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Therapeutic potential of myokines and myometabolites for brain ageing and neurodegeneration

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Neurodegeneration is not merely determined by local cues but is also influenced by systemic signals, such as factors released by peripheral tissues. Muscle-to-brain communication via muscle-secreted signalling factors is increasingly recognized as an important signalling axis. Collectively, muscle-to-brain signalling could be harnessed to impede neurodegeneration and delay cognitive decline during ageing.

Ageing is a primary risk factor for many diseases. The rise in life expectancy across many societies throughout the world has increased the burden of age-associated pathologies, such as neurodegeneration, for which therapies are either not available or have limited efficacy. Disrupted inter-tissue communication is a hallmark of ageing, and epidemiological studies indicate that muscle functional capacity is a predictor of mortality from all causes. For example, higher muscle strength correlates with a lower probability of developing neurodegeneration, whereas muscle weakness is a risk factor[1]. A possible explanation for the association between muscle and brain health was provided by the discovery of endocrine signalling factors secreted by skeletal muscle (generally known as myokines), and the finding that some of these muscle-derived signals are neuroprotective[1]. Some myokines, such as myostatin, are preferentially expressed by skeletal muscle whereas others, such as fibroblast growth factor 21 (FGF21), are expressed by multiple tissues but the muscle can be a considerable source[2].

Myokines are extremely diverse and include canonical growth factors and cytokines, myometabolites (such as lipids) and unconventional signals (such as exosomes and enzymes)[2]. The expression and/or secretion of some of these myokines can be modulated by exercise and associated processes (for example, cellular stress). However, although exercise protects against neurodegeneration and preserves cognition, muscle functional capacity generally declines with ageing, thus limiting the possibility of reaping the benefits of an active lifestyle. Moreover, patients on bed rest and/or with reduced mobility have limited exercise capabilities and are therefore precluded from the benefits that derive from physical activity. Therefore, there is a pressing need to determine how exercise preserves cognitive capacity and the key myokines that mediate protective muscle-to-brain communication. Several exercise-induced myokines (such as brain-derived neurotrophic factor (BDNF), cathepsin B, irisin, interleukin-6 and FGF21) were found to signal to the brain by crossing the blood–brain barrier, whereas others could improve brain function and impede neurodegeneration by acting on brain areas with an incomplete or weak blood–brain barrier (such as the circumventricular organs). A possible therapy could consist of the combination of top-performing myokines that benefit the central nervous system (CNS) during normal ageing and/or disease (such as BDNF, cathepsin B and irisin)[3–5]. Moreover, as well as neurons, multiple other cell types (such as microglia and astrocytes) contribute to neurodegeneration and could therefore be the target of myokine signalling. Likewise, some myokines can act indirectly on the CNS by signalling to the brain endothelium, as found for growth differentiation factor 11, and by preserving the integrity of the blood–brain barrier, which declines with ageing. Moreover, the retina might also benefit from neuroprotective myokines, given the reported benefits of exercise on this tissue[1].

Besides muscle, signalling factors secreted by other tissues, such as osteocalcin secreted by bone, are induced by exercise (possibly via myokine signalling) and cooperate with myokines to fulfil the metabolic demands of contracting muscles. Therefore, myokines might be key not only for transmitting information from the muscle to the brain but also for inducing the expression of a second tier of signalling factors by other non-muscle tissues and organs following exercise. This second tier could in turn contribute to the neuroprotective effects of physical activity. In summary, some exercise-induced myokines have been found to be neuroprotective[1,3–5], but the full compendium of myokines mediating muscle-to-brain signalling and their outcome on the CNS remains largely unexplored, especially in the context of ageing.

It is also worth considering that skeletal muscle secretes many myokines at steady state and/or in response to cues that can be disconnected from exercise, such as the nutrient-sensitive myokine erythroferrone, also known as myonectin[2]. Therefore, myokines might have a role in regulating normal brain function and behaviours, such as feeding initiation[6], as found for other peripheral tissues with important metabolic roles, such as white adipose tissue. Moreover, there might be myokines that are differentially expressed and/or secreted depending on the health status of the muscle. This differential expression could therefore transmit information to the brain about the overall fitness of this tissue.

