TYPE, DURATION, AND INTENSITY OF PHYSICAL EXERCISE MODULATE FNDC5/IRISIN EXPRESSION IN THE HIPPOCAMPUS

a Upik Rahmi, b Hanna Goenawan, c Nova Sylviana, d Setiawan, e Hamidie Ronald Daniel Ray

ABSTRACT

Introduction: Physical exercise can activate important biochemical processes in the human body, one of which is a myokine called irisin.

Objective: This review aims to identify the effect of exercise on the expression of FNDC5/irisin, a myokine secreted by skeletal muscles that is produced in response to physical activity. This hormone provides a protective function in the central nervous system, specifically the hippocampus. The effects of exercise on the brain are well known, but the duration, intensity and type of exercise as well as the underlying molecular mechanisms are not fully understood. This review will focus on Fibronectin type III domain-containing protein 5 (FNDC5) and its secreted form, myokine “irisin” with a mechanism of action in the hippocampus and the effect of exercise on irisin expression.

Method: A literature search was performed on several databases (PubMed, Scopus, and Sciencedirect) on the impact of training on irisin, resulting in 17 articles.

Results: This review shows that physical exercise increases plasma irisin levels in humans and brains in rats, including the hippocampus. Discussion: The relationship between exercise, FNDC5 (the gene that encodes irisin), and the hippocampus is an area of active research. FNDC5/irisin is a protein that has gained attention for its potential role in mediating some of the beneficial effects of exercise on the brain, including the hippocampus.

Conclusion: Irisin is expressed in plasma and hippocampus as a result of physical exercise that depends on the type, intensity, and duration of exercise that functions in the brain.

Keywords: exercise, irisin, FNDC5, hippocampus.

Received: 10/07/2023
Accepted: 11/10/2023
DOI: https://doi.org/10.55908/sdgs.v11i10.1074

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TIPO, DURAÇÃO E INTENSIDADE DA EXPRESSÃO DO MODULO DE EXERCÍCIO FÍSICO FNDC5/IRISINA NO HIPOCAMPO

RESUMO

Introdução: O exercício físico pode ativar processos bioquímicos importantes no corpo humano, um dos quais é uma miocina chamada irisina.

Objetivo: Esta revisão tem como objetivo identificar o efeito do exercício na expressão de FNDC5/irisina, uma miocina secretada pelos músculos esqueléticos que é produzida em resposta à atividade física. Este hormônio desempenha uma função protetora no sistema nervoso central, especificamente no hipocampo. Os efeitos do exercício no cérebro são bem conhecidos, mas a duração, intensidade e tipo de exercício, bem como os mecanismos moleculares subjacentes, não são totalmente compreendidos. Esta revisão se concentrará na proteína 5 contendo o domínio da fibronectina tipo III (FNDC5) e sua forma secretada, a miocina “irisina”, com mecanismo de ação no hipocampo e o efeito do exercício na expressão da irisina.

Método: Foi realizada uma pesquisa bibliográfica em diversas bases de dados (PubMed, Scopus e Sciencedirect) sobre o impacto do treinamento na irisina, resultando em 17 artigos.

Resultados: Esta revisão mostra que o exercício físico aumenta os níveis plasmáticos de irisina em humanos e no cérebro de ratos, incluindo o hipocampo. Discussão: A relação entre o exercício, o FNDC5 (o gene que codifica a irisina) e o hipocampo é uma área de pesquisa ativa. A FNDC5/irisina é uma proteína que tem ganhado atenção pelo seu papel potencial na mediação de alguns dos efeitos benéficos do exercício no cérebro, incluindo o hipocampo.

Conclusão: A irisina é expressa no plasma e no hipocampo como resultado do exercício físico que depende do tipo, intensidade e duração do exercício que funciona no cérebro.

Palavras-chave: exercício, irisina, FNDC5, hipocampo.

