






# Irisin — the future of ischemic stroke therapy?

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## Abstract

*Irisin is a recently discovered hormone, synthesized mainly by the muscles. Expression of irisin and its precursor named FNDC5 was also found in the heart, kidneys, liver, pancreas, adipose tissue, and brain including cortical neurons, hippocampus, cerebellum, hypothalamus, and spinal cord.*

*The purpose of this study is to review the latest research on the properties of the irisin and its cytoprotective effect against neuronal damage and to draw attention to its possible clinical use in the treatment of stroke. Notch pathway activity increases after ischemic damage, stimulating the repair of the affected brain area. Irisin activates the Notch pathway which inhibits the activity of microglia, secretion of inflammatory factors, and finally leads to reduction of the brain edema. Studies revealed that irisin increases levels of brain-derived neurotrophic factor (BDNF), leading to enhancement of survival and migration of the neurons, and protecting nerve cells from damage during the ischemic stroke. It was also found that irisin maintains mitochondrial integrity, reduces oxidative stress, and exerts a protective effect on the blood-brain barrier.*

*Irisin entails a neuroprotective effect, reducing the extent of the infarcted area and the degree of brain damage. Stimulation of the irisin expression by physical activity or its exogenous administration remains the subject of research that raises hope for development of the new therapeutic options for diseases, especially ischemic stroke.*

**Key words:** ischemic stroke; irisin, apoptosis; FNDC5 protein; BDNF; blood-brain barrier; brain injury; neuroprotection; exercise

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## Introduction

Ischemic stroke remains one of the most important causes of neurological morbidity and mortality all over the world. According to the data from 2021, ischemic stroke affects 9.5 million people worldwide, causing 2.7 million deaths annually [1, 2]. Recent studies have shown that stroke causes a loss of 52 million years of life as a result of premature death and disability, being one of the leading causes of reduced life expectancy,

and a deterioration in the quality of life. Over 70% of strokes remain the ischemic type. Additionally, there is a slight predominance of stroke among men [1]. The increasing incidence of stroke among young adults (45 years old, and younger) remains currently a significant issue [3, 4].

Due to the enormous importance of this problem, it is necessary to develop effective methods of preventing stroke complications. Currently, high hopes are placed on the newly discovered myokine, named irisin which

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was found to be released from skeletal muscles during physical exercises [1–6].

The aim of the study is to reveal the current state of knowledge about the cytoprotective properties of the irisin and to draw attention to the therapeutic potential and possible clinical usage of this myokine in the treatment of stroke.

We designed our literature review to include studies that addressed the role of irisin in ischemic stroke. The literature search was performed using PubMed for studies restricted to clinical trial, review, comparative and multicenter studies published from 2007 to 2022, using the following medical subject headings (MeSH) terms: ischemic stroke, irisin, apoptosis, FNDC5 protein, BDNF, blood-brain barrier, brain injury, neuroprotection, exercise. The most suitable articles were manually collected based on preliminary abstracts review on the subject of the influence of irisin on brain ischemia. The references of searched articles identified additional ones that also matched, so these were included in the final review with 36 articles and 2 websites in total.

## The current state of knowledge

The main places of irisin synthesis are skeletal muscles and its secretion takes place immediately after physical exercises [5, 6]. Studies have shown that irisin affects the liver, pancreas, adipose tissue, bone, and brain with its variety of effects [7]. First of all, irisin involves the regulation of metabolic pathways and protects cells from apoptosis [8].

Released in skeletal muscles, it stimulates the uptake of glucose and fats, and their metabolism while limiting gluconeogenesis and glycogenolysis. In the liver, it stimulates the gluconeogenesis process and inhibits glycogenolysis and lipogenesis. It regulates the level of glucose in the blood serum, not only due to the fact of aforementioned processes but also by affecting the pancreas. Irisin stimulates pancreatic cells to secrete insulin and glucagon. Furthermore, it provides protection from apoptosis and enhances the regeneration of the beta cells. Bone tissue is another site of irisin action. Bones retain adequate mass and strength because irisin reduces the activity of osteoclasts. Irisin also has a beneficial effect on white adipose tissue, turning it brown, inhibiting the accumulation of lipids, increasing glucose uptake, and inhibiting lipolysis [7].

Physical activity increases the secretion of peroxisome proliferator-activated receptor-gamma coactivator 1 alpha (PGC-1 $\alpha$ ) — which is a transcriptional coactivator and metabolic regulator [9]. The increased level of PGC-1 $\alpha$  drives the expression of FNDC5 — the irisin precursor. FNDC5 is a transmembrane glycoprotein. It consists of a signal peptide and several domains.

