Review

FNDC5/Irisin – Their Role in the Nervous System and as a Mediator for Beneficial Effects of Exercise on the Brain

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Abstract. Exercise can improve cognitive function and the outcome of neurodegenerative diseases, like Alzheimer’s disease. This effect has been linked to the increased expression of brain-derived neurotrophic factor (BDNF). However, the underlying molecular mechanisms driving the elevation of this neurotrophin remain unknown. Recently, we have reported a PGC-1α-FNDC5/irisin pathway, which is activated by exercise in the hippocampus in mice and induces a neuroprotective gene program, including Bdnf. This review will focus on FNDC5 and its secreted form “irisin”, a newly discovered myokine, and their role in the nervous system and its therapeutic potential. In addition, we will briefly discuss the role of other exercise-induced myokines on positive brain effects.

Keywords: Exercise, brain, cognition, FNDC5, irisin, BDNF, hippocampus, physical activity

INTRODUCTION

Exercise, especially endurance exercise, is known to have beneficial effects on brain health and cognitive function [11, 32, 53]. This improvement in cognitive function with exercise has been most prominently observed in the aging population [10]. Exercise has also been reported to ameliorate outcomes in neurological diseases like depression, epilepsy, stroke, Alzheimer’s and Parkinson’s Disease [2, 4, 6, 44, 56]. The effects of exercise on the brain are most apparent in the hippocampus and its dentate gyrus, a part of the brain involved in learning and memory. Specific beneficial effects of exercise in the brain have been reported to include increases in the size of and blood flow to the hippocampus in humans and morphological changes in dendrites and dendritic spines, increased synaptic plasticity and, importantly, de novo neurogenesis in the dentate gyrus in various mouse models of exercise [11, 32]. De novo neurogenesis in the adult brain occurs in only two areas; the dentate gyrus of the hippocampus is one of them and exercise is one of the few known stimuli of this de novo neurogenesis [26].

One important molecular mediator for these beneficial responses in the brain to exercise is the induction of neurotrophins/growth factors, most notably brain-derived neurotrophic factor (BDNF). In animal models, BDNF is induced in various regions of the brain with exercise, most robustly in the hippocampus [44]. BDNF promotes many aspects of brain development including neuronal cell survival, differentiation, migration, dendritic arborization, synaptogenesis and plasticity [19, 37]. In addition, BDNF is essential for synaptic plasticity, hippocampal function and learning [28]. Highlighting the relevance of BDNF in human, individuals carrying the Val66Met mutation in the BDNF gene, exhibit decreased secretion of BDNF, display a decreased volume of specific brain regions, deficits in episodic memory function as well as increased anxiety and depression [14, 20]. Blocking BDNF signaling with anti-TrkB antibodies attenuates the exercise-induced improvement of acquisition
and retention in a spatial learning task, as well as the exercise-induced expression of synaptic proteins [51, 52]. However, the underlying mechanism, by which BDNF is induced in exercise remains to be incompletely understood.

We recently described a role for the newly discovered “exercise-hormone” FNDC5 [5] and its secreted form “irisin” in the protective effects of exercise on the brain. Fndc5 expression is induced by exercise in the hippocampus in mice, which in turn, can activate BDNF and other neuroprotective genes [54]. Importantly, peripheral delivery of FNDC5 to the liver via adeno viral vectors, resulting in elevated blood irisin, induced expression of Bdnf and other neuroprotective genes in the hippocampus. These data indicate that either irisin itself can cross the blood-brain-barrier to induce these gene expression changes or irisin induces a factor x that can. This has significant implication for irisin as a novel therapeutic target. This review will examine previous literature about FNDC5/irisin as well as its therapeutic potential for treating neurodegenerative disease.

**DISCOVERY OF FNDC5/IRISIN**

In 2002, two groups independently cloned a novel gene that they termed either PeP or alternatively, Frp2, and that contained a fibronectin type III (FNIII) domain. Recently, our group identified FNDC5, as a PGC-1α-dependent myokine, that is secreted from muscle during exercise and induces some of the major metabolic benefits of exercise [5].

FNDC5 is a glycosylated type I membrane protein. It contains a N-terminal signal peptide (amino acid (aa) 1–28), a FNIII domain (aa 33–124), a transmembrane domain (aa 150–170), and a cytoplasmic tail (aa 171–209) (www.uniporot.org) (Schematic Fig. 1). The secreted form of FNDC5 contains 112 amino acids (aa 29–140), named irisin. It is generated by proteolytic cleavage and released into the circulation. The protease/sheddase responsible for that cleavage has not been identified, yet. Irisin is 100% conserved from mouse to human and is highly conserved across mammals. Irisin has been crystallized and its structure has been solved [45]. Interestingly, the FNIII-like domain shows an unusual confirmation with continuous intersubunit beta-sheet dimer, which has not been previously described for any other FNIII protein. Subsequent biochemical experiments confirmed the existence of irisin (bacterial recombinant) as a homodimer.

