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REVIEW ARTICLE

# Myokines as mediators of muscle–brain crosstalk: Implications for neuroplasticity and neurodegenerative diseases

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## Abstract

**Background:** Skeletal muscle is increasingly recognized as an endocrine organ that releases bioactive factors, termed myokines, capable of mediating inter-organ communication, including signaling to the brain. **Aim:** To summarize current evidence on key myokines involved in muscle–brain crosstalk and their potential roles in neuroplasticity, cognition, and neurodegenerative diseases. **Methods:** This narrative review synthesizes findings from experimental and clinical studies addressing exercise-induced myokines, their interaction with the blood–brain barrier, and associated intracellular signaling pathways relevant to central nervous system function. **Results:** Multiple myokines, including fibronectin type III domain-containing protein 5 (irisin), cathepsin B, insulin-like growth factor-1, interleukin-6, interleukin-1, leukemia inhibitory factor, and lactate, have been implicated in muscle–brain communication. These factors may influence brain function by crossing or modulating the blood–brain barrier and activating signaling pathways such as protein kinase B, extracellular signal-regulated kinases, and cAMP response element-binding protein. Evidence suggests that these mechanisms contribute to increased brain-derived neurotrophic factor expression, promoting neurogenesis, synaptic plasticity, and neuroprotection. Additionally, creatine, although not a myokine, may support brain function through its role in cellular energy homeostasis. **Conclusion:** Myokines represent key mediators linking physical exercise to brain health, with potential implications for the prevention and management of neurodegenerative conditions. However, further studies are required to clarify their mechanisms and clinical applicability. **Relevance for Patients:** Understanding how exercise-induced factors influence brain function may support the development of non-pharmacological and adjunct therapeutic strategies to preserve cognitive function and reduce the risk of neurodegenerative diseases.

***Keywords:*** Exercise; Cytokines; Inflammatory mediators; Signaling; Crosstalk

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## 1. Introduction

Skeletal muscle tissue corresponds to the largest endocrine organ, with the ability to produce, express, and secrete various hormones and factors in high amounts. The factors/hormones produced by it are grouped as myokines.[1,2] Myokines refer to cytokines and other peptides that are generated, expressed, and released by muscle fibers, and possess the ability to exert autocrine, paracrine, or endocrine effects.[3] The discovery of myokines provided a new perspective and a theoretical for investigating how muscle interferes with other organs and tissues.

Initially, myokines were studied by direct involvement (autocrine and paracrine) in the muscle itself. Also, they are involved in the proliferation and differentiation of satellite cells (stem cells involved in muscle regeneration and growth).[4,5] Later, new findings showed that the liver, pancreas, adipose tissue, bone, and brain, among others, had receptors for myokines, indicating signaling between muscle and various organs.[6-9] In the last decade, there has been an increase of ~97% in the publication of scientific articles that study the relationship between the production and secretion of myokines and human health.[10-12] Myokines help regulate systemic glucose homeostasis and lipid metabolism and induce phenotypic changes in white adipose tissue (WAT).[13-15] It is plausible to suppose that myokines (cytokines) in the systemic circulation access through a saturable transport system located at the brain blood barrier.[16]

The effects of myokines on neurons and glial cells, in general, occur in several ways, as illustrated in Figure 1.

