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RECEIVED 18 February 2025

ACCEPTED 10 July 2025

PUBLISHED 23 July 2025

## CITATION

Ribeiro F, Forbes SC, Candow DG, Perim P, Lira FS, Lancha AH Jr and Rosa Neto JC (2025) Creatine supplementation and muscle-brain axis: a new possible mechanism?  
*Front. Nutr.* 12:1579204.  
doi: 10.3389/fnut.2025.1579204

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# Creatine supplementation and muscle-brain axis: a new possible mechanism?

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The brain and skeletal muscle have a high energy demand, of which creatine is an important regulator. Creatine acts as both a spatial and temporal energy buffer and reduces oxidative stress and inflammation. Creatine supplementation is well-recognized to enhance exercise performance, muscular strength and lean tissue mass, with emerging research showing benefits on cognitive function. Herein, we discuss the potential muscle-brain axis and the purported benefits of creatine supplementation on myokines, with a focus on brain-derived neurotrophic factor (BDNF). Myokines and the muscle-brain axis have been implicated in strength, endurance, neuroprotection, and cognitive performance, particularly in aging and clinical conditions. Creatine is a pleiotropic molecule and the mechanisms are multifactorial, however, they appear to be associated with improved bioenergetics, muscle hypertrophy, anti-inflammatory effects and on improved glucose metabolism. Despite the growing body of research on creatine, limitations such as variability in study designs, dosages, and individual responses need to be carefully interpreted. Further research is warranted to verify this hypothesis and to establish optimal supplementation protocols, particularly, in terms of its short-term and long-term implications for neuromuscular and cognitive performance.

## KEYWORDS

creatine, supplementation, myokines, BDNF, muscle-brain axis, skeletal muscle, brain

## 1 Introduction

Creatine (methylguanidine acetic acid) is a nitrogenous compound synthesized endogenously from reactions involving the amino acids arginine, glycine and methionine in the liver and brain. Additionally, creatine can be obtained exogenously through the diet, from foods of animal origin, such as beef, fish or pork (63), or via a commercially available creatine supplement. Once endogenously synthesized or absorbed, creatine is transported into cells via a sodium-chloride dependent transporter, SLC6A8, against a concentration gradient. Inside the cell, about one-third of creatine remains free, while the remainder is phosphorylated to phosphocreatine (PCr). PCr donates its phosphate to ADP to resynthesize ATP through creatine kinase (CK) activity (1). This ATP-PCr system serves as a rapid energy buffer, especially during activities of high energy demand such as resistance exercise, by maintaining ATP levels in energy-demanding tissues like muscle, brain, and heart (2).

Beyond muscle bioenergetics, creatine appears to influence brain function. It is present in synaptic vesicles and may impact cortical neuron communication (3), while also stimulating mitochondrial activity in hippocampal neurons (4). Its potential neuroprotective effects are linked to oxidative stress modulation (5), antioxidant actions (6), electrophysiological changes (7), and neurodevelopment, are of growing interest. There is also evidence suggesting that creatine is a possible neurotransmitter in the Central Nervous System (CNS), due to its presence in synaptic vesicles, release upon stimulation, effects on cortical neurons and uptake into synaptosomes and synaptic vesicles (8).

In parallel, skeletal muscle is now recognized as an endocrine organ that releases myokines, that are cytokines and peptides that mediate crosstalk with distant organs including the brain (9, 10). As mentioned, creatine is an essential compound in cellular metabolism, especially in muscle cells, acting mainly in the rapid regeneration of ATP for muscle contractions, and myokines are released by the skeletal muscle following the muscle contraction. The communication between these molecules released by the skeletal muscle that can reach the brain can be named muscle-brain axis, which may offer a novel framework through which creatine exerts CNS effects. Thus, this mini-narrative review aims to explore the potential link between creatine supplementation and the muscle-brain axis mainly through myokine signaling.

## 2 Creatine supplementation: from sports to clinical applications

Creatine is widely recognized as one of the most effective and commonly used ergogenic aids to enhance exercise performance. In sport, creatine is recognized mainly for activities involving short bursts of high-intensity exercise or to improve resistance training adaptations (11). Mechanistically, creatine enhances exercise performance by increasing muscle PCr stores, which in turn facilitates rapid ATP resynthesis during high-intensity activities. This results in improved performance in activities such as sprinting and resistance training, where the ATP-PCr energy system predominates (1, 12, 13). Creatine supplementation combined with resistance training is associated with increased lean tissue or fat-free mass and muscular strength, likely due to enhanced training adaptations and recovery (13–15). Due to creatine's capacity to improve anaerobic work performance during repeated high-intensity efforts, in theory, this could be advantageous for endurance sports like cross-country skiing, mountain biking, cycling, running and triathlon where changes in pace and surges may impact the race (16). Furthermore, creatine may benefit short-duration events where final bursts of effort are crucial, such as rowing, kayaking, and track cycling. Beyond creatine's role in physical performance, research suggests that creatine may facilitate post-exercise recovery, support injury prevention and aid in thermoregulation (11).

Creatine supplementation also has potential benefits in various clinical contexts, including neurodegenerative disorders such as muscular dystrophy, Parkinson's disease, Huntington's disease and may contribute to neuroprotection in cases of concussions or spinal cord injuries (17). Other areas of interest include creatine's use in managing diabetes, osteoarthritis, fibromyalgia, and age-related sarcopenia, as well as its protective effects against ischemic events in

the brain and heart (18). Preliminary studies also suggest creatine's potential in reducing the risk of depression and supporting maternal health during pregnancy (19, 20). Its safety profile is well-established, with no significant adverse effects reported in healthy individuals, although caution is advised in those with pre-existing kidney conditions (21). Overall, creatine supplementation is a versatile and pleiotropic dietary strategy that may benefit both sport performance and improve health in clinical settings.

