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Review

From Exercise to Cognitive Performance: Role of Irisin

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Featured Application: Aerobic exercise has a significant impact upon cognitive function in aging, and the FNDC5/irisin system exerts an interesting role as an important exercise-related factor acting on the aging brain. Its functions are dependent on irisin of peripheral origin or by its direct expression in the CNS, both of which are induced by physical exercise. The therapeutic potential of exercise-linked irisin is very relevant, and could be very useful in preserving cognitive performance, and in improving treatment of neurodegenerative diseases.

Abstract: The beneficial effects of exercise on the brain are well known. In general, exercise offers an effective way to improve cognitive function in all ages, particularly in the elderly, who are considered the most vulnerable to neurodegenerative disorders. In this regard, myokines, hormones secreted by muscle in response to exercise, have recently gained attention as beneficial mediators. Irisin is a novel exercise-induced myokine, that modulates several bodily processes, such as glucose homeostasis, and reduces systemic inflammation. Irisin is cleaved from fibronectin type III domain containing 5 (FNDC5), a transmembrane precursor protein expressed in muscle under the control of peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α). The FNDC5/irisin system is also expressed in the hippocampus, where it stimulates the expression of the neurotrophin brain-derived neurotrophic factor in this area that is associated with learning and memory. In this review, we aimed to discuss the role of irisin as a key mediator of the beneficial effects of exercise on synaptic plasticity and memory in the elderly, suggesting its roles within the main promoters of the beneficial effects of exercise on the brain.

Keywords: irisin; FNDC5; PGC-1α; BDNF; physical exercise; brain; cognitive function; memory

1. Introduction

Physical activity refers to body movement that is produced by the contraction of Skeletal Muscle (SkM) and that increases energy expenditure. It includes activities in the workplace (e.g., typing), around the house (e.g., household chores, such as cleaning) and during leisure time (e.g., walking, swimming, dancing, cycling).

Several studies showed a relationship between physical and mental health and Physical Exercise (PE). PE is known to slow down the process of age-relatedneurodegeneration, and existing hypotheses suggest that PE represents a potential adjunctive treatment for cognitive impairment. Regular physical activity can modulate the potential risk factors of dementia and other neurodegenerative disorders, such as Alzheimer's disease (AD) and/or Parkinson disease (PD) [1].

Recently, a meta-analysis considered evidence on the safety and efficacy of PE as an additional therapeutic intervention for the quality of life, cognition, and depressive symptoms across several chronic brain disorders. Silverman and Deuster (2014) suggested that regular physical activity affects the following biological pathways: (i) optimization of neuroendocrine and physiological responses to psychosocial and physical stressors; (ii) action as a buffer against stress and stress-related diseases/chronic diseases; (iii) promotion of an anti-inflammatory state; and (iv) enhancement of neuroplasticity and growth factor expression [2].

PE exerts these effects by influencing various molecular pathways and myokines; through autocrine, paracrine, and endocrine mechanisms [3–6]. In this regard, myokines are released in response to variation in muscular contraction following exercise of different intensity, mode, and volume. Some myokines may be anabolic and have direct growth-promoting effects, while others generate signals that may mediate some of the health benefits of PE. In 2012, a new myokine expressed through the activation of transcription factor Peroxisome proliferator-activated receptor Gamma Co-activator-1α (PGC-1α) by exercise-induced effects, was discovered. The newly identified molecule has been called "irisin" and has been defined as a communicator between the SkM and adipocytes, and thus a potential bearer of positive effects of PE on other target tissues outside the muscle [7].

Irisin is cleaved from fibronectin type III domain containing 5 (FNDC5), a transmembrane precursor protein expressed in muscle under the control of PGC-1α. FNDC5 is also known to be profoundly expressed in many regions of thebrain, including cerebellar Purkinje cells, the hypothalamus, and the hippocampus, a region of the brain involved in memory and spatial awareness [7–12].

Previous work suggested that irisin may be responsible for the PE effect in some rodent models of neuropathological conditions, including cerebral ischemia and depression [13,14]. Furthermore, the overexpression of irisin and FNDC5 were associated with neuroplasticity, asthey may modulate neuronal proliferation [15], differentiation [16], and neurotrophin synthesis [8], conferring neuroprotection against amyloid peptide 1–42 (Aβ1–42) in mice [17], and having an antidepressant-like effect in rats subjected to unpredictable mild stress [13].

