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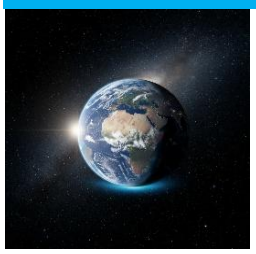

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Exercise-Induced Irisin and Its Role in Metabolic and Neurological Adaptations: A Narrative Review

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Abstract

Background. In the context of the increasing prevalence of metabolic and neurodegenerative disorders, growing attention has been directed toward biological factors mediating the beneficial effects of physical activity. Among them, irisin, a myokine released in response to muscle contraction, has emerged as a potential regulator of metabolic and neurological processes. Its role in inter-tissue communication and adaptation to exercise has become a subject of intensive research.

Aim. The aim of this study was to summarize the current state of knowledge regarding exercise-induced irisin and its role in metabolic and neurological adaptations. **Material and methods.** A narrative review was conducted using the PubMed and Web of Science databases. The analysis included systematic reviews as well as experimental and clinical studies published between 2017 and 2026 focusing on the role of irisin in metabolism, nervous system function, and responses to physical activity. **Results.** Available evidence indicates that irisin is involved in the regulation of glucose and lipid metabolism, improvement of insulin sensitivity, and induction of browning of white adipose tissue. Additionally, irisin appears to exert neuroprotective effects by influencing brain-derived neurotrophic factors (BDNF), supporting neurogenesis and cognitive function. Physical activity, particularly its intensity, type, and duration, plays a key role in modulating circulating irisin levels. However, the findings across studies remain inconsistent, likely due to methodological differences and variability in study populations. **Conclusions.** Irisin may represent an important link between physical activity and its beneficial

metabolic and neurological effects. Nevertheless, due to the heterogeneity of existing evidence, further well-designed studies are needed to better understand its mechanisms of action and potential clinical applications.

Key words: irisin, myokine, physical activity, metabolism, neuroprotection, insulin sensitivity

1. Introduction

Metabolic disorders, such as obesity, type 2 diabetes, and cardiovascular diseases, currently constitute one of the major public health challenges worldwide (Lin & Li, 2021). Their increasing prevalence encourages the search for new factors regulating metabolism and mechanisms that could be utilized in the prevention and treatment of these conditions. In recent years, particular attention has been given to the role of physical activity, not only as a lifestyle component but also as a stimulus that triggers complex hormonal responses in the body.

In this context, myokines, molecules secreted by skeletal muscles during activity, have attracted growing interest. One of these is irisin, a hormone that, since its discovery, has been the subject of numerous studies due to its potential role in regulating metabolic and neurological processes (Waseem et al., 2022). Increasing evidence suggests that irisin may influence not only energy metabolism but also neuroprotective processes, cognitive function, and the organism's adaptation to physical exercise (Natalicchio et al., 2020).

The interest in irisin is also driven by observations that modern lifestyles, characterized by low physical activity, may disrupt their secretion, potentially contributing to the development of metabolic disorders (Cigrovski Berkovic et al., 2025). Simultaneously, the role of different forms and intensities of exercise in modulating the level of this myokine and its effects on bodily function is increasingly being explored.

Despite the growing number of studies, the relationships between physical activity, irisin levels, and metabolic and neurological effects remain complex and not fully understood (Liu et al., 2022). The heterogeneity of results and limited understanding of irisin's mechanisms indicate the need for further research.

The aim of this narrative review is to present the current state of knowledge regarding exercise-induced irisin, with a particular focus on its role in metabolic and neurological adaptations.

2. Research materials and methods

A comprehensive literature search was conducted in the PubMed and Web of Science databases to identify relevant studies examining the role of irisin in metabolic regulation, neuroprotection, and exercise-induced physiological adaptations. The search included publications from 2017 to 2026. The following keywords and their combinations were used: "irisin," "FNDC5," "exercise-induced myokine," "physical activity," "metabolic health," "browning of adipose tissue," "glucose metabolism," "BDNF," "neuroprotection," and "cognitive function."

The inclusion criteria comprised original research articles, meta-analyses and systematic reviews published in English that investigated the secretion and regulation of irisin in response to physical activity, its metabolic and neurological effects. Both clinical studies on humans and experimental studies on animal models were considered. Articles not written in English, opinion pieces, conference abstracts, or studies with insufficient methodological information or without full-text availability were excluded. Data were extracted regarding exercise type, intensity, and duration, as well as irisin levels, metabolic outcomes, and neuroprotective effects.

3. Research results

3.1. Characteristics of irisin

Irisin belongs to the group of myokine hormones and is encoded by the *FNDC5* gene located on chromosome 1. This gene is responsible for the synthesis of a transmembrane protein that, upon activation, undergoes proteolytic cleavage, releasing its extracellular portion, irisin, into circulation (Deng et al., 2020).