## 3 Muscle as an endocrine organ: the muscle-brain axis

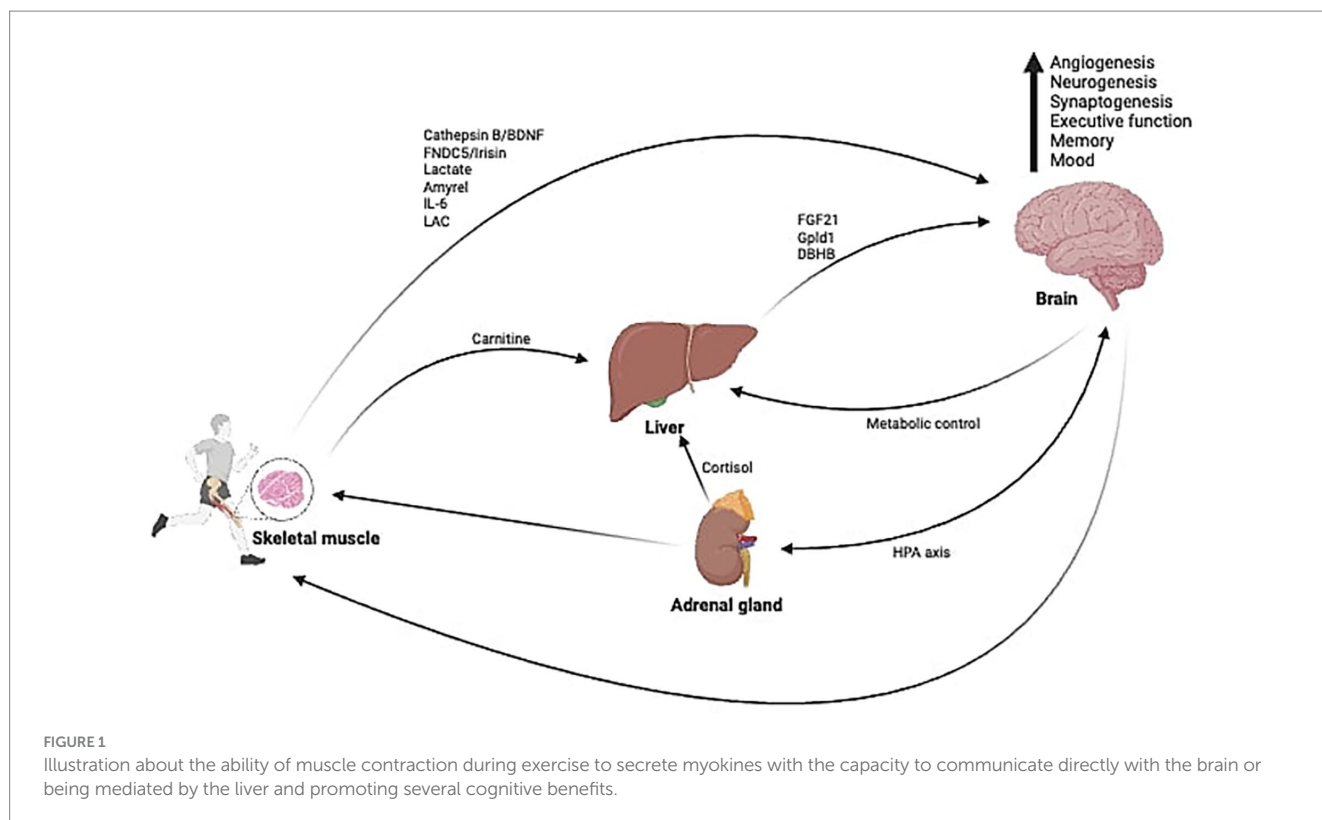
Skeletal muscle functions as an endocrine organ by releasing myokines, which are signaling proteins produced and secreted by myocytes in response to muscle contractions (10). These myokines facilitate communication between muscle and other organs, including the brain, forming what is referred to as the muscle-brain axis (22). Among the most studied myokines in this context are brain-derived neurotrophic factor (BDNF), cathepsin B, interleukin-6 (IL-6), insulin-like growth factor-1 (IGF-1), irisin and lactate. These molecules can cross the blood-brain barrier and have been shown to promote neuronal proliferation, synaptic plasticity, and cognitive improvements, as well as ameliorate behavioral alterations (22–24).

BDNF support differentiation, maturation, and survival of neurons in the CNS, so it plays a central role in synaptic plasticity, neurogenesis, and cognitive enhancement (25). Cathepsin B stimulates BDNF expression and contributes to improved memory and hippocampal function (24). IL-6, whose levels rise significantly during exercise, exhibits pleiotropic properties, acting either pro- or anti-inflammatory depending on the milieu, and is implicated in mood regulation and energy balance (23). IGF-1, transported from the periphery to the brain, has been shown to enhance neurogenesis and protect against neuronal apoptosis (26). Irisin, which is a molecule cleaved from fibronectin type III domain containing 5 (FNDC5), a precursor protein expressed in muscle, is also expressed in the hippocampus, where it stimulates the expression of the BDNF in this area that is associated with learning and memory (27). Lactate, traditionally viewed as a metabolic byproduct, is now recognized as a signaling molecule that modulates brain-derived neurotrophic pathways associated to neural development, neuroplasticity, blood-brain barrier maintenance, and lysosomal acidification (28).

