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Potential Biomarkers for Physical Exercise-Induced Brain Health

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Abstract

Physical exercise has long been recognized as an effective and economic strategy to promote brain health in humans. The cellular and structural changes in the brains of exercised animals, including enhancements of neurogenesis and synaptogenesis, dendritic remodeling, and synaptic plasticity, have been considered as the key biological alterations accounting for exercise-elicited benefits to brain health. However, what transduces body movements into the above-mentioned changes remains largely unknown. Emerging theories indicate that physical activity triggers the release of various factors into the circulation from skeletal muscle (neurotrophins, myokines, and cytokines) and/or adipose tissue (adipokines). In this chapter, we review several of these molecules that are potentially implicated in this process, including neurotrophic factors (BDNF, IGF-1, and VEGF), adipokines (adiponectin and irisin), and myokines/cytokines (IL-15). The relationship, either causal or concomitant, between levels of these molecules (particularly in the blood) and brain function after exercise may help to identify biomarkers that can serve as objective indicators to evaluate exercise therapy on diseased or ageing brain. In addition, unmasking biomarkers may be instrumental in elucidating the mechanisms mediating exercise-induced brain health, thereby contributing to novel drug discovery for treatments to maintain brain health.

Keywords: biomarkers, brain health, cognition, hippocampal plasticity, physical exercise

1. Introduction

With an ageing population worldwide, there is an increasing interest in interventions that allow for healthy ageing. Currently, physical exercise is the best known intervention that can effectively

maintain or even enhance brain health. Physical exercise is beneficial to brain health and cognitive function, especially in elderly people [1]. Clinical studies have demonstrated that more physical activity is associated with a lower risk of ageing-related neurodegenerative disorders, such as Alzheimer’s disease (AD) [2] and Parkinson’s disease (PD) [3]. Owing to the heterogeneity of exercise *per se* (in terms of the duration, frequency, intensity, type, physical fitness, and diseased state of human subjects), it is difficult to prescribe physical exercise with optimal effects on brain health in a customized way. Therefore, more research is needed to maximize exercise-elicited benefits to counteract brain ageing. In line with this goal, identification of biological markers (biomarkers) would substantially facilitate the evaluation and monitoring of the clinical effectiveness of physical exercise therapy on brain health. This information will also help with the discovery of exercise-mimetic treatments for dealing with neurodegenerative diseases, considering that there is no commercial pharmaceutical drug that can exert preventative effects on neurodegenerative diseases in ageing brains at this moment.