Irisin was first identified in the skeletal muscles of mice subjected to wheel running, where it was produced by cleavage of the extracellular domain of the FNDC5 protein (fibronectin type III domain-containing protein 5). In 2012, Boström et al. described irisin in

humans, naming it after the Greek goddess Iris, the messenger of the gods, symbolically reflecting its role as a mediator of communication between muscles and other tissues (Boström et al., 2012).

Irisin is present in various tissues, including skeletal muscles, heart, brain, liver, kidneys, pancreas, lungs, spleen, skin, secretory glands, adipose tissue, and the myelin sheaths of nerve fibers, indicating its significant role in physiological regulation (Deng et al., 2020).

Structurally, FNDC5 consists of four main regions: a signal peptide, a fibronectin type III domain, a hydrophobic transmembrane domain, and a cytoplasmic domain. Once integrated into the cell membrane, the extracellular portion of FNDC5 is cleaved by ADAM family enzymes, allowing irisin to be released into circulation. N-glycosylation of specific asparagine residues supports its stability and secretion. Once released, irisin forms homodimers that can act on various tissues, including the heart, brain, bone, and adipose tissue, inducing multiple hysiological effects (Bao et al., 2022).

Irisin is highly evolutionary conserved and exhibits nearly identical structure in humans and mice. Its main sources of secretion are skeletal muscles during physical activity and exposure to low temperatures. The expression of the *FNDC5* gene and the release of irisin are regulated by factors including the peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) and AMP-activated protein kinase (AMPK). Despite growing research, many aspects of irisin's actions remain unknown, including its receptor and downstream signaling pathways in target tissues (Lee & Kim, 2025).

Beyond exercise, certain pharmacological interventions have also been shown to influence irisin levels. Preclinical and clinical studies observed that treatment with specific drugs increases circulating irisin. For instance, healthy individuals receiving several weeks of simvastatin therapy demonstrated elevated blood irisin levels. Similar effects were seen with sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor used in type 2 diabetes treatment, which indirectly increases irisin levels via elevated GLP-1 (Wang et al., 2021).

Functionally, irisin plays an essential role in energy metabolism. One of its best-described effects is the induction of browning in white adipose tissue, increasing thermogenesis and improving energy homeostasis. Moreover, it positively affects metabolic disorders such as obesity, diabetes, and cardiovascular disease, and due to its ability to cross the blood–brain barrier, it can influence cognitive functions, including memory, via action in the hippocampus and hypothalamus. The broad tissue distribution and diverse physiological effects make irisin a crucial mediator of exercise adaptation and metabolic regulation.

3.2. Effects of irisin on the nervous system

Recent research increasingly indicates that irisin plays a key role in central nervous system function. Irisin has been detected in multiple brain structures, including the hippocampus, and in cerebrospinal fluid. It is thought to mediate some of the neurological benefits associated with regular physical activity. Exercise elevates circulating irisin levels, and the molecule can cross the blood–brain barrier to act directly on neural cells. In the hippocampus, irisin influences the expression of numerous genes in neurons and glial cells, potentially modulating processes related to neural function and protection (Lourenco et al., 2022).

A key mechanism of irisin action in the brain is its link to brain-derived neurotrophic factor (BDNF) regulation. Studies have shown that exercise increases *FNDC5* and irisin expression in the hippocampus, leading to elevated BDNF levels (Lourenco et al., 2020).

Overexpression of *FNDC5* in neurons increases BDNF expression, whereas inhibition reduces it. This mechanism involves activation of the PGC-1α/FNDC5/irisin signaling pathway, which plays a vital role in regulating neuroprotective genes. Increased BDNF enhances synaptic plasticity, supports learning and memory, and is essential for proper hippocampal function (Choi et al., 2024); (Natalicchio et al., 2020).

Growing experimental evidence indicates that irisin may exert a meaningful neuroprotective effect in the context of Parkinson's disease. In experimental models, both prior exposure to irisin and its exogenous administration have been shown to increase the activity of mitochondrial complex I and stimulate mitochondrial biogenesis, which may support neuronal function (Zhang et al., 2023). Moreover, irisin attenuates neurodegenerative processes induced by pathological forms of α-synuclein by reducing its accumulation, protecting dopaminergic neurons from damage, and preventing a decline in striatal dopamine levels. These effects are also reflected in improvements in motor function observed in behavioral assessments. Additionally, irisin levels have been found to be inversely correlated with the severity of motor symptoms and cognitive impairment, suggesting its potential clinical relevance. There is also evidence indicating that irisin may enhance L-DOPA uptake in the striatum, particularly in the hemisphere contralateral to the affected limb (Shi et al., 2024). Altogether, these findings highlight irisin as a promising target for future research in the development of novel therapeutic strategies for Parkinson's disease.

