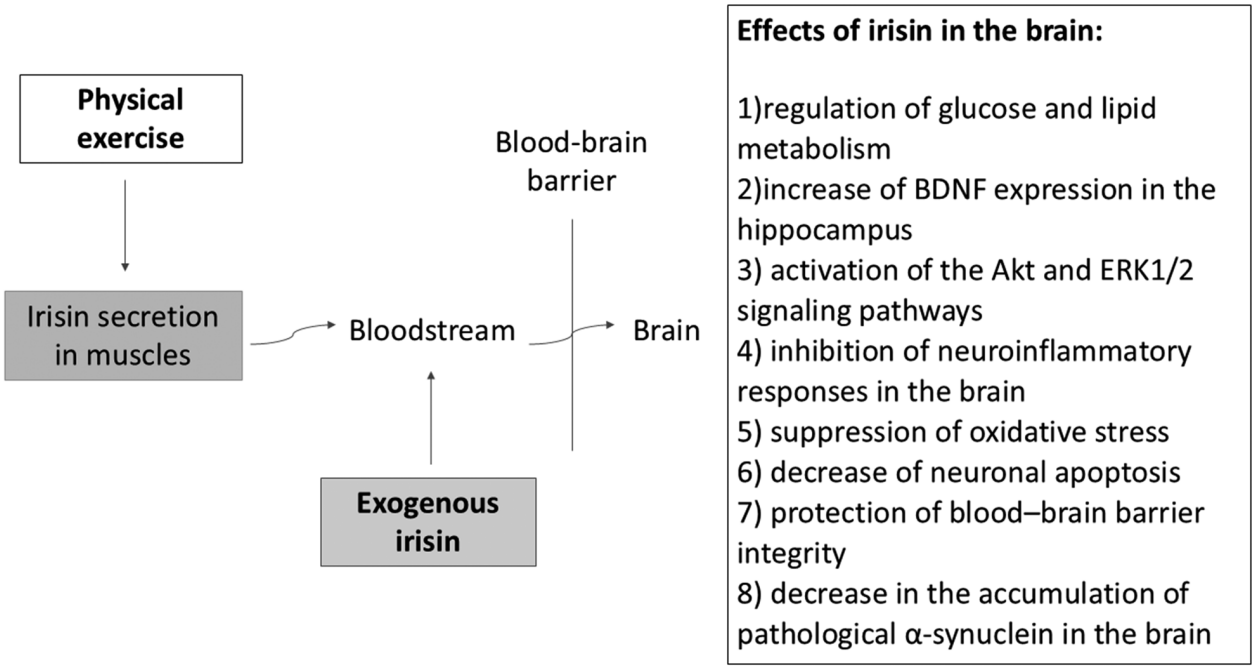

Figure 3. Irisin released into the bloodstream from skeletal muscle or administered as an exogenous pharmacological agent crosses the blood-brain barrier and exerts a range of neuroprotective effects in the brain, contributing to the alleviation of cognitive impairment and depressive symptoms.

proliferation and improving glucose tolerance [119]. Interestingly, increased endogenous ATP release from astrocytes exhibited an antidepressant-like effect in a mouse model of depression, suggesting a physiological link between ATP release from astrocytes and major depressive disorder [120].

It has been shown that, irisin stimulates UCP1 expression and the conversion of white adipose tissue to brown adipose tissue, which increases thermogenesis and energy production [50, 119]. This effect may be mediated by activation of p38 MAPK (mitogen-activated protein kinase) and extracellular signal-regulated kinase (ERK) signaling pathways [119]. The MAPK pathway is a key mechanism for the conversion of white adipocytes to brown adipocytes, neuronal differentiation, and osteoblast proliferation [65, 66, 121].

4.2. Increased BDNF Expression in the Hippocampus

BDNF, found primarily in the brain and skeletal muscle, is vital for the development and differentiation of myoblasts and myofibers. It has also been detected in various tissues and systems, including the peripheral and central nervous systems [122]. BDNF levels decrease during myoblast maturation and myogenic differentiation, thus influencing satellite cells or muscle cell progenitors and supporting early myoblast differentiation [123]. BDNF plays an important role in the CNS, controlling neuronal survival, growth, and maintenance. It also regulates synaptic plasticity, cell survival, and brain cell differentiation [124]. Studies in mice have shown that BDNF has positive effects on brain function by promoting hippocampal cell regeneration, increasing *BDNF* gene expression, improving spatial memory, enhancing motor performance, and maintaining overall brain function [125]. BDNF also acts as a key factor in exercise-induced neuroprotection and mediates increased neurotransmitter release. Even in the case of progressive memory impairment, physical activity was found to increase BDNF levels, which in turn enhances hippocampal neuroplasticity and memory function in mice of different ages [126]. A significant body of clinical and experimental evidence suggests that BDNF plays a significant role in the pathophysiology of depression. Autopsy studies of brain tissue from depressed and non-depressed patients have shown lower levels of BDNF [127]. Antidepressant treatment increases BDNF synthesis, and direct administration of BDNF to the hippocampus has an antidepressant effect [128]. Selective blockade of BDNF in the hippocampal dentate gyrus reduced the effectiveness of antidepressants [129].

Exercises induced BDNF expression in the hippocampus via the PGC-1α/FNDC5 pathway [130]. Moreover, intraperitoneal administration of recombinant irisin (0.5 μg/kg/day) increased the mRNA levels of PGC-1α, FNDC5, and BDNF in the hippocampus [131]. Peripheral delivery of irisin to the liver via adenoviral vectors also increases circulating irisin levels, promoting the expression of *BDNF* and other neuroprotective genes in the hippocampus [130]. Irisin can cross the BBB via peripheral transport and induce BDNF expression in the CNS [64]. Suppression of irisin expression in cortical neurons by siRNA resulted in a decrease in BDNF expression [130]. Further studies showed that recombinant irisin activated the cAMP/PKA/CREB pathway, crucial for BDNF synthesis, in human cortex slices and increased cAMP and pCREB expression in mouse hippocampal slices [65]. Activation of the cAMP/PKA/CREB/BDNF signaling pathway and increased BDNF expression are known to have antidepressant effects [132, 133]. A study aimed at examining the effects of central irisin administration on BDNF mRNA expression and protein levels, has shown that irisin decreased BDNF mRNA expression in the hippocampus after 1 h but increased it after 6 h [82]. BDNF mRNA expression correlated with irisin mRNA expression [82]. The latter is consistent with the notion that irisin is a positive regulator of BDNF expression [130]. Furthermore, genetic polymorphisms in BDNF (BDNF Met/Met) result in a lack of the antidepressant effect and increased BDNF and irisin mRNA levels in the hippocampal dentate gyrus [134]. Taking into consideration that BDNF expression can help mitigate the onset and progression of depression, activation of the irisin-BDNF axis in the brain may be a promising therapeutic approach for the treatment of depression.

4.3. Activation of the AKT and ERK1/2 Signaling Pathways

In patients with ischemic stroke, blood irisin concentrations inversely correlated with the severity and duration of post-stroke neurological deficit [135]. A significant decrease in serum irisin levels compared to controls was observed in patients with vascular dementia [136]. After adjustment of all clinical characteristics, statistical analysis showed a significant positive correlation between irisin levels and cognitive performance in patients with vascular dementia. A mouse ischemia/reperfusion model was established by bilateral ligation of the common carotid arteries for 20 min followed by 24 h reperfusion; this resulted in severe neurological deficits that were significantly ameliorated by irisin administration [137]. Experiments *in vivo* and *in vitro* have shown that irisin reduced hippocampal neuronal apoptosis. Furthermore, 10 μg/kg irisin significantly suppressed the expression of inflammatory cytokines such as IL-1β and tumor necrosis factor-α (TNFα), with simultaneous expression of Notch1 intracellular domain (NICD), Notch1, and Hes1. These results suggest that irisin exerts neuroprotective effects under ischemia/reperfusion conditions by modulating the Notch signaling pathway [137]. In a mouse

model of vascular dementia with chronic cerebral hypoperfusion due to bilateral stenosis of the common carotid arteries, irisin levels in the hippocampus of mice were significantly reduced. Induction of irisin expression in the hippocampus by pulsed ultrasound or injection of recombinant irisin into the hippocampus improved synaptic plasticity, mitigated neuroinflammation, and reduced the degree of cognitive impairment in mice [138]. In a study using a mouse model of stroke induced by temporary occlusion of the middle cerebral artery, intracerebroventricular injection of irisin (doses from 0.5 μg/kg to 15 μg/kg) significantly reduced infarct volume. Administration of 7.5 μg/kg irisin alleviated cerebral edema, significantly reduced the number of apoptotic cells in the ischemic cerebral cortex and increased BDNF immunoreactivity, but did not affect the BBB permeability [139]. Another study found a negative relationship between plasma irisin levels and cerebral infarction volume, neurological deficit and plasma TNFα and IL-6 concentrations [140]. Administration of irisin (0.2 μg/g) resulted in increased AKT and ERK1/2 phosphorylation levels, while inhibition of AKT and ERK1/2 weakened the neuroprotective properties of irisin. Consequently, activation of serine-threonine-specific protein kinase AKT and ERK1/2-dependent signaling pathways by irisin may be a mechanism of neuronal protection under ischemia/reperfusion conditions.

4.4. Reduction of Neuroinflammatory Responses

Neuroinflammation plays a crucial role in the pathogenesis of depression. Depressed patients have elevated levels of proinflammatory cytokines such as IL-6 and TNFα in the serum and CSF [141]. Elevated mRNA and protein levels of IL-1β, IL-6, and TNFα have also been found in the prefrontal cortex of depressed patients who died by suicide [142]. Animal studies show that depressive behavior is accompanied by increased inflammatory markers in brain regions associated with major depressive disorder [143]. Administration of lipopolysaccharide (LPS), which triggers an immune and inflammatory response, induces depressive behavior in rodents [144]. The signaling pathway involving toll-like receptor 4 (TLR4), myeloid differentiation primary response gene 8 (MyD88), and nuclear factor NF-κB is a classic inflammatory signaling pathway implicated in the development of depression [145]. It is suggested that irisin may inhibit inflammatory signaling systems and/or inflammasome activation and maturation. Irisin exhibits anti-inflammatory, anti-apoptotic, and antioxidant effects in neurological pathologies [146]. In mice with middle cerebral artery occlusion, irisin treatment suppressed microglial activation, monocyte infiltration, oxidative stress, and the expression of proinflammatory factors (TNFα and IL-6) [140]. Irisin suppressed the release of proinflammatory cytokines (IL-1β, IL-6, TNFα) and cyclooxygenase type 2 (COX-2) via the AMPK/NF-κB pathway in a rat spinal cord injury model [147]. In a cerebral hemorrhage model, irisin suppressed proinflammatory microglia/macrophage polarization, reduced neutrophil infiltration, and decreased the expression of proinflammatory cytokines TNFα and IL-1β via the integrin αVβ5/AMPK signaling pathway [66]. An *in vitro* study assessing the ability of irisin to protect neurons from beta-amyloid injury showed that irisin attenuated the release of IL-6 and IL-1β and reduced COX2 expression in astrocytes. Irisin can reduce NF-κB activation in beta-amyloid-exposed astrocytes [148]. Another study showed that irisin attenuated oxygen- and glucose-deprived inflammation by inhibiting ROS and the NLRP3 inflammatory signaling pathway [149]. In a middle cerebral artery occlusion model of cerebral ischemia, irisin inhibited neuroinflammatory responses and reduced neuronal damage by downregulating the TLR4/MyD88 cascade and inhibiting NF-κB activation [150]. Thus, it is reasonable to conclude that irisin reduces neuroinflammation and decreases the production of inflammatory factors in the brain.