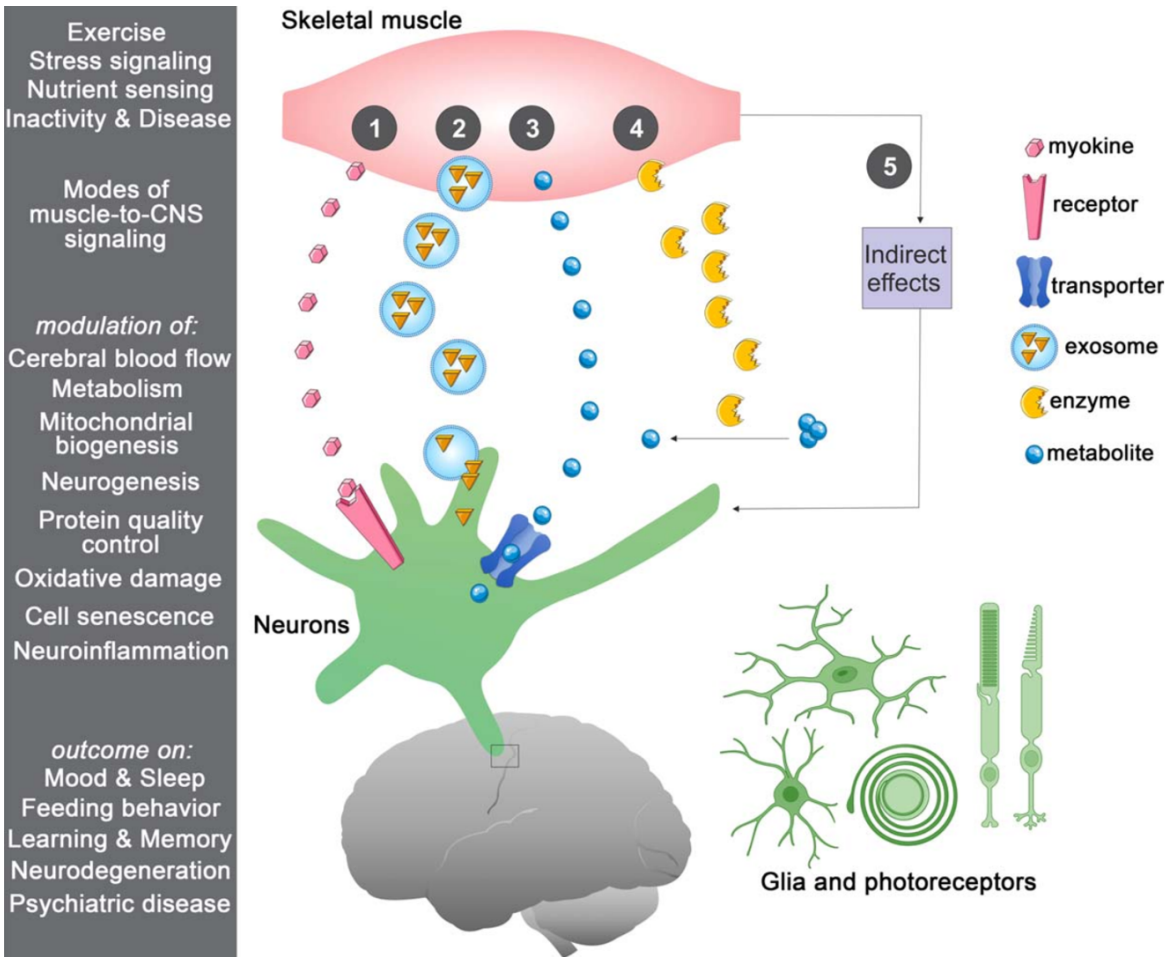



**Figure 1.** Multiple routes of muscle-to-CNS signaling: (1) by secreting signaling proteins (myokines) that can bind to receptors; (2) by releasing extracellular vesicles such as exosomes that contain signaling factors; (3) by releasing metabolites (myometabolites); (4) by secreting enzymes that produce signaling factors in the muscle, in the circulation, and/or in the brain; and (5) via indirect effects stemming from modulation of muscle metabolism and/or myokine signaling to other tissues distinct from the brain.[22]
Abbreviation: CNS: Central nervous system.

While over 600 different myokines have been extensively researched, this study aims to specifically discuss notable myokines involved in the muscle/brain crosstalk.[17] Thus, blood–brain barrier is briefly discussed to understand how these myokines enter the brain. In the next section, the following myokines were examined: Fibronectin type III domains containing protein 5 (FNDC5)/irisin, cathepsin B, insulin-like growth factor 1 (IGF1), interleukin 6 (IL-6), interleukin 1 (IL-1), leukemia inhibitory factor (LIF), and lactate. These myokines have spark debates within the scientific community. Although, creatine is not classified as a myokine, it holds relevance in the context of its effects on memory, attention, and potential mitigation of neurodegenerative diseases, similar to other myokines. The impact of these molecules on brain function is an area of ongoing discussion and research, with scientists exploring their mechanisms of action and therapeutic potential. By acknowledging the significance of creatine and its potential parallels with myokines, we can further explore its role in cognitive processes and neurodegenerative conditions. For this reason, the last section will discuss recent advances about creatine metabolism in the brain.

## 2. Methods

This study was conducted as a narrative review with a systematic search strategy aimed at identifying and synthesizing evidence on exercise-induced myokines, their interaction with the blood–brain barrier (BBB), and associated intracellular signaling pathways relevant to central nervous system function.

### 2.1. Search strategy

A comprehensive literature search was performed in electronic databases, including PubMed/MEDLINE, Scopus, and Web of Science, covering publications from January 1, 1985, to July 31, 2025. The search strategy combined controlled vocabulary and free-text terms related to the main topics of interest, including "myokines," "exercise," "skeletal muscle," "blood–brain barrier," "neuroplasticity," "brain," "signaling pathways," and specific myokines (*e.g.*, irisin, cathepsin B, IGF-1, interleukins, leukemia inhibitory factor, lactate). Boolean operators (AND/OR) were used to refine the search.

### 2.2. Eligibility criteria

Studies were considered eligible if they investigated: (i) exercise-induced myokines; (ii) mechanisms of muscle–brain crosstalk; (iii) interactions with the BBB; or (iv) intracellular signaling pathways associated with neuroplasticity, neuroprotection, or cognitive function. Both experimental (*in vitro* and *in vivo*) and clinical studies were included.

