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ORIGINAL ARTICLE

The Effects of Irisin Hormone and the FNDC5 Gene on Brain Functions and Exercise: A Systematic Review

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ABSTRACT

Introduction: The aim of this systematic review was to regroup all systematic reviews, non-systematic reviews and all original articles between 2017 and 2021 (including June) into one convenient publication that would facilitate the theoretical and applied scientific investigations directed on the efficacy of exercise and brain function on irisin hormone and FNDC5 gene.

Evidence Acquisition: The systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) method. A computer-based systematic search was conducted in July 2021 through Google Scholar, Pub Med, and Science Direct databases. The reliability of the systematic research was ensured by completely repeating the article selection process by a second author.

Evidence Synthesis: Twenty-six articles that met the criteria out of 279 articles obtained specifically for keywords were included in the review. Results show that together with different types of exercise, irisin and FNDC5 may be new biomarkers that should be considered in reducing neurodegenerative disorders and improving neuromuscular and brain functions.

Conclusion: Based on the articles included in this review, increasing the number of studies examining the potential of short and long-term exercises to stimulate irisin and FNDC5 gene in the future may help to understand the effects of exercise on Irisin and FNDC5 mediated brain functions.

Keywords: Irisin, FNDC5, exercises.

INTRODUCTION

Physical inactivity is recognized as a global health problem and ranks as the fourth-highest behavioral risk factor for death on a global scale. Adults should engage in at least 150 minutes of moderate or 75 minutes of vigorous physical activity (PA) or exercise every week, according to the World Health Organization (WHO). The other recommendation is to engage in muscle-strengthening activities twice a week and to limit inactivity [1]. Regular physical activity or exercise practices have been shown to reduce the risk of over 20 chronic diseases, including coronary heart disease, stroke, type 2 diabetes, certain types of cancer, mental health problems such as obesity and depression, and some neurological conditions such as dementia. Additionally, it has been reported that it can greatly lower the risk of disease and improve overall well-being and quality of life [2–4].

Sedentary behavior has become a widely known fact that is detrimental to not just general health but also to the brain [5,6]. Sedentary behavior, which is a risk factor in and of itself, has been linked to cognitive impairment [5–7]. Additionally, it is unclear how physical activity and sedentary behavior effect early brain function changes. Physical inactivity and sedentary behavior have been linked to structural brain alterations such as neurodegeneration and cerebral small artery disease, and there is a definite link between the variables [7–9]. While atrophy and cerebral microvascular disease are almost certainly irreversible, new indications of early reversible brain changes may be present in individuals as concerns [8]. Physical inactivity is a known global public health problem that is increasing in prevalence and has a harmful effect on disease patterns everywhere. Inactivity increases the risk of developing chronic diseases such as type II diabetes, osteoporosis, cancer, and cardiovascular disease, which are the leading causes of morbidity, mortality, and health resource usage worldwide. Sedentary behavior reduction is estimated to reduce the burden of non-communicable diseases such as coronary heart disease, type 2 diabetes, breast and colon cancers by 6% to 10% globally and increase life expectancy [10–12]. One distinction between physical inactivity and physical activity is that physical activity has an effect on the process of myelination. Myelin is a substance that surrounds the axons of neurons and enables the transmission of electrical signals throughout the central nervous system to be efficient. In general, as gray matter in the brain expands, the myelination process might begin as a result of the production of new axons [11]. However, myelination is a complex process that is also related to the number of neurons that fire. In other words, when a movement is made, impulses are delivered down the axons, and when the number of impulses along the same path increases as a result of repeated movements, more myelin is generated. Thus, the signaling between brain areas is faster, and the brain can perform this movement with less energy. However, this system is present in all muscular and cognitive functions that might be linked to the decision-making process, a critical talent in a variety of sports. A myelination mechanism also results in an increase in decision-making efficiency. If nerve transmissions between brain regions are more effective and faster, athletes can make judgments faster than their competition [12]. Increased sympathetic nervous system activity is believed to contribute to the development and progression of cardiovascular disease. Recent research indicates that physical activity versus rest modifies the architecture of neurons in brain regions related with cardiovascular control. In a study of the rostral ventrolateral medulla of the brain, which influences blood vessel activity, blood pressure, and risk of heart disease, researchers report that