Overall, these myokines demonstrate how skeletal muscle, through contraction-induced secretion, can directly affect brain physiology and cognitive health (22, 24, 29). This area of research continues to evolve, with ongoing studies aimed at elucidating the precise mechanisms and therapeutic potential of muscle-derived signals (see Figure 1).

## 4 Creatine and myokines: a new possible mechanism?

Myokines mediate communication between muscles and other organs, such as the brain, adipose tissue, liver, bone, pancreas, intestine and skin, in addition to having effects on the muscle itself. In this way, myokines exert their effects on cognition, lipid and glucose metabolism, browning of white adipose tissue, bone formation,



endothelial cell function, hypertrophy, skin structure and tumor growth (30). Creatine is an essential compound in cellular metabolism, especially in muscle cells, acting mainly in the rapid regeneration of ATP for muscle contractions. A possible relationship between creatine and myokine production occurs through different means, such as the mechanisms outlined below.

#### 4.1 Increased muscle energy

Creatine supplementation increases the availability of ATP during intense or demanding exercise (Harris et al., 1992). When contraction stimulus is received by muscle cells, ATP and  $\text{Ca}^{2+}$  are demanded for muscle function. The available ATP lasts only for a few contractions, so the cell uses creatine phosphate to resynthesize ATP (31). One of the manners to provide more creatine, so this pathway can maintain is through creatine supplementation and this increase in the availability of ATP can possibly enhance muscle energy for contraction and modify the production of myokines, such as IL-6 (interleukin-6), which are signaling proteins involved in cellular communication and the muscle recovery process (11).

IL-6 is a myokine produced that helps regulate cellular metabolism, increasing when there is a reduction in ATP synthesis. Thus, creatine supplementation could, in theory, reduce IL-6 levels, which in turn has such effects on the CNS, such as in major depressive disorder prognosis and therapeutic responses, and may affect a wide range of depressive symptomatology (32). Moreover, short-term creatine supplementation is able to induce the increase in strength, endurance, mean power output in repeated bouts from sprint tests and this short-term protocol was able to increase the mean power and speed, mainly in the second half of sprints bouts in treadmill (33–35, 61).

Interestingly, all of these studies did not show a difference in lactate concentration or other myokines into blood. It is significant because the lactate is an important metabolite associated to muscle energy and a myokine that induces directly the increase in the BDNF (36). We hypothesize that greater ATP availability as a consequence of creatine supplementation increases myokine production, which should be evaluated by future studies.

#### 4.2 Muscle hypertrophy and inflammatory response

Creatine is established to augment resistance training gains in lean tissue mass. Mechanistically, creatine promotes an anabolic environment in muscle cells, which may lead to increased translation of muscle proteins. The magnitude of the myokine-release response after muscular contraction varies with the intensity, type, and volume of exercise performed (37). Myokines, such as IL-6, are produced in response to exercise and play crucial roles in muscle recovery and growth (38). Furthermore, creatine may affect various signaling pathways that control myokine production, including the mTOR pathway, which plays a key role in muscle growth and protein synthesis (39). By modulating the secretion of myokines such as myostatin and IGF-1, creatine may indirectly influence brain-related processes including neurogenesis, synaptic plasticity, and cognitive function (29, 62). In particular, higher intramuscular IGF-1 levels, as observed following creatine supplementation (40), have been associated with enhanced neurogenesis and synaptic plasticity, owing to the ability of IGF-1 to cross the blood–brain barrier. Additionally, creatine can alter the expression of myogenic regulatory factors, enhancing satellite cell activity and muscle regeneration (41), which

may contribute to the muscle-brain cross-talk via exercise-induced myokine release. These potential pathways suggest that creatine may play a role not only in muscle anabolism, but also in modulating systemic signals that reach and influence the brain.

From an anti-inflammatory and anti-catabolic perspective, creatine can influence the inflammatory response by modulating the production of pro-inflammatory and anti-inflammatory myokines. This modulation can impact muscle recovery and adaptation to exercise, promoting a balance between inflammation and recovery (42). This modification in the inflammatory response, with reduction of muscular inflammation after exhaustive exercise, is capable of reducing plasma inflammatory markers, such as prostaglandin E2 (PGE2), which may act on the CNS and affect the muscle-brain axis (43).

### 4.3 Effects on insulin metabolism

Creatine supplementation has been associated with improved insulin sensitivity (60), which may modulate the secretion of key myokines involved in muscle-brain communication. Improved insulin signaling mediated by creatine supplementation enhances glucose uptake via GLUT-4 translocation in skeletal muscle (44), which we hypothesize that can potentiate the exercise-induced release of myokines such as irisin, IL-6 and BDNF. Irisin is upregulated by exercise and insulin signaling, and crosses the blood–brain barrier to stimulate BDNF expression in the hippocampus, promoting synaptic plasticity, memory, and neurogenesis (45, 46). IL-6, whose secretion is also influenced by insulin sensitivity and muscular glucose uptake, plays a dual role in modulating neuroinflammation and energy metabolism in the brain (23, 47). Thus, the creatine-induced

enhancement of insulin sensitivity could contribute to a favorable myokine profile, indirectly supporting brain health by amplifying neuroprotective and neuromodulatory signaling pathways associated with the muscle-brain axis (see Figure 2).