Irisin influences macrophage polarization. Macrophages are classified as conventionally activated (M1 type) or alternatively activated (M2 type), which play opposing roles in inflammation [151, 152]. M1 macrophages produce proinflammatory cytokines including TNFα, IL-6, and IL-1β, while M2 macrophages secrete anti-inflammatory cytokines such as IL-10 [152]. Exogenously administered irisin and irisin overexpression inhibit LPS-induced M1 macrophage polarization and inflammatory cytokine production via the AMPK pathway [153]. Previous studies have shown that irisin treatment can suppress the expression of proinflammatory cytokines, reduce macrophage migration, and induce a phenotypic switch of macrophages from the M1 to M2 state [154]. Irisin-mediated BDNF activation can reduce neuroinflammation by inhibiting synthesis of NF-κB and proinflammatory cytokines IL-6 and IL-1β through activation of the ERK/CREB pathway via the TrkB receptor [155]. High concentrations of irisin (50 nM, 100 nM) attenuate LPS-stimulated macrophage inflammatory activation and reduce the release of proinflammatory cytokines by inhibiting the downstream TLR4/MyD88 pathway and NF-κB phosphorylation, which is associated with the effect of irisin on MAPK phosphorylation [156]. Irisin also inhibit NF-κB phosphorylation by suppressing the TLR4/MyD88 pathway and activate the BDNF/ERK/CREB pathway, thus also reducing the proinflammatory cytokine production.

4.5. Oxidative Stress Suppression

The pathophysiology of depression is associated with dysregulated redox homeostasis [157–159]. Oxidative stress can initiate or exacerbate a number of pathogenetic processes associated with depression,

including ferroptosis, neuroinflammation, impaired autophagy, and mitochondrial dysfunction [158]. Meta-analyses have shown impaired antioxidant capacity and increased levels of oxidative damage products in patients with depression. Antioxidant levels are increased by antidepressant use [160, 161]. Thus, suppression of oxidative stress may improve depressive symptoms, as some antioxidants exhibit potential antidepressant activity [162]. Oxidative stress refers to an imbalance between ROS generation and antioxidant defense. High levels of ROS can damage proteins and DNA, promoting the release of inflammatory mediators, which ultimately leads to cell death and apoptosis [163]. Irisin reduces ROS production by activating the BDNF/UCP2 and AKT/ERK pathways and inhibiting the ROS-NLPR3 inflammatory signaling pathway. Uncoupling protein 2 (UCP2), expressed in the central nervous system, has shown potent neuroprotective effects [164]. UCP2 reduces mitochondria-mediated ROS production, increases ATP levels, mitigates free radical-induced mitochondrial damage, and helps nerve cells to use free radical energy. UCP2 deficiency has been shown to exacerbate depressive-like behavior and promote mitochondrial damage and ROS production in astrocytes in a chronic mild stress model [165]. Irisin protects against oxidative stress-induced neuronal damage in various models of neurological diseases. In a cerebral ischemia model, irisin significantly reduced the levels of nitrotyrosine, superoxide anion, and 4-hydroxynonenal in peri-infarct brain tissue through the activation of AKT and ERK1/2 signaling pathways. It also suppressed the secretion of proinflammatory factors and mitigated ischemia-induced neuronal injury [140]. In a mouse model of oxygen and glucose deficiency, irisin mitigated neuronal injury by blocking the ROS-NLRP3 inflammatory signaling pathway and reducing ROS and malondialdehyde production to inhibit oxidative stress [149]. In rat models of epilepsy, exogenous irisin significantly increased expression of BDNF and UCP2, and simultaneously reduced the levels of neuronal damage and mitochondrial oxidative stress [166, 167]. In a mouse TBI model, exogenous irisin mitigated inflammatory responses and oxidative stress by inducing UCP2 expression in neuronal mitochondrial membranes, resulting in reduced mitochondrial damage and decreased ROS production and malondialdehyde levels [168]. Consequently, irisin is a key regulator of oxidative stress and, therefore, a potential therapeutic agent for depression.

Irisin improved cognitive performance in mice with cerebral ischemia by regulating *Klotho* expression. The *Klotho* gene is a regulator of aging [169], and the protein it encodes plays a crucial role in slowing aging and improving cognitive function [170]. Mice with *Klotho* mutations have shortened lifespan, impaired synaptic integrity, and compromised cognitive function [171]. Some clinical studies have found a significant decrease of CSF Klotho concentrations in elderly individuals compared to younger individuals [172]. Moreover, these studies also found a strong correlation between *Klotho* mutations and the onset of cognitive dysfunction in the elderly [172]. Furthermore, a marked decrease in Klotho protein concentrations was observed in CSF of patients with Alzheimer's disease [173]. Another study [174] found a significant positive association between irisin levels and Klotho concentrations in CSF of stroke patients. In a mouse model of stroke with cerebral ischemia, both exercise and exogenous irisin demonstrated comparable protective effects on cognitive impairment. Compared with the cerebral ischemia group, the ischemic irisin group showed a marked increase in the expression of Klotho protein, as well as forkhead transcription factor (FOXO3a) and Mn-dependent superoxide dismutase (MnSOD). In addition, a decrease in the ROS formation was demonstrated. Subsequent studies showed that the protective effects of irisin were abolished in *Klotho* knockout mice [174]. These results indicate that irisin mitigated oxidative stress by regulating *Klotho* expression, thus improving cognitive function and clinical outcomes in a mouse cerebral ischemia model.

In summary, serum and CSF irisin are positively correlated with cognitive function in patients with vascular dementia. In various animal models of vascular dementia, irisin reduces inflammation and oxidative stress by regulating the Notch and AKT/ERK1/2 signaling pathways, while the Klotho protein protects neurons from apoptosis, thereby attenuating cognitive dysfunction in vascular dementia.

4.6. Reduction of Neuronal Apoptosis

Parkinson's disease (PD) is a neurodegenerative disease characterized by the progressive death of dopaminergic neurons in the *substantia nigra pars compacta* (SNpc). The study of the effect of irisin on this process was conducted using a PD rat model, in which the death of dopaminergic neurons was induced by intranasal administration of the toxin MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) [175]. Rats with the modeled PD were intravenously injected with bone marrow stem cells (BMSCs), irisin, or BMSCs in combination with irisin. Animals of the MPTP-treated group had 77% apoptosis of dopaminergic neurons compared with the control group animals (without MPTP). Administration of BMSCs, irisin, or irisin+BMSCs significantly reduced the number of dead cells [175]. However, no statistically significant differences were observed between the irisin group and the BMSC group, suggesting that irisin could promote the migration of stem cells to the SNpc and convert them into dopaminergic neurons. The group treated with irisin in combination with BMSCs showed the highest degree of reduction [175]. Another study has shown that after 12 weeks of regular exercises, the serum irisin concentration in PD patients increased significantly,

and their exercise capacity and balance function improved. Furthermore, irisin administration enhanced motor function in mice with MPTP-induced PD and simultaneously reduced dopaminergic neuron apoptosis [176]. Subsequent studies have shown that irisin, through activation of the ERK1/2 signaling pathway, effectively mitigated intracellular oxidative stress, suppressed mitochondrial damage, and facilitated mitochondrial respiration and biogenesis in PD models, ultimately leading to the inhibition of apoptosis [176]. The considered results suggest that irisin exhibits neuroprotective properties in PD by suppressing dopaminergic neuron apoptosis and mitigating pathological changes in mitochondria.

4.7. Protection of the Blood-Brain Barrier Integrity

A key factor in the poor clinical prognosis of TBI or stroke is the occurrence of cerebral edema resulting from the BBB disruption. A potential mechanism underlying this phenomenon may be related to morphological and functional abnormalities of neuronal mitochondria in the injured brain tissue, decreased UCP2 activity, and increased inflammatory response and oxidative stress. Irisin effectively reduces the BBB permeability after TBI. A correlation was found between the degree of brain tissue damage during injury and the CSF concentration of irisin [168]. Both physical activity and irisin administration reduced the BBB disruption in a mouse TBI model. In a UCP2 knockout mouse model, irisin administration ameliorated the impairment of mitochondrial structure and function by upregulating UCP2 expression on the neuronal mitochondrial membrane. This resulted in reduced inflammatory responses and oxidative stress, thus improving the BBB integrity and alleviating injury-induced brain edema [168]. In a one-year prospective cohort study including 656 individuals over the age of 17 years with mild TBI it was noted that 13.5% of participants demonstrated suboptimal cognitive outcomes at the end of the follow-up period; this percentage was significantly higher compared to the control group, in which only 4.5% demonstrated similar cognitive impairment [177]. A significant proportion of adult trauma patients diagnosed with intracranial hemorrhage demonstrated cognitive impairment in the early stages [178]. Similar results were obtained in a study of a pediatric group of TBI patients [179]. During the acute phase of TBI, brain cells require adequate ATP production to repair damaged cells [180]. However, damaged mitochondria lose the ability to meet this energy demand; this triggers a series of deleterious cascade reactions, including electron transport chain disruption, ATP depletion, excessive ROS generation, oxidative stress-induced damage, neuronal apoptosis, and neuroinflammation [181]. Recent *in vivo* and *in vitro* studies have demonstrated the important role of irisin in maintaining mitochondrial function and promoting mitochondrial biogenesis. Exogenous irisin administration alleviated mitochondrial dysfunction, resulting in increased ATP utilization [182, 183]. Administration of irisin (1 μg/kg) maintained mitochondrial potential and ATP levels via the involvement of AMPK-dependent pathways [184]. Irisin can stimulate mitochondrial biogenesis and inhibit mitochondrial fission, thus compensating excessive ATP consumption [183]. Irisin and its receptor integrin αVβ5 reached peak levels within 24 h of intracranial hemorrhage. Subsequent administration of irisin resulted in a reduction of cerebral edema, prevented the development of neurological deficits, and promotes the recovery of neurological functions. Notably, integrin αVβ5 is predominantly localized in microglia, and irisin administration suppresses the proinflammatory polarization of microglia/macrophages and simultaneously promotes their anti-inflammatory polarization. Moreover, irisin administration prevents neutrophil infiltration after intracerebral hemorrhage and inhibits neuronal cell apoptosis. Intranasally administered irisin significantly increased expression of integrin αVβ5, p-AMPK (phosphorylated AMPK), and Bcl-2 (B-cell lymphoma protein-2) and simultaneously decreased expression of IL-1β, TNFα, MPO (myeloperoxidase), and Bax (Bcl-2-associated protein X). Taken together, these data indicate that irisin treatment improves neurological deficits, reduces brain edema, and alleviates neuroinflammation and neuronal apoptosis through the integrin αVβ5/AMPK signaling pathway [66].

4.8. Protection Against α-syn Pathological Accumulation in the Brain

In PD patients, physical exercises improve posture, stabilize gait, improve overall mobility, and enhance cognitive abilities, including processing speed and cognitive control [185, 186]. Results of some studies indicate that this is at least partly related to irisin expression, which may serve as a basis for the development of innovative PD treatments [187]. Irisin prevents the formation of pathological α-syn aggregates and protects neurons from their neurotoxic effects. Cultivation of primary cortical neurons in the presence of preformed α-syn fibrils, was accompanied by misfolding of newly synthesized α-syn, which was toxic to the cells [188]. Irisin at concentrations of 50 ng/ml and 500 ng/ml prevented α-syn formation and α-syn-induced death of cortical neurons [189]. Injection of α-syn into the *corpus striatum* of mice resulted in the death of a portion of neurons. Two weeks later, administration of an adenoviral vector expressing irisin into the tail vein to induce irisin overexpression in the liver and increase its blood concentration reduced neuronal loss. In contrast to mice treated with blank vectors, administration of the irisin-expressing vector effectively inhibited the aggregation of insoluble α-syn and significantly ameliorated α-syn-induced behavioral impairments [189].

CONCLUSIONS

Myokines and irisin in particular, play an important role in the pathophysiology of both sarcopenia and cognitive impairment. Muscles and the brain, which are the primary organs responsible for locomotion in animals and humans, interact closely. Their developmental processes are closely linked, and in the adult organism, they cannot function without each other. Problems that still require further clarification include the precise mechanisms underlying myokine release, the dose-response relationship between exercise and muscle-induced myokine release, and the precise mechanisms underlying myokine regulation of muscle-brain interactions.