in physically inactive individuals, a number of additional branches, such as tentacles, sprout to aid neurons in connecting with one another. Regardless of how favorable this condition appears, it has been noted that unnecessary neuron terminals in this portion can result in an overactive sympathetic nervous system, resulting in hypertension and heart disease [13]. When arranging exercise routines, it is well established that intensity has a substantial influence on the organism, and it is reported that one of the most critical parts of many training designs is the process of selecting the training's intensity [14]. Because the organism develops endochronological physiological adaptations in response to external stressors [15]. These evolving modifications frequently have a direct impact on performance. In terms of exercise's effect on brain functions, it has been reported in the literature that it can benefit in neural and memory development in the dentate gyrus of the hippocampus, enhance learning abilities, act as an antidepressant, protect against age-related mental disorders such as Alzheimer's or dementia, and benefit in the formation of new neurons in the brain region [16–19]. Physical activity has an effect on the development of neural pathways, which result in physical development. Neuromuscular pathways are physiologically and anatomically connected with exercise. Exercise-induced changes occur in neuromuscular pathways' presynaptic and postsynaptic components. Exercise increases presynaptic nerve terminal branching and the number of vesicles containing more postsynaptic receptors structurally [20]. FNDC5 is highly expressed in a variety of brain areas, including cerebellar Purkinje cells, the hypothalamus, and the hippocampus [21–23]. Additionally, Western blot and mass spectrometry are used to determine the presence of irisin in human cerebrospinal fluid [24]. FNDC5 levels increase during the development of neural cells produced from human embryonic stem cells into neurons [25]. FNDC5 is also abundant in the heart and oxidative skeletal muscle [23]. Not only in skeletal muscle but also in numerous sections of brain tissue, FNDC5/irisin was discovered to be highly expressed. Irisin is a novel hormone-like myokine that is released from skeletal muscle during exercise. It is named after the Greek goddess Irisin (the messenger of the gods). This 112 amino acid peptide is cleaved from the fibronectin type III domain-containing protein 5 (FNDC5) [26]. Since its discovery in 2012, this molecule has garnered considerable attention as a potential modulator of physical exercise's health-promoting effects [27]. Exercise stimulates the expression of the FNDC5 gene in skeletal muscle, which results in an increase in circulating irisin [28]. Similarly, it has been observed that endurance exercise increases FNDC5 expression in the hippocampus. FNDC5 overexpression in the liver results in a substantial increase in the circulating irisin. The alteration of the blood iris appeared to be connected with a significant increase in BDNF and other neuroprotective gene expression in the hippocampus [29]. Irisin has been suggested to work as a neurotrophic factor, promoting the survival, maintenance, and function of neuronal cells [30]. Exercise strengthens synapses by enhancing the PGC-1/BDNF pathway (muscle/brain) via circulating irisin signaling. Irisin has neuroprotective and antidepressant properties. Exercise's neuroprotective effects are enhanced by the antioxidant properties of dissociative protein-2 (UCP2), which is produced at higher quantities in neurons during exercise. Thus, it supports a function for irisin/UCP2 in the mechanism underlying the central nervous system impacts of physical exercise. As a result, irisin/UCP2 promotes the enhancement of cognitive function. It may be a target for the prevention or treatment of neurological and neurodegenerative illnesses [31]. Additionally, because irisin is an activity-stimulated hormone (or myokine), it is unknown if irisin is responsible for the central nervous system (CNS) advantages associated with physical exercise. Irisin is a 112 amino acid peptide that is released into the bloodstream in a PGC-1α-dependent way via a muscle contraction-mediated transcription mechanism from the glycosylated type I membrane protein FNDC5 [27]. In addition, Irisin, BDNF, PGC1α and FNDC5 is also described in Table 1.