Irisin also influences neurogenesis and neuronal maturation. Enhanced *FNDC5*/irisin expression in the brain stimulates the formation of new hippocampal neurons and affects their morphology, transcriptional activity, and function. This process involves activation of BDNF and other neuroprotective genes, promoting neuronal health and proper synaptic communication (Islam et al., 2021). Consequently, irisin may support cognitive processes and counteract degenerative changes in the nervous system.

Moreover, studies suggest a potential role of irisin in mood regulation. Both irisin and BDNF exhibit antidepressant properties, as confirmed by experimental research. Individuals with depression often show reduced plasma levels of these molecules, whereas their administration in experimental models alleviates depressive-like behaviors. This indicates that irisin, through modulation of the PGC-1α–FNDC5–BDNF pathway, may play an important role in mood and cognitive function regulation (Pignataro et al., 2022).

Experimental studies also highlight irisin's potential significance in neurodegenerative diseases. In Alzheimer's disease models, increased *FNDC5*/irisin expression improved synaptic plasticity and reduced memory deficits (Pahlavani, 2023). Peripheral administration of irisin ameliorated cognitive impairments even in the presence of neuropathological changes characteristic of the disease, suggesting irisin as a promising therapeutic target, though further clinical studies are necessary.

3.3. Role of irisin in the metabolic regulation

Irisin exhibits pleiotropic effects in metabolic regulation across multiple organs and tissues. In skeletal muscles, it enhances insulin sensitivity via PI3K/AKT pathway activation, promoting glucose transport into myocytes through GLUT4 translocation (Song et al., 2021); (Wu et al., 2023). It also stimulates glycogenesis and indirectly regulates gluconeogenesis, supporting glucose homeostasis and improving muscle energy efficiency (Yano et al., 2021). These mechanisms are crucial for maintaining systemic energy balance and preventing metabolic disorders such as insulin resistance and type 2 diabetes.

In adipose tissue, irisin induces browning of white adipocytes, increasing energy expenditure and reducing lipid accumulation. This process is mediated through ERK1/2 and p38 MAPK signaling pathways, leading to upregulation of UCP1, which drives non-shivering thermogenesis. Mouse models lacking irisin show reduced WAT browning and disrupted lipid

and carbohydrate metabolism, emphasizing its therapeutic potential for obesity and related metabolic disorders (Y. Chen et al., 2021). Furthermore, irisin intervention in high-fat diet models improved metabolic profiles by lowering blood glucose and cholesterol levels and reducing WAT volume and fat fraction.

The liver is another key target organ, where irisin regulates glucose homeostasis through modulation of production, uptake, and storage, as well as glycogen synthesis and degradation. In hepatocytes, irisin activates PI3K/AKT signaling, promoting glycogenesis while inhibiting gluconeogenesis via AMPK–PEPCK mechanisms. This action reduces excessive glucose production and enhances hepatic insulin sensitivity. However, irisin receptors in hepatocytes and precise signaling mechanisms remain largely unknown, representing a significant area for further study (Liu et al., 2022).

Irisin's effects extend beyond muscle, liver, and adipose tissue. It stimulates osteocyte proliferation and osteogenesis, supports bone health, exhibits neuroprotective properties, and promotes neuronal differentiation (Storlino et al., 2020). Additionally, irisin enhances insulin synthesis in pancreatic β-cells, inhibits adipogenesis, and reduces lipogenesis, collectively improving metabolic profiles. Through these multi-organ effects, irisin integrates signals across tissues, maintaining metabolic homeostasis, body weight regulation, and systemic energy balance (Z. Chen et al., 2020).

Irisin also modulates inflammation and oxidative stress in metabolic tissues, including muscle, liver, adipose tissue, and intestines. By influencing macrophages, it decreases reactive oxygen species (ROS) and pro-inflammatory cytokines (IL-1β, TNFα, IL-6, MCP-1), supporting metabolic homeostasis. FNDC5 overexpression and elevated irisin promote M2 macrophage polarization, reduce M1 recruitment, and enhance endothelial barrier function via AMPK-α and Src kinase activation (Mazur-Bialy et al., 2017).

Moreover, irisin stimulates the NRF2 pathway in intestinal cells, inhibiting NF-κB transcription and increasing heme oxygenase-1 (HO-1) production, supporting anti-inflammatory and antioxidant mechanisms (Du et al., 2019). These effects collectively enhance tissue metabolic function, reduce oxidative and inflammatory stress, stabilize glucose and lipid metabolism, and support muscle, liver, and adipocyte function.