Proteolytic cleavage of FNDC5 is necessary for the formation of functional irisin. The final step is post-translational modification including glycosylation [10].

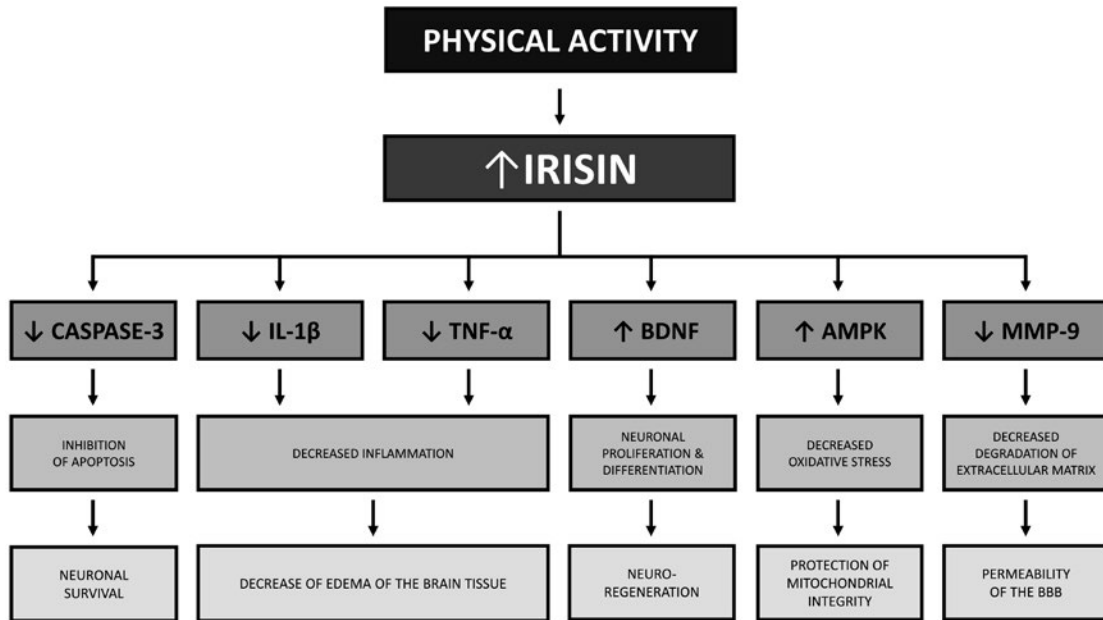
Neural stem cell proliferation, neuronal differentiation, gliogenesis, and microglial activity are regulated by the Notch pathway [11]. Its activity increases following ischemic damage and stimulates the repair of the affected areas of the brain.

Administration of irisin activates the Notch pathway that inhibits the activity of microglia and secretion of inflammatory factors such as IL-1 $\beta$ , and TNF- $\alpha$ , and finally reduces edema of the brain tissue. Caspase-3 activity is also reduced, inhibiting thereby neuronal apoptosis [11] (Fig. 1).

Studies have shown that the activity of the Notch intracellular domain (NICD) increases 24 hours after ischemic stroke, which proves an increased activity of the aforementioned Notch pathway. The process of neuronal differentiation can be demonstrated by labeling nerve cells with NeuN dye. Studies revealed that the levels of NeuN-positive cells increase after prior administration of exogenous irisin. The NeuN dye binds to mature neurons, indicating that neuronal differentiation takes place. On the other hand, the concentration of pro-inflammatory factors, including TNF- $\alpha$  and IL-1 $\beta$ , is significantly reduced after the administration of irisin [11]. This allows us to conclude that irisin reduces inflammation in the course of a stroke.

## Irisin influence on caspase-3 levels and neural cells apoptosis

Caspase-3 appears to be a crucial enzyme in the pathways of cerebral cell apoptosis. Brain ischemia leads to the involvement of two overall apoptosis pathways, intrinsic — initiated by mitochondria injury, and extrinsic — initiated by cell surface death receptors, both mediated by caspase-3 [12, 13]. An important role in cell death through apoptosis plays oxidative stress that leads to blood-brain barrier (BBB) dysfunction through structural and functional disturbances of endothelial cells' mitochondria [14, 15]. Thereby, cytochrome C (Cyt-c) is released from the mitochondrial membrane to the cell's cytoplasm, whereas proapoptotic Bax protein shifts inversely, activating the caspase family (including caspase-3), and inducing endothelial apoptosis. These events cause BBB damage and following dysfunction that leads to brain edema [15, 16]. Guo et al. (2021) revealed that exogenous irisin administration inhibits Bax and Cyt-C transits that lead to a decrease in caspase-3 activity and a reduction of endothelial cell apoptosis [15]. The above-mentioned study used a mouse model of traumatic brain injury (TBI), exploring both exogenous irisin and in vivo irisin synthesis, triggered by endurance exercise, influencing BBB after TBI. Both