Similarly, to PE, the peripheral delivery of FNDC5 to the liver, via adenoviral vectors (resulting in elevated blood irisin levels), induced the expression of brain-derived neurotrophic factor (BDNF) and other neuroprotective genes in the hippocampus of mice [8]. In line with these results, the neurotrophin BDNF plays an important role in the homeostatic function and survival of the neurons; particularly in synaptic plasticity and neurogenesis. Decreased levels of BDNF have been identified in serum, as well as in hippocampal and cortex samples of AD and PD patients [18,19].

Since its discovery, irisin has been the subject of extensive research, which has enabled several insights to be gained about its pleiotropic properties. The role of irisin on memory and cognitive performance has been studied only recently, particularly during the last 5 years. Given the rising significance of irisin as a mediator of the beneficial effects of PE, in this review, we providean update onthe literature focusing on the relationship between FNDC5/irisin system and cognitive functions.

2. Cognitive Functions Memory and Aging

During the last decade, the aging brain has been at the center of intensive research. The cognitive domains represent the more important elements of studying the aging brain. It is encouraging that several studies have suggested that specific environmental factors can increase the brain plasticity in all ages of life, opening up the possibility of

definite intervention to maintain the cognitive performance in older adults. In particular, cognitive stimulation and regular PE have been successfully related to improvement in brain plasticity [20,21]. However, age-related cognitive decline continues to occur, including in the deterioration of memory [22].

Memory enables the storage and recovery of data in order to adapt to environmental stimuli. In 1968, Atkinson and Shiffrin suggested the "modal" model of memory, in which memory was characterized by (i) sensory store, (ii) short-term memory (STM), and (iii) long-term memory (LTM). Therefore, memory has the capacity to archive the sensory inputs. Furthermore, through STM, memory can archive and use data for a brief period. STM is also defined as primary or active memory, and comprises different memory systems. LTM permits us to collect an indefinite amount of information for an indefinite time [23,24].

The anatomic side of memory is mainly situated in the hippocampus [25]. It is a neural structure with complex efferent and afferent connections with various brain cortices, that exerts a fundamental role in learning [26]. Consequently, STM and LTM are archived mainly in the hippocampus, but also in other cortex regions. This memory network allows us to more rapidly understand environmental stimuli, planning and acting adaptive responses. The brain can create new memories to learn more and/or use previous memories to inform behavior [27–29].

Recent studies have shown that functional and morphological changes occur in parallel in the aging brain, most importantly at hippocampal and pre-frontal cortex levels [30]. At present, numerous interventions have been proposed to ameliorate the deficit in memory and slow down the acquirement of mild cognitive impairment or dementia. Withinthese multifactorial interventional factors, approaches include stress reduction (e.g., meditation), diet regimen, and regular PE [31]. PE has been described as having particularly beneficial effects. In fact, regular PE helps to prevent serious diseases including diabetes, cancer, cardiovascular and neurodegenerative diseases. Moreover, PE can improve mood, quality of sleep and reinforce immune response [32–37].

Older adults are characterized by significant atrophy of grey and white matter primarily in the hippocampus and pre-frontal cortex. PE is associated with improvement of cardiorespiratory fitness and reduced loss of grey and white matter in the temporal, frontal and pre-frontal regions [38]. At cellular and molecular levels, PE increases neurogenesis, cerebral plasticity and synaptogenesis in the hippocampus. In these processes, PE acts on the expression and release of BDNF downstream, improving cerebral oxygen uptake, and in turn, enhancing memory formation [39]. Also, PE has been shown to promote memory by increasing dopaminergic activity in the basal ganglia [40].

Several studies support the hypothesis that a multifactorial approach is more effective in counteracting aging related memory decay. The combination of PE and mental exercises is more effective in improving cognitive function in the healthy elderly with respect to treatment with one stimulus alone. Specifically, the application ofa combination of home-based PE and digitalized cognitive stimulation for 16 weeks ameliorated the performance of verbal episodic memory [41]. Additionally, elderly who were submitted to a combined intervention for 12 weeks showed higher levels of improvement in executive and memory functions [42].