Table 1: Hormones affecting brain functions

Irisin	The concentration level of the central irisin plays a role in the regulation of neural differentiation and proliferation, neurobehavior, energy expenditure and cardiac function. Elevated peripheral irisin level stimulates hippocampal genes related to neuroprotection, learning and memory [30].
BDNF	BDNF can affect memory through BDNF-induced changes in membrane receptor expression and translocation, as well as activating several pathways (PLC-y, PI3K, ERK) that act together to facilitate cellular effects influencing synaptic plasticity [32].
PGC1α	PGC1α is a highly conserved coactivator of transcription factors that protect neurons against destruction [33].
FNDC5	FNDC5 is expressed in many regions of the brain, including cerebellar Purkinje cells, hypothalamus, and also hippocampus [34].

PGC-1α functions as a transcriptional coactivator and does not directly bind to DNA; it must interact with another transcription factor in order to promote neuronal FNDC5 gene expression [35]. Numerous evidence indicate that PGC-1α' s binding partner is nuclear estrogen-related receptor alpha (ERRα) [36]. Additionally, in a positive feedback loop, irisin boosts PGC-1α expression in the hippocampus and prefrontal brain of mice [37]. It is hypothesized that the irisin travels through the bloodstream in vesicles containing other components such as proteins, miRNA, and nucleic acids until it reaches target tissues such as adipose tissue and the brain [38]. The release of peptides and nucleic acids by skeletal muscle during exercise (together referred to as 'exercises') contributes to systemic biological changes [38]. Wrann et al. (2013) discovered that two weeks of exercise on exercise wheels increased FNDC5 expression in hippocampal neurons. Additionally, increasing FNDC5 expression enhanced the expression of genes encoding BDNF, Arc, cFos, and Zif268, all of which are triggered by neural activity. FNDC5 expression is counterbalanced by BDNF expression in a negative feedback system [23]. This feedback mechanism may represent a CNS training approach that requires continuous exercise to maintain its neurological benefits. This research suggests that FNDC5 activation is a component of the transcriptional response to exercise in the central nervous system, including

neuroplasticity and neuroprotection. By stimulating the Akt and ERK1/2 signaling pathways, exercise-induced irisin has been demonstrated to protect neurons from ischemia-induced damage in mice [39]. Additionally, exercise-induced irisin has been demonstrated to reduce the size of brain cerebral infarction, neurological deficits, brain edema, and body weight loss in mice with middle cerebral artery occlusion [40]. Irisin may be crucial for neuronal survival following cerebral ischemia.

Evidence Acquisition: The purpose of this study is to conduct a systematic review of the irisin hormone and the FNDC5 gene in order to determine the association between brain function and acute-chronic exercise. The current systematic review was conducted to identify using the findings of previous studies (studies that had ethical approval) conducted by the authors of the article. As a consequence, this study does not require ethical approval. This systematic review was conducted in accordance with Prisma's principles. The Prisma is a checklist with 27 items and a four-phase flowchart. According to Prisma, the first 11 items were found to be sufficient and should be followed in the preparation of this systematic review. The title, abstract, and introduction all contain the first 1-4 items of the Prisma directive. The Prisma directive's items 5 to 11 were incorporated into the contribution of this review's methodological model [41].

Prisma-Item 5: Protocol and Registration: There is no record of the present systematic review.

Prisma-Item 6: Eligibility Criteria: The following criteria were used to assess eligibility for this study: (1) Research involving FNDC5 and Irisin, as well as the brain and exercise. (2) Prospective cohort studies and systematic reviews of FNDC5 and Irisin that shed light on the mechanisms underlying the brain-exercise relationship. (3) Randomized control group studies and pretest-posttest investigations evaluating the effects of acute, chronic, aerobic, and anaerobic exercise on the levels of irisin and FNDC5. (4) Articles published in the period from 2016 to 2021. (5) Human and rat/mouse studies.

Prisma-Item 7. Information Resources: Between April and July 2021, the electronic databases Pubmed, Google Academic, and Science Direct were scanned for their products in order to improve consumer intent and competence.

Prisma-Item 8. Literature Search: The electronic databases Pubmed, Google Scholar, and Science Direct were searched for items relevant to the study using the terms "FNDC5 and brain", "Irisin and brain", "Irisin and exercise", and "FNDC5 and exercise".

