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Editorial

The multi-tissue benefits of exercise on aging human physiology

1. Introduction to the special issue

Aging severely impacts functional, metabolic, and cognitive health of older adults, leading to an increased risk of various diseases including heart disease, type 2 diabetes, and dementia. Aging also significantly impairs quality of life in an ever-growing older adult population via reduced functional capacity and an inability to perform activities of daily living. Interestingly, these derangements stem in part from a sedentary lifestyle, with exercise training leading to improvements in overall health of older adults. In this Special Issue on Exercise Gerontology: The Multi-Tissue Benefits of Exercise on Aging Human Physiology, we present a collection of reviews and original research that explore both the benefits, mechanisms, and the latest key findings on sedentary aging and exercise training via their impact on multi-organ systems physiology in older adults. The accompanying papers present a range of works by independent investigators highlighting: a) the impact of exercise and aging on chronic inflammation and alterations in NAD^+ biology, b) the potential role of exercise-induced extracellular vesicles as a regenerative therapeutic approach for aging muscle, c) a series of reviews on exercise and tissue crosstalk covering muscle, liver, brown and white adipose tissue, and the cardiovascular system, and d) an examination of the complex relationships between brain health and sedentary/physical activity behaviors. Collectively, this issue provides a ranging view of the many beneficial properties of exercise and multi tissue benefits in aging and underlies the need for continued translational investigations of exercise and aging.

2. Skeletal muscle heath and exercise in aging

The first articles in this special issue focus on skeletal muscle, the largest organ in the human body which plays a key role in posture and capacity for locomotion, as well as serving as a bona fide endocrine organ (Pedersen and Febbraio, 2012). Muscle mass starts to decline by the third decade of life, with ~10 % decrease by the age of 50 years (Lexell et al., 1988). Older adults (>60 years) have an acceleration in muscle loss, with ~0.7–0.8 % decrease in leg muscle mass each year (Lexell et al., 1988). The loss of muscle mass with age results from atrophy of type II muscle fibers and loss of both type I and II muscle fibers due to neurodegenerative processes including alpha motor neuron death and peripheral denervation (Lexell, 1995; Lexell et al., 1986; Lexell et al., 1983; Lexell et al., 1988). Along with muscle mass, muscle strength is also reduced with age. While associated with loss in muscle mass, declines in muscle strength are three times more rapid than the loss in mass (Goodpaster et al., 2006). Additionally, aging causes changes in muscle composition, with an increased prevalence of hybrid muscle fibers (Purves-Smith et al., 2014), decreased protein content, including lower total, sarcoplasmic, and myofibrillar protein (Trappe et al., 2003), and increased infiltration of adipose tissue (Visser et al., 2002). Clinically, sarcopenia increases the risk of falls and fractures, hospitalization, and mobility disability, collectively resulting in a reduced ability to perform activities of daily living.

The first review article by Kunz and Lanza details the multifactorial molecular mechanisms that contribute to age-associated inflammation or "inflammaging" (Kunz and Lanza, 2023). Increased circulating mediators of chronic low-grade inflammation are well recognized to play an important role in the etiology of many age-associated diseases (Freund et al., 2010). More recently, there is a growing appreciation for the role of muscle specific inflammatory responses and cascades in contributing to lower muscle mass and function in older adults. The role of innate immune receptors TLR and NLPR, both pattern recognition receptors, to induce expression of pro-inflammatory cytokines in mediation muscle inflammation are described. The specific role of macrophage infiltration and polarization may also have profound implications for skeletal muscle inflammation in older adults. Kunz and Lanza review the evidence that muscle inflammation contributes to a blunted anabolic response to acute exercise, a key effect of exercise needed to maintain muscle health. In addition, several studies have examined the potential of therapeutics to enhance exercise responsiveness in older adults, including NSAIDs, n-3 PUFA's and senolytics. Indeed, there is a growing appreciation for the importance of reducing inflammation to enhance responsiveness to acute exercise and exercise training. While the interplay between exercise and inflammation is complex, further understanding of how both interact in aging hold potential for developing new therapeutic strategies to maximize health benefits of exercise in aging.

The second review, by Chubanava and Treebak, focuses on the role of NAD^+ biology in aging muscle (Chubanava and Treebak, 2023). NAD^+ plays an obligatory role as a cofactor for hundreds of different redox enzymes. More recently, interest in NAD^+ has peaked because NAD^+ was identified as a co-substrate for sirtuins and PARPs, two enzyme classes that mediate a host of different biological effects, but at a cost of NAD^+ consumption, and that have been implicated in aging and longevity. The review details the evidence on how acute and chronic exercise may impact NAD^+ levels in skeletal muscle in rodent studies and importantly how these findings translate to humans. The effects of NAD^+ precursor supplementation (NR, NMN, and NAM) and exercise training combined on skeletal muscle aging are also addressed. Finally, the authors provide a critical discussion on the challenges and limitations in the field, including the need for improved standardization of NAD^+ extraction and analysis to make cross study comparisons more

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meaningful.