In summary, irisin is a multifunctional metabolic hormone that coordinates signaling across muscles, adipose tissue, liver, bones, and pancreas to maintain energy balance, improve

insulin sensitivity, and protect organs from metabolic stress. Its therapeutic potential includes obesity, diabetes, lipid disorders, bone loss, and overall metabolic health support.

3.4. Effect of physical activity on irisin levels

Physical activity is one of the primary regulators of circulating irisin. Produced by proteolytic cleavage of FNDC5, irisin is mainly secreted by skeletal muscles in response to activity. This mechanism involves activation of the PGC-1α/FNDC5 pathway, which intensifies during muscle contraction, leading to increased irisin release.

Exercise intensity is a key determinant of irisin levels. High-intensity activities, including high-intensity interval training (HIIT), result in higher irisin concentrations compared to moderate-intensity exercise, particularly in young, normal-weight individuals. In overweight or obese individuals, the hormonal response may be less pronounced, potentially due to different metabolic changes during exercise, such as increased levels of AMP, ADP, or lactate, which may regulate irisin secretion (Mohammad Rahimi et al., 2022).

Exercise type also modulates irisin levels. Both endurance and resistance training can increase circulating irisin, though results are not always consistent. Some studies report the greatest increase following strength training or combined aerobic–resistance programs, while aerobic-only training may not significantly alter levels (Mohammad Rahimi et al., 2022).

Other forms of activity, including functional training (e.g., TRX) or Pilates over several weeks, have been shown to significantly elevate irisin compared to inactive controls (Rahimi et al., 2021).

Duration and regularity of training further influence irisin levels. Long-term programs, lasting several to dozens of weeks, increase *FNDC5* expression and circulating irisin. Single prolonged exercise bouts show transient irisin elevation in early and mid-phases, but excessive duration may reduce the effect, highlighting the dynamic nature of irisin response. Environmental factors, such as low temperature, may enhance irisin secretion compared to moderate conditions, suggesting a role in thermogenesis and cold adaptation (Ulupinar et al., 2021).

The irisin response to exercise may also vary by health status. In individuals with metabolic disorders, such as obesity or type 2 diabetes, exercise-induced irisin elevation may improve lipid metabolism and glucose regulation. However, some studies report inconsistent changes in metabolic syndrome, indicating a need for further investigation (Cheng et al., 2024).

In summary, physical activity is a crucial regulator of irisin, but its effects depend on

multiple factors, including exercise intensity, type, duration, environmental conditions, and metabolic status. Irisin appears to mediate beneficial metabolic adaptations to exercise, making it a potential target for prevention and treatment of metabolic disorders.

4. Discussion

Available evidence indicates that irisin plays an important role in regulating metabolic processes and exercise-induced adaptation. Its effects are largely mediated through multiple target organs, including muscles, liver, adipose tissue, bone, and brain (Muzaffar et al., 2025).

Dysregulated irisin expression or signaling may lead to impaired glucose homeostasis, unfavorable lipid metabolism, and increased risk of insulin resistance, obesity, and cardiovascular diseases (Paoletti & Coccurello, 2024).

However, study results are not fully consistent. Methodological differences, including intervention duration, exercise intensity and type, and participant health status, limit direct comparisons. Data heterogeneity from observational and interventional studies of varying quality and sample size further complicates interpretation. In many analyses, it is difficult to separate irisin effects from other factors, such as diet, sleep, or overall physical activity. Lack of standardization in exercise protocols and differences in irisin measurement methods also challenge result interpretation.

Future research should include well-designed, long-term interventional studies to evaluate the durability and effectiveness of interventions modulating irisin. Individual differences, such as age, metabolic status, body mass, and genetic predispositions, should be considered. It is also essential to deepen the understanding of molecular and hormonal mechanisms underlying irisin's metabolic, neuroprotective, and anti-inflammatory effects, providing a foundation for personalized preventive and therapeutic strategies for metabolic and neurodegenerative diseases.

5. Conclusions

Irisin is an important mediator of exercise-induced effects, linking muscle activity to metabolic regulation and nervous system function. Its actions encompass a wide range of effects, including improved insulin sensitivity, modulation of glucose and lipid metabolism, browning of white adipose tissue, and support of neuroprotective and cognitive processes.

Its effects are complex and influenced by exercise type and intensity, metabolic status, and individual characteristics. Given the heterogeneity of study findings and methodological limitations, interpretation of available data should be cautious. Further well-designed studies are necessary to clarify the role of irisin and assess its potential in preventive and therapeutic strategies, particularly regarding metabolic and neurological disorders.

Disclosure

Author Contributions

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The authors deny any conflict of interest.

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In preparing this work, the author(s) used ChatGPT for language improvement and grammatical correction. After using this tool/service, the author(s) have reviewed and edited the content as needed and accept full responsibility for the substantive content of the publication.

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