1 INTRODUCTION

Sedentary behaviour (1) due to infrequent exercise, activity intolerance, and low level of knowledge about health (2) can cause a decrease in the ability of cognitive function and memory (1)(3). On the one hand, endurance sports are known to have an effect on brain health and cognitive function (4) and non-endurance sports have an effect on spatial learning (5). Exercise can increase brain plasticity (6), enhances neurogenesis, synaptogenesis, angiogenesis, and release of neurotrophins as neural mechanisms that mediate cognitive effects (7).

This cognitive enhancement is regulated by a protein known as FNDC5/irisin (8). FNDC5/irisin was first described as an exercise-induced myokine (9). FNDC5/Irisin expression during exercise in skeletal muscle is mediated by the transcriptional coactivator Peroxisome proliferator-activated receptor-gamma coactivator (PGC)-1alpha (PGC-1α) (9)(10). FNDC5/Irisin plasma then circulates in the blood (11) then goes to neurons in the central nervous system by crossing the blood-brain barrier (11)(12)(13).
Apart from skeletal muscle, FNDC5/Irisin is also expressed in the brain including the hippocampus (4), hypothalamus (15), and Purkinje cells of the cerebellum (16). In the hippocampus, the exercise-activated PGC-1α-FNDC5/irisin pathway then induces the neuroprotective gene Brain Derived Neurotropic Factor (BDNF) (14) function on neural, cognitive, learning and memory plasticity (15) in humans and animals (16)(17).

However, the mechanism of irisin activation for memory remains unclear. Therefore, we conducted a review of irisin activity in the hippocampus resulting from physical exercise of various types, durations and intensities.

2 METHOD

We searched online literature databases, including Scopus, PubMed-Medline, and ScienceDirect. The original article in English uses the following keywords in the title: (Exercise OR physical activity) AND (Irisin) AND (Brain), (Exercise OR physical activity) AND (FNDC5) AND (Brain), between 2013 and 2023. We limited our analysis to experimental studies with exercise interventions. Articles in English published between 1987 and 2022, were included. Figure 1

Animals and Human studies in subjected to exercise interventions, with neurocognitive impairment included, did not include systematic reviews or literature articles, simplified and expanded abstracts published in the proceedings and book chapters. Studies with neurodegenerative disease. Traumatic Brain Injury, Diabetes mellitus. Figure 1

3 RESULT

A total of 17 articles were selected for the systematic review, whose authorship, year of publication, study population, techniques used, most important results are show in Table 1, Table 2, Table 3.
3.1 REGULATION OF THE EXPRESSION OF FNDC5/IRISIN

FNDC5/irisin expression in the hippocampal is modulated by aerobic and resistance exercise in rodents (21)(20). Aerobic and anaerobic exercise improves cognitive function (21)(22) with increased expression of FNDC5/irisin (23) in primary and hippocampal neurons (4), induces synaptic plasticity, neurogenesis (24), (25), improve spatial memory, and learning (26).

Studies have shown that endurance exercise protects neurons from injury, induces neurogenesis, and increases brain activity (27)(28). Stimulation of irisin signaling due to exercise in the brain may be useful in people with Alzheimer's disease (AD), because irisin activates neuronal protective pathways in the hippocampal (29). Endurance exercise also increases irisin and can reduce brain edema after Trauma Brain Ischemia (TBI) by increasing the expression of uncoupling protein 2 (UCP2) in the mitochondrial membrane of neurons and contributing to neuroprotection (30). Irisin also reduces ischemia-induced nerve injury through activation of the Akt and ERK1/2 signaling.

It is well known that PGC-1α controls FNDC5 expression in the hippocampus and primary neurons in culture (4). In the hippocampus, it is dependent on the cAMP/PKA signaling pathway (36). Furthermore, lactate released from skeletal muscle during exercise induces FNDC5 expression in the hippocampus (37). Further analysis has shown a putative ERRα binding element (ERRE) located upstream to the FNDC5 promoter. In primary cortical neurons, PGC-1α activates ERRα and increases FNDC5 expression in the brain, which is then negatively fed back to PGC-1α/ERRα (4).

