J Musculoskel Neuron Interact 2004; 4(2):175-178

Review Article

Hylonome

The effects of exercise on skeletal muscle in the aged

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Abstract

Age-related sarcopenia leads to muscle weakness and a concomitant increase in gait problems and the risk of hip fracture due to falling in the elderly. Muscle weakness reduces general activity levels in elderly individuals which in turn elevates the risk of osteoporosis due to a decrease in overall mechanical loading of the skeleton. At the same time, age-related sarcopenia is also linked to an increase in the risk of metabolic disorders such as adult onset (Type II) diabetes. However, it is widely accepted that increased mechanical loading of the musculoskeletal system (e.g., resistive exercise) can have a beneficial effect on both skeletal muscle and the supporting skeleton resulting in a significant reduction in the risk of developing all of the above age-related problems. As such, unloading models that exhibit many if not all of the same responses observed in aged muscle, including the capacity of exercise to reverse these responses, may provide valuable insight into the skeletal muscle aging process.

Keywords: Aging, Resistive Exercise, Skeletal Muscle, Sarcopenia, Unloading Models

Introduction

In general, the effects of the aging process on skeletal muscle function can be characterized as being intrinsic or extrinsic. For example, aging-related decrements in cardiovascular/pulmonary/hormonal status can negatively impact skeletal muscle function and thus can be viewed as extrinsic effects. Conversely, aging-related reductions in myofiber cross-sectional area due to the loss of contractile protein (i.e., sarcopenia) and alterations in myofiber myosin heavy chain (MHC) expression profiles can be viewed as intrinsic effects. However, it is essential that such a characterization does not lead to the view that the extrinsic and intrinsic effects of the aging process on skeletal muscle function are isolated and unrelated. This perspective is useful when considering the effects of exercise on aging muscle. For example, exercise-induced transient increases in the levels of circulating hypertrophic hormones (i.e., GH or testosterone) in aged individuals[1,2], or the enhanced delivery of nutrients to skeletal muscle due to exercise-induced prevention of aging-related cardiovascular de-conditioning[3,4], both extrinsic effects, are capable of modulating intrinsic effects such as protein synthesis rates in individual myofibers[5].

One common component of physical activity/exercise is an increase in the levels of mechanical load placed on the body as a whole and skeletal muscle in particular. Currently, it is unclear whether or not the aging process *per se*, or the reduced levels of mechanical loading associated with age-related reductions in physical activity, results in the changes observed in the skeletal muscle tissue of older individuals[6-9]. However, it is clear that exercise/increased physical activity levels can prevent or reverse some of the phenotypic alterations commonly observed in aged skeletal muscle[6,10]. In addition, a large number of these alterations can also be seen in the skeletal muscle of younger individuals as a response to mechanical unloading of the musculoskeletal system[11-13]. These observations tend to support the concept that physical de-conditioning/reduction in mechanical loading plays a major role in some of the changes reported in aging muscle. This review will focus on specific intrinsic alterations reported in aging muscle, the effects of exercise on these aging-induced alterations, and the parallels, if any, that can be drawn between the aging process and the effects of mechanical unloading on younger muscle.

Myofiber sarcopenia

Sarcopenia, defined as an age-related loss in myofiber cross-sectional area (CSA), is characterized by a loss of contractile protein from the aging myofiber[14]. Sarcopenia results in functional decrements such as muscle weakness[15], disrup-

The author has no conflict of interest.

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Accepted 28 May 2004

tion in gait and an increase in the risk of falling in the elderly[16]. Recent studies employing resistive exercise protocols, such as weight training of the lower limbs, have suggested that sarcopenia can be reversed in aged (< 65 years old) individuals[14,17-19]. These studies have indicated that resistive exercise increases contractile protein synthesis resulting in an increase in myofiber CSA and muscle strength in aged muscle. Mechanical unloading of younger individuals (i.e., bed rest, unilateral leg suspension) decreases myofiber CSA in a similar fashion to that observed in individuals with age-related sarcopenia[11]. As in the aged, such unloading–induced myofiber atrophy can also be reversed by resistive exercise[20,21]. In both instances, the hypertrophic stimulus of mechanical loading appears to push the myofiber protein synthesis/protein degradation balance towards the synthetic side[22].