Priority was given to experimental studies to better elucidate mechanistic pathways. When necessary to contextualize findings or provide broader interpretation, relevant review articles were also included.

### 2.3. Study selection

Titles and abstracts were screened to identify potentially relevant studies. Full texts of selected articles were then assessed for eligibility based on the inclusion criteria. Reference lists of included articles were also manually screened to identify additional relevant studies.

### 2.4. Data extraction and synthesis

Data were extracted qualitatively, focusing on: (i) type of myokine; (ii) source and stimulus (*e.g.*, exercise modality/intensity); (iii) ability to cross or modulate the BBB; and (iv) intracellular signaling pathways and neurobiological outcomes (*e.g.*, BDNF expression, neurogenesis, synaptic plasticity).

Given the heterogeneity of study designs, models, and outcomes, a quantitative synthesis was not performed. Instead, findings were narratively integrated, emphasizing converging evidence from experimental and clinical studies.

### 2.5. Approach to evidence integration

The synthesis was structured to align with the biological framework of muscle–brain communication. Particular emphasis was placed on mechanistic insights derived from experimental models, while clinical studies were used to support translational relevance. This approach allowed for a comprehensive understanding of how exercise-induced myokines may influence brain function through BBB interactions and intracellular signaling pathways.

## 3. Physiological and pathological regulation of the blood–brain barrier permeability

The BBB serves as a protective barrier for the brain, selectively allowing the passage of essential molecules while restricting larger substances like cytokines.[18] Myokines, which are cytokines or peptides released by muscle fibers, have been investigated in relation to the BBB, but our knowledge in this area is still limited.[3] The interactions between myokines and the BBB are complex and not fully understood. While small molecules and gases can passively diffuse through the BBB, larger molecules like cytokines typically require specialized transport mechanisms.[19]

Under normal conditions, the BBB restricts the entry of cytokines into the brain. However, during inflammatory or pathological states, the BBB can become compromised,

enabling the passage of cytokines and other immune-related molecules.[20]

Under specific conditions, pro-inflammatory cytokines can activate transport systems or receptors on the endothelial cells of the BBB, enabling their passage into the brain.[16,21,22] Additionally, certain cytokines have the ability to stimulate the production of other molecules that can disrupt BBB integrity, facilitating their own entry.[16,21,22] Emerging research suggests that select myokines, such as interleukin-6 (IL-6) and brain-derived neurotrophic factor (BDNF) induced by exercise, may influence BBB integrity and function.[16] These exercise-induced myokines have been implicated in regulating BBB permeability and facilitating communication between muscle cells and the brain.[23]

Intense exercise, particularly endurance activities, has been associated with transient increases in BBB permeability, allowing the passage of certain substances, including small molecules and cytokines.[21] The exact mechanisms underlying exercise-induced BBB alterations are not fully understood but may involve factors such as increased blood flow, changes in blood pressure, and the release of substances during exercise.[24,25] Oxidative stress and inflammation associated with intense exercise can also impact BBB integrity.[18,21,23,25,26]

It is important to note that exercise-induced BBB disruption is typically temporary and reversible, with limited evidence suggesting long-term detrimental effects on brain health.[20,25] In addition, regular exercise has been associated with positive effects on BBB integrity, promoting neurovascular health and releasing factors that support neurogenesis and brain plasticity.

While cytokines can influence BBB integrity and some may facilitate their own entry into the brain, the passage of cytokines through the BBB is tightly regulated.[3,16,21] Factors, such as size, charge, concentration, and specific transport mechanisms, play a role in determining whether cytokines can cross the BBB.[16,19,24]

## 4. Endocrine profile and biological functions of exercise-induced myokines

It is essential to clarify the conceptual framework regarding the molecules discussed herein. Strictly defined, myokines are cytokines or peptides that are synthesized, expressed, and released by skeletal muscle fibers, exerting autocrine, paracrine, or endocrine effects. To maintain conceptual precision, this review distinguishes myokines from other signaling molecules such as classic growth factors, muscle-derived metabolites—notably lactate, which acts as a metabolic substrate rather than a signaling protein—and systemic pro-inflammatory cytokines. While these diverse factors collectively orchestrate the muscle–brain crosstalk, they operate through distinct biological mechanisms and secretion pathways. Therefore, this section organizes these mediators based on their molecular nature and their specific role in bridging physical exercise and neurobiological adaptations.