3.2 SIGNALING PATHWAYS INVOLVED AND FUNCTION FNDC5/IRISIN

The action of FNDC5/irisin induces BDNF by crossing the blood-brain barrier to regulate synaptic plasticity (4)(38) thereby modulating the differentiation and maturation of neurons (39), regulation of neuronal differentiation and proliferation, neural behavior, neuroprotection, learning, and memory (40).

Several studies have shown that changes in certain genes in neurons are affected by the expression levels of FNDC5/Irisin, for example, the differentiation of mouse embryonic stem cells into nerve cells is influenced by the FNDC5 gene (41)(42). Furthermore, the expression of BDNF, Neuronal PAS Domain Protein 4 (Npas4), cFos, and Arc in primary cortical neurons is induced by overexpression of FNDC5 (4). Interestingly, BDNF mRNA levels increased in the hippocampus but decreased in the prefrontal cortex after intracerebroventricular (icv) administration of Irisin (1ng) in male rats (34).

An important question that remains unanswered is whether Irisin can control FNDC5 expression in the brain. A recent study showed that administration of Irisin caused a brief decrease in FNDC5 expression in the prefrontal cortex and hippocampus after 1 hour. However, FNDC5 expression was increased in the hippocampus without changes in the prefrontal cortex 6 hours after Irisin administration (34). The mechanism of action for these changes is not fully understood. Increased proliferation of the rat
3.3 INTEGRINS AS IRISIN RECEPTORS

Irisin delivered to the nervous system will cross the blood-brain barrier (36), circulates in the nervous system, and potentially binds to integrin receptors. Nonetheless, studies have yet to confirm that irisin receptors in the central nervous system are integrins (44). Until now there have been no research results that explain irisin receptors in the brain.

Figure 2: Irisin induces a signaling mechanism in the brain.

Irisin is produced in skeletal muscle and the brain by the FNDC5 protein. Irisin acts on neurons via receptors that have yet to be identified. The irisin functions include stimulating (cAMP) accumulation, cAMP-PKA activation, CREB phosphorylation, and BDNF expression (36). Exercise further stimulates FNDC5 production in the brain through a coactivator-dependent mechanism PPARγ 1α (PGC-1α), leading to synaptic plasticity and cognition, precisely in the hippocampus. (45)

3.4 IMPACTS OF PHYSICAL EXERCISE TYPES, INTENSITY, AND DURATION ON FNDC5/IRISIN EXPRESSION AT HIPPOCAMPUS

3.4 IMPACTS OF PHYSICAL EXERCISE TYPES, INTENSITY, AND DURATION ON FNDC5/IRISIN EXPRESSION AT HIPPOCAMPUS
### 3.4 Impacts of Physical Exercise Types, Intensity, and Duration on FNDC5/Irisin Expression at Hippocampus