## 5 BDNF and creatine supplementation

Cytokines have several physiological effects in humans, including IL-6, interleukin-10 (IL-10), tumor necrosis factor-alpha (TNF-alpha), adiponectins and BDNF (10). The secretion of these cytokines is influenced by physical exercise, as exercise stimulates the release of neurotransmitters and neurotrophins (such as serotonin and dopamine) in an activity-dependent manner, which acutely enhances neural function and induces a cascade of events that promote structural and functional plasticity of the brain (48). Thus, creatine supplementation can influence key neurotransmitter systems, such as serotonin and dopamine, which are fundamental to mood regulation (49). These mechanisms suggest that creatine might help reduce depressive symptoms by restoring energy balance in brain cells and protecting them from neuroinflammation and oxidative damage. This set of mechanisms contributes to brain plasticity, with BDNF being one of the main mechanisms responsible for increasing neurogenesis and memory (50). BDNF is a protein that belongs to the neurotrophin family and is abundantly expressed in the hippocampus and cerebral cortex (51). BDNF plays a role in the formation and maintenance of neural synapses, as well as the ability of the CNS to adapt and regenerate to potential damage (52).

Approximately 70–80% of the BDNF present in the blood is produced by the brain at rest and during physical exercise (51). Therefore, increasing BDNF secretion is extremely important, and

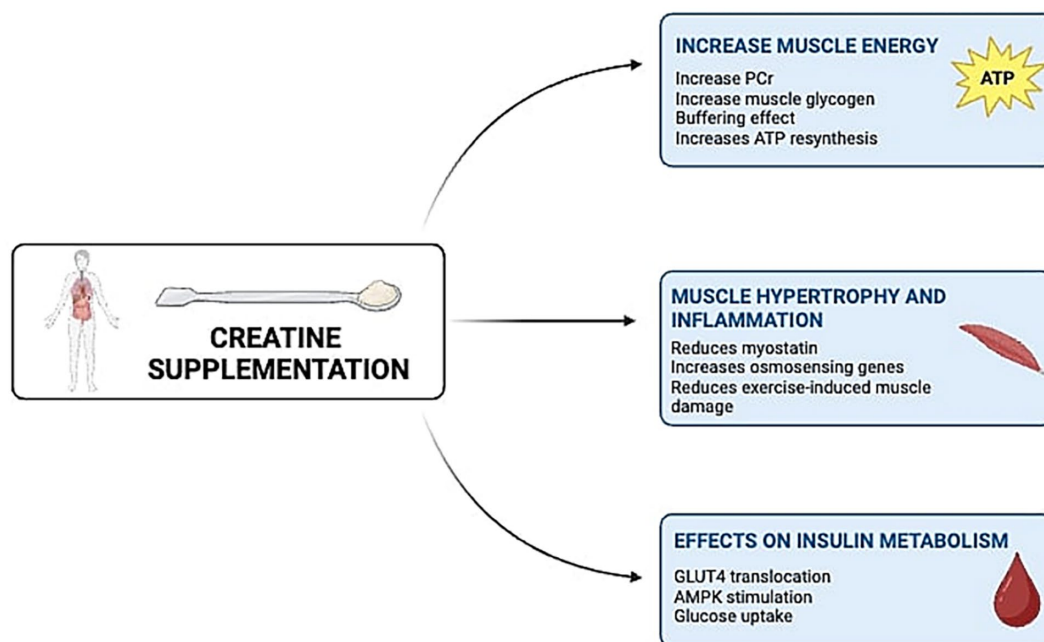


FIGURE 2

Multiple mechanisms that creatine supplementation in humans can promote metabolic responses. PCr, phosphocreatine; ATP, adenosine triphosphate; AMPK, adenosine monophosphate-activated protein kinase.



one of the main stimulants is exercise or muscular contractions. Regarding its relationship with physical exercise, acute exercise has been able to promote a temporary improvement in cognitive function, while long-term exercise training is associated with the stimulation of brain plasticity, improvement of brain function and prevention of neurological disorders (53). The most robust evidence available indicates that acute aerobic exercise promotes a transient increase in circulating levels of BDNF. Recently, Edman et al. (36) showed that the acute exercise increases the expression of pro-BDNF and the infusion of lactate induces the huge elevation in mature form of BDNF. In contrast, chronic exercise training appears to have variable effects on basal concentrations of BDNF (53, 54).

In the CNS, BDNF is primarily synthesized in the hippocampus, but can also be found in the cerebral cortex, midbrain, thalamus, hypothalamus, pons, and medulla oblongata (55). Thus, due to its low molecular weight (13 kDa) in its mature form, BDNF can cross the blood–brain barrier, and variations in the concentration of circulating BDNF likely originate from neurons and glial cells of the CNS (51). As such, BDNF plays an important role in neuronal survival and growth, acts as a neurotransmitter modulator and participates in neuronal plasticity, essential for learning and memory (56).

As previously mentioned, creatine can impact muscle function, which appears to be associated with improved training volume via increasing energy capacity and calcium uptake in the sarcoplasmic reticulum, or through the main pathways related to protein kinetics and protein degradation (57). The link between creatine and BDNF release may be explained through multiple interconnected pathways. First, creatine supplementation enhances phosphocreatine availability and ATP resynthesis, supporting higher training volumes and intensities, which are known stimuli for myokine release, including BDNF.

