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Commentary

Training muscles to keep the aging brain fit

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1. Aging and exercise

Aging is associated with the decline of cellular, tissue, and systemic functions and is characterized by at least 7 highly interdependent molecular pillars of aging[1] (Fig. 1). Besides compromised genetic functions (telomer shortening and epigenetic dysregulation), metabolic efficiency (impaired mitochondrial functions and nutrient sensing), and cellular stress responses deteriorate. Consequential disruption of normal protein regulation (proteostasis) in combination with impaired cellular waste clearance leads to the accumulation of macromolecular damage (and in some cases to specific protein aggregation pathologies, like in Alzheimer's dementia brains), chronic inflammation, and stem cell exhaustion ensue. Less efficient communication between cells and tissues contributes to age-related decline of physical and cognitive performance and increased vulnerability to age-related diseases. Sufficient physical activity or regular exercise (i.e., physical activity to systematically increase fitness) can counteract many cellular aging effects, by improving cellular stress responses, mitochondrial functions, and waste-disposal efficiency.[1] Accordingly, it constitutes a potent protective factor against age-related symptoms and diseases, including cognitive decline and dementia.[2]

But why? Is exercising at an older age still efficient? And don't these molecular effects occur mainly locally, in the working skeletal muscle? So how does this affect the brain?

2. Do older people still benefit from exercise?

Today, the old dogma claiming that exercise yields reduced benefits at an older age, when the cardiovascular plasticity and muscle hypertrophy in response to exercise may be blunted, is largely refuted. It is well-established that regular exercise attenuates muscle-mass reduction and physical and cognitive performance decline, preserves higher cardiorespiratory fitness (CRF), and protects from all-cause mortality also at old age.[3,4]

CRF (i.e., maximal oxygen uptake) is a measure of endurance exercise performance and decreases continuously from the age of ∼30−40 years. The losses become greater at older age, reaching decreases of more than 21% per decade at ages of more than 70 years[3] and even 46% per decade in highly trained old athletes who stop training.[5] At such rates, the exercise capacity quickly falls below the levels necessary for performing daily life activities, such as cleaning and cooking. CRF is also correlated with preserved cognitive function;[6] thus, overall the maintenance of a high CRF is crucial for functional independence and quality of life.

Concomitantly, skeletal muscle mass decreases by about 1% per year starting from mid-adulthood.[3] In combination with a decline of the neuronal components of muscle force generation, this compromises strength-dependent activities, such as lifting, standing up, or climbing stairs, as well as balance, increasing the risk of falls.[3]

Regular exercise attenuates this decline.[5] Highly active athletes can maintain CRF similar to those of inactive mid-age adults even in their 80s.[3] In less active adults, starting exercise late in life is still efficient. Optimized aerobic training interventions can increase CRF by up to at least 46% in people older than 70 years.[3] Similarly, strength and hypertrophy can be reasonably trained even at old age:[3] average increases of maximum leg extension strength by close to 50% have been reported in people older than 85 years after 12 weeks of progressive whole-body resistance exercise training.[7]

Both endurance and resistance exercise are beneficial in old age and appropriate training programs can elicit similar relative strength and CRF outcomes as in young adults.

These effects refer mainly to skeletal muscles and the cardiorespiratory system: What about the brain?

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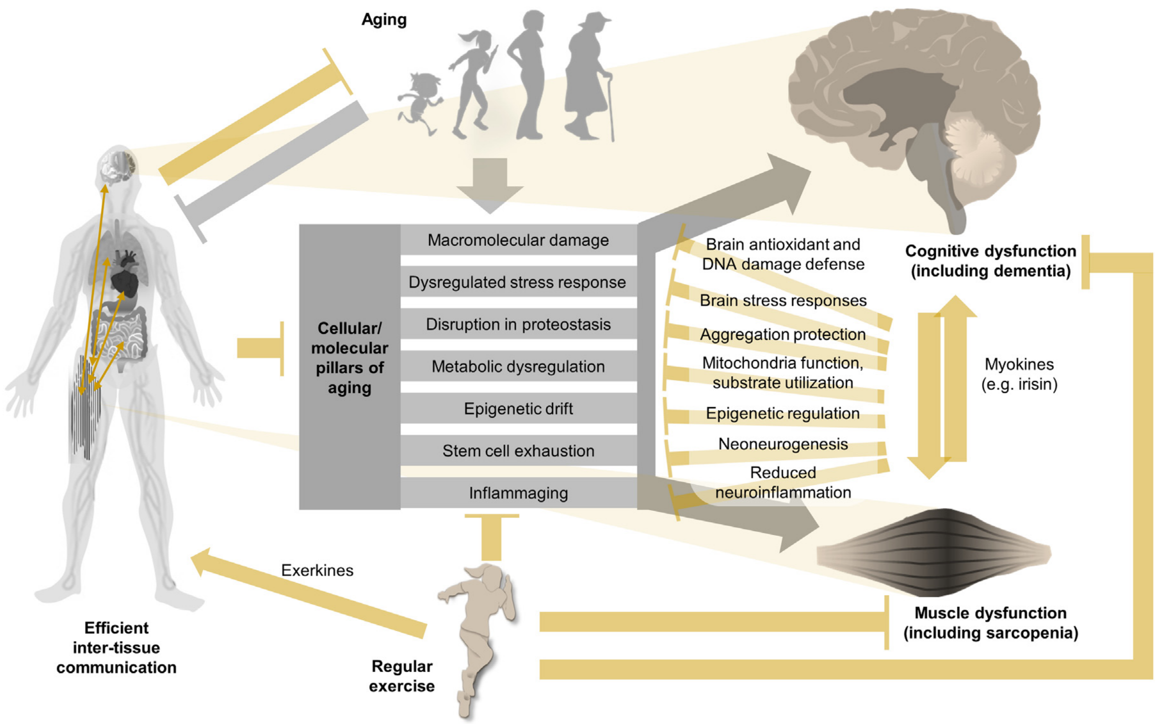