### 4.1. Fibronectin type III domains containing protein 5 (FNDC5)/irisin

Fibronectin type III domains containing protein 5 (FNDC5) is a type I glycosylated membrane protein.[27] Irisin (a 112 amino acid peptide) arises from the proteolytic cleavage of FNDC5, which is subsequently released into circulation.[28] FNDC5/Irisin is described as an exercise-induced myokine, and it is widely reported that skeletal muscle is mainly responsible for total circulating levels of irisin. Studies have suggested that irisin may promote neurogenesis, enhance synaptic plasticity, and protect against neurodegenerative diseases. It is believed to exert its effects on the brain by crossing the BBB and interacting with specific receptors or signaling pathways.[27]

Skeletal muscle contraction induces the activation of the peroxisome proliferator-activated receptor-γ coactivator (PGC)-1α, a transcriptional coactivator described as a master regulator of mitochondrial biogenesis and function. Furthermore, after exercise, PGC-1α induces irisin generation and secretion.[29] Several studies have shown that physical exercise in mice and humans increases the production of *FNDC5* mRNA in skeletal muscle fibers.[30-32]

Irisin can also stimulate neurogenesis in specific brain regions, notably the hippocampus, which is essential for memory formation and spatial awareness. The expression of FNDC5 in the hippocampus is dependent on PGC-1α, a transcriptional coactivator involved in regulating energy metabolism and exercise response. This relationship between FNDC5 and PGC-1α has been highlighted in studies utilizing genetically modified mice lacking PGC-1α, which subsequently showed a lack of FNDC5 expression.[20] These findings provide evidence for the interplay between PGC-1α, FNDC5, and the induction of neurogenesis in the hippocampus, further emphasizing the link between exercise, irisin production, and brain function.

Studies have shown that irisin can reduce the accumulation of amyloid-beta plaques in Alzheimer's disease and alpha-synuclein in Parkinson's disease in the brain.[33,34] It has been demonstrated to inhibit the formation of amyloid-beta plaques and reduce the levels of alpha-synuclein in experimental models. In this way, irisin may help to preserve neuronal function and prevent neurodegeneration.[33,34]

Irisin stimulates both neuronal proliferation and differentiation. It has been shown that the neuroprotective effects of exercise occur via irisin, which activates the signaling pathway of protein kinase B (PKB) and extracellular signal-regulated kinases (ERK).[35]

Another function described for irisin is increased BDNF expression by neural cells. BDNF modulates the nervous system's plasticity through the growth, differentiation, and repair of neurons, thus acting on cognitive function and reducing the likelihood of neurodegenerative diseases.[36]

Despite the compelling preclinical evidence highlighting the neuroprotective potential of irisin, several caveats must be considered. Firstly, the measurement of circulating irisin in humans remains a subject of intense scientific debate, with substantial methodological heterogeneity reported across studies. Furthermore, the majority of the mechanistic insights regarding irisin-mediated neuroprotection originate from *in vitro* or rodent models; therefore, the direct causal translation to human cognitive health requires cautious interpretation. While irisin appears to be associated with neuroplasticity markers, current findings should be interpreted as correlative rather than definitively causative, emphasizing the need for robust, standardized human clinical trials to validate these findings.

### 4.2. Cathepsin B

Cathepsin B (CTSB) belongs to a family of lysosomal cysteine proteases.[37] Physical exercise causes the expression of the *CTSB* gene in the muscle.[38] This gene is also responsible for encoding a protein called cathepsin B, which acts in the hippocampus and responds by promoting the synthesis of BDNF.[38]

Cathepsin B can be released from muscle cells during exercise and reach the brain through various mechanisms. One proposed mechanism is through the bloodstream, where cathepsin B can be transported across the BBB or through fenestrated capillaries in brain regions that lack a strict BBB.[39] Another possible route is through the release of exosomes or other extracellular vesicles containing cathepsin B, which can be taken up by neighboring cells, including neurons.[22,40]

As already described in the previous topic, BDNF is involved in neural plasticity, and the effect of cathepsin B in the brain is exerted through PKB activation and cAMP response element binding protein (CREB) signaling, a mechanism that induces increased production of BDNF.[41] BDNF acts on the phosphoinositide phospholipase gamma (PLC-γ), phosphoinositide 3-kinase (PI3K), and ERK activation chains that together affect synaptic plasticity and cognitive response.[42]

Another mechanism related to increased BDNF by muscle cathepsin B is increased growth and proliferation of cells in the dentate gyrus of the hippocampus.[38,43] This function enhances neuronal differentiation, plasticity, cell survival, and hippocampal function[38,43], thereby highlighting the role of physical exercise in the mediation of cognitive changes.[43,44]

It is important to emphasize that skeletal muscle can produce BDNF.[45] However, studies are still inconclusive about a possible muscle/brain endocrine effect mediated by muscle BDNF.[45]

It has been proposed that muscle-derived cathepsin B facilitates the synthesis of BDNF in the brain. However, it is important to note that the direct causal link between peripheral cathepsin B levels and hippocampal BDNF upregulation remains to be fully established in humans. Most evidence derives from experimental models where high-intensity physical activity is the primary trigger. Consequently, while cathepsin B represents a promising signaling molecule, we must exercise restraint in assuming a direct, unidirectional promotion of BDNF synthesis by this protease in clinical populations without further longitudinal investigation.