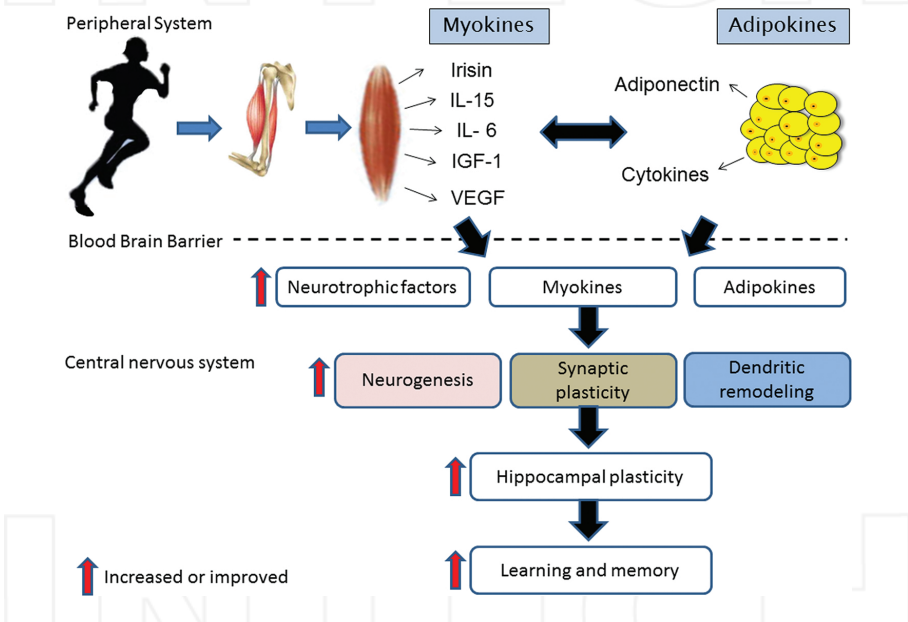


Figure 1. Exercise enhances hippocampal plasticity and hence improves cognitive performance. Physical activities promote the production and release of a variety of mediators in both central and periphery nervous systems, such as neurotrophic factors, myokines, adipokines, and cytokines. These molecules enter the brain and regulate hippocampal plasticity by affecting neurogenesis, synaptic plasticity, and dendritic remodeling, eventually improving learning and memory performance.

Effects of physical exercise on the brain are most apparent in the hippocampus, a brain region involved in learning and memory. Animal studies have indicated that physical exercise robustly improves hippocampal structural and functional plasticity by enhancing the generation of adult-born neurons (adult neurogenesis) in the hippocampal dentate gyrus (DG) [4, 5], increasing dendritic complexity and spine density [6-8], as well as promoting synaptic

plasticity [5]. It is thought that important mediators for these exercise-triggered beneficial effects include neurotrophic factor produced in the brain such as brain-derived neurotrophic factor (BDNF) [9], as well as factors secreted by peripheral organs, such as insulin-like growth factor 1 (IGF-1) [10] and vascular endothelial growth factor (VEGF) [11]. In addition to these well-known factors, emerging evidence has suggested that many other peripheral molecules known to be induced by physical exercise may also affect brain health, particularly those secreted by skeletal muscle and/or adipose tissues, termed myokines (e.g., irisin), cytokines (e.g., interleukin-5 (IL-15)), and adipokines (e.g., adiponectin)(**Figure 1**).

Biomarkers are measurable indicators of normal biological and pathogenic states, as well as pharmacological responses to treatment intervention [12]. They can be used for clinical assessment of treatment effect or disease state. The biomarker should be present at baseline and its levels should be changed in response to treatment or disease state such that its levels can be used to predict the ultimate response. The ideal biomarkers should be easy to measure and quantify, and most importantly, they should closely correlate with the parameters being measured. Unfortunately, there are no conclusions on any one of the biomarkers that can fulfill the characteristics so far. Multiple biomarkers are likely needed for measurements in clinical studies, since using multiple biomarkers may be able to increase sensitivity, specificity, and predictive abilities for clinical diagnosis [13]. With the necessity to develop a biomarker panel to better evaluate exercise-induced cognitive enhancement, in this chapter, we first summarize the influences of physical exercise training on brain health, involving both animals and humans, and discuss the possible underlying mechanisms. Next, we summarize the effect of physical exercise on regulating potential peripheral biomarker candidates. Finally, we address the relationship between exercise-biomarkers and hippocampal plasticity with available literatures.

2. Beneficial effect of physical exercise on learning and memory in animals and humans

Extensive evidence from animal studies has reliably shown that the enhancement of adult-born neurons in the hippocampus, termed as hippocampal neurogenesis, may underlie the exercise-induced improvements on cognitive function. Seminal studies by van Praag and collaborators (1999) have shown that exercise in the form of wheel running not only increased hippocampal neurogenesis [4, 5], but also improved performance in the Morris water maze, and selectively increased the long-term potentiation (LTP) in the mouse DG [5]. These initial studies showed that not only does physical activity upregulate hippocampal neurogenesis, but it can also improve the capacity for hippocampal neurons to undergo synaptic plasticity and facilitate hippocampal-dependent learning and memory behavior in the same animals. Three months of physical exercise in humans was correlated with the increased blood volume in the DG, as measured by functional magnetic resonance imaging (fMRI) and improved cognitive function [14]. Exercise is indeed known to increase the cerebral blood flow [15], blood-brain-barrier permeability [16], and angiogenesis [17-20]. Given the relationship between angiogenesis and neurogenesis [21, 22], cognition improvement [14] following

exercise can be interpreted as a result of increased hippocampal angiogenesis and therefore neurogenesis.