<table>
<thead>
<tr>
<th>No</th>
<th>Author, Year</th>
<th>Population:</th>
<th>Exercise Type</th>
<th>Duration</th>
<th>Result</th>
<th>Importance</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mohammad Azimi, et al., 2017</td>
<td>AD</td>
<td>Treadmill</td>
<td>Low to Moderate 10-15m/min, 60 min/day, 5 days/week</td>
<td>4 weeks (5 groups)</td>
<td>↑ mRNA PGC-1α, ↑mRNA FNDC5, ↑mRNA BDNF</td>
<td>Moderate intensity treadmill exercise increases AMPK activity causing an increase in PGC-1α/FNDC5/BDNF levels which can improve spatial learning and memory deficits</td>
</tr>
<tr>
<td>2</td>
<td>Mychael V. Lourenco, et al., 2019</td>
<td>AD</td>
<td>Swimming</td>
<td>Moderate to High (60 cm depth × 45 cm diameter), 10 - 60 min/day, 20 min/session, 5 days/week,</td>
<td>5 weeks (2 groups)</td>
<td>↑ Protein irisin</td>
<td>Exercise stimulates transient activation of extracellular signal-regulated kinase 1/2 (ERK 1/2), and prevents oxidative stress induced by amyloid-β oligomers in primary hippocampal neurons of AD patients with increased irisin expression, so that the Neuroprotective pathway is active in the hippocampal via BDNF.</td>
</tr>
<tr>
<td>3</td>
<td>Dong-Jie Li., 2016</td>
<td>Mice; n = 30</td>
<td>Treadmill</td>
<td>Moderate to High 10 m/min for 90 min</td>
<td>2 minggu (3 group)</td>
<td>↑ Protein irisin</td>
<td>Physical exercise effects are equivalent to irisin on infarct area, brain function, IL-6 because Irisin reduces ischemia-induced nerve injury through activation of the Akt and ERK1/2 signaling pathways and contributes to the neuroprotective effect of exercise against cerebral ischemia.</td>
</tr>
<tr>
<td>4</td>
<td>Xianshengjie Lang., 2020</td>
<td>T2DM (high-fat diet and Mice n= 36</td>
<td>Treadmill</td>
<td>Moderate 13.3 m / min, 15 min / d, 5 days/week</td>
<td>8 weeks</td>
<td>↑ SIRT1/ NF-κB dan SIRT1/PGC-1α/ FNDC5/ BDNF</td>
<td>Moderate-intensity treadmill exercise over a long period of time can reduce the inflammatory response in the hippocampus and</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>STZ injection.</th>
<th>Mice</th>
<th>Treadmill</th>
<th>Low to moderate 2 m/min/week 45min/days, 5days/week</th>
<th>4 week (3 Groups)</th>
<th>↑ FNDC5</th>
<th>Increase BDNF expression in T2DM mice by activating SIRT1.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aline Siteneski., 2020</td>
<td>Mice n = 15</td>
<td>Treadmill</td>
<td>Low to moderate 2 m/min/week 45min/days, 5days/week</td>
<td>4 week (3 Groups)</td>
<td>↑ FNDC5</td>
<td>Endurance exercise increased the number of FNDC5-positive cells in the hippocampal DG and increased FNDC5 C-terminal and FNDC5/irisin immunocontent throughout the hippocampus.</td>
</tr>
<tr>
<td>Muaz Belviranli., 2018</td>
<td>Female wistar n=16</td>
<td>Voluntary free wheel running</td>
<td>Low MAY RW2508</td>
<td>90 hari (4 kelompok)</td>
<td>↑ protein</td>
<td>Exercise training improves spatial learning and memory in aged mice. Increases expression of BDNF, FNDC5, PGC-1α, mTOR, ARC, c-Fos, ERK, SIRT, FOXO dan PE ↑ Protein</td>
</tr>
<tr>
<td>M.R Islam., 2021</td>
<td>AD F5KO (global Fndc5 knock-out KO) Mice; n = 42</td>
<td>Running wheel</td>
<td>Low 30-min intervals</td>
<td>90 mins (2 kelompok WT, F5KO)</td>
<td>↑ irisin</td>
<td>Exercise increases Irisin which functions as a potential therapeutic agent to treat cognitive impairment in AD sufferers.</td>
</tr>
<tr>
<td>Peipei Guo., 2021</td>
<td>Traumatic Brain Injury Mice; n = 16</td>
<td>Treadmill</td>
<td>Low 6 m/min, 30 min/2 days, 8 m/min, 10 m/min, 30 min 15 days/week,</td>
<td>6 weeks</td>
<td>Exercise Endurance ↑ protein irisin</td>
<td>Exercise Endurance and exogenous irisin can reduce BBB damage in the mouse model of TBI. Irisin reduces brain edema after TBI by promoting the expression of uncoupling protein 2 UCP2 in the mitochondrial membrane of neurons and contributes to neuroprotection</td>
</tr>
<tr>
<td>Babaei., 2021</td>
<td>Rat; n=44</td>
<td>Treadmill</td>
<td>Low to Hight 16 m/min, 2min/day, 5days/week</td>
<td>5 week (3 group)</td>
<td>↑ Protein</td>
<td>Interval exercise training increases PGC-1α and FNDC5. HIIT increases the hippocampal proteins PGC-1α, FNDC5, and BDNF and has a neuroprotective effect.</td>
</tr>
</tbody>
</table>
Type, Duration, and Intensity of Physical Exercise Modulate FNDC5/Irisin Expression in the Hippocampus