### 4.3. Insulin-like growth factor 1

Insulin-like growth factor 1 (IGF-1) is one of the essential anabolic factors in bone growth, muscle growth, brain neurogenesis, and cognitive function.[46,47] Initially, it was verified that the primary source of IGF-1 is the liver, which produces IGF-1 induced both by the concentration of growth hormone (GH) and by variations in energy metabolism. Subsequently, new findings showed that skeletal muscle fibers can produce and secrete IGF-1, with autocrine, paracrine, and endocrine effects. Muscle contraction (both by mechanical and metabolic effects) is a potent stimulator of IGF-1 production and secretion, with the autocrine effect being the most evident. However, as part of the IGF-1 produced during exercise reaches the bloodstream, IGF-1 signaling may play a key role in muscle-brain communication.[48] The moderate-intensity and medium/long-duration (<20 min) exercise increases neuronal uptake of IGF-1 and stimulates intracellular factor signaling pathways. One of the neural mechanisms of IGF-1 is the increase in the expression of BDNF mediated by PKB-CREB, favoring neurogenesis and the survival of neurons.[49]

Studies have shown that, in the elderly, moderate/long-term exercise increases IGF-1 and BDNF, significantly improving the hippocampus's volume and connectivity capabilities.[50]

### 4.4. Interleukin 6

Interleukin 6 (IL-6) is a protein of the interleukin family that acts as a pro-inflammatory cytokine (mainly produced by macrophages) and an anti-inflammatory myokine, in addition to being produced in other tissues. Muscle contractions can induce up to 100-fold increases in plasma IL-6 concentration.[51] An interesting finding is that IL-6 secretion is independent of exercise-induced muscle micro-injuries, as would be expected.[52] Physical exercise increases IL-6 mRNA expression and protein levels in the brain.[53,54] Two weeks of wheel exercise increased IL-6 expression in the hippocampus in mice, resulting in a decrease in pro-inflammatory cytokines and inflammation, allowing us to deduce that IL-6 can protect neural tissue, mitigating harmful inflammatory responses.[55]

Moreover, it seems that IL-6 may act metabolically, not only in an inflammatory response. It was proposed that blood glucose and glycogen storage regulate IL-6 in blood during exercise due to muscle contraction and cell ATP provision.[51,56] In addition, injection of four-fold IL-6 doses intraperitonnally compared to intracerebroventricular injections showed reduced food intake in mice, suggesting possible appetite control.[57] Thus, contracting muscle and glucose levels regulate IL-6 response, which may act as a regulator of food intake, suggesting that it may participate in glucose homeostasis.

*In vitro* studies have shown that IL-6 contributes to the integrity of neural cells[58,59], potentially through protection against $Ca^{2+}$-mediated excitotoxicity and attenuation of reactive oxygen species (ROS).[60] Contradictorily, *in vitro* studies have shown that IL-6 increases the neurotoxicity caused by β-amyloid (Aβ) protein plaques, which induce Alzheimer's disease. However, in *in vivo* studies, IL-6 increased the activation of astrocytes and cells of the microglia, inducing clearance of Aβ plaques and showing neuroprotective properties.[61]

### 4.5. Interleukin 1

Interleukin 1 (IL-1) is synthesized in many tissues, *i.e.*, endothelial and airway cells, fibroblasts, and cells such as macrophages, monocytes, and neutrophils. Two main types of IL-1 α and β are known and bind to two types of IL-1 receptors (IL-1RI and IL-1RII) found in nearly all tissue.[62] These cytokines are essential to inflammatory response, and their receptor modulates this response.[62] In a series of papers, Carmichael *et al.*[63-65] explore the relationship between muscle damage and central nervous system. Thus, eccentric-biased downhill running resulted in an increase in plasma creatine kinase and delayed recovery in running performance. This mechanism was explained eccentric-biased downhill running was associated more with increased levels of IL-1β in the cortex and cerebellum responsible for movement, coordination, motivation, perception of effort, and pain than uphill running, which requires more metabolically demand.[63] Thus, running performance was closely associated with brain IL-1β levels following muscle damage, potentially through signaling by brain macrophages that contributes to central nervous system fatigue in male mice.[64,65] In contrast, IL-R doses and macrophage depletion in the brain were able to improve running performance in rats during strenuous exercise..[64,65] However, this is not the only mechanism that involves the muscle, IL-1, and the brain. The muscle-brain relationship is complex and intricate.