The beneficial effects of physical exercise on cognitive function imply that it may be used as a treatment to prevent of cognitive decline in age-related neurodegenerative diseases. Exercise has been shown to prevent a number of factors that decline with age, such as the decreases in hippocampal cell proliferation, neurogenesis [23], LTP, and neurotrophin levels [24]. Moreover, in aged mice, physical exercise can enhance hippocampal-dependent learning [25]. The benefits of exercise are not limited to midlife or aged adulthood, as rats submitted to a physical exercise regime during early postnatal development retained increases in hippocampal neurogenesis and improvement in spatial memory into their adult lives [26], highlighting the long-lasting benefits of physical exercise on brain plasticity throughout the lifespan [27].

Physical exercise has emerged in recent years as one of the most effective, affordable, and simple strategies for healthy aging, and therefore has the potential as a preventative treatment for cognitive decline associated with neurodegenerative diseases [28]. A meta-analysis has shown that 1–12 months of exercise in healthy adults is associated with significant behavioral benefits including ameliorated memory, processing speed, and attention [29]. Moreover, a regular exercise regime during not only adulthood [30], but also midlife [31] reduce the risk of developing dementia and preserve cognition later in life, which suggests that physical exercise may play a role in preventing age-related cognitive decline. In fact, a recent observational study has found a reduction in the risk of developing AD and other forms of dementia in individuals that exercise regularly, as opposed to those that did not engage in physical activity [32]. Physical exercise is beneficial to cognition across the life span, with its most significant effect on cognitive tasks involving the prefrontal cortex and the hippocampus [33].

3. Mechanism of physical exercise-induced hippocampal plasticity

Animal studies have suggested that physical exercise increases structural (e.g., neurogenesis and dendritic remodeling) and functional plasticity (e.g., synaptic plasticity) in the hippocampus (**Figure 2**).

3.1. Neurogenesis

Running distance is used as the physical assessment of voluntary running in animal studies, where a positive correlation between running distance and levels of neurogenesis in the hippocampus have been reliably shown in the literature using mice [34–36]. However, running distance is not the only variable that can affect the exercise-induced increases in hippocampal neurogenesis. Additional factors such as the genetic background [34, 37], age of the animals [38, 39], whether the running is forced or voluntary [4, 40–42], whether the animals are housed alone or in a group [43], and the duration of the running regime [44] can all affect neurogenesis following exercise. While there is some variability among studies of exercise, increases in neurogenesis are consistently reported in the literature [4, 25, 45, 46]. Long-term wheel running (2–4 months) with female C57 mice significantly increases the process of neuronal survival and neurogenesis concomitant with enhanced synaptic plasticity and improved performance

in the Morris water maze [4]. Others have found that there appear to be discrete stages at which voluntary running affects cell proliferation and differentiation. Namely, voluntary running in adult male C56B/L mice results in an increase in proliferating cells that peaks at 3 days following short-term running, which returns to basal levels following running for 32 [47] or 35 days [48]. Meanwhile, significant increases in neuronal differentiation are only observed following 10 days of voluntary running [23]. These data indicate that voluntary-running-induced increases in cell proliferation occurs during the earliest stages of running while a longer period of running promotes neuronal differentiation of adult-born cells.