**TRANSCRIPTIONAL REGULATION OF FNDC5 EXPRESSION**

The FNDC5 gene is located on human chromosome 1 and mouse chromosome 4, respectively. *In silico* analysis by Seifi et al. suggests that the putative core promoter of the mouse Fndc5 gene ranges from –551 to +101 with respect to the transcriptional start sites and that it contains exon 1 and intron 1 of Fndc5 gene. This murine Fndc5 core promoter lacks a TATA box and is GC rich [46].

Fndc5 has been shown to be regulated by the transcriptional co-activator PGC-1α in skeletal muscle.
FNDC5/IRISIN IN EXERCISE

FNDC5/irisin were first described as an exercise-induced myokine by Bostrom et al. in 2012 [5], who observed upregulation of FNDC5 gene expression in skeletal muscle and increases in serum irisin levels after prolonged endurance exercise in mice and humans. Increasing the circulating levels of irisin by overexpressing FNDC5 from adenoviral vectors in the liver, led to increased of “browning” of the white inguinal adipose tissue, i.e. the upregulation of mitochondrial gene expression, especially of Ucp1, and to increased glucose tolerance in mice – two of the major metabolic benefits of endurance exercise. By now, there are have been around 50 papers published that investigate FNDC5 and/or irisin in exercise in rodent studies and clinical trials in humans. Induction of Fndc5 mRNA in skeletal by endurance exercise has been confirmed in several studies in mice [41, 50, 54] and humans [3, 29, 34] using QPCR or RNA sequencing. As with all clinical studies, there are a lot of variables to consider, such as retrospective studies vs. intervention trials, age and fitness level of the subjects and, most importantly, the type of exercise protocol used and time point of sampling. However, there is a consensus building that studies that reported positive associations between irisin plasma level and exercise, performed early sampling and high intensity training protocols levels [12, 22, 27, 34]. The brief rise in circulating irisin levels after exercise is suggestive of an acute shedding event of irisin during exercise. There is little or no evidence so far that FNDC5 or irisin is upregulated by resistance exercise in mice or human; which is not unexpected since endurance exercise activates a different isoform of PGC-1α than resistance exercise [43].

FNDC5/IRISIN IN METABOLISM

Initially, irisin was described as acting preferentially on the subcutaneous ‘beige’ fat and to cause ‘browning’ by increasing the expression of UCP-1 and other thermogenic genes [5, 55]. The result is increased thermogenesis and energy expenditure, with improved whole body glucose metabolism in obese mice [5]. A recent study in myostatin mutant mice suggests that the leaner body composition and reduced fat mass in those mice maybe caused by browning of the white adipose tissue by higher levels of irisin (Fndc5)
secreted from the skeletal muscle [47]. Many studies have described the relationship of FNDC5/irisin and various metabolic parameters, such as BMI, obesity, type 2 diabetes, age, or pregnancy etc. Recent reviews from Chen J.Q. et al. and Chen N. et al. nicely summarize the results of those studies [8, 9].

FNDC5/IRISIN IN NEURONAL DEVELOPMENT

*Fndc5* is highly expressed in the brain, including the Purkinje cells of the cerebellum [13, 16, 49]. Irisin, the shed form of FNDC5 was identified in human cerebrospinal fluid by WB [40]. In addition, immunoreactivity against the extracellular domain of FNDC5/irisin was detected in human hypothalamic sections, especially paraventricular neurons [40]. Other tissues with high FNDC5 levels include skeletal muscle and the heart. *Fndc5* gene expression increases during differentiation of rat pheochromocytoma-derived PC12 cells into neuron-like cells [35]. FNDC5 levels are enhanced after differentiation of human embryonic stem cell-derived neural cells into neurons [18] as well as during the maturation of primary cortical neurons in culture and during brain development *in vivo* [54].

Knockdown of FNDC5 in neuronal precursors impaired their development into mature neurons (and astrocyte), suggesting a developmental role of FNDC5 in neurons [21]. On the other hand, forced expression of FNDC5 during neuronal precursor formation from mouse embryonic stem cells increased mature neuronal markers (Map2, b-tubulinIII and Neurocan) and astrocyte marker (GFAP) and BDNF. However, overexpression of FNDC5 in undifferentiated mouse embryonic stem cells did not have these effects, indicating that FNDC5 supports neural differentiation rather than lineage commitment [17]. Pharmacological doses of recombinant irisin increased cell proliferation in the mouse H19-7 hippocampal cell line [33]. Furthermore, forced expression of FNDC5 in primary cortical neurons increased cell survival in culture, whereas knockdown of FNDC5 had the opposite effect [54].