The mechanisms by which PE exerts its positive effects on health are numerous, howeverthe expression and release of myokines represent one of the most important. In 2007, Pedersen and coworkers were early proponents of the idea that SkM releases a largenumber of molecules, which werenamed myokines [43]. Some years after this, the same authors suggested a new model in which SkM is a secretory organ, synthesizing and secreting myokines in response to muscle contraction. The main function of these factors is to regulate the muscular function and metabolism [44]. Subsequently, myokines have been increasingly recognized as a protective element against the negative effects of physical inactivity and physiological aging. The most important myokines include acid β-aminoisobutyric acid, BDNF, decorin, fibroblast growth factor-21, follistatin-like

protein-1, insulin-like growth factor-1, irisin, leukaemia inhibitory factor, meteorin-like, myonectin, myostatin, and immune mediators IL-4, IL-6, IL-7, IL-8, and IL-15 [45,46].

The myokines act at a systemic level, exerting specific roles in different organs and tissues, including modulatory activity of the central nervous system (CNS) [47]. Many of the protective effects of PE on CNS are facilitated bycomponents of the neurothrophin family, particularly BDNF. As ascertained by studies on animal models, it acts in a paracrine or autocrine manner on energy balance, improving insulin signaling, regulating motoneuron survival, playing an essential role insynaptic plasticity, neuronal survival and differentiation [48–50]. Inhumans, several studies on healthy subjects suggested a significant association between PE, peripheral levels of BDNF, cognitive performance, and the volume of the hippocampus [51–53]. Growing evidence is accumulating on the pleiotropic functions of irisin, and on its precise mechanism of action in the brain. However, evidence regarding the correlation between PE and irisin effects at a systemic level, as well as the association between irisin response and cognitive functions in older populations, is still limited. In the following sections, we describe irisin structure and expression, and speculate on its role in contributing to cognitive performance improvement by PE.

3. Irisin

3.1. Irisin Structure

About 20 years ago, two independent groups identified FNDC5 as a protein exerting a role in the differentiation of myoblast. These first findings suggested that the gene was highly expressed in the SkM, but also in cerebral and cardiac tissues [54,55]. Human FNDC5 is a type I membrane protein of 212 amino acids (aa). The N-terminal is a signal sequence needed for final maturation and cleavage, the C-terminal is the cytoplasmatic domain, and in the middle there is a fibronectin III (FNIII) domain, an unknown domain, and a hydrophobic transmembrane domain [7,56,57]. The irisin represents the segment of FNDC5 that is cleaved under stimuli such as PE or cold. The portion contains 112 aa, formed by the residues from 29 to 140, including the tail at the C-terminus, the central FNIII domain, and the tail at the N-terminus [7,57]. The resulting peptide is characterized by a molecular weight of 12 kDa, and is dimerizing through the FNIII domain [56]. The irisin undergoes post-translational modification by N-glycosylation at two different residues. This modification, in addition to dimerization, determines a molecular weight reaching 35 kDa. The protein stability and the irisin secretion are regulated by the N-glycosylation. The process is strictly dependent on the presence of the signal peptide at the N-terminal, and is important for the irisin activity. The loss of glycosylation does not allow irisin to exert its main function in the browning stimulation of white adipose tissue (Figure 1) [58].

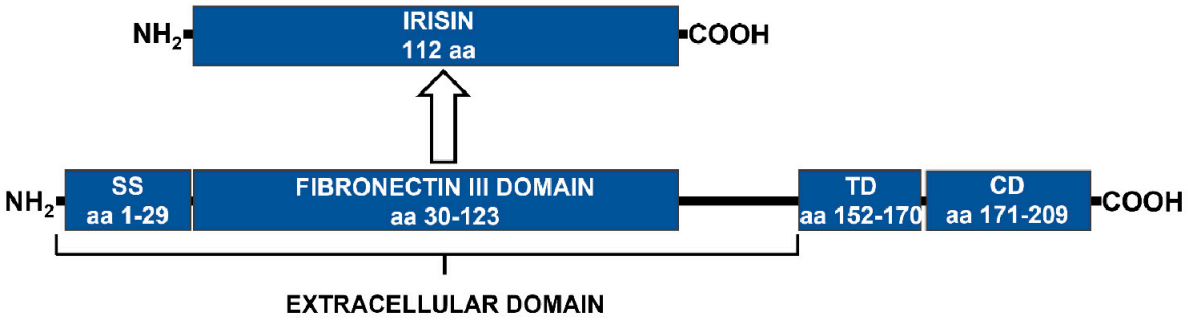

Figure 1. FNDC5/Irisin structure. Schematic structure of FNDC5. CD: Cytosolic Domain; FNDC5: Fibronectin type III Domain Containing 5; SS: Signal Sequence; TD: Transmembrane Domain.