Studies have shown that irisin plays a key role in muscle-brain interactions. In this review, we have summarized the putative mechanisms underlying the irisin neuroprotective effect in the brain of humans with cognitive impairment and/or depression. Developing drugs that mimic the therapeutic effects of exercise is now a feasible goal. Irisin levels increase during physical activity, but implementing regular exercise regimens for people with cognitive impairment can be challenging and potentially dangerous, as in untrained individuals, physical activity also triggers the release of other myokines with proinflammatory effects, particularly IL-6. Improvement of cognitive function by increasing irisin levels after exercises may not be a practical approach for these patients. Numerous studies have demonstrated the ability of irisin to cross the BBB, suggesting that exogenous irisin administration is a promising therapeutic approach for addressing cognitive impairments. Therefore, for patients with cognitive impairments who cannot afford regular exercises, exogenous irisin administration may be a viable option.

In the context of perspectives of further studies, certain areas need more intensive research. Currently, data from large-scale clinical trials on the safety and efficacy of irisin, as well as the dosage range and time window for clinical use, are still absent. The use of irisin in clinical practice still represents a serious problem due to its short half-life *in vivo*. Several approaches exist to extend the half-life of protein drugs *in vivo*, such as chemical or genetic conjugation to albumin [190]. The emergence of nanotechnological delivery strategies may offer a solution to prolong the therapeutic effect and reduce the frequency of administration [76]. Future research should aim to improve the stability of irisin using these innovative technologies to optimize therapeutic outcomes and expand its clinical potential. Finally, the complex interplay between physical activity, gut microbiota, and cognitive function has attracted considerable attention in recent years. However, studies exploring the possible role of myokines, including irisin, in these interactions have not yet been conducted.

FUNDING

The work was performed within the framework of the Program for Basic Research in the Russian Federation for a long-term period (2021–2030) (no. 122022800499-5).

COMPLIANCE WITH ETHICAL STANDARDS

This article does not contain any research involving humans or the use of animals as objects.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

REFERENCES

1. *Gale S.A., Acar D., Daffner K.R.* (2018) Dementia. Am. J. Med., **131**(10), 1161–1169. DOI: 10.1016/j.amjmed.2018.01.022
2. *López-Lluch G., Rattan S.I.S.* (2015) Facing challenges in an ageing world. Biogerontology, **16**(5), 567–568. DOI: 10.1007/s10522-015-9597-5
3. *Herrman H., Kieling C., McGorry P., Horton R., Sargent J., Patel V.* (2019) Reducing the global burden of depression: a Lancet-World Psychiatric Association Commission. Lancet, **393**(10189), e42–e43. DOI: 10.1016/S0140-6736(18)32408-5
4. *Friedrich M.J.* (2017) Depression is the leading cause of disability around the world. JAMA, **317**(15), 1517. DOI: 10.1001/jama.2017.3826
5. *Richmond-Rakerd L.S., d'Souza S., Milne B.J., Caspi A., Moffitt T.E.* (2022) Longitudinal associations of mental disorders with dementia: 30-year analysis of 1.7 million New Zealand citizens. JAMA Psychiatry, **79**(4), 333–340. DOI: 10.1001/jamapsychiatry.2021.4377
6. *Singh-Manoux A., Dugravot A., Fournier A., Abell J., Ebmeier K., Kivimäki M., Sabia S.* (2017) Trajectories of depressive symptoms before diagnosis of dementia: a 28-year follow-up study. JAMA Psychiatry, **74**(7), 712–718. DOI: 10.1001/jamapsychiatry.2017.0660
7. *Dafsari F.S., Jessen F.* (2020) Depression — an underrecognized target for prevention of dementia in Alzheimer's disease. Transl. Psychiatry, **10**(1), 160. DOI: 10.1038/s41398-020-0839-1
8. *Lorenzetti V., Allen N.B., Fornito A., Yücel M.* (2009) Structural brain abnormalities in major depressive disorder: a selective review of recent MRI studies. J. Affect. Disord., **117**(1–2), 1–17. DOI: 10.1016/j.jad.2008.11.021
9. *Cotter D., Mackay D., Chana G., Beasley C., Landau S., Everall I.P.* (2002) Reduced neuronal size and glial cell density in area 9 of the dorsolateral prefrontal cortex in subjects with major depressive disorder. Cereb. Cortex, **12**(4), 386–394. DOI: 10.1093/cercor/12.4.386
10. *Duman R.S., Shinohara R., Fogaça M.V., Hare B.* (2019) Neurobiology of rapid acting antidepressants: convergent effects on GluA1-synaptic function. Mol. Psychiatry, **24**(12), 1816–1832. DOI: 10.1038/s41380-019-0400-x

11. *Kang H.J., Voleti B., Hajszan T., Rajkowska G., Stockmeier C.A., Licznerski P., Lepack A., Majik M.S., Jeong L.S., Banasr M., Son H., Duman R.S.* (2012) Decreased expression of synapse-related genes and loss of synapses in major depressive disorder. Nat. Med., **18**(9), 1413–1417. DOI: 10.1038/nm.2886
12. *Peng T.-C., Chen W.-L., Wu L.-W., Chang Y.-W., Kao T.-W.* (2020) Sarcopenia and cognitive impairment: a systematic review and meta-analysis. Clin. Nutr., **39**(9), 2695–2701. DOI: 10.1016/j.clnu.2019.12.014
13. *Sugimoto T., Ono R., Murata S., Saji N., Matsui Y., Niida S., Toba K., Sakurai T.* (2016) Prevalence and associated factors of sarcopenia in elderly subjects with amnestic mild cognitive impairment or Alzheimer disease. Curr. Alzheimer Res., **13**(6), 718–726. DOI: 10.2174/1567205013666160211124828
14. *Tyndall A.V., Clark C.M., Anderson T.J., Hogan D.B., Hill M.D., Longman R.S., Poulin M.J.* (2018) Protective effects of exercise on cognition and brain health in older adults. Exerc. Sport Sci. Rev., **46**(4), 215–223. DOI: 10.1249/JES.0000000000000161
15. *Cassilhas R.C., Tufik S., de Mello M.T.* (2015) Physical exercise, neuroplasticity, spatial learning and memory. Cell. Mol. Life Sci., **73**(5), 975–983. DOI: 10.1007/s00018-015-2102-0
16. *de Sousa R.A.L., Rocha-Dias I., de Oliveira L.R.S., Improta-Caria A.C., Monteiro-Junior R.S., Cassilhas R.C.* (2021) Molecular mechanisms of physical exercise on depression in the elderly: a systematic review. Mol. Biol. Rep., **48**(4), 3853–3862. DOI: 10.1007/s11033-021-06330-z
17. *Wong-Goodrich S.J.E., Pfau M.L., Flores C.T., Fraser J.A., Williams C.L., Jones L.W.* (2010) Voluntary running prevents progressive memory decline and increases adult hippocampal neurogenesis and growth factor expression after whole-brain irradiation. Cancer Res., **70**(22), 9329–9338. DOI: 10.1158/0008-5472.CAN-10-1854
18. *Pietropaolo S., Sun Y., Li R., Brana C., Feldon J., Yee B.K.* (2008) The impact of voluntary exercise on mental health in rodents: a neuroplasticity perspective. Behav. Brain Res., **192**(1), 42–60. DOI: 10.1016/j.bbr.2008.03.014
19. *Heissel A., Heinen D., Brokmeier L.L., Skarabis N., Kangas M., Vancampfort D., Stubbs B., Firth J., Ward P.B., Rosenbaum S., Hallgren M., Schuch F.* (2023) Exercise as medicine for depressive symptoms? A systematic review and meta-analysis with meta-regression. Br. J. Sports Med., **57**(16), 1049–1057. DOI: 10.1136/bjsports-2022-106282
20. *Noetel M., Sanders T., Gallardo-Gómez D., Taylor P., del Pozo Cruz B., van den Hoek D., Smith J.J., Mahoney J., Spathis J., Moresi M., Pagano R., Pagano L., Vasconcellos R., Arnott H., Varley B., Parker P., Biddle S., Lonsdale C.* (2024) Effect of exercise for depression: systematic review and network meta-analysis of randomised controlled trials. BMJ, **384**, e075847. DOI: 10.1136/bmj-2023-075847
21. *Hu M.X., Turner D., Generaal E., Bos D., Ikram M.K., Ikram M.A., Cuijpers P., Penninx B.W.J.H.* (2020) Exercise interventions for the prevention of depression: a systematic review of meta-analyses. BMC Public Health, **20**(1), 1255. DOI: 10.1186/s12889-020-09323-y
22. *Singh B., Bennett H., Miatke A., Dumuid D., Curtis R., Ferguson T., Brinsley J., Szeto K., Eglitis E., Zhou M., Simpson C.E.M., Petersen J.M., Firth J., Maher C.A.* (2025) Systematic umbrella review and meta-meta-analysis: effectiveness of physical activity in improving depression and anxiety in children and adolescents. J. Am. Acad. Child Adolesc. Psychiatry, S0890-8567(25)00208-4. DOI: 10.1016/j.jaac.2025.04.007 Epub ahead of print.
23. *Hamer M., Chida Y.* (2009) Physical activity and risk of neurodegenerative disease: a systematic review of prospective evidence. Psychol. Med., **39**(1), 3–11. DOI: 10.1017/S0033291708003681
24. *Nichol K.E., Poon W.W., Parachikova A.I., Cribbs D.H., Glabe C.G, Cotman C.W.* (2008) Exercise alters the immune profile in Tg2576 Alzheimer mice toward a response coincident with improved cognitive performance and decreased amyloid. J. Neuroinflammation, **5**, 13. DOI: 10.1186/1742-2094-5-13
25. *Little H.C., Tan S.Y., Cali F.M., Rodriguez S., Lei X., Wolfe A., Hug C., Wong G.W.* (2018) Multiplex quantification identifies novel exercise-regulated myokines/cytokines in plasma and in glycolytic and oxidative skeletal muscle. Mol. Cell. Proteomics, **17**(8), 1546–1563. DOI: 10.1074/mcp.RA118.000794
26. *Eaton M., Granata C., Barry J., Safdar A., Bishop D., Little J.P.* (2018) Impact of a single bout of high-intensity interval exercise and short-term interval training on interleukin-6, FNDC5, and METRNL mRNA expression in human skeletal muscle. J. Sport Health Sci., **7**(2), 191–196. DOI: 10.1016/j.jshs.2017.01.003
27. *Cai L., Tan M., Tan W., Zeng X., Wan N., Wong S.H.-S., O'Reilly J., Sun F., Yang J., Chen Y.* (2019) Associations of circulating irisin concentrations with cardiometabolic risk factors among children vary by physical activity or sedentary time levels. Front. Endocrinol., **10**, 549. DOI: 10.3389/fendo.2019.00549
28. *Bettariga F., Taaffe D.R., Galvão D.A., Lopez P., Bishop C., Markarian A.M., Natalucci V., Kim J.-S., Newton R.U.* (2024) Exercise training mode effects on myokine expression in healthy adults: a systematic review with meta-analysis. J. Sport Health Sci., **13**(6), 764–779. DOI: 10.1016/j.jshs.2024.04.005
29. *Cordingley D.M., Anderson J.E., Cornish S.M.* (2023) Myokine response to blood-flow restricted resistance exercise in younger and older males in an untrained and resistance-trained state: a pilot study. J. Sci. Sport Exerc., **5**, 203–217. DOI: 10.1007/s42978-022-00164-2
30. *Vints W.A.J., Šeikinaitė J., Gökçe E., Kušleikienė S., Šarkinaite M., Valatkeviciene K., Česnaitienė V.J., Verbunt J., Levin O., Masiulis N* (2024) Resistance exercise effects on hippocampus subfield volumes and biomarkers of neuroplasticity and neuroinflammation in older adults with low and high risk of mild cognitive impairment: a randomized controlled trial. GeroScience, **46**(4), 3971–3991. DOI: 10.1007/s11357-024-01110-6
31. *Morishita S., Tsubaki A., Nakamura M., Nashimoto S., Fu J.B., Onishi H.* (2019) Rating of perceived exertion on resistance training in elderly subjects. Expert Rev. Cardiovasc. Ther., **17**(2), 135–142. DOI: 10.1080/14779072.2019.1561278
32. *Kim Y.-P., Kim H.-B., Jang M.-H., Lim B.-V., Kim Y.-J., Kim H., Kim S.-S., Kim E.-H., Kim C.-J.* (2003) Magnitude- and time-dependence of the effect of treadmill exercise on cell proliferation in the dentate gyrus of rats. Int. J. Sports Med., **24**(2), 114–117. DOI: 10.1055/s-2003-38202
33. *Blumenthal J.A., Babyak M.A., Doraiswamy P.M., Watkins L., Hoffman B.M., Barbour K.A., Herman S., Craighead W.E., Brosse A.L., Waugh R., Hinderliter A., Sherwood A.* (2007) Exercise and pharmacotherapy in the treatment of major depressive disorder. Psychosom. Med., **69**(7), 587–596. DOI: 10.1097/PSY.0b013e318148c19a