Myofiber type alterations

Alterations in myofiber characteristics due to aging appear to involve an increase in the relative numbers of Type I myofibers present, along with selective atrophy of Type II myofibers[23,24]. Jointly, this effect can explain the dramatic strength losses observed after the sixth decade of life in humans[25]. In addition to the classic histochemical ATPase fiber typing approach, the use of modern immunochemical and molecular techniques to investigate myosin heavy chain (MHC) protein expression has led to a clearer understanding of the effects of exercise in aging skeletal muscle[5,18,26,27]. Decreased number of Type II myofibers relative to Type I myofibers in aged muscle can be explained by either a complete loss of Type II fibers or an increase in the number of Type II fibers that undergo fiber type shifting. The increased number of hybrid myofiber exhibiting co-expression of both MHC I and MHC II proteins in aged muscle indicate that myofiber type shifting may be the true underlying cause of this Type I myofiber predominance in aged muscle, rather than a loss of Type II myofibers *per se*[28]. In addition, the Type IIb to Type IIa fiber type shifting observed during progressive resistance exercise in older men further indicates that aged muscle retains the capacity to respond to exercise in a similar fashion to young muscle[26]. Short-term unloading of skeletal muscle in younger individuals induces myofiber atrophy and decreases in muscle strength[13,29] but does not appear to induce the overt Type I myofiber shifting observed during aging, with the exception that a significant number of MHC hybrid fibers have been reported in such unloaded muscle[12]. However, as in the case of aged muscle, the use of resistive exercise protocols can reverse the decrements in whole muscle strength, myofiber cross-sectional area and modify MHC expression levels induced by unloading in younger muscle[12,21].

Excitation-contraction (E-C) coupling

One potential site where the aging process may have an adverse effect on contractile properties of skeletal muscle is during the process of E-C coupling. Recent information concerning the negative effects of reactive oxygen species (ROS) on the cellular machinery involved in controlling E-C coupling suggests that a number of calcium channels and their respective control systems may be a target for ROS-mediated damage[7,30-33]. In addition, modifications in the lipid composition of membrane systems within skeletal muscle, such as sarcoplasmic reticulum (SR) membranes, have been shown to modulate calcium channel function in a wide number of experimental models[34]. Preliminary results from our laboratory using an immuno-staining technique to spatially localize cholesterol in frozen sections[35], suggest that SR membrane cholesterol content is significantly increased in both aged and unloaded young muscle over control levels, a response that can be reversed by resistive exercise. In addition, we have shown that increased SR membrane cholesterol content results in the inhibition of SR Ca2+ ATPase activity in vesicle preparations obtained from soleus muscle. Conversely, we have also demonstrated that elevated membrane cholesterol content results in an increase in the activity of calcium release channels (RyR-1) present in a lipid bilayer model of the SR membrane. Such observations may explain the decrements in SERCA activity previously reported in both aged and unloaded muscle[36,37]. They may also provide a molecular basis for explaining the increase in calcium-mediated processes, such as calcium-dependent proteolysis, important in the sarcopenic response.

Summary

It is becoming more apparent that skeletal muscle is a tissue that remains responsive to exercise intervention throughout the lifespan. The ability of aged skeletal muscle to respond to exercise, especially resistive exercise, in the same fashion as younger muscle suggests that skeletal muscle retains an inherent plasticity not necessarily observed in other aging tissues. The close parallel in the responses of skeletal muscle to unloading indicates that there are many components of the aged muscle phenotype that result from reduced mechanical loading rather than from the aging process itself. As such, skeletal muscle unloading paradigms provide a useful model for studying several important facets of the aging process in skeletal muscle and its response to exercise.

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