### 4.6. Leukemia inhibitory factor

Leukemia inhibitory factor (LIF) is a pleiotropic glycoprotein belonging to the family of ligands, including IL-6, IL-11, oncostatin M, and others. It is produced by different organs or tissues, such as cardiac, neuronal, and skeletal muscle tissue.[66] LIF is involved in astrocyte development, oligodendrocyte survival, and spinal cord injury regeneration in mice.[21] LIF is an exercise-induced myokine, and evidence suggests it induces hypertrophy and regeneration of skeletal muscle fibers.[67-69] LIF, via PKB-mediated c-Fos induction, has also been shown to protect against Aβ-induced neurotoxicity.[69]

### 4.7. Lactate

Lactate is a metabolite from glycolysis produced by virtually all cell types.[70] Skeletal muscle fibers produce lactate at rest in small amounts; however, during muscle contractions, increased energy demands stimulate greater lactate production and its release into the bloodstream.[70]

Lactate can be considered a myokine or a myometabolite and is an essential energy substrate for metabolism in general and neural metabolism in particular.[71] Lactate produced in exercised mice crossed the BBB and induced BDNF expression. The already described neuroprotective effects of BDNF are potentiated by the tropomyosin kinase B receptor of the BDNF receptor (TrkB) in the hippocampus, favoring learning and memorization.[72]

The acute production of lactate in short-duration, high-intensity exercise promotes angiogenesis in the brain by binding to the 1-hydroxycarboxylic acid receptor (HCAR1).[21] The mechanism is not fully understood. However, exercise and daily lactate injections increased vascular endothelial growth factor (VEGF) levels and consequently enhanced microvascular density in the dentate gyrus of mice.[73] Mice with HCAR1 knockout did not exhibit an increase in microvascular density[73], highlighting the important role of lactate signaling through HCAR1 in regulating microvascular density.

The action of N-methyl-D-aspartate (NMDA) receptors present in glutamatergic neurons is potentiated in the presence of lactate, stimulating neuronal plasticity and memory. Lactate also activates a cascade of molecular events that stimulate the expression of genes related to synaptic plasticity, such as activity-regulated cytoskeleton-associated protein (Arc), c-Fos, and Zif268[74], thus acting on dendritic density, associated with better cognitive function.

Figure 2 provides an illustrative overview of myokine signaling pathway and its effects on angiogenesis, neural and dendritic plasticity, and hippocampal neurogenesis.

## 5. A perspective approach to creatine supplementation, neuroprotection, and neuroplasticity

Initially, the role of creatine supplementation was almost exclusively linked to sports performance or static improvement, primarily known for its role in energy metabolism within muscle cells.[75,76] However, more recently, creatine has been recognized as an important metabolite involved in brain function.[77] In the brain or muscle cells, creatine functions as a crucial energy buffer by replenishing ATP (adenosine triphosphate), which is the primary source of cellular energy.[75-77] It helps maintain energy levels in the brain or muscle, especially during periods of increased energy demand or stress.[75-77]

We cannot classify creatine as a myokine, but it is closely associated with the mitigation of sarcopenia[78,79], especially when associated with physical exercise. While there is still an ongoing debate regarding the impact of creatine supplementation on brain function, recent observational clinical studies have indicated an interesting association. Specifically, these studies have found that older adults who consume higher amounts of creatine through their diet (not through supplementation) tend to exhibit better performance in visuospatial memory tests.[80] However, it is important to note that further scientific research is necessary to establish a conclusive consensus on the effects of creatine on brain function.[80]

Furthermore, it has been suggested that creatine supplementation may have neuroprotective effects and potential benefits for various neurological conditions.[81,82] Studies have shown that creatine supplementation can improve cognitive performance, enhance memory and attention, and potentially mitigate the effects of neurodegenerative diseases.[81,82]

Additionally, creatine is involved in the synthesis of phosphocreatine, which acts as an energy reserve in the brain and facilitates the rapid regeneration of ATP.[81,82]

