Review Article
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Inflammatory response induced by resistance exercise

Abstract

Inflammatory response after resistance exercise occurs mainly in untrained subjects with exercises involving eccentric actions. Skeletal muscle is crucial in precise movement and your cells have a robust capacity of regenerated after injury, however, exercises involving eccentric actions, mainly in untrained subjects, induce muscular damage. This damage arises from muscle injury and may cause rupture and inflammation of muscle, connective or nervous tissues and produces a stereotyped inflammatory process. The inflammatory response is followed by muscle repair, regeneration, and growth, which involve activation, proliferation, and differentiation of satellite cells. Thus, this inflammatory response after muscle damage is fundamental to the adaptation of the skeletal muscle to exercise. Moreover, muscle damage decreases when a person performs the same exercise consistently and an attenuated inflammatory response to a repeated bout reflects in an adaptation to avoid the proliferation of the mechanical disruption of myofibrils. In addition, regular exercise is beneficial to upregulating defense mechanisms against oxidative stress, increased resistance against infection and a lower risk of appearance of disease.

Keywords: sskeletal muscle, muscle inflammation, eccentric actions, oxidative stress, sarcomeric, contractile, cytoskeletal proteins, dystrophin, desmin, leucocyte accumulation, calcium homeostasis, cytoskeletal proteins, myostatin inhibitor, follistatin, inflammatory myopathies.

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Introduction

In the body human, there are around 640 skeletal muscles which together account for ~38% of total body mass for men and 30% for women.[1] Skeletal muscle is crucial in precise movement and your functional unit cell (muscle fibre) has a vigorous regenerative capacity, with rapid reestablishment (by 3 weeks) of full power occurring even after severe damage that causes widespread myofibre necrosis.[2] Exercise-induced muscle damage (EIMD) in humans frequently occurs after unaccustomed exercise, particularly if the exercise involves a large amount of eccentric contractions. There are three types of muscle actions: concentric, eccentric and isometric. The eccentric actions occur during the lowering phase of any weightlifting exercise and are defined as muscle actions at the places where the muscle lengthens because the contraction force is less than the resistive force.[3] Initial resistance exercise stress affects muscle homeostasis promoting changes in muscle morphology, loss of sarcomeric structural proteins (e.g. desmin and dystrophin), muscle fibre segmental necrosis, alterations in connective tissue, in T-tubules and sarcoplasmic reticulum.[4,5] Muscle damage is commonly defined by disruption of the extracellular matrix, basal lamina, and sarcolemma as well as damage within the muscle fiber to the contractile and cytoskeletal proteins. Sarcolemma disruption is confirmed by an increase in blood-borne levels of intramuscular proteins such as creatine kinase (CK), which in turn has been linked to production of an inflammatory response.[6] The severity of the inflammation depends on the type, duration and intensity of exercise. Moreover, exercise with eccentric contractions will cause more damage and inflammation than concentric exercise of equal intensity and duration.[7] In addition, regular exercise is beneficial to up regulating defense mechanisms against oxidative stress and to increased resistance against infection and a lower risk of appearance of disease. The aim in this review was to focus attention in inflammatory process caused by muscle damage after resistance exercises and, in addition, show the benefits of regular intensity exercise against oxidative stress, infections and some diseases.

Discussion

Muscle damage is dependent on the choice of exercise protocol,[8] resistance exercise (with equal concentric and eccentric loads) and eccentrically-biased exercise, such as downhill running (~8°) and running downstairs, generally do not cause severe muscle damage or significant leucocyte accumulation in the exercised muscles. On the other hand, tissue accumulation of leucocytes occurs consistently after single joint, maximal eccentric exercise across a large range of motion. Stepping exercise (i.e., isolated eccentric work for one leg, very steep downhill running (e.g., 16° in and very long distance running appear to induce moderate or severe muscle damage and leucocyte accumulation (at least if the exercise is unaccustomed). The eccentric action is characterized by the ability to achieve high muscle forces, an enhancement of the tissue damage that is associated with muscle soreness and perhaps requires unique control strategies by the central nervous system.[9] In addition, there is evidence of damages such as delayed onset muscle soreness (DOMS), elevated intracellular enzymes in the blood (e.g., creatine kinase, lactate dehydrogenase, and myoglobin), loss of calcium homeostasis, reduced joint range of motion (ROM) and muscle swelling (increasing limb circumference). Generally, muscle soreness becomes noticeable about 8 hours post-exercise and peaks 12-36 hours later, although the exact time course can vary.[10] Additionally, eccentric exercise also shows a larger increase in plasma creatine kinase (CK) activity, whereas concentric and isometric exercise did not increase this enzyme.[11] DOMS, CK activity, decreased in ROM, increase in limb circumference and decreased in muscle strength are considered indirect markers of muscle damage.