<table>
<thead>
<tr>
<th>No</th>
<th>Author</th>
<th>Species, n</th>
<th>Type</th>
<th>Intensity</th>
<th>Duration</th>
<th>Result</th>
<th>Importance</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>Lee., 2022</td>
<td>Rat; n=32</td>
<td>Treadmill</td>
<td>Moderate</td>
<td>12 weeks</td>
<td>↑ Protein FNDC5/irisin</td>
<td>Combined treadmill and resistance training, reduces β-amyloid plaques, the main cause of decreased brain function, and increases the expression of PGC-1α, FNDC5, and BDNF proteins in the hippocampus</td>
<td>(52)</td>
</tr>
<tr>
<td>11</td>
<td>Wrann., 2013</td>
<td>Mice; n=6</td>
<td>Running-wheel</td>
<td>Low</td>
<td>30 days</td>
<td>↑ mRNA FNDC5/irisin</td>
<td>Endurance exercise increased the expression of FNDC5 and BDNF proteins in the rat hippocampus.</td>
<td>(8)</td>
</tr>
<tr>
<td>12</td>
<td>Gruhn., 2021</td>
<td>Mice; n=20</td>
<td>Treadmill</td>
<td>Low to moderate</td>
<td>4 week</td>
<td>↑ Protein FNDC5/irisin</td>
<td>Exercise increased the number of phosphorylated mTORC1 (Ser2448) positive cells in the whole and ventral subgranular zone of the dentate hippocampal gyrus, increasing hippocampal FNDC5/irisin immunoreactivity, but rapamycin administration did not alter this effect.</td>
<td>(32)</td>
</tr>
</tbody>
</table>

Source: Prepared by the authors

Table 2: Aerobic exercise of different types, duration, and intensities that modulated FNDC5/Irisin expression in the Rat/Mice at hippocampus
Table 3: Aerobic exercise of different types, duration, and intensities that modulated FNDC5/Irisin expression in the Human at hippocampus

<table>
<thead>
<tr>
<th>No</th>
<th>Author, Year</th>
<th>Dx</th>
<th>Population</th>
<th>Exercise</th>
<th>Duration</th>
<th>Result</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ji-Hyeon Kim, et al., 2018</td>
<td>Human; Elderly women n= 26</td>
<td>Aquarobic</td>
<td>40–50% HRR/RPE 11-12</td>
<td>16 week (2 Group)</td>
<td>↑Serum irisin and serum BDNF</td>
<td>Aquarobic exercise increases serum levels of irisin and BDNF which function effectively to prevent degenerative brain diseases and improve brain function in elderly women</td>
</tr>
<tr>
<td>2</td>
<td>Ghodrati., 2023</td>
<td>T2D Type 2 Diabetess Mellitus; n= 21</td>
<td>aerobic, resistance, and balance exercises</td>
<td>%HRR, 55%-75%, 5 minutes, 3 times/week</td>
<td>12 weeks</td>
<td>↑Irisin serum levels did not change significantly in the exercise</td>
<td>Physical fitness and cognitive function improve with combined aerobic exercise and resistance exercise, but not significantly to the increase in BDNF in women with T2D</td>
</tr>
<tr>
<td>3</td>
<td>Tsai., 2021</td>
<td>HIIT MICE</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Note: MICE: Moderate-intensity continuous exercise
Source: Prepared by the authors
a. The Impacts of Physical Exercise Type on FNDC5/Irisin Regulation.