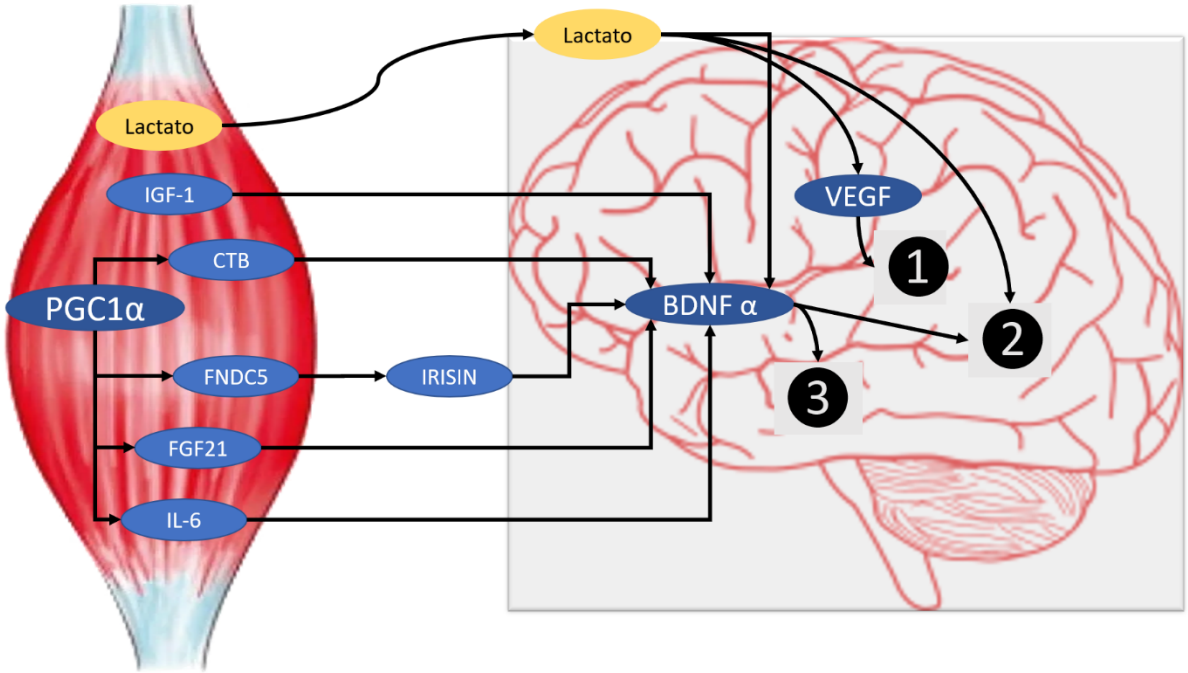



**Figure 2.** Myokine signaling pathway and its effects on: ❶ angiogenesis; ❷ neural and dendritic plasticity; ❸ hippocampal neurogenesis.

This is particularly important in situations where the brain requires immediate bursts of energy, such as during cognitive tasks or periods of mental exertion.[81,82]

As already mentioned, creatine is not a signaling molecule and myokines. However, some studies on fish have pointed out that creatine may modulate signaling pathways indirectly by affecting cellular energetics, gene expression, and protein synthesis.[83,84] For instance, creatine supplementation has been associated with increased expression of certain genes related to muscle growth and adaptation.[84] To date, there are no studies in humans. However, creatine may be a signaling molecule in humans.

Creatine supplementation, initially known for its role in muscle energy metabolism, has shown implications for brain function.[75,76] While not classified as a myokine, it plays a vital role in replenishing ATP and maintaining energy levels in both the brain and muscles.[75-77] Recent studies suggest potential benefits for visuospatial memory and neuroprotection.[80] However, creatine's involvement in phosphocreatine synthesis and potential modulation of signaling pathways further contribute to its multifaceted role.[83,84] Taken together, creatine's significance extends beyond its initial associations, with relevance in both muscle and brain cells.

## 6. Exercise and myokines

The impact of physical activity on the muscle-brain axis is significantly modulated by the exercise modality employed. Aerobic exercise is primarily associated with sustained upregulation of neurotrophic factors and enhanced cerebral vascularization, largely driven by the metabolic demand of the muscle. In contrast, resistance training facilitates distinct neuromuscular adaptations, promoting the secretion of myokines involved in muscle hypertrophy and protein synthesis, which indirectly support neural homeostasis. Furthermore, high-intensity interval training (HIIT) induces a more rapid and robust secretory response, often leading to a transient, high-amplitude release of systemic factors that promote metabolic efficiency. These modalities, by inducing different mechanical and metabolic stresses on skeletal muscle, create specific 'myokine signatures' that influence neuroplasticity and brain health in unique ways, suggesting that diversified training protocols may be necessary to optimize the neurobiological benefits of exercise.

## 7. Sarcopenia and neurodegenerative diseases

The interplay between sarcopenia and neurodegenerative diseases underscores a critical pathological link in the muscle–brain crosstalk axis. As skeletal muscle undergoes age-related atrophy and metabolic dysfunction (sarcopenia), the loss of its endocrine function results in a diminished release of protective myokines, thereby depriving the central nervous system of essential trophic support. This muscle–brain disconnection may exacerbate neurodegenerative processes, such as impaired synaptic plasticity and neuroinflammation. Consequently, reversing sarcopenia through targeted interventions—including resistance training and adequate nutritional support—represents a promising therapeutic strategy. By curbing catabolic processes and restoring the muscular secretory capacity, it is possible to modulate molecular targets that stabilize the BBB and potentially slow the progression of central nervous system diseases, highlighting the therapeutic potential of preserving muscle mass as an adjunct treatment for cognitive health.