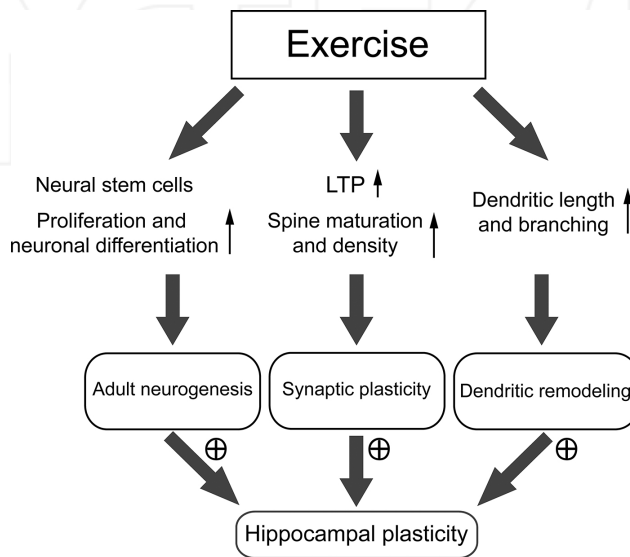


Figure 2. Potential mechanisms mediating exercise-induced hippocampal plasticity. Adult neurogenesis in the dentate gyrus of hippocampus is enhanced by exercise through increasing proliferation and neuronal differentiation of neural stem cells. Physical activities also alter synaptic plasticity by facilitating the induction of long-term potentiation and promoting the spine density and maturation in the hippocampus. Additionally, exercise modulates dendritic complexity by increasing the length and branching of dendrites. The above-mentioned changes may contribute to exercise-exerted effects on hippocampal plasticity.

3.2. Synaptic plasticity

Synaptic plasticity refers to changes in the way in which neurons communicate as a result of prior experience. Two forms of synaptic plasticity have been shown in the hippocampus, the LTP, where synaptic responses to a particular input are increased following a conditioning episode for memory formation, and the long-term depression (LTD), where synaptic responses to an input are decreased following a conditioning episode, which is recently implicated in memory clearance. The effects of exercise on *in vitro* hippocampal DG recordings were first shown in female mice by van Praag and colleagues in 1999, where 1 week of voluntary wheel running resulted in a greater LTP in the DG. Enhancement of LTP in the DG by exercise may

occur by lowering the induction threshold for LTP [49]. However, a longer period of running is required to observe the exercise effect on synaptic plasticity in the DG [50] and CA3 [51] of rats.

3.3. Dendritic remodeling and synaptogenesis

In addition to increasing neurogenesis in the DG, voluntary wheel running can promote increased dendritic complexity or spine density in hippocampal subregions including the DG, CA1, CA3, and entorhinal cortex (EC) subregions [8]. Retroviral labeling of newborn neurons in the DG showed that voluntary running accelerates spine maturation with increased proportions of mushroom spines [52], which suggests that running may enhance the functional integration of newborn neurons into existing neuronal circuits. Moreover, voluntary wheel running increases both spine density and dendritic length of dentate granule cells [7]. Particularly, running increases the proportion of cells with higher dendritic complexity [53]. Two months of voluntary running also increase spine density in the CA1 subregion and layer III of the EC [8]. However, a longer period of running may be needed to trigger structural changes in the CA3 region because running for 2 weeks increases spine density in the DG and CA1 regions, but not in the CA3 region [54]. Increases of dendritic branching and spine density of CA3 pyramidal neurons are only observed after running for 4 weeks [55].

4. Potential biomarkers of physical exercise-promoted brain health

4.1. Neurotrophic factors

4.1.1. BDNF

4.1.1.1. Animal studies

BDNF levels can be increased by exercise [56, 57], with the increase occurring as early as 2–7 days of running [56], and it remains elevated for the whole duration of running [9], even extending to an additional 2 weeks following the end of the running period [58]. Increases in BDNF are important not only for the promotion of neurogenesis but also the enhancement of functional plasticity in the forms of LTP and behavioral learning and memory performance [5, 59, 60]. A direct link between BDNF and neurogenesis has been revealed by acutely knocking down BDNF in the DG by the lentivirus-mediated RNA interference, which resulted in a remarkable reduction in adult neurogenesis [61]. Additionally, 1 month following 2 weeks of BDNF overexpression significantly increases neuronal differentiation [62].