One specific mechanism involves the upregulation of Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1 Alpha (PGC-1 $\alpha$ ) in skeletal muscle during exercise, a key regulator of mitochondrial biogenesis and oxidative metabolism, which also stimulates the expression of FNDC5, the precursor of irisin (46). Irisin, in turn, crosses the blood–brain barrier and induces BDNF expression in the hippocampus, contributing to neuroplasticity and cognitive improvements (45). Moreover, creatine may influence calcium signaling and mTOR pathway activation within muscle fibers, both of which are involved in activity-dependent myokine expression and may contribute to the enhanced release of neurotrophic factors like BDNF (64, 65). Thus, creatine's ergogenic effects can indirectly support neuromodulation through myokine-mediated signaling from muscle to brain.

Pazini et al. (58) evaluated the antidepressant effect of creatine in mice with corticosterone-induced depression (20 mg/kg, orally, for 21 days). After treatment, creatine (10 mg/kg) and ketamine (1 mg/kg) reduced the immobility time in the tail suspension test, while fluoxetine (10 mg/kg) was not effective. The inhibitors of the PI3K/Akt/mTOR pathway (wortmannin and rapamycin) abrogated the antidepressant effects of creatine and ketamine. Both compounds restored BDNF levels in the hippocampus and increased synaptic proteins, such as PSD95. These results suggest that creatine, like ketamine, exerts a rapid antidepressant effect through the PI3K/Akt/mTOR pathway and BDNF modulation, being a potential alternative for the treatment of depression in mice.

More recently, Sherpa et al. (59) analyzed the efficacy and safety profile of oral creatine monohydrate combined with cognitive-behavioral therapy (CBT) on depression. An 8-week pilot, double-blind, randomized, placebo-controlled protocol was conducted in 100 adults with depression. Patient Health Questionnaire-9 (PHQ-9) scores improved in both groups over 8 weeks, with a significantly greater reduction in the creatine+CBT group. Findings suggest that 5 g of creatine supplementation for 8 weeks is a safe and potentially effective adjunct to CBT for depression, warranting further investigation in larger trials. However, there are still no clinical trials that have evaluated whether creatine supplementation influences the production of myokines, such as BDNF.

## 6 Future directions and conclusion

The relationship between creatine supplementation, physical exercise and the concentration of myokines, such as IL-6, BDNF, among others, is a topic of increasing relevance. Beyond the muscle, creatine can influence the health of the CNS, which may be associated with the modulation of the levels of BDNF, IL-6, IL-10, serotonin and dopamine. IL-6 and IL-10 have crucial roles in the inflammatory response and muscle recovery.

As future directions, it would be important to investigate if creatine supplementation, by increasing energy availability in cells, may favor the production of IL-10 and attenuate the negative effects of IL-6 in situations of oxidative stress and muscle inflammation. Furthermore, the relationship between creatine and neurotransmitters such as serotonin and dopamine warrants attention. So investigating the effects of creatine on cytokines and neurotransmitters is relevant to understanding creatine's implications for health and physical performance, in addition to enhancing nutritional intervention and physical training strategies. Also, no clinical trials evaluated whether creatine supplementation has the potential to amplify BDNF effects, acting synergistically with physical exercise. The study of the interaction between creatine supplementation, exercise and BDNF levels can provide valuable outcomes for health promotion and prevention of diseases that affect the CNS. Finally, this interaction could be investigated in different interventions (e.g., dosage, time of administration, and population) because it can be relevant mainly as an adjuvant treatment of depression, sarcopenia, mood and neurological disorders, such as Alzheimer disease. There is a gap in the scientific literature that requires an investigation of the hypothesis that creatine supplementation can modify the expression of myokines released by muscle contraction induced by physical exercise.

In conclusion, we propose that creatine possible effects on the muscle-brain axis are a new possible mechanism, potentially modifying the production of BDNF and other neurotransmitters. The relevance of this field lies in the possibility of developing intervention strategies that can benefit mental and physical health, contributing to a better understanding of the relationship between nutrition, physical exercise and neurological function.

## Author contributions

FR: Conceptualization, Methodology, Supervision, Writing – original draft, Writing – review & editing. SF: Writing – review &

editing. DC: Writing – review & editing. PP: Resources, Software, Writing – review & editing. FL: Writing – review & editing. AL: Investigation, Writing – review & editing. JR: Funding acquisition, Supervision, Writing – original draft, Writing – review & editing.

## Funding

The author(s) declare that financial support was received for the research and/or publication of this article. JR has been financially supported by Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) (2022/06073-9).

## Acknowledgments

The authors would like to thank Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPQ) and FAPESP who contributed to the research involved in this manuscript.

## Conflict of interest

SF is a scientific advisor for BearBalanced, a company that sells creatine products. SF has also received creatine monohydrate donations for research purposes. SF is a sport nutrition advisor and

advisory board member for the International Society of Sports Nutrition (ISSN). DC has conducted industry-sponsored research involving creatine supplementation and received creatine donations for scientific studies and travel support for presentations involving creatine supplementation at scientific conferences. In addition, DC serves as an expert witness/consultant in legal cases involving creatine supplementation.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