Prisma-Item 9. Study Selection: Using the inclusion criteria outlined above, the titles and full texts of studies in the indicated databases were individually searched in a non-blind fashion by one person (ÖE). The researcher generated a table with the term "environment" in the title and kept track of the search results. The author assessed independently which papers were appropriate for the study's purpose. Comparing the selected articles resulted in the creation of a new list. The final choice was taken after obtaining the complete text for the verification category articles. Studies that were excluded following a full-text examination were classified as excluded studies, with the grounds for exclusion specified (studies written in different languages and conducted in different fields were excluded).

Prisma-Article 10. Data Collection Process: The author of this review collected data and inferred conclusions. The necessary Pub Med articles were emailed to the researcher's e-mail address via the database's "E-mail" section, and the articles were recorded in Word format. The articles were converted to Word format by examining the text of the studies in the Science Direct and Google Scholar databases and converting them to author, title, abstract, reference, and doi number. Additionally, the computer environment stored the complete texts of all articles.

Article 11. Data Items: The following information items were extracted from each publication that met the eligibility criteria of the study and were included in the study and were reviewed within the article:

1 In research evaluating the link between FNDC5 and exercise-induced brain activities: (a) the article's authors and publication year. (b) sample population (mean age, gender). b) regimen for exercise (content, duration, type and intensity of exercise). (d) exercise's influence on FNDC5.

2 Research evaluating the association between irisin and physical activity and cognitive function: (a) the article's authors and publication year. (b) sample population (mean age, gender). b) regimen for exercise (content, duration, type and intensity of exercise). (d) the Irisin's response to exercise.

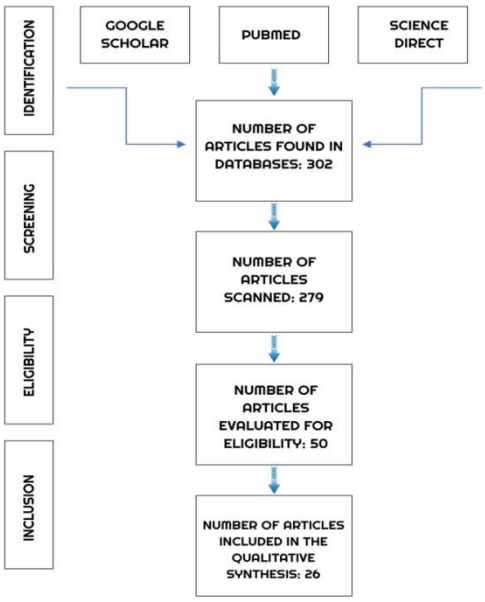

Figure 1: Prisma flowchart of review with literature search and number of articles included and excluded in the selection process

Evidence Analysis: Figure 1 describes the flowchart of the procedure used to identify articles relevant to the review's objective. A total of 302 studies were located through the use of databases such as Google Scholar, Pubmed, and Science Direct. After evaluating the abstracts and contents

of the 302 papers obtained, it was decided that 185 of them did not match the review's qualifying criteria. A total of 50 papers that satisfied the inclusion criteria were included in the systematic review, as 23 of the remaining 117 publications were not in other languages (Chinese, Russian, etc.) or involved the interaction between FNDC5 and Irisin and exercise and the brain (Figure 1).

The study reviewed nine papers on the influence of FNDC5 and irisin on neurodegenerative illnesses; 10 reviews on FNDC5, irisin, and the effects of exercise on brain functions; and seven reviews that were appropriate for this material.