3. Exercise and interorgan crosstalk

Exercise elicits molecular cross talk between organs via release of "exerkines", signaling moieties which exert their effects through endocrine, paracrine and/or autocrine pathways (Chow et al., 2022). Since the discovery that muscle contraction releases IL-6 (Steensberg et al., 2000), the number of exercise-associated signaling molecules that have been identified has multiplied. Exerkines have potential roles in improving cardiovascular, metabolic, immune and neurological health (Chow et al., 2022). Recent studies have revealed that skeletal muscle can also release extracellular vesicles (EVs) into circulation following a bout of exercise (Vechetti et al., 2021). EVs are small membrane-bound vesicles capable of delivering biomolecules (including exerkines) to recipient cells and subsequently altering their metabolism. The original research article by Bean and colleagues furthers our understanding of how EVs role in exercise induced skeletal muscle regeneration (Bean et al., 2023). Using a targeted muscle contractile protocol, the authors show that skeletal muscle contraction in aged animals alters EV profiles using Raman spectroscopy. The findings suggest that intermittent bouts of repetitive skeletal muscle contractions improve the potential of serum EVs to improve functional recovery of acutely injured skeletal muscle in aged mice.

Expanding on the concept of interorgan communication, the review by Cao and Thyfault focuses on exercise and its ability to improve skeletal muscle, liver and adipose metabolism in an integrated manner to improve overall metabolic health in older adults (Cao and Thyfault, 2023). In the past, studies have predominantly focused on the effects of exercise on muscle and the cardiovascular system. However, there is a growing appreciation that exercise is a metabolic challenge for almost every organ system in the body. The authors describe the "dynamic trio" of skeletal muscle, liver and adipose tissue as key organ systems that work in concert to manage glucose and lipid supply and demand to fuel exercise metabolism. The resulting chronic adaptations protect older adults against cardiometabolic disease and while the mechanisms that mediate this protection are incompletely understood, IL-6 plays a prominent role along with other to be discovered exerkines. The review closes with a discussion on novel concepts in the field including time of day for optimal exercise response and the importance of considering interactions between pharmacotherapies commonly prescribes to older adults and exercise response.

The review by Nirengi and Stanford addresses the impact of aging on brown adipose tissue function and how exercise can counteract these negative effects (Nirengi and Stanford, 2023). BAT is a thermogenic organ that is controlled by the sympathetic nervous system and physiological stimuli. UCP-1 dependent thermogenesis in BAT is fueled by lipids, glucose and amino acids. In addition, BAT also functions as an endocrine organ and has been shown to impact systematic metabolism and cardiac health via a growing list of secreted endocrine factors. Aging causes a decrease in BAT mass and activity and this review concisely details the various aspects of BAT biology that are impaired with aging. Importantly, as with many other physiological systems, exercise can benefit BAT health by stimulating activity via the sympathetic nervous system and increasing endocrine function of BAT which can improve metabolic and cardiac health in aging.

The review by Murray and colleagues describes the molecular mechanisms underlying arterial dysfunction with aging and the beneficial effect that aerobic exercise can have on cardiovascular health (Murray et al., 2023). The barriers to engaging in aerobic exercise are reviewed along with alternative time and resource efficient therapies that promote healthy cardiovascular aging, including high resistance inspiratory muscle strength training and chronic passive heat therapy. Finally, pharmacological interventions that promote healthy aging are discussed, including NAD^{+} boosters, mitoquinol and senolytics. The review details evidence based alternative strategies that mimic aspects of exercise or target fundamental aging mechanisms that are impacted by exercise, with the caveat that further translational research is required before any of these options can be considered viable therapies to improve cardiovascular health with aging.

4. Sedentary behavior, exercise and brain health

The final review in this special issue by Collins and colleagues addresses the complex interactions between physical activity and sedentary behaviors and their impact on brain health (Collins et al., 2023). While the benefits of physical activity on brain health in adulthood and old age are reasonable well defined, there is a paucity of evidence investigating how sedentary behavior might impact brain health of older adults. Current evidence is mixed and future research is needed to more clearly define the role of sedentary behavior on brain health. The review includes a detailed discussion on the definition of key terms, including detailing the difference between sedentary behavior, physical inactivity, physical activity and how each relate to brain health. Investigations on the impact of sedentary behavior on brain health are burgeoning, and there has been speculation that sedentary behavior leads to biological and behavioral decline in brain health. The totality of literature however, paints a mixed picture. Studies of sedentary behavior are complicated, for example cognitively stimulating activities performed while sedentary may reduce the risk for dementia, independently of physical activity. The review concludes with the suggestion that future studies should consider conceptual models in which sedentary and physical activity behaviors are related together to provide a more holistic public heath message to promote brain health in late adulthood.

In summary, the collection of reviews and original research presented herein highlight key current concepts on the benefits of exercise in aging and identified important knowledge gaps. Though it is generally recognized that engagement in exercise induces multiple health benefits and can slow some of the negative effects of aging, there are important nuances in exercise modality, special populations, intervention combinations (pharmaceutical and exercise, etc.), and implementation strategies that may modulate the efficacy of exercise in older adults. Further investment in translational research at the juncture of exercise and aging are needed to advance our understanding from the molecular level to multi organ communication to optimize healthy aging.

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Andrew Philp[a,b], Paul M. Coen[c,*]
[a] *Centre for Healthy Ageing, Centenary Institute, Sydney, NSW, Australia*
[b] *School of Sport, Exercise and Rehabilitation Sciences, University of Technology Sydney, NSW, Australia*
[c] *AdventHealth Translational Research Institute, Orlando, FL, USA*

[*] Corresponding author at: AdventHealth Translational Research Institute, 301 East Princeton Street, Orlando, FL 32804, USA.
E-mail address: paul.coen@adventhealth.com (P.M. Coen).