In contrast to rodents, the human FNDC5 gene has an ATA as a start codon instead of ATG, generating a transcript that results in a very low efficiency of translation [59]. More recently, Albrecht et al. (2020), identifying other non-canonical start codon, suggested that in SkM there are several transcripts for the human FNDC5 gene [60]. Studies on

transcriptome profiling through RNA-sequencing (RNA-Seq) by the Functional Annotation of the Mammalian Genome/Genotype-Tissue Expression Project, established that the FNDC5 gene is mainly expressed in SkM, the heart, and several regions of the brain, mainly in the cerebellum, but also in hippocampus, cortex, and medulla oblongata [61].

A receptor for irisin has not yet been identified. The only evidence is provided by an interesting study by Kim et al. (2018), whichshowed that this myokine exerts its biological function by binding the integrins' family of proteins. The integrins are ubiquitously expressed transmembrane receptors, consisting of eighteen α- and eight β-subunits, forming a total of 24 different heterodimers able to recognize also soluble ligands. Kim and coworkers described how the binding of irisin with the αVβ5 integrin heterodimer occurs in human adipocytes and osteocytes. Using the integrin inhibitor RGD peptide, which binds to αVβ5 in a selective manner, they also showed that any signaling response induced by irisin was significantly suppressed in these cells [62].

3.2. Irisin Functions

Bostrom and colleagues were the first to showthat irisin levels in the blood increase after PE, describing an increase of 65% in blood concentration in mice submitted to regular running for 21 days [7]. The level of irisin after PE is dependent on the type of physical activity, where training based on aerobic exercise is a higher inductor of serum irisin compared to resistance exercise [63,64].

In general, the level of irisin is influenced by lifestyle, characterized by specific residential place and associated activities, as suggested by the differences recorded between rural and urban inhabitants. Irisin concentration is lower in urban citizens, with a mean value of 3.6 ng/mL, while active individuals that live in rural areashad amean value of 4.3 ng/mL [65]. PE increases the level of irisin in the blood of healthy people [7], and in people with metabolic disorders [66]. Its circulating level is also related to the phenotype of different disease, as well obesity, type 2 diabetes [67], chronic renal disease [68] and hypothyroidism [69].

The first identified function of irisin was the "browning" of adipose tissue, in which irisin increases the expression of the mitochondrial protein uncoupling protein-1 (UCP-1) in mature fat cells, allowing the conversion of the white adipose tissue (WAT) to the brown adipose tissue (BAT) phenotype. The process ends with the formation of a third type of adipose tissue phenotype, named beige/brite adipose tissue. Irisin and PGC-1α regulate the expression of UCP-1 and thermogenesis in BAT, driving the metabolism of glucose and lipids toward the increase in energy consumption [70,71]. Furthermore, irisin is implicated in glucose homeostasis, by acting on different cell types and tissues involved in glucose metabolism, such as adipose tissue, SkM, liver, and pancreatic β cells. Due to this property, irisin is able to improve insulin sensitivity under insulin resistance (IR) conditions [72]. A decrease in irisin levels was associated with an increased risk of presenting metabolic syndrome and hyperglycemia in obese adults. This myokine shows negative associations with fasting insulin and glycosylated hemoglobin [73]. Previous studies also suggested its negative correlation with fasting glucose and HOMA-IR in school-age students of both genders [74], and positive associations with insulin concentration, fasting glucose, and HOMA-IR [66,75–77].

Irisin has other specific functions, including in the heart and liver, where it exerts antiapoptotic effects on cardiomyocytes and hepatocytes through the induction of autophagy [45], and protects cells from ischemia-reperfusion injury [78,79]. At bone level, it has a favorable effect and represents a key molecule in the crosstalk between this tissue and SkM. Specifically, irisin increases the mass and strength of the cortical bones, positively modifying their geometry by reducingthe secretion of osteoblast inhibitors, and driving the expression of bone-specific genes [80]. In immune system functioning, irisin mediates the positive effect of regular/moderate physical activity, contributing to a reduction in systemic inflammation, and consequently protecting from the development of diseases associated with chronic inflammation [81].

The functions of irisin on the brain are described in more detail in the section "Irisin: a new bridge between exercise and cognitive functions". In brief, this myokine increases the proliferation of hippocampal neuronal cells [15], and reduces the neuronal damage mediated by pro-oxidant stimuli [14]. The FNDC5/irisin system is important for long-term potentiation and memory in mouse hippocampal region, being involved in establishing synaptic plasticity and memory [82], and may contribute to the antidepressant effect of PE together with serotonin, by the activation of the PGC-1α/BDNF pathway [83].