34. *Lee J., Gierc M., Vila-Rodriguez F., Puterman E., Faulkner G.* (2021) Efficacy of exercise combined with standard treatment for depression compared to standard treatment alone: a systematic review and meta-analysis of randomized controlled trials. J. Affect. Disord., **295**, 1494–1511. DOI: 10.1016/j.jad.2021.09.043
35. *Mammen G., Faulkner G.* (2013) Physical activity and the prevention of depression: a systematic review of prospective studies. Am. J. Prev. Med., **45**(5), 649–657. DOI: 10.1016/j.amepre.2013.08.001
36. *Pearce M., Garcia L., Abbas A., Strain T., Schuch F.B., Golubic R., Kelly P., Khan S., Utukuri M., Laird Y., Mok A., Smith A., Tainio M., Brage S., Woodcock J.* (2022) Association between physical activity and risk of depression:a systematic review and meta-analysis. JAMA Psychiatry, **79**(6), 550–559. DOI: 10.1001/jamapsychiatry.2022.0609
37. *Cunha M.P., Oliveira Á., Pazini F.L., Machado D.G., Bettio L.E.B., Budni J., Aguiar A.S., Martins D.F., Santos A.R.S., Rodrigues A.L.S.* (2013) The antidepressant-like effect of physical activity on a voluntary running wheel. Med. Sci. Sports Exerc., **45**(5), 851–859. DOI: 10.1249/MSS.0b013e31827b23e6
38. *Lin T.-W., Kuo Y.-M.* (2013) Exercise benefits brain function: the monoamine connection. Brain Sci., **3**(1), 39–53. DOI: 10.3390/brainsci3010039
39. *Euteneuer F., Dannehl K., del Rey A., Engler H., Schedlowski M., Rief W.* (2017) Immunological effects of behavioral activation with exercise in major depression: an exploratory randomized controlled trial. Transl. Psychiatry, **7**(5), e1132. DOI: 10.1038/tp.2017.76
40. *Sigwalt A.R., Budde H., Helmich I., Glaser V., Ghisoni K., Lanza S., Cadore E.L., Lhullier F.L.R., de Bem A.F., Hohl A., de Matos F.J., de Oliveira P.A., Prediger R.D., Guglielmo L.G., Latini A.* (2011) Molecular aspects involved in swimming exercise training reducing anhedonia in a rat model of depression. Neuroscience, **192**, 661–674. DOI: 10.1016/j.neuroscience.2011.05.075
41. *Luca M., Luca A.* (2019) Oxidative stress-related endothelial damage in vascular depression and vascular cognitive impairment: beneficial effects of aerobic physical exercise. Oxid. Med. Cell. Longev., **2019**, 8067045. DOI: 10.1155/2019/8067045
42. *Brocardo P.S., Boehme F., Patten A., Cox A., Gil-Mohapel J., Christie B.R.* (2012) Anxiety- and depression-like behaviors are accompanied by an increase in oxidative stress in a rat model of fetal alcohol spectrum disorders: protective effects of voluntary physical exercise. Neuropharmacology, **62**(4), 1607–1618. DOI: 10.1016/j.neuropharm.2011.10.006
43. *Liang X., Tang J., Qi Y.-Q., Luo Y.-M., Yang C.-M., Dou X.-Y., Jiang L., Xiao Q., Zhang L., Chao F.-L., Zhou C.-N., Tang Y.* (2022) Exercise more efficiently regulates the maturation of newborn neurons and synaptic plasticity than fluoxetine in a CUS-induced depression mouse model. Exp. Neurol., **354**, 114103. DOI: 10.1016/j.expneurol.2022.114103
44. *Liang X., Tang J., Chao F.-L., Zhang Y., Chen L.-M., Wang F.-F., Tan C.-X., Luo Y.-M., Xiao Q., Zhang L., Qi Y.-Q., Jiang L., Huang C.-X., Gao Y., Tang Y.* (2019) Exercise improves depressive symptoms by increasing the number of excitatory synapses in the hippocampus of CUS-induced depression model rats. Behav. Brain Res., **374**, 112115. DOI: 10.1016/j.bbr.2019.112115
45. *Micheli L., Ceccarelli M., d'Andrea G., Tirone F.* (2018) Depression and adult neurogenesis: positive effects of the antidepressant fluoxetine and of physical exercise. Brain Res. Bull., **143**, 181–193. DOI: 10.1016/j.brainresbull.2018.09.002
46. *Steib K., Schäffner I., Jagasia R., Ebert B., Lie D.C.* (2014) Mitochondria modify exercise-induced development of stem cell-derived neurons in the adult brain. J. Neurosci., **34**(19), 6624–6633. DOI: 10.1523/JNEUROSCI.4972-13.2014
47. *Meyer J.D., Koltyn K.F., Stegner A.J., Kim J.-S., Cook D.B.* (2016) Relationships between serum BDNF and the antidepressant effect of acute exercise in depressed women. Psychoneuroendocrinology, **74**, 286–294. DOI: 10.1016/j.psyneuen.2016.09.022
48. *Baj G., d'Alessandro V., Musazzi L., Mallei A., Sartori C.R., Sciancalepore M., Tardito D., Langone F., Popoli M., Tongiorgi E.* (2012) Physical exercise and antidepressants enhance BDNF targeting in hippocampal CA3 dendrites: further evidence of a spatial code for BDNF splice variants. Neuropsychopharmacology, **37**(7), 1600–1611. DOI: 10.1038/npp.2012.5
49. *Teufel A., Malik N., Mukhopadhyay M., Westphal H.* (2002) Frcp1 and Frcp2, two novel fibronectin type III repeat containing genes. Gene, **297**(1–2), 79–83. DOI: 10.1016/s0378-1119(02)00828-4
50. *Boström P., Wu J., Jedrychowski M.P., Korde A., Ye L., Lo J.C., Rasbach K.A., Boström E.A., Choi J.H., Long J.Z., Kajimura S., Zingaretti M.C., Vind B.F., Tu H., Cinti S., Højlund K., Gygi S.P., Spiegelman B.M.* (2012) A PGC1-α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. Nature, **481**(7382), 463–468. DOI: 10.1038/nature10777
51. *Nie Y, Dai B., Guo X., Liu D.* (2020) Cleavage of FNDC5 and insights into its maturation process. Mol. Cell. Endocrinol., **510**, 110840. DOI: 10.1016/j.mce.2020.110840
52. *Schumacher M.A., Chinnam N., Ohashi T., Shah R.S., Erickson H.P.* (2013) The structure of irisin reveals a novel intersubunit β-sheet fibronectin type III (FNIII) dimer: implications for receptor activation. J. Biol. Chem., **288**(47), 33738–33744. DOI: 10.1074/jbc.M113.516641
53. *Huh J.Y., Panagiotou G., Mougios V., Brinkoetter M., Vamvini M.T., Schneider B.E., Mantzoros C.S.* (2012) FNDC5 and irisin in humans: I. Predictors of circulating concentrations in serum and plasma and II. mRNA expression and circulating concentrations in response to weight loss and exercise. Metabolism, **61**(12), 1725–1738. DOI: 10.1016/j.metabol.2012.09.002
54. *Wojtaszewski J.F.P., Nielsen P., Hansen B.F., Richter E.A., Kiens B.* (2000) Isoform-specific and exercise intensity-dependent activation of 5′-AMP-activated protein kinase in human skeletal muscle. J. Physiol., **528**(Pt 1), 221–226. DOI: 10.1111/j.1469-7793.2000.t01-1-00221.x
55. *Witczak C.A., Sharoff C.G., Goodyear L.J.* (2008) AMP-activated protein kinase in skeletal muscle: from structure and localization to its role as a master regulator of cellular metabolism. Cell. Mol. Life Sci., **65**(23), 3737–3755. DOI: 10.1007/s00018-008-8244-6
56. *Liang H., Ward W.F.* (2006) PGC-1α: a key regulator of energy metabolism. Adv. Physiol. Educ., **30**(4), 145–151. DOI: 10.1152/advan.00052.2006
57. *Dun S.L., Lyu R.-M., Chen Y.-H., Chang J.-K., Luo J.J., Dun N.J.* (2013) Irisin-immunoreactivity in neural and non-neural cells of the rodent. Neuroscience, **240**, 155–162. DOI: 10.1016/j.neuroscience.2013.02.050