Accordingly to Paulsen et al.[8] decreases in muscle strength are correlated to the level of Z-band streaming after muscle damage-inducing protocols, and reflect the magnitude of myofibrillar disruption, inflammation, and necrosis better than any other indirect marker. Furthermore, eccentric exercise can increase serum levels of pro- and anti-inflammatory cytokines such as the tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6) and interleukin-10 (IL-10).[12] The interleukins (ILs) are a class of cytokines released by numerous body tissues to control and coordinate immune responses,[13] showed that muscle damage (demonstrated by loss of muscle strength) was greater after maximal versus submaximal eccentric actions of the elbow flexors, but cytokine responses were similar between the two trials. The immune system plays a role in the degeneration and regeneration process of muscle and surrounding connective tissue after EIMD. In a few words, neutrophils are rapidly mobilized into the circulation after exercise and soon invade the damaged muscle tissue. Natural killer (NK) cells and lymphocytes are also mobilized, and anti-inflammatory cytokines are released into the systemic circulation during and immediately after eccentric exercise. About one day after exercise, neutrophils are replaced in damaged muscle tissue by macrophages, and pro-inflammatory cytokines are produced in muscle.[14]

Cytokines are traditionally regarded as messenger molecules associated with leucocytes and inflammatory and immunological reactions. However, researchers demonstrate that these cytokines are not only produced by leucocytes, but also by myofibres and peritendinous tissue.[8,15] The cytokines and other peptides that are produced, expressed and released by muscle fibers, and exert autocrine, paracrine or endocrine effects, are classified as myokines. Some myokines are involved in muscle hypertrophy, such as leukaemia inhibitory factor (LIF), IL-4, IL-6, IL-7 and IL-15. Myostatin inhibits muscle hypertrophy, and exercise provokes the release of a myostatin inhibitor, follistatin, from the liver. Brain-derived neurotropic factor (BDNF) and IL-6 are involved in AMPK-mediated fat oxidation; IL-6 stimulates lipolysis and IL-15 stimulates in particular lipolysis of visceral fat. IL-6 is involved in glucose and lipid metabolism. Furthermore, IL-6 stimulates cortisol production and hence neutrocytosis and lymphopenia.[16]

Skeletal muscle contains resident immune cell populations and their abundance and type are altered in inflammatory myopathies, endotoxemia or other different types of muscle injury.[15] There are several isoforms of ILs and the most known is interleukin-6 (IL-6), an early-stage myokine that might play important role in exercise-induced muscular growth. IL-6 is a pleiotropic cytokine associated with the control and coordination of immune responses, inflammation, hematopoiesis, and oncogenesis, which regulates cell growth, survival, and differentiation.[17] In addition, IL-6 exert anti-inflammatory effects during exercise by inhibiting the production of the pro-inflammatory cytokine tumor necrosis factor (TNF)-α and stimulating the synthesis of other anti-inflammatory cytokines such as IL-1 receptor antagonist (IL-1ra), IL-10 and soluble TNF-α receptor 1 (sTNF-αR1).[13] Another myokine that has significant increase after acute resistance exercise is IL-15. This interleukin that has received considerable interest for its potential role in skeletal muscle growth. This cytokine is one of the most abundantly released in skeletal muscle.[18] In animals, IL-15 stimulates protein accretion and leads to myosin heavy chain (MHC) accumulation in differentiated myocytes and myotubes, while reducing protein degradation. This ability of IL-15 to inhibit myotube protein degradation suggests that it may be of great utility in treating muscle wasting characteristics of some cases of cachexia cancer, muscular dystrophies, or aging (i.e. sarcopenia),[19, 20] showed in mice that IL-10 is required for normal growth and regeneration of muscle following injury, and the loss of IL-10 or the application of superphysiological levels of IL-10 can impede muscle growth and repair following injury. In addition, the authors showed that the negative effect of supraphysiological levels of IL-10 may reflect the dose dependency of IL-10 effects on leukocyte activation. For example, IL-10 generally functions as an anti-inflammatory cytokine, but supraphysiological levels of IL-10 administered during sepsis exacerbate the inflammatory response.