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## References

- Terjung RL, Clarkson P, Eichner ER, Greenhaff PL, Hespel PJ, Israel RG, et al. American College of Sports Medicine roundtable. The physiological and health effects of oral creatine supplementation. *Med Sci Sports Exerc.* (2000) 32:706–17. doi: 10.1097/00005768-200003000-00024
- Wallimann T, Tokarska-Schlattner M, Schlattner U. The creatine kinase system and pleiotropic effects of creatine. *Amino Acids.* (2011) 40:1271–96. doi: 10.1007/s00726-011-0877-3
- Bian X, Z J, J X, L W, Y S, L Z, et al. Suggestion of creatine as a new neurotransmitter by approaches ranging from chemical analysis and biochemistry to electrophysiology. *eLife.* (2023) 12:RP89317
- Li Z, Okamoto K-I, Hayashi Y, Sheng M. The importance of dendritic mitochondria in the morphogenesis and plasticity of spines and synapses. *Cell.* (2004) 119:873–87. doi: 10.1016/j.cell.2004.11.003
- Genius J, Geiger J, Bender A, Möller HJ, Klopstock T, Rujescu D. Creatine protects against excitotoxicity in an in vitro model of neurodegeneration. *PLoS One.* (2012) 7:e30554. doi: 10.1371/journal.pone.0030554
- Sartini S, Sestili P, Colombo E, Martinelli C, Bartolini F, Ciuffoli S, et al. Creatine affects in vitro electrophysiological maturation of neuroblasts and protects them from oxidative stress. *J Neurosci Res.* (2012) 90:435–46. doi: 10.1002/jnr.22762
- Sartini S, Lattanzi D, Ambrogini P, di Palma M, Galati C, Savelli D, et al. Maternal creatine supplementation affects the morpho-functional development of hippocampal neurons in rat offspring. *Neuroscience.* (2016) 312:120–9. doi: 10.1016/j.neuroscience.2015.11.017
- Mallik B, Frank CA. Is creatine a CNS neurotransmitter? *eLife.* (2023) 12:e91824. doi: 10.7554/eLife.91824
- Burtscher J, Millet GP, Place N, Kayser B, Zanou N. The muscle-brain axis and neurodegenerative diseases: the key role of mitochondria in exercise-induced neuroprotection. *Int J Mol Sci.* (2021) 22:6479. doi: 10.3390/ijms22126479
- Severinsen MCK, Pedersen BK. Muscle-organ crosstalk: the emerging roles of myokines. *Endocr Rev.* (2020) 41:594–609.
- Kreider RB, Kalman DS, Antonio J, Ziegenfuss TN, Wildman R, Collins R, et al. International society of sports nutrition position stand: safety and efficacy of creatine supplementation in exercise, sport, and medicine. *J Int Soc Sports Nutr.* (2017) 14:18. doi: 10.1186/s12970-017-0173-z
- Rodriguez NR, Di Marco NM, Langley S. American College of Sports Medicine position stand: nutrition and athletic performance. *Med Sci Sports Exerc.* (2009) 41:709–31. doi: 10.1249/MSS.0b013e31890eb86
- Wax B, Kerkick CM, Jagim AR, Mayo JJ, Lyons BC, Kreider RB. Creatine for exercise and sports performance, with recovery considerations for healthy populations. *Nutrients.* (2021) 13:1915. doi: 10.3390/nu13061915
- Ribeiro F, Longobardi I, Perim P, Duarte B, Ferreira P, Gualano B, et al. Timing of creatine supplementation around exercise: a real concern? *Nutrients.* (2021) 13:2844. doi: 10.3390/nu13082844
- Wu SH, Chen KL, Hsu C, Chen HC, Chen JY, Yu SY, et al. Creatine supplementation for muscle growth: a scoping review of randomized clinical trials from 2012 to 2021. *Nutrients.* (2022) 14:1255. doi: 10.3390/nu14061255
- Forbes SC, Candow DG, Falk Neto JH, Kennedy MD, Forbes JL, Machado M, et al. Creatine supplementation and endurance performance: surges and sprints to win the race. *J Int Soc Sports Nutr.* (2023) 20:2204071. doi: 10.1080/15502783.2023.2204071
- Clark JF, Cecil KM. Clinical applications of creatine supplementation in health and disease. *Nutrients.* (2021) 13:58.
- Kreider RB, Stout JR. Creatine in health and disease. *Nutrients.* (2021) 13:447. doi: 10.3390/nu13020447
- Rawson ES, Venezia AC. Use of creatine in the elderly and evidence for effects on cognitive function in young and old. *Amino Acids.* (2018) 50:1401–10. doi: 10.1007/s00726-011-0855-9
- Tarnopolsky MA. Creatine as a therapeutic strategy for myopathies and other conditions. *Amino Acids.* (2011) 40:1397–407. doi: 10.1007/s00726-011-0876-4
- Longobardi I, Gualano B, Seguro AC, Roschel H. Is it time for a requiem for creatine supplementation-induced kidney failure? A narrative review. *Nutrients.* (2023) 15:1466. doi: 10.3390/nu15061466
- Kostka M, Morys J, Malecki A, Nowacka-Chmielewska M. Muscle-brain crosstalk mediated by exercise-induced myokines—insights from experimental studies. *Front Physiol.* (2024) 15:1488375. doi: 10.3389/fphys.2024.1488375
- Isaac AR, Lima-Filho RAS, Lourenco MV. How does the skeletal muscle communicate with the brain in health and disease? *Neuropharmacology.* (2021) 197:108744. doi: 10.1016/j.neuropharm.2021.108744