58. *Aydin S., Kuloglu T., Aydin S., Kalayci M., Yilmaz M., Cakmak T., Albayrak S., Gungor S., Colakoglu N., Ozercan I.H.* (2014) A comprehensive immunohistochemical examination of the distribution of the fat-burning protein irisin in biological tissues. Peptides, **61**, 130–136. DOI: 10.1016/j.peptides.2014.09.014
59. *Ruan Q., Huang Y., Yang L., Ruan J., Gu W., Zhang X., Zhang Y., Zhang W., Yu Z.* (2019) The effects of both age and sex on irisin levels in paired plasma and cerebrospinal fluid in healthy humans. Peptides, **113**, 41–51. DOI: 10.1016/j.peptides.2019.01.004
60. *Zhao R.* (2022) Irisin at the crossroads of inter-organ communications: challenge and implications. Front. Endocrinol., **13**, 989135. DOI: 10.3389/fendo.2022.989135
61. *Jedrychowski M.P., Wrann C.D., Paulo J.A., Gerber K.K., Szpyt J., Robinson M.M., Nair K.S., Gygi S.P., Spiegelman B.M.* (2015) Detection and quantitation of circulating human irisin by tandem mass spectrometry. Cell Metab., **22**(4), 734–740. DOI: 10.1016/j.cmet.2015.08.001
62. *Ruan Q., Zhang L., Ruan J., Zhang X., Chen J., Ma C., Yu Z.* (2018) Detection and quantitation of irisin in human cerebrospinal fluid by tandem mass spectrometry. Peptides, **103**, 60–64. DOI: 10.1016/j.peptides.2018.03.013
63. *Roca-Rivada A., Castelao C., Senin L.L., Landrove M.O., Baltar J., Belén Crujeiras A., Seoane L.M., Casanueva F.F., Pardo M.* (2013) FNDC5/irisin is not only a myokine but also an adipokine. PLOS One, **8**(4), e60563. DOI: 10.1371/journal.pone.0060563
64. *Islam M.R., Valaris S., Young M.F., Haley E.B., Luo R., Bond S.F., Mazuera S., Kitchen R.R., Caldarone B.J., Bettio L.E.B., Christie B.R., Schmider A.B., Soberman R.J., Besnard A., Jedrychowski M.P., Kim H., Tu H., Kim E., Choi S.H., Tanzi R.E., Spiegelman B.M., Wrann C.D.* (2021) Exercise hormone irisin is a critical regulator of cognitive function. Nat. Metab., **3**(8), 1058–1070. DOI: 10.1038/s42255-021-00438-z
65. *Lee J.M., Sim T.H., Kim S.H., Choi Y.J., Lee J.H., Yeo S.G., Kim Y.-J.* (2025) Exercise-induced FNDC5/irisin ameliorates cognitive impairment in aged mice, associated with antioxidant and neurotrophic responses. Antioxidants, **14**(10), 1239. DOI: 10.3390/antiox14101239
66. *Wang Y., Tian M., Tan J., Pei X., Lu C., Xin Y., Deng S., Zhao F., Gao Y., Gong Y.* (2022) Irisin ameliorates neuroinflammation and neuronal apoptosis through integrin αVβ5/AMPK signaling pathway after intracerebral hemorrhage in mice. J. Neuroinflammation, **19**, 82. DOI: 10.1186/s12974-022-02438-6
67. *Lee P., Linderman J.D., Smith S., Brychta R.J., Wang J., Idelson C., Perron R.M., Werner C.D., Phan G.Q., Kammula U.S., Kebebew E., Pacak K., Chen K.Y., Celi F.S.* (2014) Irisin and FGF21 are cold-induced endocrine activators of brown fat function in humans. Cell Metab., **19**(2), 302–309. DOI: 10.1016/j.cmet.2013.12.017
68. *Waseem R., Shamsi A., Mohammad T., Hassan M.I., Kazim S.N., Chaudhary A.A., Rudayni H.A., Al-Zharani M., Ahmad F., Islam A.* (2022) FNDC5/irisin: physiology and pathophysiology. Molecules, **27**(3), 1118. DOI: 10.3390/molecules27031118
69. *Pang M., Yang J., Rao J., Wang H., Zhang J., Wang S., Chen X., Dong X.* (2018) Time-dependent changes in increased levels of plasma irisin and muscle PGC-1α and FNDC5 after exercise in mice. Tohoku J. Exp. Med., **244**(2), 93–103. DOI: 10.1620/tjem.244.93
70. *Babaei A., Nourshahi M., Fani M., Entezari Z., Jameie S.B., Haghparast A.* (2021) The effectiveness of continuous and interval exercise preconditioning against chronic unpredictable stress: involvement of hippocampal PGC-1α/FNDC5/BDNF pathway. J. Psychiatr. Res., **136**, 173–183. DOI: 10.1016/j.jpsychires.2021.02.006
71. *Brenmoehl J., Albrecht E., Komolka K., Schering L., Langhammer M., Hoeflich A., Maak S.* (2014) Irisin is elevated in skeletal muscle and serum of mice immediately after acute exercise. Int. J. Biol. Sci., **10**(3), 338–349. DOI: 10.7150/ijbs.7972
72. *Norheim F., Langleite T.M., Hjorth M., Holen T., Kielland A., Stadheim H.K., Gulseth H.L., Birkeland K.I., Jensen J., Drevon C.A.* (2014) The effects of acute and chronic exercise on PGC-1α, irisin and browning of subcutaneous adipose tissue in humans. FEBS J., **281**(3), 739–749. DOI: 10.1111/febs.12619
73. *Flori L., Testai L., Calderone V.* (2021) The "irisin system": from biological roles to pharmacological and nutraceutical perspectives. Life Sci., **267**, 118954. DOI: 10.1016/j.lfs.2020.118954
74. *Yen C.-H., Chang P.-S., Chang Y.-H., Lin P.-T.* (2022) Identification of coenzyme Q10 and skeletal muscle protein biomarkers as potential factors to assist in the diagnosis of sarcopenia. Antioxidants, **11**(4), 725. DOI: 10.3390/antiox11040725
75. *Kim H.-J., So B., Choi M., Kang D., Song W.* (2015) Resistance exercise training increases the expression of irisin concomitant with improvement of muscle function in aging mice and humans. Exp. Gerontol., **70**, 11–17. DOI: 10.1016/j.exger.2015.07.006
76. *Tsou Y.-H., Wang B., Ho W., Hu B., Tang P., Sweet S., Zhang X.-Q., Xu X.* (2019) Nanotechnology-mediated drug delivery for the treatment of obesity and its related comorbidities. Adv. Healthc. Mater., **8**(12), e1801184. DOI: 10.1002/adhm.201801184
77. *Pardo M., Crujeiras A.B., Amil M., Aguera Z., Jiménez-Murcia S., Baños R., Botella C., de la Torre R., Estivill X., Fagundo A.B., Fernández-Real J.M., Fernández-García J.C., Fruhbeck G., Gómez-Ambrosi J., Rodríguez R., Tinahones F.J., Fernández-Aranda F., Casanueva F.F.* (2014) Association of irisin with fat mass, resting energy expenditure, and daily activity in conditions of extreme body mass index. Int. J. Endocrinol., **2014**, 857270. DOI: 10.1155/2014/857270
78. *Hecksteden A., Wegmann M., Steffen A., Kraushaar J., Morsch A., Ruppenthal S., Kaestner L., Meyer T.* (2013) Irisin and exercise training in humans — results from a randomized controlled training trial. BMC Med., **11**, 235. DOI: 10.1186/1741-7015-11-235
79. *Tsuchiya Y., Ando D., Takamatsu K., Goto K.* (2015) Resistance exercise induces a greater irisin response than endurance exercise. Metabolism, **64**(9), 1042–1050. DOI: 10.1016/j.metabol.2015.05.010
80. *He Z., Tian Y., Valenzuela P.L., Huang C., Zhao J., Hong P., He Z., Yin S., Lucia A.* (2018) Myokine response to high-intensity interval vs. resistance exercise: an individual approach. Front. Physiol., **9**, 1735. DOI: 10.3389/fphys.2018.01735
81. *Ruas J.L., White J.P., Rao R.R., Kleiner S., Brannan K.T., Harrison B.C., Greene N.P., Wu J., Estall J.L., Irving B.A., Lanza I.R., Rasbach K.A., Okutsu M., Nair K.S., Yan Z., Leinwand L.A., Spiegelman B.M.* (2012) A PGC-1α isoform induced by resistance training regulates skeletal muscle hypertrophy. Cell, **151**(6), 1319–1331. DOI: 10.1016/j.cell.2012.10.050

82. *Siteneski A., Cunha M.P., Lieberknecht V., Pazini F.L., Gruhn K., Brocardo P.S., Rodrigues A.L.S.* (2018) Central irisin administration affords antidepressant-like effect and modulates neuroplasticity-related genes in the hippocampus and prefrontal cortex of mice. Prog. Neuropsychopharmacol. Biol. Psychiatry, **84**(Pt A), 294–303. DOI: 10.1016/j.pnpbp.2018.03.004
83. *Pignataro P., Dicarlo M., Zerlotin R., Storlino G, Oranger A., Sanesi L., Lovero R., Buccoliero C., Mori G., Colaianni G., Colucci S., Grano M.* (2022) Antidepressant effect of intermittent long-term systemic administration of irisin in mice. Int. J. Mol. Sci., **23**(14), 7596. DOI: 10.3390/ijms23147596
84. *Bilek F., Cetisli-Korkmaz N., Ercan Z., Deniz G., Demir C.F.* (2022) Aerobic exercise increases irisin serum levels and improves depression and fatigue in patients with relapsing remitting multiple sclerosis: a randomized controlled trial. Mult. Scler. Relat. Disord., **61**, 103742. DOI: 10.1016/j.msard.2022.103742
85. *Tu W.-J., Qiu H.-C., Liu Q., Li X., Zhao J.-Z., Zeng X.* (2018) Decreased level of irisin, a skeletal muscle cell-derived myokine, is associated with post-stroke depression in the ischemic stroke population. J. Neuroinflammation, **15**, 133. DOI: 10.1186/s12974-018-1177-6
86. *Yardimci A., Ertugrul N.U., Ozgen A., Ozbeg G, Ozdede M.R., Ercan E.C., Canpolat S.* (2023) Effects of chronic irisin treatment on brain monoamine levels in the hypothalamic and subcortical nuclei of adult male and female rats: an HPLC-ECD study. Neurosci. Lett., **806**, 137245. DOI: 10.1016/j.neulet.2023.137245
87. *Clelland C.D., Choi M., Romberg C., Clemenson G.D., Fragniere A., Tyers P., Jessberger S., Saksida L.M., Barker R.A., Gage F.H., Bussey TJ.* (2009) A functional role for adult hippocampal neurogenesis in spatial pattern separation. Science, **325**(5937), 210–213. DOI: 10.1126/science.1173215
88. *Anacker C., Luna V.M., Stevens G.S., Millette A., Shores R., Jimenez J.C., Chen B., Hen R.* (2018) Hippocampal neurogenesis confers stress resilience by inhibiting the ventral dentate gyrus. Nature, **559**(7712), 98–102. DOI: 10.1038/s41586-018-0262-4
89. *Tapia-Rojas C., Aranguiz F., Varela-Nallar L., Inestrosa N.C.* (2016) Voluntary running attenuates memory loss, decreases neuropathological changes and induces neurogenesis in a mouse model of Alzheimer's disease. Brain Pathol., **26**(1), 62–74. DOI: 10.1111/bpa.12255
90. *Moreno-Jiménez E.P., Flor-García M., Terreros-Roncal J., Rábano A., Cafini F., Pallas-Bazarra N., Ávila J., Llorens-Martín M.* (2019) Adult hippocampal neurogenesis is abundant in neurologically healthy subjects and drops sharply in patients with Alzheimer's disease. Nat. Med., **25**(4), 554–560. DOI: 10.1038/s41591-019-0375-9
91. *McAvoy K.M., Scobie K.N., Berger S., Russo C., Guo N., Decharatanachart P., Vega-Ramirez H., Miake-Lye S., Whalen M., Nelson M., Bergami M., Bartsch D., Hen R., Berninger B., Sahay A.* (2016) Modulating neuronal competition dynamics in the dentate gyrus to rejuvenate aging memory circuits. Neuron, **91**(6), 1356–1373. DOI: 10.1016/j.neuron.2016.08.009
92. *Oakley H., Cole S.L., Logan S., Maus E., Shao P., Craft J., Guillozet-Bongaarts A., Ohno M., Disterhoft J., van Eldik L., Berry R., Vassar R.* (2006) Intraneuronal beta-amyloid aggregates, neurodegeneration, and neuron loss in transgenic mice with five familial Alzheimer's disease mutations: potential factors in amyloid plaque formation. J. Neurosci., **26**(40), 10129–10140. DOI: 10.1523/JNEUROSCI.1202-06.2006
93. *Hashemi M.-S., Ghaedi K., Salamian A., Karbalaie K., Emadi-Baygi M., Tanhaei S., Nasr-Esfahani M.H., Baharvand H.* (2013) *Fndc5* knockdown significantly decreased neural differentiation rate of mouse embryonic stem cells. Neuroscience, **231**, 296–304. DOI: 10.1016/j.neuroscience.2012.11.041
94. *Forouzanfar M., Rabiee F., Ghaedi K., Beheshti S., Tanhaei S., Shoaraye Nejati A., Jodeiri Farshbaf M., Baharvand H., Nasr-Esfahani M.H.* (2015) Fndc5 overexpression facilitated neural differentiation of mouse embryonic stem cells. Cell Biol. Int., **39**(5), 629–637. DOI: 10.1002/cbin.10427
95. *Ebadi R., Rabiee F., Kordi-Tamandani D.M., Nasr-Esfahani M.H., Ghaedi K.* (2021) *Fndc5* knockdown significantly decreased the expression of neurotrophins and their respective receptors during neural differentiation of mouse embryonic stem cells. Human Cell, **34**(3), 847–861. DOI: 10.1007/s13577-021-00517-z
96. *Lourenco M.V., Frozza R.L., de Freitas G.B., Zhang H., Kincheski G.C., Ribeiro F.C., Gonçalves R.A., Clarke J.R., Beckman D., Staniszewski A., Berman H., Guerra L.A., Forny-Germano L., Meier S., Wilcock D.M., de Souza J.M., Alves-Leon S., Prado V.F., Prado M.A.M., Abisambra J.F., Tovar-Moll F., Mattos P., Arancio O., Ferreira S.T., de Felice F.G.* (2019) Exercise-linked FNDC5/irisin rescues synaptic plasticity and memory defects in Alzheimer's models. Nat. Med., **25**(1), 165–175. DOI: 10.1038/s41591-018-0275-4
97. *Lourenco M.V., de Freitas G.B., Raony H., Ferreira S.T., de Felice F.G.* (2022) Irisin stimulates protective signaling pathways in rat hippocampal neurons. Front. Cell. Neurosci., **16**, 953991. DOI: 10.3389/fncel.2022.953991
98. *Chen K., Wang K., Wang T.* (2022) Protective effect of irisin against Alzheimer's disease. Front. Psychiatry, **13**, 967683. DOI: 10.3389/fpsyt.2022.967683
99. *Lourenco M.V., Ribeiro F.C., Sudo F.K., Drummond C., Assunção N., Vanderborght B., Tovar-Moll F., Mattos P., de Felice F.G., Ferreira S.T.* (2020) Cerebrospinal fluid irisin correlates with amyloid-β, BDNF, and cognition in Alzheimer's disease. Alzheimers Dement. (Amsterdam), **12**, e12034. DOI: 10.1002/dad2.12034
100. *Gonçalves R.A., Sudo F.K., Lourenco M.V., Drummond C., Assunção N., Vanderborght B., Ferreira D.D.P., Ribeiro F.C., Pamplona F.A., Tovar-Moll F., Mattos P., Ferreira S.T., de Felice F.G.* (2023) Cerebrospinal fluid irisin and lipoxin A4 are reduced in elderly Brazilian individuals with depression: insight into shared mechanisms between depression and dementia. Alzheimers Dement., **19**(6), 2595–2604. DOI: 10.1002/alz.12893
101. *Otte C., Gold S.M., Penninx B.W., Pariante C.M., Etkin A., Fava M., Mohr D.C., Schatzberg A.F.* (2016) Major depressive disorder. Nat. Rev. Dis. Primers, **2**, 16065. DOI: 10.1038/nrdp.2016.65
102. *Schuch F.B., Vancampfort D., Firth J., Rosenbaum S., Ward P.B., Silva E.S., Hallgren M., Ponce de Leon A., Dunn A.L., Deslandes A.C., Fleck M.P., Carvalho A.F., Stubbs B.* (2018) Physical activity and incident depression: a meta-analysis of prospective cohort studies. Am. J. Psychiatry, **175**(7), 631–648. DOI: 10.1176/appi.ajp.2018.17111194
103. *Pignataro P., Dicarlo M., Suriano C., Sanesi L., Zerlotin R., Storlino G., Oranger A., Zecca C., dell'Abate M.T., Mori G., Grano M., Colucci S., Colaianni G.* (2023)