Aerobics is exercise using large, rhythmic muscles, including brain vitalization, developed to improve cognitive abilities (57). Aerobic exercise can improve heart and brain health, especially the hippocampus as a cognitive center. Endurance exercise includes yard work (mowing the lawn, sweeping), dancing, swimming, cycling, climbing stairs or hills, brisk walking or jogging, using the treadmill, and playing tennis or basketball (58).

FNDC5/Irisin expression in the Central Nervous System (CNS) is induced by various types of exercise. Jening Running exercise in mice increases FNDC5 expression in the hippocampus which causes an increase in BDNF expression (4). These results confirm previous research that exercise increases BDNF levels in the hippocampus (59)(60)(61). This is relevant because the formation of memory and cognition is associated with hippocampal BDNF, and hippocampal neurogenesis which is a process involved in exercise-induced memory function and BDNF(62)(63)(64). BDNF expression in the hippocampus is influenced by various factors that could mediate the relationship between exercise and neurogenesis (65), for example, PGC-1α/FNDC5/BDNF which is activated in the hippocampus due to the voluntary running wheel (4).

In treadmill running type exercise, the exercise parameters (intensity, duration, etc.) are determined which cause increased stress due to increased running intensity, so this has an effect on memory and spatial learning decreases in animals compared to (66) with the type of voluntary running wheel, because on the running wheel, rats can run freely in their cages (67) thereby enhancing cognitive function and learning (68), more precisely improve spatial memory, and hippocampal neurogenesis due to intermittent voluntary wheel running in middle-aged rats (69).

Study (70) the type of treadmill exercise with the type of voluntary wheel running has the same effect (70)(71). Likewise, the expression of FNDC5/Irisin increases in the hippocampus with the type of voluntary wheel running exercise (54)(72)(4)(73).

b. The Impacts of Physical Exercise of Different Intensities on FNDC5/Irisin Regulation

Aerobic exercise is generally classified as high, moderate, and low intensity, based on percentage of maximum heart rate or VO2 max (74)(58). Moderate intensity treadmill exercise increases PGC-1α/FNDC5/BDNF levels, can improve spatial learning and
memory deficits accompanied by increased AMPK activity in the hippocampus (75) and long-term moderate-intensity treadmill exercise can reduce the inflammatory response in the hippocampus and increase BDNF expression in T2DM mice by activating SIRT1 (48).

In anaerobic exercise, interval exercise training increases the hippocampal proteins PGC-1α, FNDC5, and BDNF which also have a protective effect against chronic stress (51). Likewise in Resistance training, the expression of the neuronal gene FNDC5 which is regulated by PGC-1α, a previously identified muscle protein that is induced by exercise and cleaved and secreted as irisin, also increased in the rat hippocampus (4). Additionally, levels of key brain plasticity markers increased in the hippocampus after 8 weeks of High Interval Intensity Training (HIIT)(76).

Significant increases in irisin levels were only observed after the HIIT intervention although serum BDNF levels increased significantly in both the HIIT intervention and the acute Moderate Intensity Cognitive Exercise (MICE) (77). However, changes in Irisin and BDNF levels before and after the intervention did not correlate with changes in neurocognitive performance. Irisin may have a potential facilitating role in neuropsychological performance and working memory(56). The increasing intensity of exercise will also increase the expression of FNDC5/irisin in the hippocampus as a neuroprotective, synaptic function and to prevent cognitive decline in AD (36). So it can be concluded that FNDC5/irisin levels increase with increasing exercise intensity (78).