24. Pedersen BK. Physical activity and muscle-brain crosstalk. *Nat Rev Endocrinol.* (2019) 15:383–92. doi: 10.1038/s41574-019-0174-x
25. Matthews VB, Aström MB, Chan MH, Bruce CR, Krabbe KS, Prelovsek O, et al. Brain-derived neurotrophic factor is produced by skeletal muscle cells in response to contraction and enhances fat oxidation via activation of AMP-activated protein kinase. *Diabetologia.* (2009) 52:1409–18. doi: 10.1007/s00125-009-1364-1
26. Wrigley S, Arafa D, Tropea D. Insulin-like growth factor 1: at the crossroads of brain development and aging. *Front Cell Neurosci.* (2017) 11:14. doi: 10.3389/fncel.2017.00014
27. Pesce M, La Fratta I, Paolucci T, Grilli A, Patrino A, Agostini F, et al. From exercise to cognitive performance: role of Irisin. *Appl Sci.* (2021) 11:7120. doi: 10.3390/app11157120
28. Zhang S, Xia J, He W, Zou Y, Liu W, Li L, et al. From energy metabolism to mood regulation: the rise of lactate as a therapeutic target. *J Adv Res.* (2025). doi: 10.1016/j.jare.2025.04.018
29. Delezie J, Handschin C. Endocrine crosstalk between skeletal muscle and the brain. *Front Neurol.* (2018) 9:698. doi: 10.3389/fneur.2018.00698
30. Benatti FB, Pedersen BK. Exercise as an anti-inflammatory therapy for rheumatic diseases—myokine regulation. *Nat Rev Rheumatol.* (2015) 11:86–97. doi: 10.1038/nrrheum.2014.193
31. Hargreaves M, Spriet LL. Exercise metabolism: fuels for the fire. *Cold Spring Harb Perspect Med.* (2018) 8:a029744. doi: 10.1101/cshperspect.a029744
32. Ting EY, Yang AC, Tsai SJ. Role of interleukin-6 in depressive disorder. *Int J Mol Sci.* (2020) 21:2194. doi: 10.3390/ijms21062194
33. Bogdanis GC, Nevill ME, Aphasidis G, Stavrinou PS, Jenkins DG, Giannaki CD, et al. Effects of oral creatine supplementation on power output during repeated treadmill sprinting. *Nutrients.* (2022) 14:1140. doi: 10.3390/nu14061140
34. Furtado ETF, Oliveira JPL, Pereira ISB, Veiga EP, Silva SFD, Abreu WC. Short term creatine loading improves strength endurance even without changing maximal strength, RPE, fatigue index, blood lactate, and mode state. *An Acad Bras Cienc.* (2024) 96:e20230559. doi: 10.1590/0001-3765202420230559
35. Glaister M, Rhodes L. Short-term creatine supplementation and repeated sprint ability—a systematic review and meta-analysis. *Int J Sport Nutr Exerc Metab.* (2022) 32:491–500. doi: 10.1123/ijnsnem.2022-0072
36. Edman S, Horwath O, Van der Stede T, Blackwood SJ, Moberg I, Ström Lind H, et al. Pro-brain-derived neurotrophic factor (BDNF), but not mature BDNF, is expressed in human skeletal muscle: implications for exercise-induced neuroplasticity. *Function (Oxf).* (2024) 5:zqae005. doi: 10.1093/function/zqae005
37. Peake JM, Della Gatta P, Suzuki K, Nieman DC. Cytokine expression and secretion by skeletal muscle cells: regulatory mechanisms and exercise effects. *Exerc Immunol Rev.* (2015) 21:8–25. Available at: <http://eir-isei.de/2015/eir-2015-008-article.pdf>
38. Petersen AMW, Pedersen BK. The anti-inflammatory effect of exercise. *J Appl Physiol.* (2005) 98:1154–62. doi: 10.1152/japplphysiol.00164.2004
39. Dreyer HC, Fujita S, Cadenas JG, Chinkes DL, Volpi E, Rasmussen BB. Resistance exercise increases protein synthesis and phosphorylation of mTOR signaling components in human skeletal muscle. *J Physiol.* (2006) 576:525–32. doi: 10.1113/jphysiol.2006.116451
40. Burke DG, Candow DG, Chilibeck PD, MacNeil LG, Roy BD, Tarnopolsky MA, et al. Effect of creatine supplementation and resistance-exercise training on muscle insulin-like growth factor in young adults. *Int J Sport Nutr Exerc Metab.* (2008) 18:389–98. doi: 10.1123/ijnsnem.18.4.389
41. Farshidfar F, Pinder MA, Myrie SB. Creatine supplementation and skeletal muscle metabolism for building muscle mass: review of the potential mechanisms of action. *Curr Protein Pept Sci.* (2017) 18:1273–87. doi: 10.2174/1389203718666170606105108
42. Cordingley, DM, Cornish, SM, Candow, DG. Anti-Inflammatory and Anti-Catabolic Effects of Creatine Supplementation: A Brief Review. *Nutrients.* (2022) 14:544. doi: 10.3390/nu14030544
43. Kalinski P. Regulation of immune responses by prostaglandin E2. *J Immunol.* (2012) 188:21–8. doi: 10.4049/jimmunol.1101029
44. Solis MY, Artioli GG, Gualano B. Potential of creatine in glucose management and diabetes. *Nutrients.* (2021) 13:570. doi: 10.3390/nu13020570
45. Lourenco MV, Frozza RL, de Freitas GB, Zhang H, Kincheski GC, Ribeiro FC, et al. Exercise-linked FND5/irisin rescues synaptic plasticity and memory defects in Alzheimer's models. *Nat Med.* (2019) 25:165–75. doi: 10.1038/s41591-018-0275-4