Once-daily subcutaneous irisin administration mitigates depression- and anxiety-like behavior in young mice. Int. J. Mol. Sci., **24**(7), 6715. DOI: 10.3390/ijms24076715
104. *Hou Z., Zhang J., Yu K., Song F.* (2020) Irisin ameliorates the postoperative depressive-like behavior by reducing the surface expression of epidermal growth factor receptor in mice. Neurochem. Int., **135**, 104705. DOI: 10.1016/j.neuint.2020.104705
105. *Wang S., Pan J.* (2016) Irisin ameliorates depressive-like behaviors in rats by regulating energy metabolism. Biochem. Biophys. Res. Commun., **474**(1), 22–28. DOI: 10.1016/j.bbrc.2016.04.047
106. *Ernst J., Hock A., Henning A., Seifritz E., Boeker H., Grimm S.* (2017) Increased pregenual anterior cingulate glucose and lactate concentrations in major depressive disorder. Mol. Psychiatry, **22**(1), 113–119. DOI: 10.1038/mp.2016.73
107. *Chan K.L., Cathomas F., Russo S.J.* (2019) Central and peripheral inflammation link metabolic syndrome and major depressive disorder. Physiology (Bethesda), **34**(2), 123–133. DOI: 10.1152/physiol.00047.2018
108. *Qin Y., Jiang X., Li W., Li J., Tian T., Zang G., Fang L., Zhou C., Xu B., Gong X., Huang C., Yang X., Bai M., Fan L, Xie P.* (2019) Chronic mild stress leads to aberrant glucose energy metabolism in depressed *Macaca fascicularis* models. Psychoneuroendocrinology, **107**, 59–69. DOI: 10.1016/j.psyneuen.2019.05.007
109. *Liu L., Zhou X., Zhang Y., Pu J., Yang L., Yuan S., Zhao L., Zhou C., Zhang H., Xie P.* (2018) Hippocampal metabolic differences implicate distinctions between physical and psychological stress in four rat models of depression. Transl. Psychiatry, **8**(1), 4. DOI: 10.1038/s41398-017-0018-1
110. *Chen G, Yang D., Yang Y., Li J., Cheng K., Tang G, Zhang R., Zhou J., Li W., Liu Z., Fan S., Xie P.* (2015) Amino acid metabolic dysfunction revealed in the prefrontal cortex of a rat model of depression. Behav. Brain Res., **278**, 286–292. DOI: 10.1016/j.bbr.2014.05.027
111. *Luo Y., Qiao X., Ma Y., Deng H., Xu C.C., Xu L.* (2020) Disordered metabolism in mice lacking irisin. Sci. Rep., **10**, 17368. DOI: 10.1038/s41598-020-74588-7
112. *Xiong X.-Q., Chen D., Sun H.-J., Ding L., Wang J.-J., Chen Q., Li Y.-H., Zhou Y.-B., Han Y., Zhang F., Gao X.-Y., Kang Y.-M., Zhu G.-Q.* (2015) FNDC5 overexpression and irisin ameliorate glucose/lipid metabolic derangements and enhance lipolysis in obesity. Biochim. Biophys. Acta, **1852**(9), 1867–1875. DOI: 10.1016/j.bbadis.2015.06.017
113. *Moreno-Navarrete J.M., Ortega F., Serrano M., Guerra E., Pardo G., Tinahones F., Ricart W., Fernández-Real J.M.* (2013) Irisin is expressed and produced by human muscle and adipose tissue in association with obesity and insulin resistance. J. Clin. Endocrinol. Metab., **98**(4), E769–E778. DOI: 10.1210/jc.2012-2749
114. *Zhang W., Chang L., Zhang C., Zhang R., Li Z., Chai B., Li J., Chen E., Mulholland M.* (2015) Irisin: a myokine with locomotor activity. Neurosci. Lett., **595**, 7–11. DOI: 10.1016/j.neulet.2015.03.069
115. *Kleinridders A., Cai W., Cappellucci L., Ghazarian A., Collins W.R., Vienberg S.G., Pothos E.N., Kahn C.R.* (2015) Insulin resistance in brain alters dopamine turnover and causes behavioral disorders. Proc. Natl. Acad. Sci. USA, **112**(11), 3463–3468. DOI: 10.1073/pnas.1500877112
116. *Kimbrell T.A., Ketter T.A., George M.S., Little J.T., Benson B.E., Willis M.W., Herscovitch P., Post R.M.* (2002) Regional cerebral glucose utilization in patients with a range of severities of unipolar depression. Biol. Psychiatry, **51**(3), 237–252. DOI: 10.1016/s0006-3223(01)01216-1
117. *Xin C., Liu J., Zhang J., Zhu D., Wang H., Xiong L., Lee Y., Ye J., Lian K., Xu C., Zhang L., Wang Q., Liu Y., Tao L.* (2016) Irisin improves fatty acid oxidation and glucose utilization in type 2 diabetes by regulating the AMPK signaling pathway. Int. J. Obes., **40**(3), 443–451. DOI: 10.1038/ijo.2015.199
118. *Lee H.J., Lee J.O., Kim N., Kim J.K., Kim H.I., Lee Y.W., Kim S.J., Choi J.-I., Oh Y., Kim J.H., Suyeon-Hwang, Park S.H., Kim H.S.* (2015) Irisin, a novel myokine, regulates glucose uptake in skeletal muscle cells via AMPK. Mol. Endocrinol., **29**(6), 873–881. DOI: 10.1210/me.2014-1353
119. *Zhang Y., Li R., Meng Y., Li S., Donelan W., Zhao Y., Qi L., Zhang M., Wang X., Cui T., Yang L.-J., Tang D.* (2014) Irisin stimulates browning of white adipocytes through mitogen-activated protein kinase p38 MAP kinase and ERK MAP kinase signaling. Diabetes, **63**(2), 514–525. DOI: 10.2337/db13-1106
120. *Cao X., Li L.-P., Wang Q., Wu Q., Hu H.-H., Zhang M., Fang Y.-Y., Zhang J., Li S.-J., Xiong W.-C., Yan H.-C., Gao Y.-B., Liu J.-H., Li X.-W., Sun L.-R., Zeng Y.-N., Zhu X.-H., Gao T.-M.* (2013) Astrocyte-derived ATP modulates depressive-like behaviors. Nat. Med., **19**(6), 773–777. DOI: 10.1038/nm.3162
121. *Rabiee F., Lachinani L., Ghaedi S., Nasr-Esfahani M.H., Megraw T.L., Ghaedi K.* (2020) New insights into the cellular activities of Fndc5/irisin and its signaling pathways. Cell Biosci., **10**, 51. DOI: 10.1186/s13578-020-00413-3
122. *Ribeiro D., Petrigna L., Pereira F.C., Muscella A., Bianco A., Tavares P.* (2021) The impact of physical exercise on the circulating levels of BDNF and NT 4/5: a review. Int. J. Mol. Sci., **22**(16), 8814. DOI: 10.3390/ijms22168814
123. *Mousavi K., Jasmin B.J.* (2006) BDNF is expressed in skeletal muscle satellite cells and inhibits myogenic differentiation. J. Neurosci., **26**(21), 5739–5749. DOI: 10.1523/JNEUROSCI.5398-05.2006
124. *Aguado F., Carmona M.A., Pozas E., Aguiló A., Martínez-Guijarro F.J., Alcantara S., Borrell V., Yuste R., Ibañez C.F., Soriano E.* (2003) BDNF regulates spontaneous correlated activity at early developmental stages by increasing synaptogenesis and expression of the K^+/Cl^- co-transporter KCC2. Development, **130**(7), 1267–1280. DOI: 10.1242/dev.00351
125. *Marlatt M.W., Potter M.C., Lucassen P.J., van Praag H.* (2012) Running throughout middle-age improves memory function, hippocampal neurogenesis, and BDNF levels in female C57BL/6J mice. Dev. Neurobiol., **72**(6), 943–952. DOI: 10.1002/dneu.22009
126. *Tsai S.-F., Ku N.-W., Wang T.-F., Yang Y.-H., Shih Y.-H., Wu S.-Y., Lee C.-W., Yu M., Yang T.-T., Kuo Y.-M.* (2018) Long-term moderate exercise rescues age-related decline in hippocampal neuronal complexity and memory. Gerontology, **64**(6), 551–561. DOI: 10.1159/000488589
127. *Sheldrick A., Camara S., Ilieva M., Riederer P., Michel T.M.* (2017) Brain-derived neurotrophic factor (BDNF) and neurotrophin 3 (NT3) levels in post-mortem brain tissue from patients with depression compared to healthy individuals — a proof of concept study. Eur. Psychiatry, **46**, 65–71. DOI: 10.1016/j.eurpsy.2017.06.009
128. *Zavvari F., Nahavandi A.* (2020) Fluoxetine increases hippocampal neural survival by improving axonal transport in stress-induced model of depression male rats. Physiol. Behav., **227**, 113140. DOI: 10.1016/j.physbeh.2020.113140