FNDC5/IRISIN – OTHER EFFECTS IN THE CNS

The group of Dr. Mulholland had taken in interest in the central nervous effects of irisin. In a first study, they injected irisin either into 3rd ventricle of rats or intravenously and measured the effects on blood pressure and cardiac contractibility [57]. Central administration of irisin activated neurons in the paraventricular nuclei of the hypothalamus as indicated by increased c-fos immunoreactivity. Central irisin administration also increased blood pressure and cardiac contractibility. In contrast, i.v. injection of irisin reduced blood pressure in both, control and spontaneously hypertensive rats. In a second study, Zhang et al. showed that central treatment of rats with irisin-Fc led to an increase in physical activity compared to control animals receiving IgG-Fc peptide [58]. In addition, the centrally applied irisin also induced significant increases in oxygen consumption, carbon dioxide production and heat production, indicating an increase in metabolic activity- possibly through SNS activation.

EXERCISE INDUCES HIPPOCAMPAL BDNF THROUGH A PGC-1α/FNDC5 PATHWAY

In a recent study, we have shown that FNDC5 is also elevated in the hippocampus of mice undergoing an endurance exercise regimen of 30-days free-wheel running. Neuronal *Fndc5* gene expression is regulated by PGC-1α and Pgc1α−/− mice show reduced *Fndc5* expression in the brain. Forced expression of FNDC5 in primary cortical neurons increases *Bdnf* expression, whereas RNAi-mediated knockdown of FNDC5 reduces *Bdnf*. Importantly, peripheral delivery of FNDC5 to the liver via adenoviral vectors, resulting in elevated blood irisin, induces expression of *Bdnf* and other neuroprotective genes in the hippocampus. Interestingly, a recent study investigating the effects of the flavonoid quercetin and hypobaric hypoxia, reported that quercetin administration to hyperbaric hypoxic rats increased expression of PGC-1α, FNDC5, and BDNF in the hippocampus [31].

Taken together, our findings link endurance exercise and the important metabolic mediators, PGC-1α and FNDC5, with BDNF expression in the brain. While more research will be required to determine whether the FNDC5/irisin protein actually improves cognitive function in animals, this study suggest that a natural substance given in the bloodstream might mimic some of the effects of endurance exercise on the brain.

FUTURE DIRECTIONS FOR FNDC5/IRISIN IN EXERCISE AND THE BRAIN

However, this first study opens up important questions that need to be addressed in the future.
1) Can irisin itself cross the blood brain barrier? Molecules can cross the blood brain barrier either through free diffusion if the molecular weight is <400 Da and it forms <8 hydrogen bonds. However, recent studies suggest that other molecules can use either carrier- or receptor-mediated transport (RMT) through the blood brain barrier; a concept that is currently being explored by the pharmaceutical industry for drug delivery [36].

2) Does a prolonged elevation of peripheral irisin confer neuroprotective effects and can this be achieved by peripheral administration of recombinant protein? So far there have been only two studies that injected recombinant irisin either into 3rd ventricle of rats or intravenously and monitored acute effects on blood pressure or activity within minutes [57, 58]. But no chronic long-term studies using a genetic model or repeated injections have been reported. Longer term administration of irisin will also allow to evaluate the effects on synaptic plasticity and cognition.

3) FNDC5 is expressed in at highest levels in oxidative muscle, like skeletal muscle and heart, as well as the nervous tissue. Endurance exercise induces FNDC5 in skeletal muscle as well as in the hippocampus in mice [54]. Which tissue contributes to what extend to the beneficial effects of exercise on the brain? Tissue-specific deletion of Fndc5 in the skeletal muscle and the hippocampus will help to delineate the effects of skeletal muscle- vs. hippocampal-induced Fndc5 on central BDNF expression as well as on improvement of learning and memory by endurance exercise.

4) What is the identity of the irisin receptor and intracellular signaling pathways used by irisin? Finding the irisin receptor will help to identify all possible target tissues of irisin effects and therefore targeted drug development.

OTHER CIRCULATING FACTORS FROM THE MUSCLE

While FNDC5/irisin is a very interesting molecule with therapeutic promise, this is not to say that we think that FNDC5/irisin captures all the benefits of exercise on the brain or that it is the only important secreted molecule from muscle in exercise. In fact, other such molecules have been described, including BDNF, IGF-1, and VEGF, kynurenic acid, and a variety of cytokines and chemokines, to name a few [1, 39, 53]. We expect that in the future additional molecules will be discovered and that some of those will fulfill their therapeutic potential.

ACKNOWLEDGMENTS

C.D.W. was supported by a K99/R00-NIH Pathway to Independence (PD) Award (NS087096). Part of this work is funded by the JPB Foundation and NIH grants (DK31405 and DK08681) to Bruce M. Spiegelman. I thank Dr. Bruce Spiegelman for critical scientific discussions. I also thank Dr. Mark Jedrychowski for support with the art work.

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