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The unexplored potential of exosomes in the muscle–brain axis

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To the editor,

In the article "Neuronal innervation regulates the secretion of neurotrophic myokines and exosomes from skeletal muscle," Huang et al. demonstrate that innervated skeletal muscle produces neurotrophic myokines and exosomes, enhancing communication between brain cells (1).

This research sheds light on the neuromuscular interface, essential for understanding muscle physiology and neurodegenerative diseases.

The system developed in this study is truly remarkable, offering significant insights into neuromuscular cross talk and paving the way for an enhanced understanding of the morphofunctional alterations associated with neurodegenerative diseases. By demonstrating the role of neuronal innervations in regulating muscle metabolism and enhancing the secretion of neurotrophic factors, including myokines and exosomes, the authors have illuminated a critical aspect of neuron–muscle interface. This study not only highlights the importance of such interactions but also sets the stage for future investigations into exactly how the neuron–muscle interface and exercise might synergistically influence muscle secretion.

One relevant aspect that the authors did not explore in their study is the potential role of exosome secretion from muscle tissue as part of a broader muscle–brain axis. Exosomes, due to their structural properties, can carry signals across long distances, linking distant organs like muscle and brain. A key factor supporting this muscle–brain axis is the ability of exosomes to cross the blood–brain barrier (BBB) (2–4). Under specific inflammatory conditions, often associated with increased permeability of the BBB, peripheral Extracellular Vesicles (EVs) can enter the central nervous system more easily, modulating the genetic profile of their target cells (5). This highlights the potential for muscle-derived EVs to directly influence brain function, further reinforcing the concept of a muscle–brain communication axis that warrants deeper exploration.

Among the organs–brain axes mediated by EVs, the gut–brain axis is particularly well-documented (6). Emerging evidence supports that EVs derived from the gut microbiota can traverse the BBB, carrying molecular signals that influence brain physiology and pathology (6, 7). Despite the physical distance between the two organs, the gut–brain axis has been shown to affect key processes, such as neurotransmitter production, neuroinflammation, and the regulation of stress-related pathways. Our previous studies have provided the first mechanistic evidence of this axis, showing that gut microbiota and probiotics influence tryptophan metabolism via exosomal signaling (8). These findings have major implications for neurological health and suggest potential therapeutic interventions, such as using probiotics to modulate exosome-mediated communication.

Applying this concept to muscle–brain communication could expand the scope of the author's findings. Muscle-derived exosomes may play a vital role in how exercise and muscle metabolism affect brain function. Exploring this muscle–brain axis could open avenues of research, particularly useful for an enhanced understanding of how systemic factors contribute to the pathophysiology of neurodegenerative diseases. This discovery holds considerable implications for neurological health and may lead to therapeutic interventions centered around probiotic intake. These considerations could help stimulate growing research in the field and optimize models aiming to demonstrate that organs communicate with each other via exosomes.

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The authors declare no competing interest.

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