Letter to the Editor

Unveiling the orchestrators: The novel role of specific micronutrients in mediating muscle-brain crosstalk during exercise

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Dear Editor-in-Chief

While the critical role of macronutrients and established myokines (e.g., BDNF, Irisin) in muscle-brain communication during exercise is increasingly recognized, a significant and underexplored frontier lies in the specific, active modulation of this bidirectional crosstalk by essential micronutrients. This letter proposes a novel conceptual framework: that certain micronutrients act not merely as metabolic co-factors, but as dynamic orchestrators or gatekeepers of the signaling pathways fundamental to muscle-brain communication in response to acute and chronic exercise.

Beyond their classical roles in energy metabolism or antioxidant defense within each organ, compelling emerging evidence suggests specific micronutrients directly influence the production, release, stability, and reception of key signaling molecules traversing the muscle-brain axis: Vitamin D receptors (VDR) are expressed in both skeletal muscle and brain regions crucial for motor control and cognition. Recent work indicates vitamin D sufficiency potentiates exercise-induced BDNF release from muscle and brain, enhances sensitivity to neuroprotective myokines like Irisin, and may regulate muscle-derived kynurenine metabolism, shifting it away from neurotoxic metabolites (e.g., quinolinic acid) towards neuroprotective pathways (Pan et al., 2022). Deficiency may thus disrupt this protective signaling axis.

Certain polyphenols (e.g., flavonoids, curcumin) cross the BBB and exhibit potent anti-inflammatory and antioxidant effects. Novel evidence suggests they may protect neuronal receptors involved in sensing muscle-derived signals (e.g., AMPK activation) from exercise-induced oxidative stress, enhancing signal fidelity. Furthermore, they may modulate microglial activation states triggered by muscle-derived inflammatory signals during intense exercise, preventing excessive neuroinflammation (Gao et al., 2024; Gomez-Pinilla & Nguyen, 2012; Wang et al., 2024).

B-vitamins (particularly B6, B9, B12) are essential co-factors in one-carbon metabolism, critically influencing the synthesis of neurotransmitters (serotonin, dopamine) known to modulate central fatigue, motivation, and motor output. Exercise alters neurotransmitter turnover. Crucially, B-vitamin status impacts the brain's response to peripherally derived signals like IL-6, which has dual pro-inflammatory and anti-inflammatory/neuroprotective roles depending on context and magnitude (Gomez-Pinilla & Nguyen, 2012; Kato et al., 2024). Optimal B-vitamin levels may be key for interpreting muscle-derived IL-6 as an anti-fatigue signal within the CNS.

Therefore, we propose that specific micronutrients (e.g., Vitamin D, B-vitamins, polyphenols) act as dynamic modulators of the muscle-brain signaling axis during exercise, moving beyond their classical metabolic roles. Understanding this "Micronutrient Crosstalk Matrix" offers novel avenues to optimize exercise benefits for brain health and performance through targeted nutrition.

References

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