**Figure 1.** The effect of increased irisin concentration on various neural cell pathways; IL-1 $\beta$  — interleukin-1 beta, TNF- $\alpha$  — tumor necrosis factor-alpha; BDNF — brain-derived neurotrophic factor, AMPK — AMP-activated protein kinase, MMP-9 — matrix metalloproteinase-9

exogenous irisin and endurance exercise appeared to diminish BBB damage in mice. Furthermore, the authors demonstrated that irisin may ameliorate BBB dysfunction after TBI by uncoupling protein 2 (UPC2) expression enhancement on the neural mitochondrial membrane [15]. Uncoupling proteins remarkably affects mitochondrial physiology, engaging in, inter alia, redox signaling. UPC2 might decrease reactive oxygen species production, reducing mitochondrial membrane potential [17]. It may result in a reduction of oxidative stress and inflammatory response [15].

Jin et al. (2019) investigated the influence of irisin on cleaved caspase-3, using in vivo and in vitro ischemia/reperfusion (I/R) brain injury models. The investigators found that pretreatment of irisin was associated with a significant reduction of the cleaved caspase-3 levels after I/R brain injury in comparison with the I/R injury group without irisin treatment in both in vivo and in vitro models. These results point out the neuroprotective properties of irisin that are associated with the inhibition of neural cell apoptosis [11].

### The role of BDNF and AMPK

Brain-derived neurotrophic factor (BDNF) is a protein synthesized in the neurons as a pro-isoform and released after proteolytic changes. BDNF expression in the central and peripheral nervous systems is dependent on various factors, such as stress, nutrition, metabolism, or behavior. BDNF mediates neuronal differentiation,

axonal sprouting, or dendritic arbor proliferation, and controls synaptic plasticity, long-term depression (LTD), and long-term potentiation (LTP), playing a very important role in the learning and memory processes [18]. Irisin may affect BDNF through PGC-1 $\alpha$ /FNDC5 axis during endurance exercise, exerting a neuroprotective effect [19, 20]. Asadi et al. (2018) explored the influence of recombinant irisin on the BBB permeability, infarct size, neurological outcomes, BDNF expression, and apoptosis, using a mouse model of ischemic stroke by occlusion middle cerebral artery with following reperfusion. The study revealed that intracerebroventricular administration of recombinant irisin at doses of 0,5; 2,5; 7,5 and 15  $\mu$ g/kg significantly decreased the size of infarction; however, better neurological outcomes were observed at doses of 7,5 and 15  $\mu$ g/kg. At level 7,5  $\mu$ g/kg irisin significantly reduced brain edema, lowered apoptotic cells, and enhanced BDNF immunoreactivity in the infarcted brain regions. It was found that the irisin administration did not affect BBB interruption.

The authors concluded that irisin reduces brain damage following ischemic stroke in a dose-dependent manner, diminishing apoptosis and leading to increasing BDNF expression in the ischemic brain area [21]. BDNF appears as an essential regulating factor following irisin action during ischemic stroke. It may also have a beneficial impact on neuronal survival and migration [19, 22] (Fig. 1).

Regarding 5'-AMP-activated protein kinase (AMPK), it appears as an endogenous protective protein, responding to deleterious stimuli, including cerebral ischemia, or neurodegenerative diseases. It regulates energy metabolism in the brain, influencing cell survival, growth, obsolescence, and death. AMPK plays an important role in ischemic stroke, reducing oxidative stress, ameliorating neuron apoptosis, affecting autophagy, improving mitochondrial dysfunction, protecting neurons from excitotoxicity of glutamate, reducing neuroinflammation, and promoting angiogenesis [23] (Fig. 1).

It was shown that irisin may mediate the expression of both BDNF and AMPK through physical activity [19]. Fan et al. (2020) revealed, in their *in vitro* study, that irisin activates the AMPK pathway, leading to the protection of cardiomyocytes and mitochondria against hypoxia-reoxygenation injury, under high glucose stress conditions [24].

Similarly, Zhang et al. (2020) revealed a protective irisin role against ischemia/reperfusion acute kidney injury, mediating by AMPK [25]. Despite poor evidence in the literature, linking directly neuroprotective role of irisin, mediating by AMPK in ischemic stroke, the above-mentioned studies indicate this possibility and further investigations are needed [19].