129. *Björkholm C., Monteggia L.M.* (2016) BDNF — a key transducer of antidepressant effects. Neuropharmacology, **102**, 72–79. DOI: 10.1016/j.neuropharm.2015.10.034
130. *Wrann C.D., White J.P., Salogiannnis J., Laznik-Bogoslavski D., Wu J., Ma D., Lin J.D., Greenberg M.E., Spiegelman B.M.* (2013) Exercise induces hippocampal BDNF through a PGC-1α/FNDC5 pathway. Cell Metab., **18**(5), 649–659. DOI: 10.1016/j.cmet.2013.09.008
131. *Kim M.-H., Leem Y.-H.* (2019) The effects of peripherally-subacute treatment with irisin on hippocampal dendritogenesis and astrocyte-secreted factors. J. Exerc. Nutr. Biochem., **23**(4), 32–35. DOI: 10.20463/jenb.2019.0029
132. *Wu L., Zhang T., Chen K., Lu C., Liu X.F., Zhou J.L., Huang Y.K., Yan H., Chen Y., Zhang C.J., Li J.F., Shi S.Q., Ren P., Huang X.* (2021) Rapid antidepressant-like effect of Fructus Aurantii depends on cAMP-response element binding protein/brain-derived neurotrophic facto by mediating synaptic transmission. Phytother. Res., **35**(1), 404–414. DOI: 10.1002/ptr.6812
133. *Cai M.-Y., Yang Z., Huang X.-J., Li J., Bao W.-Y., Hurilebagen, Wulanqiqige, Wuyunsiriguleng, Cui J.-W., Ma L.-Q.* (2022) Mongolian medicine Areca Thirteen Pill (GY-13) improved depressive syndrome via upregulating cAMP/PKA/CREB/BDNF signaling pathway. J. Ethnopharmacol., **293**, 115310. DOI: 10.1016/j.jep.2022.115310
134. *Ieraci A., Madaio A.I., Mallei A., Lee F.S., Popoli M.* (2016) Brain-derived neurotrophic factor Val66Met human polymorphism impairs the beneficial exercise-induced neurobiological changes in mice. Neuropsychopharmacology, **41**(13), 3070–3079. DOI: 10.1038/npp.2016.120
135. *Tu W.-J., Qiu H.-C., Cao J.-L., Liu Q., Zeng X.-W., Zhao J.-Z.* (2018) Decreased concentration of irisin is associated with poor functional outcome in ischemic stroke. Neurotherapeutics, **15**(4), 1158–1167. DOI: 10.1007/s13311-018-0651-2
136. *Zhang F., Hou G., Hou G., Wang C., Shi B., Zheng Y.* (2021) Serum irisin as a potential biomarker for cognitive decline in vascular dementia. Front. Neurol., **12**, 755046. DOI: 10.3389/fneur.2021.755046
137. *Jin Z., Guo P., Li X., Ke J., Wang Y., Wu H.* (2019) Neuroprotective effects of irisin against cerebral ischemia/reperfusion injury via Notch signaling pathway. Biomed. Pharmacother., **120**, 109452. DOI: 10.1016/j.biopha.2019.109452
138. *Song D., Chen X., Zhou N., Yuan Y., Geng S., Zhang C., Zhao Z., Wang X., Bao X., Lan X., Zhang X.* (2023) Low-intensity pulsed ultrasound triggers a beneficial neuromodulation in dementia mice with chronic cerebral hypoperfusion via activation of hippocampal Fndc5/irisin signaling. J. Transl. Med., **21**, 139. DOI: 10.1186/s12967-022-03824-7
139. *Asadi Y., Gorjipour F., Behrouzifar S., Vakili A.* (2018) Irisin peptide protects brain against ischemic injury through reducing apoptosis and enhancing BDNF in a rodent model of stroke. Neurochem. Res., **43**(8), 1549–1560. DOI: 10.1007/s11064-018-2569-9
140. *Li D.-J., Li Y.-H., Yuan H.-B., Qu L.-F., Wang P.* (2017) 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, **68**, 31–42. DOI: 10.1016/j.metabol.2016.12.003
141. *Haapakoski R., Mathieu J., Ebmeier K.P., Alenius H., Kivimäki M.* (2015) Cumulative meta-analysis of interleukins 6 and 1β, tumour necrosis factor α and C-reactive protein in patients with major depressive disorder. Brain Behav. Immun., **49**, 206–215. DOI: 10.1016/j.bbi.2015.06.001
142. *Pandey G.N., Rizavi H.S., Zhang H., Bhaumik R., Ren X.* (2018) Abnormal protein and mRNA expression of inflammatory cytokines in the prefrontal cortex of depressed individuals who died by suicide. J. Psychiatry Neurosci., **43**(6), 376–385. DOI: 10.1503/jpn.170192
143. *Lu Y., Ho C.S., Liu X., Chua A.N., Wang W., McIntyre R.S., Ho R.C.* (2017) Chronic administration of fluoxetine and pro-inflammatory cytokine change in a rat model of depression. PLOS One, **12**(10), e0186700. DOI: 10.1371/journal.pone.0186700
144. *Franklin T.C., Xu C., Duman R.S.* (2018) Depression and sterile inflammation: essential role of danger associated molecular patterns. Brain Behav. Immun., **72**, 2–13. DOI: 10.1016/j.bbi.2017.10.025
145. *Xiao X., Zhang H., Ning W., Yang Z., Wang Y., Zhang T.* (2022) Knockdown of FSTL1 inhibits microglia activation and alleviates depressive-like symptoms through modulating TLR4/MyD88/NF-κB pathway in CUMS mice. Exp. Neurol., **353**, 114060. DOI: 10.1016/j.expneurol.2022.114060
146. *Askari H., Rajani S.F., Poorebrahim M., Haghi-Aminjan H., Raeis-Abdollahi E., Abdollahi M.* (2018) A glance at the therapeutic potential of irisin against diseases involving inflammation, oxidative stress, and apoptosis: an introductory review. Pharmacol. Res., **129**, 44–55. DOI: 10.1016/j.phrs.2018.01.012
147. *Jiang X., Shen Z., Chen J., Wang C., Gao Z., Yu S., Yu X., Chen L., Xu L., Chen Z., Ni W.* (2020) Irisin protects against motor dysfunction of rats with spinal cord injury via adenosine 5′-monophosphate (AMP)-activated protein kinase-nuclear factor kappa-B pathway. Front. Pharmacol., **11**, 582484. DOI: 10.3389/fphar.2020.582484
148. *Wang K., Li H., Wang H., Wang J.-H., Song F., Sun Y.* (2018) Irisin exerts neuroprotective effects on cultured neurons by regulating astrocytes. Mediators Inflamm., **2018**, 9070341. DOI: 10.1155/2018/9070341
149. *Peng J., Deng X., Huang W., Yu J.-H., Wang J.-X., Wang J.-P., Yang S.-B., Liu X., Wang L., Zhang Y., Zhou X.-Y., Yang H., He Y.-Z., Xu F.-Y.* (2017) Irisin protects against neuronal injury induced by oxygen-glucose deprivation in part depends on the inhibition of ROS-NLRP3 inflammatory signaling pathway. Mol. Immunol., **91**, 185–194. DOI: 10.1016/j.molimm.2017.09.014
150. *Yu Q., Li G., Ding Q., Tao L., Li J., Sun L., Sun X., Yang Y.* (2020) Irisin protects brain against ischemia/reperfusion injury through suppressing TLR4/MyD88 pathway. Cerebrovasc. Dis., **49**(4), 346–354. DOI: 10.1159/000505961
151. *Duan H., Jing L., Xiang J., Ju C., Wu Z., Liu J., Ma X., Chen X., Liu Z., Feng J., Yan X.* (2022) CD146 associates with Gp130 to control a macrophage pro-inflammatory program that regulates the metabolic response to obesity. Adv. Sci. (Weinheim), **9**(13), e2103719. DOI: 10.1002/advs.202103719
152. *van den Bossche J., Baardman J., Otto N.A., van der Velden S., Neele A.E., van den Berg S.M., Luque-Martin R., Chen H.-J., Boshuizen M.C.S., Ahmed M., Hoeksema M.A., de Vos A.F., de Winther M.P.* (2016) Mitochondrial dysfunction prevents repolarization of inflammatory macrophages. Cell Rep., **17**(3), 684–696. DOI: 10.1016/j.celrep.2016.09.008