3.3. Expression of FNDC5/Irisin

In this section, the mechanisms involved in regulating FNDC5/Irisin expression in SkM and CNS are considered. Although the expression of the FNDC5 gene occurs in several tissues both in humans and rodents, we have focused on the SkM because it represents the major source of irisin from a peripheral origin [7,66]. We also considered the expression in the brain, due to the relevant role of irisin of CNS origin on cognitive functions.

4. Skeletal Muscle

The expression of the FNDC5 gene in SkM cells is differentiated between muscle fiber types. Generally, slow type fibers show a higher expression compared to fast type fibers at rest; PE is able to induce FNDC5 expression in all type of fibers, following an expression pattern regulated by exercise type and duration. For example, in a mouse model, aerobic exercise (i.e., running wheel) induces equal expression of FNDC5 in different muscle fibers [7,84–86].

While the FNDC5 gene is expressed in different tissues, the main sources of circulating irisin are the SkM during PE, and adipose tissue. Therefore, irisin can be considered both a myokine and an adipokine [7,84]. In the SkM, irisin expression is mainly mediated by PGC-1α through its interaction with a number of transcription factors implicated in energy requirement [87–89]. These proteins can induce the expression of FNDC5 in a different manner: Yang et al. (2018) recently suggested in vitro that in C2C12 myotubes the expression of FNDC5 is modulated by the cAMP response element-binding protein (CREB) through its binding with PGC-1α [90]. It's important to remember that CREB is activated by aerobic exercise and that the signaling of cAMP activates CREB in the SkM during exercise to manage metabolic adaptation [91,92]. In addition, endurance exercise induces the expression of FNDC5 in the quadriceps via the PGC-1α/estrogen related receptor alpha (ERRa) pathway [8]. The retinoic acid (RA) is another inductor of FNDC5 expression in muscle. RA is a natural ligand for retinoid X receptor (RXR). This receptor also represents a transcription factor activated by a ligand that binds to RA responsive elements (RARE) in the regulatory sequences of genes regulated by PGC-1α [93]. The expression of FNDC5 is increased by treatment with RA in differentiated C2C12 myocytes, also in an independent manner from PGC-1α [94] (Figure 2). During PE, PGC-1α accelerates mitochondrial biogenesis and regulates the glucose/fatty acid metabolism, favoring the switch from fast to slow fiber contraction. Under this process, the increased expression and activity of PGC-1α is mediated by the increase of Ca^{2+} influx into fibers' cytoplasm [95].

Conversely, other conditions can inhibit the expression of FNDC5 in SkM. For example, FNDC5 expression is reduced by Myostatin. This myokine exerts a reverse effect to FNDC5, inhibiting the differentiation of myoblast [96], and significantly increasing the mRNA expression levels of PGC-1α and FNDC5 when it is silenced [97] (Figure 2). Comparably, the expression of PGC-1α and FNDC5 may be suppressed by the protein Mothers against decapentaplegic homolog 3 (SMAD3) in C2C12 mouse myoblasts, while in knockout Smad3 mice, aerobic exercise increases serum irisin in comparison to wild-type mice [86]. Furthermore, Varela-Rodriguez et al. (2016) showed that 48 h of fasting decreased the circulating level of irisin and expression level of FNDC5 in SkM, while the intraperitoneal injection of insulin for 2 weeks has a comparable action on FNDC5/irisin level in plasma and SkM [98].