4.1.1.2. Human studies

Erickson and colleagues reported that physical exercise as an intervention for the aging population not only attenuated the age-related loss of hippocampal volume but also increased the serum levels of BDNF in these individuals [63]. Increases in hippocampal BDNF levels are

thought to contribute to the upregulation of hippocampal neurogenesis seen with antidepressant treatment [64]. In fact, clinical studies have reported decreased serum BDNF levels in depressive patients, which were improved following treatment with antidepressants [65]. Given the well-established link between neurotrophins and adult hippocampal neurogenesis, it is reasonable to speculate that peripheral levels of these factors may be used as biomarkers of hippocampal neurogenesis. While the exact relationship between peripheral levels of neurotrophic factors and hippocampal neurogenesis has not reliably been established, progress has been made in this respect. Rasmussen and colleagues provided the first evidence that BDNF in the brain is a major contributor to the increase in plasma BDNF in response to exercise [66]. More recently, Yau and colleagues (2012) investigated the interaction of hippocampal neurogenesis, plasma neurotrophin levels, and cognitive performance in a rat stress model. They found that acute stress enhanced spatial learning as well as both hippocampal and plasma BDNF levels, but these findings were independent of hippocampal neurogenesis [67]. When chronic stress was administered, it significantly decreased hippocampal BDNF levels, hippocampal neurogenesis, and impaired spatial learning without affecting plasma BDNF levels [67]. While 28 days of voluntary running increased hippocampal neurogenesis and spatial learning, plasma BDNF levels were not significantly altered by exercise in rats [67]. While there is still possibility to use peripheral levels of neurotrophins as biomarkers correlating to changes in hippocampal neurogenesis, the interaction between these two factors remains to be understood and is far from a simple, linear relationship. It is possible that in order to fully depict changes in hippocampal neurogenesis at the periphery, we must examine multiple neurotrophins simultaneously, as peripheral BDNF changes may only be evident once substantial changes in BDNF levels have first occurred in the brain. This dissociation between central and peripheral BDNF levels shown in animals has also been reported in human subjects. Following 3 months of endurance training in healthy individuals, blood samples from the internal jugular vein but not the peripheral vessels showed increased BDNF levels [68]. Understandably, the responses of plasma or serum levels of BDNF varied considerably between studies; however, many reported a transient increase in plasma/serum levels of BDNF following exercise [69]. Lee and colleagues (2014) recently showed that adolescent athletes have lower resting serum levels of both BDNF and VEGF, and also showed improved brain function in the medial-temporal and frontal areas specifically compared to age-matched controls [70].

4.1.2. IGF-1

4.1.2.1. Animal studies

IGF-1 is another important growth factor that is shown to increase as a result of exercise [10]. This growth factor is taken up by the hippocampus from the bloodstream; however, if this process is blocked by subcutaneous infusions of IGF-1 antiserum, the exercise-mediated increase in neurogenesis is inhibited [10]. When IGF-1 is injected systemically in sedentary rats, it can mimic the effects of exercise and lead to enhancements in neurogenesis [71]. When IGF-1 is taken up by neurons, it can lead to increased firing and sensitivity of the neuron, which

may stimulate BDNF and c-fos expression [71], which can, in turn, increase neurogenesis in the surrounding area.

4.1.2.2. *Human studies*

IGF-1 is a neurotrophic factor that is primarily secreted from the liver [72] that can readily be transported across the blood-brain and blood-cerebrospinal fluid barriers [73]. In the brain, IGF-1 plays a critical role in the creation of new neurons and synapses where transgenic overexpression of IGF-1 promotes neurogenesis and synaptogenesis in the hippocampus during postnatal development [74]. Both 6 and 20 days after exogenous IGF-1 is administered, there is an increase in the number of hippocampal cell proliferation [75]. Clinical studies have established a positive correlation between serum IGF-1 levels and cognitive function [76-78]. Additionally, following two 60-minute cycling sessions, middle-aged men show increased peripheral IGF-1 levels [79], which has also been replicated in road cyclists [80]. While there is evidence to suggest that there is a link among peripheral IGF-1, exercise and cognitive function, a direct relationship among peripheral IGF-1, brain IGF-1, hippocampal neurogenesis, and hippocampus-specific function has yet to be established. In contrast to studies of acute exercise, sustained physical exercise has been shown to either have no effect [81] or reduce peripheral IGF-1 levels in healthy subjects [82], regardless of previous experience as athletes [70] or exercise intensity [83]. As with BDNF, the relationship between IGF-1 in the body and brain in response to exercise is ambiguous.