153. *Xiong X.-Q., Geng Z., Zhou B., Zhang F., Han Y., Zhou Y.-B., Wang J.-J., Gao X.-Y., Chen Q., Li Y.-H., Kang Y.-M., Zhu G.-Q.* (2018) FNDC5 attenuates adipose tissue inflammation and insulin resistance via AMPK-mediated macrophage polarization in obesity. Metabolism, **83**, 31–41. DOI: 10.1016/j.metabol.2018.01.013
154. *Dong J., Dong Y., Dong Y., Chen F., Mitch W.E., Zhang L.* (2016) Inhibition of myostatin in mice improves insulin sensitivity via irisin-mediated cross talk between muscle and adipose tissues. Int. J. Obes., **40**(3), 434–442. DOI: 10.1038/ijo.2015.200
155. *Madhu L.N., Somayaji Y., Shetty A.K.* (2022) Promise of irisin to attenuate cognitive dysfunction in aging and Alzheimer's disease. Ageing Res. Rev., **78**, 101637. DOI: 10.1016/j.arr.2022.101637
156. *Mazur-Bialy A.I., Pocheć E., Zarawski M.* (2017) Anti-inflammatory properties of irisin, mediator of physical activity, are connected with TLR4/MyD88 signaling pathway activation. Int. J. Mol. Sci., **18**(4), 701. DOI: 10.3390/ijms18040701
157. *Pandya C.D., Howell K.R., Pillai A.* (2013) Antioxidants as potential therapeutics for neuropsychiatric disorders. Prog. Neuropsychopharmacol. Biol. Psychiatry, **46**, 214–223. DOI: 10.1016/j.pnpbp.2012.10.017
158. *Zuo C., Cao H., Song Y., Gu Z., Huang Y., Yang Y., Miao J., Zhu L., Chen J., Jiang Y., Wang F.* (2022) Nrf2: an all-rounder in depression. Redox Biol., **58**, 102522. DOI: 10.1016/j.redox.2022.102522
159. *Bhatt S., Nagappa A.N., Patil C.R.* (2020) Role of oxidative stress in depression. Drug Discov. Today, **25**(7), 1270–1276. DOI: 10.1016/j.drudis.2020.05.001
160. *Palta P., Samuel L.J., Miller E.R. 3rd, Szanton S.L.* (2014) Depression and oxidative stress: results from a meta-analysis of observational studies. Psychosom. Med., **76**(1), 12–19. DOI: 10.1097/PSY.0000000000000009
161. *Liu T., Zhong S., Liao X., Chen J., He T., Lai S., Jia Y.* (2015) A meta-analysis of oxidative stress markers in depression. PLOS One, **10**(10), e0138904. DOI: 10.1371/journal.pone.0138904
162. *Eren I., Naziroğlu M., Demirdaş A.* (2007) Protective effects of lamotrigine, aripiprazole and escitalopram on depression-induced oxidative stress in rat brain. Neurochem. Res., **32**(7), 1188–1195. DOI: 10.1007/s11064-007-9289-x
163. *Juszczyk G., Mikulska J., Kasperek K., Pietrzak D., Mrozek W., Herbet M.* (2021) Chronic stress and oxidative stress as common factors of the pathogenesis of depression and Alzheimer's disease: the role of antioxidants in prevention and treatment. Antioxidants, **10**(9), 1439. DOI: 10.3390/antiox10091439
164. *Wang D., Zhai X., Chen P., Yang M., Zhao J., Dong J., Liu H.* (2014) Hippocampal UCP2 is essential for cognition and resistance to anxiety but not required for the benefits of exercise. Neuroscience, **277**, 36–44. DOI: 10.1016/j.neuroscience.2014.06.060
165. *Du R.-H., Wu F.-F., Lu M., Shu X.-D., Ding J.-H., Wu G., Hu G.* (2016) Uncoupling protein 2 modulation of the NLRP3 inflammasome in astrocytes and its implications in depression. Redox Biol., **9**, 178–187. DOI: 10.1016/j.redox.2016.08.006
166. *Yu J., Cheng Y., Cui Y., Zhai Y., Zhang W., Zhang M., Xin W., Liang J., Pan X., Wang Q., Sun H.* (2022) Anti-seizure and neuronal protective effects of irisin in kainic acid-induced chronic epilepsy model with spontaneous seizures. Neurosci. Bull., **38**(11), 1347–1364. DOI: 10.1007/s12264-022-00914-w
167. *Cheng Y., Cui Y., Zhai Y., Xin W., Yu Y., Liang J., Li S., Sun H.* (2021) Neuroprotective effects of exogenous irisin in kainic acid-induced status epilepticus. Front. Cell. Neurosci., **15**, 738533. DOI: 10.3389/fncel.2021.738533
168. *Guo P, Jin Z., Wang J., Sang A., Wu H.* (2021) Irisin rescues blood-brain barrier permeability following traumatic brain injury and contributes to the neuroprotection of exercise in traumatic brain injury. Oxid. Med. Cell. Longev., **2021**, 1118981. DOI: 10.1155/2021/1118981
169. *Kuro-o M., Matsumura Y., Aizawa H., Kawaguchi H., Suga T., Utsugi T., Ohyama Y., Kurabayashi M., Kaname T., Kume E.* (1997) Mutation of the mouse klotho gene leads to a syndrome resembling ageing. Nature, **390**(6655), 45–51. DOI: 10.1038/36285
170. *Zhao Y., Zeng C.-Y., Li X.-H., Yang T.-T., Kuang X., Du J.-R.* (2020) Klotho overexpression improves amyloid-β clearance and cognition in the APP/PS1 mouse model of Alzheimer's disease. Aging Cell, **19**(10), e13239. DOI: 10.1111/acel.13239
171. *Dubal D.B., Zhu L., Sanchez P.E., Worden K., Broestl L., Johnson E., Ho K., Yu G.-Q., Kim D., Betourne A., Kuro-o M., Masliah E., Abraham C.R., Mucke L.* (2015) Life extension factor klotho prevents mortality and enhances cognition in hAPP transgenic mice. J. Neurosci., **35**(6), 2358–2371. DOI: 10.1523/JNEUROSCI.5791-12.2015
172. *Semba R.D., Moghekar A.R., Hu J., Sun K., Turner R., Ferrucci L., O'Brien R.* (2014) Klotho in the cerebrospinal fluid of adults with and without Alzheimer's disease. Neurosci. Lett., **558**, 37–40. DOI: 10.1016/j.neulet.2013.10.058
173. *Erickson C.M., Schultz S.A., Oh J.M., Darst B.F., Ma Y., Norton D., Betthauser T., Gallagher C.L., Carlsson C.M., Bendlin B.B., Asthana S., Hermann B.P., Sager M.A., Blennow K., Zetterberg H., Engelman C.D., Christian B.T., Johnson S.C., Dubal D.B., Okonkwo O.C.* (2019) *KLOTHO* heterozygosity attenuates *APOE4*-related amyloid burden in preclinical AD. Neurology, **92**(16), e1878–e1889. DOI: 10.1212/WNL.0000000000007323
174. *Jin Z., Zhang Z., Ke J., Wang Y., Wu H.* (2021) Exercise-linked irisin prevents mortality and enhances cognition in a mice model of cerebral ischemia by regulating klotho expression. Oxid. Med. Cell. Longev., **2021**, 1697070. DOI: 10.1155/2021/1697070
175. *Zarbakhsh S., Safari M., Aldaghi M.R., Sameni H.R., Ghahari L., Khaleghi Lagmouj Y., Rahimi Jaberi K., Parsaie H.* (2019) Irisin protects the substantia nigra dopaminergic neurons in the rat model of Parkinson's disease. Iran. J. Basic Med. Sci., **22**(7), 722–728. DOI: 10.22038/ijbms.2019.33444.7987
176. *Zhang X., Xu S., Hu Y., Liu Q., Liu C., Chai H., Luo Y., Jin L., Li S.* (2023) Irisin exhibits neuroprotection by preventing mitochondrial damage in Parkinson's disease. NPJ Parkinsons Dis., **9**, 13. DOI: 10.1038/s41531-023-00453-9
177. *Schneider A.L.C., Huie J.R., Boscardin W.J., Nelson L., Barber J.K., Yaffe K., Diaz-Arrastia R., Ferguson A.R., Kramer J., Jain S., Temkin N., Yuh E., Manley G.T., Gardner R.C.* (2022) Cognitive outcome 1 year after mild traumatic brain injury: results from the TRACK-TBI study. Neurology, **98**(12), e1248–e1261. DOI: 10.1212/WNL.0000000000200041
178. *Delaplain P.T., Albertson S., Grigorian A., Williams B., Smith M., Inaba K., Lekawa M., Nahmias J.* (2020) Early cognitive impairment is common after intracranial

hemorrhage with mild traumatic brain injury. J. Trauma Acute Care Surg., **89**(1), 215–221. DOI: 10.1097/TA.0000000000002641

179. *Keys M.E., Delaplain P., Kirby K.A., Boudreau K.I., Rosenbaum K., Inaba K., Lekawa M., Nahmias J.* (2021) Early cognitive impairment is common in pediatric patients following mild traumatic brain injury. J. Trauma Acute Care Surg., **91**(5), 861–866. DOI: 10.1097/TA.0000000000003266
180. *Hagberg H., Mallard C., Rousset C.I., Thornton C.* (2014) Mitochondria: hub of injury responses in the developing brain. Lancet Neurol., **13**(2), 217–232. DOI: 10.1016/S1474-4422(13)70261-8
181. *Chou S.H.-Y., Lan J., Esposito E., Ning M., Balaj L., Ji X., Lo E.H., Hayakawa K.* (2017) Extracellular mitochondria in cerebrospinal fluid and neurological recovery after subarachnoid hemorrhage. Stroke, **48**(8), 2231–2237. DOI: 10.1161/STROKEAHA.117.017758
182. *Fan J., Zhu Q., Wu Z., Ding J., Qin S., Liu H., Miao P.* (2020) Protective effects of irisin on hypoxia-reoxygenation injury in hyperglycemia-treated cardiomyocytes: role of AMPK pathway and mitochondrial protection. J. Cell. Physiol., **235**(2), 1165–1174. DOI: 10.1002/jcp.29030
183. *Bi J., Zhang J., Ren Y., Du Z., Li Q., Wang Y., Wei S., Yang L., Zhang J., Liu C., Lv Y., Wu R.* (2019) Irisin alleviates liver ischemia-reperfusion injury by inhibiting excessive mitochondrial fission, promoting mitochondrial biogenesis and decreasing oxidative stress. Redox Biol., **20**, 296–306. DOI: 10.1016/j.redox.2018.10.019
184. *Chen K., Xu Z., Liu Y., Wang Z., Li Y., Xu X., Chen C., Xia T., Liao Q., Yao Y., Zeng C., He D., Yang Y., Tan T., Yi J., Zhou J., Zhu H., Ma J., Zeng C.* (2017) Irisin protects mitochondria function during pulmonary ischemia/reperfusion injury. Sci. Transl. Med., **9**(418), eaao6298. DOI: 10.1126/scitranslmed.aao6298
185. *Tsukita K., Sakamaki-Tsukita H., Takahashi R.* (2022) Long-term effect of regular physical activity and exercise habits in patients with early Parkinson disease. Neurology, **98**(8), e859–e871. DOI: 10.1212/WNL.0000000000013218
186. *Johansson M.E., Cameron I.G.M., van der Kolk N.M., de Vries N.M., Klimars E., Toni I., Bloem B.R., Helmich R.C.* (2022) Aerobic exercise alters brain function and structure in Parkinson's disease: a randomized controlled trial. Ann. Neurol., **91**(2), 203–216. DOI: 10.1002/ana.26291
187. *Avgerinos K.I., Liu J., Dalamaga M.* (2023) Could exercise hormone irisin be a therapeutic agent against Parkinson's and other neurodegenerative diseases? Metabol. Open, **17**, 100233. DOI: 10.1016/j.metop.2023.100233
188. *Kam T.-I., Mao X., Park H., Chou S.-C., Karuppagounder S.S., Umanah G.E., Yun S.P., Brahmachari S., Panicker N., Chen R., Andrabi S.A., Qi C., Poirier G.G., Pletnikova O., Troncoso J.C., Bekris L.M., Leverenz J.B., Pantelyat A., Ko H.S., Rosenthal L.S., Dawson T.M., Dawson V.L.* (2018) Poly(ADP-ribose) drives pathologic α-synuclein neurodegeneration in Parkinson's disease. Science, **362**(6414), eaat8407. DOI: 10.1126/science.aat8407
189. *Kam T.-I., Park H., Chou S.-C., van Vranken J.G., Mittenbühler M.J., Kim H., A M., Choi Y.R., Biswas D., Wang J., Shin Y., Loder A., Karuppagounder S.S., Wrann C.D., Dawson V.L., Spiegelman B.M., Dawson T.M.* (2022) Amelioration of pathologic α-synuclein-induced Parkinson's disease by irisin. Proc. Natl. Acad. Sci. USA, **119**(36), e2204835119. DOI: 10.1073/pnas.2204835119
190. *Sleep D., Cameron J., Evans L.R.* (2013) Albumin as a versatile platform for drug half-life extension. Biochim. Biophys. Acta, **1830**(12), 5526–5534. DOI: 10.1016/j.bbagen.2013.04.023

Received: 14.11.2025.
Revised: 04.12.2025.
Accepted: 05.12.2025.

МИОКИН ИРИЗИН: ВОЗДЕЙСТВИЕ НА ГОЛОВНОЙ МОЗГ И ТЕРАПЕВТИЧЕСКИЙ ПОТЕНЦИАЛ В ЛЕЧЕНИИ ДЕПРЕССИИ И НЕЙРОДЕГЕНЕРАТИВНЫХ ЗАБОЛЕВАНИЙ

А.М. Гисина*, К.Н. Ярыгин

Научно-исследовательский институт биомедицинской химии имени В.Н. Ореховича,
119121, Москва, ул. Погодинская, 10; *эл. почта: alisa.gisina@ibmc.msk.ru

Эпидемиологические исследования показывают, что во всём мире, в том числе в РФ, наблюдается устойчивый рост числа пациентов с когнитивными нарушениями, связанными с нейродегенеративными заболеваниями и различными аффективными расстройствами. В связи с этим существует запрос на разработку более действенных терапевтических подходов к их коррекции. Установлено, что регулярная физическая нагрузка способствует улучшению когнитивных функций и подавляет симптомы депрессии. Работающие мышцы секретируют биологически активные вещества — миокины, регулирующие восстановление самих мышц, а также регулирующие функции внутренних органов, желёз внутренней секреции, иммунной системы и мозга. Результатом является скоординированный ответ органов и систем, направленный на восстановление функциональной активности организма после физической нагрузки. В частности, улучшается память и способность к обучению. Пациенты с когнитивными нарушениями или депрессией часто не способны вовлечься в регулярную физическую активность из-за физических ограничений или ослабления мотивации. В связи с этим фармацевтические препараты, имитирующие эффекты мышечной активности, являются перспективной терапевтической опцией. Одним из направлений может стать создание препаратов на основе миокина иризина, который вырабатывается во время физической нагрузки и оказывает целый ряд благотворных эффектов на когнитивные функции и настроение. В этом обзоре представлены данные по влиянию физической нагрузки на когнитивные функции в норме и при патологии, описано физиологическое действие иризина, представлены предполагаемые механизмы действия иризина на когнитивные функции и симптомы депрессии.

Полный текст статьи на русском языке доступен на сайте журнала (http://pbmc.ibmc.msk.ru).

Ключевые слова: миокины; иризин; депрессия; нейродегенеративные заболевания

Финансирование. Работа выполнена в рамках Программы фундаментальных научных исследований в Российской Федерации на долгосрочный период (2021–2030 годы) (№ 122022800499-5).

Поступила в редакцию: 14.11.2025; после доработки: 04.12.2025; принята к печати: 05.12.2025.