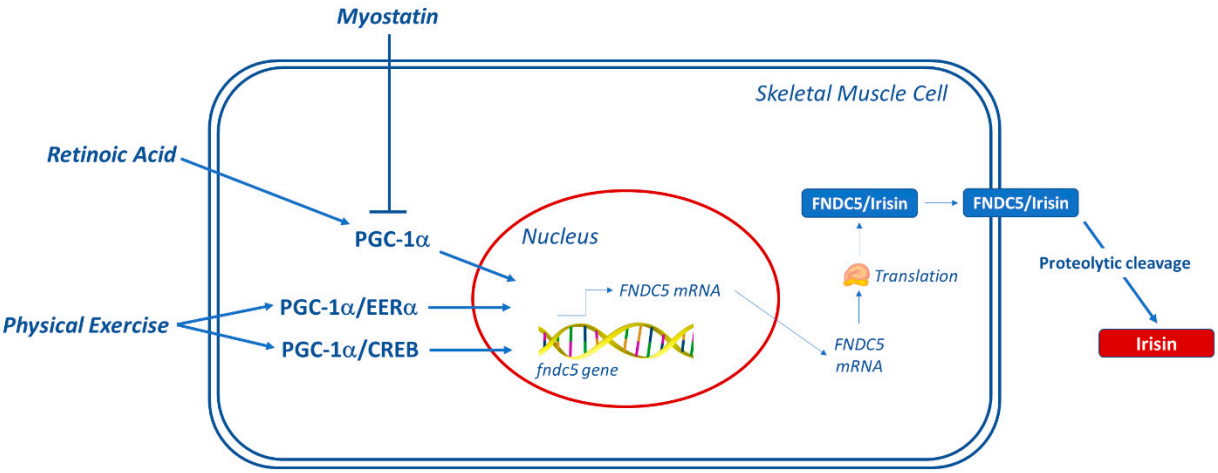

Figure 2. FNDC5/Irisin expression in Skeletal Muscle (SkM) mediated by PGC-1a. Schematic representation of irisin expression modulating factor in SkM occurring by activation or inhibition of PGC-1a. CREB: cAMP response element-binding protein; ERRα: Estrogen-related receptor α; FNDC5: Fibronectin type III Domain Containing 5; PGC-1α: PPARγ coactivator 1α.

Finally, it is worth mentioning the growing interest in the potential use of irisin as a bona fide biomarker and potential target for the complex management of sarcopenia and muscle loss even in subjects after spinal cord injury [80,99–101]. Future studies are warranted to investigate the role of irisin as a biological bridge among exercise and muscle metabolism.

5. Brain

Several studiessuggested that the FNDC5/irisin system is expressed in the brain, where its specific roles have not yet been well established. Studies on animal models showed that this expression is dependenton the region of the brain, in which irisin is expressed in ventromedial nuclei and hypothalamic arcuate in primates [102], and in cortex, hippocampus, and other areas such as the vestibular nuclei of the medulla oblongata and Purkinje cells of the cerebellum in mice [9].

The irisin expression in the CNS is regulated by several environmental, physiological and pathological conditions. Aerobic PE significantly increases the mRNA of FNDC5 in the mouse hippocampus [8,103]. Recently, Yu et al. (2020) suggested that additional stimuli, such as environmental enrichment (EE), can increase the expression of FNDC5 in the pre-frontal cortex [104], where it is useful in promoting neurogenesis and general cerebral activity, increasing the neuronal capacity to recover from wounds [105,106]. In regard topathological conditions, the expression of FNDC5 is reduced in AD patients in the pre-frontal cortex and hippocampus [107]. Nevertheless, the injection of recombinant irisin reduces stress-mediated anxiety, depression and memory disfunction in the hippocampus and/or in the lateral ventricle of rodents' model [108–110].

There is increasing evidence relating to FNDC5/irisin brain expression. Wrann et al. (2013) described that PGC-1α is responsible for FNDC5 expression induction in the primary neurons and hippocampus [8]. More recently, it was foundthat FNDC5 induction in the hippocampus is regulated by the activation of the cAMP/PKA [104], and that the hippocampal FNDC5 expression is also induced by the lactate released from SkM during PE [107]. The FNDC5 promoter has been described in the presence of an ERRαbinding element (ERRE) sited in the upstream region, where PGC-1α increased FNDC5 expression activating ERRα, and then triggered a negative feedback onto PGC-1α/ERRα in primary cortical neurons [8]. Further studies are needed to investigatethe upstream regulatory sequences of the FNDC5 promoter, in order to better define how different stimuli can influence FNDC5 expression in the brain. These analyses could clarify which binding elements are regulated by different transcription factors.

A number of studies suggested that irisin can also be endocytosed and that it exerts a role in mediating endocytosis and exocytosis. Regarding the endocytosis process, Lourenco et al. (2019) suggested that irisin bound to unrecognized receptor in CNS, particularly on the surface of hippocampal neurons and astrocytes, starting an endocytosis process [107]. In addition, the subcutaneous injection of irisin increased glucose uptake at brain level, suggesting its potential role in augmenting the endocytosis of glucose transporters [13]. Relating to exocytosis, the only evidences come from Zhang et al. (2018) showing that irisin increased insulin secretion in mouse pancreatic islet cells in response to glucose [111].