Fig. 1. Regular exercise and the molecular hallmarks of aging (based on Goh et al.[1]): the muscle–brain axis' involvement in brain benefits from exercise. Inter-tissue coordination is essential for healthy aging, in particular, to manage metabolic stress, such as in exercise. Regular exercise keeps the required communication between organs efficient and thereby likely contributes to the systemic effects of exercise. Many organs are important for the management of systemic metabolic health and crosstalk between all of them (including the gut, liver, cardiovascular, respiratory, and immune systems, as well as the brain; for clarity, only crosstalk of those organs with skeletal muscle are indicated, and not among themselves, although they are important as well) and the muscle–brain axis is 1 important example that is emerging as integral for the cognitive benefits of exercise.

3. Maintaining healthy inter-organ communication via the muscle–brain axis

Linked to increasing life expectancies, age-related neurological diseases—such as dementia—are among the fastest-growing morbidities worldwide. Regular exercise is a powerful measure to improve brain health and prevent cognitive decline and dementia[8] but how this works mechanistically remains poorly understood.[9]

Improved inter-organ communication is increasingly acknowledged as an intriguing health advantage of exercise. The many signaling molecules mediating organismal exercise responses and health benefits are called exerkines.[10] Exerkines are released by acute or chronic exercise from different organs and can act locally and/or systemically. If released by skeletal muscle, they are termed "myokines". The emerging concept of a "muscle–brain axis" appears to play a major role in the brain's responses to exercise and is based on crosstalk via myokines directly or indirectly affecting the brain.[8,10] The myokine irisin has gained particular attention recently as a potential major mediator of cognitive benefits of exercise, based on observations that irisin mimics and its deficiency abolishes exercise effects on cognition in animal models.[11] While the topic of adult neurogenesis is a heavily debated one, in rodents myokines seem to increase hippocampal neurogenesis and neurotrophins.[10] Exerkines released from other tissues and changing systemic conditions (e.g., pH, temperature) by physical effort certainly also play roles in exercise-induced effects on the brain.[8,10]

4. Finish line

Regular appropriate exercise benefits many organs, including the brain. Exercise-stimulated muscle–brain crosstalk likely constitutes an important factor for brain health, attenuation of cognitive decline, and prevention of dementia. Like for other exercise outcomes, the design of exercise programs (including the choice of the exercise dose) is essential also for brain effects. The generally recommended minimum exercise volumes for older adults are (1) 150 min of moderate-intensity or 75 min of vigorous-intensity aerobic activity per week, (2) muscle strength training on 2 days per week, and (3) balance and flexibility training on 2 days per week. Exceeding these recommendations yields additional benefits and should be aimed at, according to individual abilities and limitations,[3,4] also if the aim is to improve brain health. Progressive resistance training programs are generally required to improve strength and induce hypertrophy and if chosen well, they can be very effective in older people.[3,7] Importantly, for all exercise types, an appropriate diet and sufficient regeneration are essential. To improve brain health, the combination of cognitive and social stimulation is probably central as well.

Keeping muscles and the muscle−brain axis in shape when getting older helps to stay physically and mentally healthy. In the race of life, an end spurt will not bring you to the finish line faster but instead, it will make you enjoy the run longer and in better metabolic, cardiovascular, muscular, and cerebral health.

Authors' contributions

JB contributed to the conceptualization, wrote the original draft, designed the figure, and contributed writing (review and editing); MB contributed to the conceptualization and contributed writing (review and editing). Both authors have read and approved with the final version of the manuscript, and agree with the order of presentation of the authors.

Competing interests

Both authors declare that they have no competing interests.

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