DISCUSSION

Recent studies have shown that FNDC5 and irisin levels fluctuate in response to exercise and can impair cognitive functions [42–44]. The expression of the hippocampal FNDC5 protein was found to be significantly lower in aged control rats than in young control, young exerciser, and old exerciser rats ($P < 0.05$). These findings imply that cognitive dysfunction associated with aging is connected with decreased hippocampus expression of PGC-1, FNDC5, and BDNF, and that exercise can restore cognitive performance by activating these genes and proteins. Exercises, whether voluntary or mandatory, have been shown to increase hippocampal-dependent spatial learning and memory in mice [44,45]. Voluntary running has been shown to increase neuronal re-sprouting in the entorhinal cortex [44] and synaptic formation and function, perhaps via the transcription factor metastasis suppressor 1-like (Mtss1L) activity in the dentate gyrus [46]. Neuroimaging studies in older adults have revealed that exercise enhances hippocampus volume and boosts the functional connectivity of the putative mode network [44,47]. Belviranli and Okudan (2018) demonstrate that aging-related cognitive dysfunction is connected with decreased hippocampus expression of PGC-1, FNDC5, and BDNF, and that exercise can restore cognitive performance by activating these genes and proteins. Belviranli and Okudan (2018) discovered that exercise improves cognitive functions in the hippocampus by activating the FNDC5 and BDNF genes and protein expression [42]. Belviranli et al. (2016) found that sedentary athletes' cognitive performance and circulating BDNF and irisin concentrations were higher than those in the control group, and that there was a positive correlation between cognitive performance and BDNF and irisin [43]. Irisin, a myokine secreted by skeletal muscle in response to exercise, has protective functions in both the central and peripheral neurological systems, including the control of brain-derived neurotrophic factors. Irisin, in particular, is capable of protecting the hippocampus. Given that this region of the brain is particularly sensitive to Alzheimer's disease (AD), such a favorable effect may help prevent or delay the beginning of neurodegenerative disorders such as AD. Additionally, it has been discovered that factors involved in irisin production decrease A aggregation, a pathogenic characteristic of AD [48]. According to Kim and Kim (2018), aquarobic exercises increase serum irisin and BDNF levels, suggesting that they may be beneficial in avoiding degenerative brain illnesses and increasing cognitive performance in older women [49]. Uysal et al. (2018) showed that rats that engaged in voluntary aerobic exercise on a regular basis had reduced levels of anxiety. Irisin is a myokine generated by a variety of tissues in response to exercise; its involvement in anxiolytic behavior is unknown. According to certain reports, the decrease in anxiolytic behavior associated with regular voluntary exercise may be due to locally produced brain irisin. Six weeks of continuous and intermittent exercise increases PGC-1/FNDC5/BDNF protein expression in the male rat hippocampus, and while intermittent exercise raises PGC-1 and FNDC5 more than continuous exercise, anxiety- and depression-like behaviors are found to improve. Three weeks of chronic unexpected stress following exercise has been shown to decrease PGC-1, FNDC5, and BDNF protein levels and behavioral scores [50]. Tsai et al. (2021) showed that when compared to high-intensity interval training, moderate-intensity continuous exercise (MICE) improved working memory accuracy (HIIT). Following HIIT, a substantial increase in irisin levels was found. Acute high-intensity interval training (HIIT) and MICE have been shown to have distinct impacts on neurocognitive and molecular parameters [51].

CONCLUSION

When research are evaluated, it is discovered that no studies have been conducted on the effects of individual and team sports on irisin, FNDC5, and brain functions. Additionally, it is critical to do studies exploring the impact of various types of exercise on neurodegenerative illnesses in order to close the gap in the literature. Additionally, water activities have been shown to benefit the prevention of neurodegenerative illnesses. Other reviewed studies have described the impact of irisin and FNDC5 on neuronal conduction pathways in the brain and how they work. Irisin is a newly found hormone that was identified in 2012. The majority of investigations have concentrated on the conversion of this hormone and FNDC5 from brown to white adipose tissue. There are relatively few studies evaluating the effects of irisin and FNDC5 on neurodegenerative illnesses and brain functions. When research are evaluated, it is discovered that no studies have been conducted on the effects of individual and team sports on irisin, FNDC5, and brain functions. Additionally, it is critical to do studies exploring the impact of various types of exercise on neurodegenerative illnesses in order to close the gap in the literature. Aquatic workouts have been shown to be beneficial in the prevention of neurodegenerative disorders. Other research investigated the influence of irisin and FNDC5 on neuronal conduction routes in the brain, as well as the mechanism through which this effect was seen. It is critical, however, to duplicate these research using a variety of different sorts of exercises, with a variety of different volunteer groups, and at various times. It is critical to study this topic further in future research.

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