6. Irisin: A New Bridge between Exercise and Cognitive Functions

As mentioned above, irisin exerts its role at a systemic level, including the CNS [46,47]. Since 2016, several findings on irisin's impacts on cognitive functions have been made. These findings suggest that the beneficial effects of PE in counteracting memory degradationare mediated by irisin from a peripheral and central origin. In turn, the impactof irisin on cognition is to a large extent elicited by the induction of the neurothrophin BDNF.

In general, BDNF is essential for brain development due to its actions in neuronal survival, differentiation, and migration, and in exerting a role in dendritic arborization and in regulating synapse genesis and plasticity. Consequently, BDNF is fundamental for hippocampal function and learning [112–114]. It has been widely described that higher levels of BDNF have a beneficial effect on many cognitive processes, such as verbal, recognition, spatial, and episodic memory [115,116]. In humans, mutation in the BDNF gene (i.e., Val66Met) is associated with a decreased level of BDNF, with the affected subjects characterized by a higher level of mood disturbances, such as increased anxiety and depression, alterations in episodic memory, and reduced volume in specific regions of the brain [117,118].

BDNF is related to the positive effect of PE on CNS, in particular acting on the above cited neuronal survival/differentiation, and synaptic plasticity [48,49,53]. In humans, circulating BDNF was successfully associated with PE, cognitive performance and hippocampal volume [51,52]. In a several studies, Vaynman and colleagues suggested that the blockage of BDNF signaling with a specific antibody (ant-TrkB) significantly reduced the improvement in acquisition and retention during spatial memory tasks induced by PE; this inhibition was paralleled by a decrease in expression of synaptic proteins [119,120]. In accordance, other studies suggested associations between PE, circulating BDNF levels and the hippocampal volume [121,122], whose systemic decline is associated with advanced age [123].

Notably, the activation of the FNDC5/irisin system in the brain is an important inductor of BDNF. The overexpression of FNDC5 in primary cortical neurons increases BDNF expression, and in a similar manner the BDNF expression is significantly abrogated by RNAi-mediated knockdown of the FNDC5 gene [124]. An animal model showed that the irisin precursor FNDC5 could mediate beneficial CNS effects of endurance exercise by upregulating BDNF expression in the hippocampus [8]. Accordingly, the above-mentioned human polymorphism of BDNF, Val66Met, was shown to affect both BDNF and FNDC5 expression in the brain after PE [125]. Nevertheless, in a mouse model of AD, the neurogenesis mediated by PE in the hippocampus was associated with similar induction of expression of BDNF and FNDC5, facilitating improvement in cognitive functions [126]. Schnyder et al., (2015), suggested that endurance PE elevates systemic irisin levels, inducing the expression of FNDC5 in the hippocampus by PGC-1a, and leading to BDNF expression. This process culminates in neurogenesis induction in this region [127]. In two recent studies, Lourenco and coworkers investigated the relationship between the potential alteration of the FNDC5/irisin system and AD. They showed that silencing FNDC5 with specific small hairpin RNA in a mouse brain, determined the loss of long-term potential (LTP) at hippocampal level. A similar loss of LTP was induced in a model of AD obtained by injecting amyloid-β oligomers (AβOs) and causing memory and behavioral defects. The injection of the recombinant irisin in the glycosylated form was able to reverse these

processes on LTP loss and behavioral alterations. In an additional approach, the same authors used an adenovirus expressing FNDC5 into the brain, injecting AβOs after six days, and obtaining analog recovery of animals. PE also reversed the behavioral defects of the AβO injection, supporting the idea from previous data, that the induction of FNDC5 in the hippocampus was mediated by PE. The following year (2020), Lourenco and colleagues suggested a positive correlation between cerebrospinal fluid irisin and BDNF levels, and memory, during a study on AD patients and control subjects [107,128]. These findings supported earlier evidence in animals of a relationship between FNDC5/irisin-BDNF and neuroplasticity in brain, as an element of the linking pathway between PE and cognitive functions [8,15]. Nevertheless, irisin may contribute to the antidepressant effect of PE together with serotonin, via the upstream activation of the PGC-1α/BDNF pathway [83].

Altogether, these findings suggest that the brain activation of the FNDC5/irisin system could be the mediator by which PE induces neurogenesis at a molecular level, highlighting that an important association exists between irisin and BDNF [116]. See Figure 3 for a summary representation.