46. Wrann CD, White JP, Salogiannnis J, Laznik-Bogoslavski D, Wu J, Ma D, et al. Exercise induces hippocampal BDNF through a PGC-1 $\alpha$ /FND5 pathway. *Cell Metab.* (2013) 18:649–59. doi: 10.1016/j.cmet.2013.09.008
47. Pedersen BK, Febbraio MA. Muscle–organ crosstalk: the emerging roles of myokines. *Nat Rev Endocrinol.* (2012) 8:457–65. doi: 10.1210/endrev/bnaa016
48. Hamilton GF, Rhodes JS. Exercise regulation of cognitive function and neuroplasticity in the healthy and diseased brain. *Prog Mol Biol Transl Sci.* (2015) 135:381–406. doi: 10.1016/bs.pmbts.2015.07.004
49. Cunha MP, Machado DG, Capra JC, Jacinto J, Bettio LE, Rodrigues AL. Antidepressant-like effect of creatine in mice involves dopaminergic activation. *J Psychopharmacol.* (2012) 26:1489–501. doi: 10.1177/0269881112447989
50. Cotman CW, Berchtold NC, Christie LA. Exercise builds brain health: key roles of growth factor cascades and inflammation. *Trends Neurosci.* (2007) 30:464–72. doi: 10.1016/j.tins.2007.06.011
51. Rasmussen P, Brassard P, Adser H, Pedersen MV, Leick L, Hart E, et al. Evidence for a release of brain-derived neurotrophic factor from the brain during exercise. *Exp Physiol.* (2009) 94:1062–9. doi: 10.1113/expphysiol.2009.048512
52. Song M, Martinowich K, Lee FS. BDNF at the synapse: why location matters. *Mol Psychiatry.* (2017) 22:1370–5. doi: 10.1038/mp.2017.144
53. Knaepen K, Goekint M, Heyman E, Meeusen R. Neuroplasticity—exercise-induced response of peripheral brain-derived neurotrophic factor: a systematic review of experimental studies in human subjects. *Sports Med.* (2010) 40:765–801. doi: 10.2165/11534530-000000000-00000
54. Dinoff A, Herrmann N, Swardfager W, Lanctôt KL. The effect of acute exercise on blood concentrations of brain-derived neurotrophic factor in healthy adults: a meta-analysis. *Eur J Neurosci.* (2017) 46:1635–46. doi: 10.1111/ejn.13603
55. Lu B, Nagappan G, Lu Y. BDNF and synaptic plasticity, cognitive function, and dysfunction. *Handb Exp Pharmacol.* (2014) 220:223–50. doi: 10.1007/978-3-642-45106-5\_9
56. Bathina S, Das UN. Brain-derived neurotrophic factor and its clinical implications. *Arch Med Sci.* (2015) 11:1164–78. doi: 10.5114/aoms.2015.56342
57. Candow DG, Forbes SC, Chilibeck PD, Cornish SM, Antonio J, Kreider RB. Variables influencing the effectiveness of creatine supplementation as a therapeutic intervention for sarcopenia. *Front Nutr.* (2019) 6:124. doi: 10.3389/fnut.2019.00124
58. Pazini FL, Cunha MP, Rosa JM, Colla AR, Lieberknecht V, Oliveira Á, et al. Creatine, similar to ketamine, counteracts depressive-like behavior induced by corticosterone via PI3K/Akt/mTOR pathway. *Mol Neurobiol.* (2016) 53:6818–34. doi: 10.1007/s12035-015-9580-9
59. Sherpa NN, De Giorgi R, Ostinelli EG, Choudhury A, Dolma T, Dorjee S. Efficacy and safety profile of oral creatine monohydrate in add-on to cognitive-behavioural therapy in depression: an 8-week pilot, double-blind, randomised, placebo-controlled feasibility and exploratory trial in an under-resourced area. *Eur Neuropsychopharmacol.* (2025) 90:28–35. doi: 10.1016/j.euroneuro.2024.10.004
60. Pinto CL, Botelho PB, Pimentel GD, Campos-Ferraz PL, Mota JF. Creatine supplementation and glycemic control: a systematic review. *Amino Acids.* (2016) 48:2103–29. doi: 10.1007/s00726-016-2277-1
61. Stroud MA, Holliman D, Bell D, Green AL, Macdonald IA, Greenhaff PL. Effect of oral creatine supplementation on respiratory gas exchange and blood lactate accumulation during steady-state incremental treadmill exercise and recovery in man. *Clin Sci (Lond).* (1994) 87:707–10. doi: 10.1042/cs0870707
62. Turner CE, Byblow WD, Gant N. Creatine supplementation enhances corticomotor excitability and cognitive performance during oxygen deprivation. *J Neurosci.* (2015) 35:1773–80. doi: 10.1523/JNEUROSCI.3113-14.2015
63. Harris RC, Söderlund K, Hultman, E. Elevation of creatine in resting and exercised muscle of normal subjects by creatine supplementation. *Clin Sci (Lond).* (1992) 83:367–74. doi: 10.1042/cs0830367
64. Deldicque L, Atherton, P, Patel, R, Theisen, D, Nielsens, H, Rennie, MJ, et al. Effects of resistance exercise with and without creatine supplementation on gene expression and cell signaling in human skeletal muscle. *J Appl Physiol* (2008) 104:371–8. doi: 10.1152/japplphysiol.00873.2007
65. Eijnde B, Ursø, B, Richter, EA, Greenhaff, PL, Hespel, P. Effect of oral creatine supplementation on human muscle GLUT4 protein content after immobilization. *Diabetes.* (2001) 50:18–23. doi: 10.2337/diabetes.50.1.18