4.1.3. *VEGF*

4.1.3.1. *Animal studies*

Angiogenesis and vascular function are enhanced in response to exercise in many brain areas, which may improve normal neural function, and also potentially offer protection during insult [84]. Magnetic resonance imaging of both mice and humans has suggested a correlation between exercise, DG blood flow, and neurogenesis; however, histological examination of the vasculature did not show exercise-induced changes in mice [14]. Increased blood flow can also increase the exposure to growth factors [56, 85] that can influence neurogenesis, such as VEGF. This neurotrophin, which is known for its role in stimulating angiogenesis, is increased following exercise [11] and may play a role in enhancing neurogenesis [21, 86]. Interestingly, new neurons in the DG tend to cluster around the local microvasculature [11, 87], and if VEGF is blocked, the exercise-induced increase in neurogenesis is abolished [11].

4.1.3.2. *Human studies*

VEGF is a 45-kDa heparin-binding homodimeric glycoprotein that is secreted by skeletal muscles and can be released into the vascular system [88]. Levels of VEGF have been shown to increase in skeletal muscle following acute physical exercise [89, 90]. VEGF mRNA expression in human muscle is elevated after 30 minutes of exercise [89]. Plasma VEGF levels are decreased in the femoral vein following 3 hours of two-legged kicking exercise meanwhile skeletal muscle VEGF mRNA expression was increased [91]. Similarly, arterial VEGF plasma

levels are decreased following 10 days of exercise [89]. Kraus and colleagues have reported increased plasma VEGF levels following 2 hours of exercise in well-trained endurance athletes, but not sedentary controls at any time points [92]. The first link between exercise-induced functional improvements in the temporal cortex and changes of BDNF, IGF-1, and VEGF has recently been reported in healthy elderly subjects [93]. Following a 7-week regime of aerobic exercise, there was increased connectivity between the bilateral parahippocampi and the bilateral temporal gyri, which was associated with increased peripheral levels of BDNF, IGF-1, and VEGF. In teens that exercise regularly, Lee and colleagues showed improved frontal and temporal lobe cognitive function when compared to age-matched teens that did not exercise [70]. In contrast to what was seen in the study of elderly subjects, in the teen study there was a negative correlation between peripheral levels of BDNF and VEGF with temporal and frontal lobe functions. These studies raise critical questions regarding the type and duration of exercise as well as the age and previous exercise experience of the subjects.

5. Changes of other potential peripheral factors in response to physical exercise

Skeletal muscle and adipose tissues have recently been identified as major secretory organs in the maintenance of metabolic functions of the body. Myokines are identified as peptides and cytokines that are released by muscle fibers and can act in a paracrine or endocrine manner [94]. Adipokines are identified as hormones that are involved in metabolic functions and mediate the crosstalk between adipose tissues and the brain [95]. In response to physical exercise, these factors may have a crosstalk to regulate the secretion of myokines and adipokines, and work in concert to regulate many biological activities such as immune responses, neuroplasticity, and neurogenesis. Although linkage between hippocampal neurogenesis and levels of myokines or adipokines are still unclear, emerging animal studies have given us hints regarding their potential role in mediating the effect of exercise on regulating hippocampal plasticity.