Figure 2: Exercise modulates irisin expression in the hippocampus (78).
c. The Impacts of Physical Exercise Duration on FNDC5/Irisin Regulation

FNDC5/Irisin expression can also be regulated by exercise duration (81)(82), for example, Duvivier et al showed that 30 minutes of exercise, three times a week can improve one's health status (79)(80) especially increasing performance and maximal cognitive fitness (81). Meanwhile, 30 minutes of treadmill can improve the accuracy of the intensity of the exercise, thus improving cognitive and memory function (82). In addition, running wheels for 30 days increased FNDC5 mRNA expression (83) and enhancing the role of FNDC5/irisin in neurogenesis, morphology and maturity, and levels of secretion in dendritic spines (74), increase synaptic hippocampal neurons (36).

Increased exercise duration increased the expression of the FNDC5/irisin gene in the hippocampal of young and old rats (26). In the voluntary wheel running exercise, not many neurons are induced because of the short duration and less intensity (19), although duration affects the expression of FNDC5/Irisin in voluntary wheel running exercises (84).

The duration or dose of acute aerobic exercise affects cognitive function (85)(86)(87), spatial working memory increases after 30 minutes of practice (88), the duration of the exercise affects the accuracy and response time of the stroop task on cognitive (88). In the end, it can be concluded that the intensity, duration, and type of exercise affect the expression of FNDC5/irisin protein and irisin mRNA in the hippocampus. (29)(48).

4 DISCUSSION

The relationship between exercise, FNDC5 (the gene that encodes irisin), and the hippocampus is an area of active research. FNDC5/irisin is a protein that has gained attention for its potential role in mediating some of the beneficial effects of exercise on the brain, including the hippocampus.

Several studies, both in animals and humans, show a positive relationship between exercise and FNDC5/irisin expression in the hippocampus (29)(21). Animal studies have shown that exercise can increase FNDC5/irisin expression in the hippocampus, for example, in rodents, voluntary exercise or running on a treadmill has been associated with increased FNDC5/irisin levels in the hippocampus (14).

In human studies, the evidence is more limited and mixed. Several studies have reported a positive correlation between exercise and FNDC5/irisin expression in the
hippocampus, suggesting that exercise can increase irisin production in this brain region. (89). Research on humans examined irisin only on serum and plasma, so that the correlation between exercise and FNDC5/irisin expression in the hippocampus did not find a significant relationship. Variations in study designs, participant characteristics, exercise protocols, and measurement methods can account for these differences.

The hippocampus is the main brain region involved in learning, memory and cognitive function(90). Exercise has consistently been shown to have a positive effect on the structure and function of the hippocampus. It promotes neurogenesis, synaptic plasticity, and the release of various growth factors and neurotrophins that support hippocampal health (91). FNDC5/irisin has been proposed as a potential mediator of these exercise-induced effects on the hippocampus.(92)

While the exact mechanisms and specific effects of FNDC5/irisin on the hippocampus are still being elucidated, it is clear that exercise has multiple benefits for hippocampal health and cognitive function. Regular exercise is associated with improved memory, increased neuroplasticity, and reduced risk of age-related cognitive decline and neurodegenerative diseases.(92)

5 CONCLUSION

Irisin, which is expressed in plasma and in the hippocampus due to physical exercise that depends on the type, intensity and duration of exercise, functions in the brain. improve cognitive and prevent degenerative diseases dan sebagai neuroprotective.

SUGGESTION

The need for further research on irisin receptors in hippocampal neurons

ACKNOWLEDGMENTS

This work was supported by funding from the Research Fund Management Institute (LPDP) from the Indonesian Ministry of Finance, located in the Danadyaksa Cikini Building. Jl. Cikini Raya No. 91 Jakarta Indonesia.
AUTHOR CONTRIBUTIONS

Conceptualization, investigation, formal analysis and writing of the manuscript: Upik Rahmi. Conceptualization, investigation and data curation: Hanna Goenawan Investigation, validation and writing the draft of the manuscript: Upik Rahmi, Hanna Goenawan, Nova Sylviana, Setiawan, Hamidi Ronald Daniel Ray. Conceptualization, formal analysis and critical revision of the manuscript: Upik Rahmi. All authors reviewed and approved the final version of the submitted manuscript.
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