## 8. Conclusion

The effects of myokines, which are cytokines produced by skeletal muscle tissue, on the brain are an area of active research. However, for myokines to exert their effects on the brain, they need to cross the BBB, which is a selective barrier that restricts the entry of certain molecules into the brain.[7,18]

The BBB allows the passage of small molecules and gases through passive diffusion but restricts larger substances like cytokines.[19] However, during inflammatory or pathological states, the BBB can become compromised, allowing the passage of cytokines and other immune-related molecules.[16,20,21] Pro-inflammatory cytokines can activate transport systems or receptors on the endothelial cells of the BBB, enabling their passage into the brain. Additionally, cytokines can stimulate the production of other molecules that disrupt BBB integrity, facilitating their own entry.[21,23,25,26]

Among the notable myokines involved in muscle/brain crosstalk are FNDC5/irisin, cathepsin B, IGF-1, IL-6, IL-1, LIF, and lactate. Irisin, derived from the proteolytic cleavage of FNDC5, has been shown to promote neurogenesis, enhance synaptic plasticity, and protect against neurodegenerative diseases.[27] Cathepsin B, released from muscle cells during exercise, can reach the brain and promote the synthesis of BDNF, a protein involved in neuronal plasticity.[41] IGF-1, produced by skeletal muscle, plays a role in bone growth, muscle growth, brain neurogenesis, and cognitive function.[46,47] IL-6 has both pro-inflammatory and anti-inflammatory effects and may influence neural tissue protection and appetite control.[55,57] IL-1, another cytokine, is associated with the inflammatory response and has been linked to muscle damage and central nervous system.[63-65]

Emerging evidence indicates that muscle-to-brain signaling via BDNF exhibits a sex-dependent dimorphic profile, reflecting distinct adaptive responses between males and females. Recent studies have highlighted that muscle-derived BDNF plays a critical role in orchestrating inter-organ crosstalk in a manner influenced by biological sex, with significant implications for neuroplasticity and cognitive health. Furthermore, differential regulation of metabolic and neurotrophic pathways suggests that exercise-induced BDNF release may not be uniform across populations, necessitating a more personalized approach when assessing muscle–brain communication. Understanding these sex-specific mechanisms is essential for elucidating the heterogeneity observed in exercise-mediated cognitive benefits and for developing tailored therapeutic strategies for neurodegenerative conditions.[85,86]

Although not classified as a myokine, the impact of creatine on brain function and its potential parallels with myokines were explored. The discussion also acknowledges the relevance of creatine in the context of its effects on memory, attention, and potential mitigation of neurodegenerative diseases.[81,82]

The specific bioactivity of myokines remains undescribed and poorly understood.[87] Further clarifying how they are secreted and released from muscle fiber, as well as elucidating their effect on the brain, will help decipher the link between muscle, exercise, and brain function. These findings have the potential to enhance the prescription of exercise and facilitate the development of drugs interventions for the treatment of neurodegenerative disorders.

Despite the robust mechanistic insights provided by preclinical investigations utilizing cell cultures and rodent models, a critical appraisal of the current literature reveals a heavy reliance on non-human data. Much of our understanding regarding myokine transport, intracellular signaling pathways, and neuroprotection stems from experimental models, while direct clinical trials, human observational studies, and structured exercise interventions remain comparatively scarce. Consequently, translating these findings to human physiology—particularly in clinical populations suffering from neurodegenerative or metabolic disorders—must be approached with caution. There is an urgent need for future research to prioritize large-scale randomized controlled trials, longitudinal observational studies, and targeted exercise prescription protocols in human cohorts to validate the translational relevance of myokines and establish definitive clinical evidence.

## 9. Relevance for patients

Regular physical exercise is widely recognized as a key strategy for maintaining overall health, and emerging evidence suggests that its benefits extend to brain function through molecules released by skeletal muscle, known as myokines. These exercise-induced factors may influence processes such as memory, learning, and brain resilience by promoting communication between muscle and the central nervous system.

From a clinical and practical perspective, this highlights the importance of incorporating structured physical activity into daily routines as a non-pharmacological approach to support cognitive health. Exercise may be particularly relevant for individuals at risk of cognitive decline, older adults, or patients with neurodegenerative conditions, as it can stimulate biological pathways associated with neuroprotection and brain plasticity.

Furthermore, understanding the role of myokines may contribute to the development of future therapeutic strategies that mimic or enhance the beneficial effects of exercise. Although these applications are still under investigation, they may eventually complement existing treatments for neurological disorders.

In summary, promoting regular exercise represents an accessible, low-cost, and safe intervention that can support both physical and brain health, reinforcing its role in preventive and integrative healthcare.

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The authors declare that they have no competing interests.

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Not applicable.

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Not applicable.

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