5.1. Adipokine-adiponectin

5.1.1. Animal studies

Adiponectin, which is a protein secreted by adipose tissue, is well-known for its effects on metabolism and the cardiovascular system including antidiabetic, antiinflammatory, and antiatherosclerosis functions [96, 97]. Recent work has uncovered a role for adiponectin, as a peripheral factor mediating exercise-induced hippocampal cell proliferation [46]. Adiponectin has previously been shown to stimulate proliferation but not differentiation of adult hippocampal progenitor cells *in vitro* [98]. Acute administration via intracerebroventricular injections of either recombinant adiponectin [99] or an adenovirus expressing recombinant adiponectin [46] mimics the antidepressant effects of physical exercise. In the adenovirus experiment, administration also increased hippocampal neurogenesis, while knocking out

adiponectin attenuated the antidepressant and neurogenic effects of physical exercise [46]. Following 14 days of running in mice, hippocampal adiponectin levels are elevated paired with increases in hippocampal cell proliferation [46]. Lower levels of adiponectin are associated with cognitive dysfunction [100]. Knockdown of adiponectin in aged animals results in cognitive deficits and AD pathogenesis such as A β -aggregate deposition, Tau hyperphosphorylation, excess neuroinflammation, and synaptic loss in frontal cortex [101], suggesting adiponectin may have an important influence on ageing-associated neurodegeneration.

5.1.2. Human studies

Levels of plasma adiponectin are positively correlated with physical activity [102]. However, effects of acute or chronic exercise training on modulating adiponectin levels are inconsistent and require further study. Circulating concentrations of adiponectin in normal individuals range from 5 to 20 $\mu\text{g/ml}$ [103]. In clinical studies of acute exercise training, the reported levels of adiponectin have been varied, where some groups report increases [104, 105], decreases [106], or no changes [107-109]. The effect of exercise on adiponectin seems to be intensity dependent, because the acute effect of exercise in the form of volume-extended rowing training significantly increases adiponectin levels in elite athletes immediately and 30 minutes postexercise, but leads to decreased adiponectin levels in less elite athletes [106]. Both aerobic and resistance training with moderate to high intensity have been reported to significantly increase adiponectin levels [110], suggesting that the intensity of physical exercise is important to modulate adiponectin levels. Since adequate duration and intensity of physical training may be needed to augment circulating adiponectin levels, more detailed examinations of how adiponectin levels are manipulated by different forms and durations of exercise are necessary to provide insight regarding the role of adiponectin as a useful biomarker for evaluating the beneficial effects of physical exercise on the brains.

5.2. Adipokine-FNDC5/Irisin

5.2.1. Animal studies

In 2012, irisin was discovered as a novel exercise hormone for mediating the beneficial effects of exercise on metabolism [111]. Irisin is encoded by the *Fndc5* gene and is produced with the cleavage of its precursor FNDC5, and is then secreted from muscle during exercise [111]. Bostrom and colleagues identified irisin as a peroxisome proliferator-activated receptor γ coactivator-1 α (PGC-1 α)-dependent myokine secreted by skeletal muscle. In response to exercise, it circulates in the blood stream to reach fat tissue, where it triggers the browning of white adipose tissue [111]. Emerging animal studies have implicated irisin as a potential mediator for exercise-induced brain health. Irisin facilitates glucose and lipid metabolism in human muscle through AMP kinase phosphorylation [112]. It is known that administration of an AMPK agonist in wild-type mice, but not skeletal muscle-specific AMPK mutant mice, improves brain plasticity and memory function [113], suggesting that skeletal muscle-secreted factors that activate AMPK may influence brain and behavior. Irisin promotes cell proliferation

in a mouse H19–7 hippocampal cell line in a dose-dependent manner [114]. Irisin was elevated in serum and skeletal muscle immediately after acute exercise [115]; however, whether its levels were increased in the hippocampus has not yet been explored. Notably, its precursor, FNDC5, is elevated by endurance exercise in the mouse hippocampus [116]. Increased FNDC5 in the hippocampus can in turn upregulate PGC-1 α and BDNF expressions in the brain [116]. Knockdown of FNDC5 significantly decreases neural differentiation in mouse embryonic stem cells [117] and reduces *Bdnf* gene expression in hippocampal neurons [116], whereas peripheral delivery of FNDC5 by adenoviral vectors increases BDNF expression in the hippocampus [116]. These findings have suggested that FNDC5 may have a direct or indirect role in regulating hippocampal neurogenesis in response to physical training.