Although there is an emphasis on identifying protective myokines, it is equally important to consider the detrimental effects that the lack of physical activity has on cognitive capacity during ageing. Whereas a sedentary life could impair brain function simply because of reduced levels of protective myokines, it is also possible that detrimental myokines not normally expressed by a functional muscle (such as haemopexin) might become preponderant during muscle wasting and

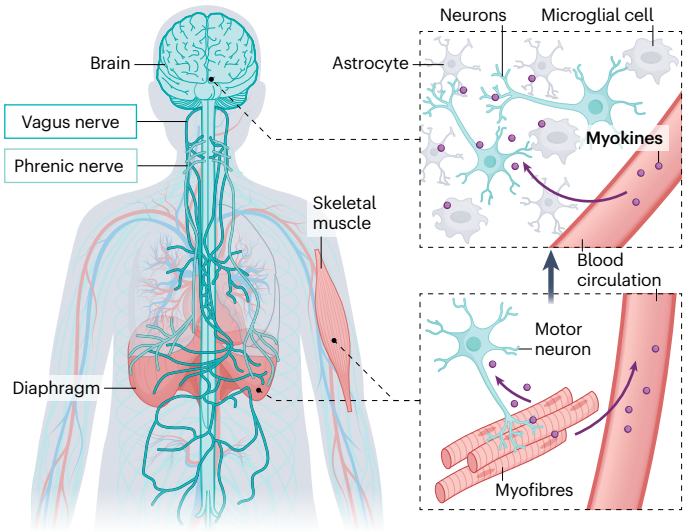

Fig. 1 | General overview of muscle-to-brain signalling. Muscle-secreted signalling factors (myokines) can reach the brain via the circulation and potentially also via retrograde signalling through the neuromuscular junction and spinal cord. The diaphragm might also signal to the brain through its connection via the vagus nerve and phrenic nerve.

weakness associated with ageing and disease[7]. Protective myokines might counteract the function of such detrimental myokines, but, alternatively, this protection could be obtained by depleting deleterious myokines and/or by impeding their signalling. Likewise, it has been proposed that aggregation-prone proteins responsible for neurodegeneration in the brain might be secreted by peripheral sources, including the skeletal muscle, and that such a circulating pool of pathogenic proteins could contribute to brain disease. Although the quantitative relevance and pervasiveness of such a phenomenon remains largely unexplored[8], it could represent an additional axis of muscle-to-brain detrimental signalling that could be targeted therapeutically.

Apart from the circulation, alternative routes of muscle-to-brain signalling are also possible. For example, stimulation of specific brain areas and neuronal circuits in response to exercise might occur because of retrograde transport of signalling factors through the neuromuscular junction and spinal cord or because of signalling from muscles to motor neurons via myokines such as neurturin[9] (Fig. 1).

Although all skeletal muscles are typically considered equal sources of myokines, it is also worth considering that some skeletal muscles could have more prominent roles than others. The diaphragm is key for respiration and hence for exercise capacity. This muscle influences breathing through its contractions and so affects neuronal oscillations associated with learning, memory and behaviour. The diaphragm is connected to the brain via the phrenic nerve and vagus nerve, which transmit motor information to the diaphragm and report information back to the brain. Interestingly, the vagus nerve is a recognized route of gut-to-brain signalling and can mediate the spread of pathogenic proteins from the gut to the brain: on this basis, the vagus (and possibly also the phrenic) nerve could constitute an overlooked route for muscle-to-brain communication and for the seeding of pathogenic proteins from the diaphragm to the CNS. The diaphragm might also express a different portfolio of myokines compared to other skeletal muscles. Specifically, the close connection of the diaphragm with breathing and, by extension, exercise, suggests a potentially unique role of protective myokines that are preferentially expressed by the diaphragm versus other skeletal muscles.

In conclusion, a comprehensive understanding of the signalling axes that mediate muscle-to-brain communication could uncover pivotal myokines and myometabolites that might help preserve brain function. Recombinant myokines, administration of exogenous myometabolites and myokine-based gene therapies might provide opportunities for delaying or preventing the onset and development of age-related dementias but might also find a more general application in maintaining brain health and function during normal ageing.

It has been suggested that human brains evolved to their current size because of a lifestyle change dependent on muscle, that is, the increased physical activity associated with the long-distance hunting strategies of *Homo erectus*[10]. It might be time for the skeletal muscle to help the brain cope with lifestyle changes again, such as the modern-day challenge of maintaining a healthy brain over a longer lifespan. Boosting the levels of protective myokines and myometabolites while blocking detrimental signals released by wasting muscles might provide a therapeutic opportunity to increase brain healthspan.

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Competing interests

The authors declare no competing interests.