### The role of MMP-9

The scope of damage caused by ischemia and reperfusion is significantly dependent on blood-brain barrier (BBB) disruption and subsequent edema formation. Matrix metalloproteinase MMP-9, by participating in the degradation of the extracellular matrix, leads to an increase in the permeability of the blood-brain barrier, which can cause early brain edema, inflammatory infiltration, and, consequently, neuronal injury [26, 27].

In the studies using the middle cerebral artery occlusion (MCAO) ischemic stroke model in rats, it was shown that intravenous administration of irisin prior to the induction of stroke significantly improved parameters related to the extent of the stroke. A significant reduction in the volume of infarcted cerebral tissue was observed in the irisin pretreatment group (23.00% vs. 34.83%). In the pathomorphological analysis using Evans blue, a decrease in permeability of the blood-brain barrier and a decrease in the activity of MMP-9 metalloproteinase was observed in this group. Maintaining the integrity of the blood-brain barrier resulted in a reduction of edema and limited excessive build-up of water in the brain tissue (Fig. 1). Also, the neurological deficit score was lower in irisin-treated rats. The above results suggest that increased concentrations of irisin, by inhibiting MMP-9, may have a neuroprotective effect, leading to a reduction in the level of neurological deficit [28].

### Irisin as a prognostic factor

There are indications that serum levels of irisin may be used as a prognostic marker in patients with ischemic stroke. Irisin level in patients with 6-month survival was significantly higher compared to patients who died. Moreover, irisin had a higher predictive value as compared to FBG, Hs-CRP, HCY, IL-6, and clinical assessment according to the NIHSS scale. Most noteworthy, among patients with high concentrations of irisin, poor functional outcome (i.e. modified Rankin Scale (mRS) of 3–6) is less frequent, resulting in higher chances of recovery [29, 30].

### Neuroprotection of the physical activity in ischemic stroke

It is commonly known that exercises have a beneficial effect on brain function. Physical activity causes releasing of many molecules, proteins, and metabolites involved in cell metabolism and the repair of their injuries. Exercises stimulate a series of changes to ensure the amelioration of the brain's vascularization and release neuroprotective and angiogenesis factors, which are promoting increased brain blood flow and avoidance of injuries [31]. According to the same study active subjects show statistically significant reductions in vessel tortuosity and an increased number of small vessels in comparison to less active persons [32]. In combination with creating new collateral vessels that might explain the role of activity in neuroprotection. Preconditioning exercise as a mild stressor protects the brain from injury by inhibiting apoptosis and induces brain ischemic tolerance. These effects have a lot of mechanisms. Preconditioning exercises reduce infarct volume and neurological deficits, activate the protective and repair functions of astrocytes, and reduce oxidative damage in neurons [33]. Moreover, this activity has a positive impact on the components of the blood-brain barrier preventing its interruption and subsequent formation of edema [34].

During physical exercise, many metabolic pathways are activated, including the release of osteocalcin by bones, beta-hydroxy-butyrate by the liver and FNDC5/irisin by muscles. All of the aforementioned substances are responsible for increasing the level of BDNF, which shows a neuroprotective effect, reducing the scope of cognitive impairment due to ischemia, as studies concluded [35]. Studies have shown that irisin can decrease inflammatory factors, such as IL-6 and TNF- $\alpha$ , which may limit inflammation-related damage to the brain. The protective properties of irisin are also associated with a decrease in the concentration of MMP-9 responsible for the destruction of the blood-brain barrier. The similarity of irisin effects to other neuroprotective substances secreted during exercise leads to the conclusion

that irisin is also an important mediator of the protective effect on the brain. This conclusion is supported by the fact that low serum irisin level was a predictor of poor early functional outcomes in patients with ischemic stroke. As irisin is mainly secreted by muscles during physical activity, it may play a key role in connecting exercise with the protection of brain function [36].

## Conclusions

Irisin secretion is associated with physical activity. This myokine plays a key role in relieving inflammation, inhibiting apoptosis, as well as maintaining mitochondrial integrity, and reducing oxidative stress which is connected with cell injury. Irisin exerts a cytoprotective effect on neurons, reducing the extent of infarcted area and the degree of brain damage. There is a correlation between physical activity, irisin levels, and the likelihood of a positive neurological outcome during ischemic stroke. Irisin also has an effect similar to other neuroprotective substances secreted during physical activity, suggesting its importance in alleviating the effects of ischemia on brain tissue. Its multidimensional effect raises hope that it can be used as a prognostic factor, which may enable the development of new therapeutic strategies in patients after ischemic stroke. However, further investigations are still needed, in particular on large groups of patients, which in the future may provide a foundation for the development of new therapeutic options for ischemic stroke.

## Conflict of interest

None.

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