5.2.2. Human studies

Circulating irisin and its levels in adipose tissue are significantly associated with *Fndc5* gene expression in adipose tissue. The *Fndc5* gene is more strongly expressed in muscle than in adipose tissue by a 200-fold increase. Of note, obese patients and those with type 2 diabetes have lower circulating levels of irisin and *Fndc5* gene expression in adipose tissue [118, 119]. Circulating levels of irisin in sedentary individuals is ~3.6 ng/ml [120]. Its levels can be reduced in response to a 12-week training, and increased (~1.2-fold) just after acute exercise; however, FNDC5 and serum irisin levels did not change after acute aerobic and long-term endurance training. Interestingly, salivary and serum irisin increased significantly after moderate exercise [121]. Circulating irisin increased immediately after high-intensity interval exercise and declined 1 hour postexercise, suggesting that the increase in irisin levels may be transient and dose-/duration-dependent in humans.

5.3. Myokines/cytokine-interleukin 15 (IL-15)

5.3.1. Animal studies

IL-15 is a proinflammatory cytokine which can be secreted by muscle cells. IL-15 is stable in the circulation and can reach the parenchyma through the blood-brain barrier [122]. Beck and colleagues observed increases in hippocampal IL-15 expression and concurrent neurogenesis in IL-2-null mice [123]. Direct administration of IL-15 modulated neuronal differentiation of rat neural stem cells *in vitro* [124]. The suppression on olfactory neurogenesis was also found in a mouse model lacking the IL-15 receptor (IL-15R) [125]. Furthermore, IL-15 was shown to regulate neural stem cell proliferation through the MEK and JAK pathways [126]. In terms of depression-like behaviors, IL-15 treatment in wild-type mice shortened immobility time in the forced swim test. Conversely, IL-15R-deficient mice displayed increased immobility in the tail suspension and the forced swim tests, indicating that IL-15 signaling is essential to prevent neuropsychiatric symptoms [127]. Additionally, the IL-15/IL-15R pathway is also important for maintaining normal hippocampal activity and reducing anxiety-like behaviors in mice [128, 129].

5.3.2. Human studies

How IL-15 level is modulated by physical exercise is still unclear. An acute endurance exercise failed to elevate muscle IL-15 levels [130], whereas acute resistance exercise was reported to increase IL-15 mRNA expression without affecting its protein content in muscle [131]. Interestingly, a prolonged 12-week endurance exercise only raised the muscle IL-15 protein content without any changes at its mRNA levels [130]. This suggests divergent regulatory mechanisms mediating IL-15 production during muscle contraction. Plasma IL-15 concentrations were elevated by acute resistance exercise [132]. However, chronic resistance exercise seemed to have no such effect [133]. Therefore, more studies with the unified training paradigm are needed to identify the dynamic changes of IL-15.

6. Conclusion

In summary, the changes of central and/or peripheral neurotrophins, adipokines, myokines, or cytokines in response to physical training are still inconclusive so far. In human subjects, it is important to consider that age, health status, and previous exercise experience as well as general fitness can all play a role. Exercise with insufficient duration or intensity or form may not necessarily affect the expression of the above-mentioned factors. Therefore, answering the questions that by which type of and to what extent the exercise should be performed in the specific population are of particular significance. Further research is required to validate the use of exercise-modulated peripheral factors as the potential biomarkers for monitoring brain health following exercise intervention. Future direction should be focused on characterizing changes of aforementioned potential biomarkers and cognitive performance in different targeted groups. Identifying different biomarker panels may be necessary to examine the beneficial effect of exercise on targeted populations, since this will provide a more complete assessment with a better characterization on the effect of exercise on brain health.

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