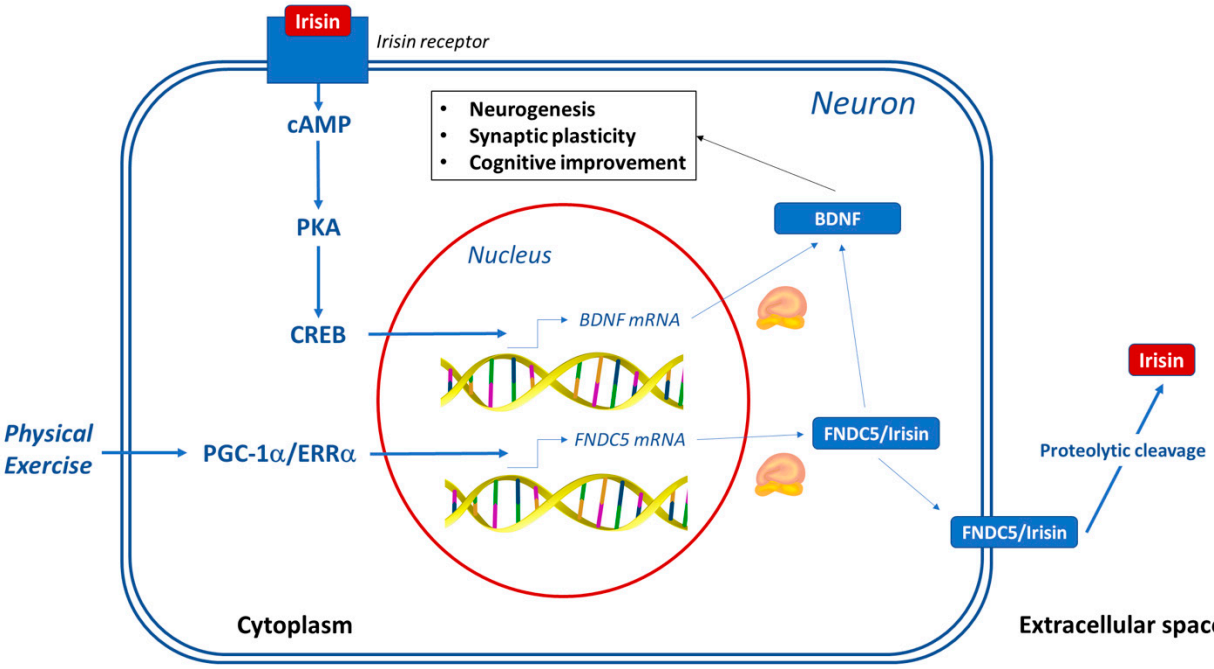

Figure 3. FNDC5/Irisin signaling in the brain. Schematic representation of irisin action on neuron. Irisin stimulates synaptic plasticity, neurogenesis and cognitive improvement by induction of expression of brain-derived neurotrophic factor (BDNF). Physical exercise further induces brain FNDC5 and irisin release. cAMP: cyclic adenosine monophosphate; CREB: cAMP response element-binding protein; ERRα: Estrogen-related receptor α; FNDC5: Fibronectin type III domain containing 5; PGC-1α: PPARγ coactivator 1α; PKA: cAMP-dependent protein kinase.

In another study, Li et al. (2017) described a role for irisin in the brain and cognitive modulation without mentioning BDNF, suggesting that irisin also has a protective effect againstadverse environmental stimuli. They described a reduction mediated by irisin of obtained neuronal damage inducing an oxidative stress condition; this beneficial effect was caused bythe inhibition of expression and secretion of canonical proinflammatory cytokines [14].

7. Conclusions

This comprehensive review has shown how the interest in the myokine irisin has grown exponentially. Aerobic exercise has a significant impact upon cognitive function in aging. The FNDC5/irisin system exerts an interesting role as an important exercise-related factor acting on the aging brain. Its functions are dependenton irisin of peripheral origin or

by its direct expression in the CNS, both of which are induced by PE. The administration of glycosylated recombinant irisin may improve cognitive function in animals, mimicking the effect of endurance exercise on specific brain regions such as the hippocampus. The physiological expression of irisin levels decreases with age, albeit irisin expression in muscle is higher in elderly high-fitness men than in elderly low-fitness men. This is not true for the young [129–132]. Thus, it is possible that the aging-induced reduction in circulating irisin level can be restored by sustained endurance training, and that this effect might be age-specific.

In the future, it will be imperative to completely bridge the gap in scientific literature on the relationship betweenexercise-linked irisin and consequences on cognition in aging, considering that the therapeutic potential of exercise-linked irisin is very relevant, and that it could be highly useful in preserving cognitive performance, and in improving treatment of neurodegenerative diseases.

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