The inflammatory process caused by muscle damage has an overall beneficial or detrimental effect on muscle function depending on the magnitude of the response, the injury-specific interactions between the muscle and inflammatory cells and previous exposure to the applied stimulus.[21] However, the muscle damage decreases when a person performs the same exercise consistently, this phenomenon is commonly known as the "repeated bout effect" or "protective effect". This effect occurs after a single training session and this benefit is found within a period as short as 24 hours and can remain for up to six months,[22, 23] observed that when performing eccentric training sessions with different intensities (40%, 60%, 80% and maximal strength) all damage markers analyzed were more attenuated at higher intensities (80% and 100%) in a second training session performed 2-3 weeks later. According to Brentano and Kruel,[21] several factors are thought to be responsible for the repeated bout effect, including an adaptive strengthening of connective tissue, increased efficiency in the recruitment of motor units, enhanced synchronization of motor units, a more even distribution of the workload among fibers and a greater contribution of muscle synergists. In addition,[24] showed that the initial inflammatory response to the initial bout may contribute to the induction of a protective mechanism,[25] suggest that one key feature for adaptation may be an increase in monocyte chemoattractant protein-1 (MCP1) that co-localized with macrophages and satellite cells, which could play a role in promoting recovery. The authors demonstrated a significant upregulation in MCP1 mRNA after a single exercise bout and an even greater upregulation after a second bout, with a trend toward greater numbers of satellite cells expressing MCP1. Satellite cells are muscle precursor cells that lie between the basal lamina and the sarcolemma of skeletal muscle fibers. In normal adult muscle, satellite cells are mitotically and metabolically quiescent, which are known as stem cells.[26] These cells are involved in the repair of muscle fibers after injurious eccentric contractions and with appropriate environmental signals, satellite cells enter into the cell cycle, (i.e. are activated) to provide the precursors needed for new muscle formation in growth and repair.[25,27] In addition,[27] observed that satellite cell proliferation is required for approximately half of the force recovery after eccentric contraction-induced injury,[28] have found that an increase in the area of muscle fibres can occur without the addition of new myonuclei, however, myonuclear addition is required when hypertrophy reaches 26%. Thus, the hypertrophic response is an adaptation promoted by muscle damage. However,[4] showed that initial increases in muscle protein synthesis (MPS) post-resistance exercise are likely directed to muscle repair and remodeling due to damage and do not correlate with eventual muscle hypertrophy induced by several resistance exercise weeks. Increases in MPS post-resistance exercise session only contribute to muscle hypertrophy after a progressive attenuation of muscle damage and even more significantly when damage is minimal.

With regard to training adaptation, regular exercise training reduces basal IL-6 production as well as the magnitude of the acute exercise IL-6 response by counteracting several potential stimuli of IL-6. Thus, a decreased plasma IL-6 concentration at rest as well as in response to exercise appears to characterize normal training adaptation.[16] A single bout of exercise can increase reactive oxygen species (ROS) concentration and promote oxidative damage of lipids, proteins and DNA, however, these pathways are obligatory for adaptive responses to occur,[29] demonstrated that administration of allopurinol, a potent inhibitor of xanthine oxidase, a type of enzyme that generates ROS, prevents exercise-induced adaptation. This study showed the importance of ROS, at least in the concentration generated during moderate exercise to induce adaptation, and questions the uncontrolled administration of antioxidants. On the other hand, high-intensity or long-term exercise can cause immunosuppression and increase susceptibility to infection. In fact, upper respiratory tract infections are often reported after strenuous exercise.[30–32] showed that the level of exercise load is associated with glutamate debt, which could alter the efficiency of the immune system. In addition, prolonged exercise results in increased secretion of cortisol, which can also lead to immunosuppression.[33] High-intensity and long-duration exercise suppresses the activity of natural killer (NK) cells to below pre-exercise values.[34] On the other hand, moderate intensity and duration exercise can be considered a positive up-regulator of the immune system, leading to increased resistance against infections and lower risk of disease onset, including certain types of cancer.[35]

Conclusion

In summary, the immune system is fundamental and plays a crucial role in the degeneration and regeneration process of skeletal muscle after EIMD. Moreover, the inflammatory response to the initial bout can contribute to the muscular adaptation to stress caused by exercise and in the induction of a protective mechanism, a phenomenon known as the "repeated bout effect" or "protective effect" Thus, muscle damage decreases when a person performs the same exercise consistently. In addition, the activation and proliferation of satellite cells are essential in the repair of muscle damage after exercise and the addition of new myonuclei is required when hypertrophy reaches 26%. The knowledge about EIMD and the inflammatory process in the human and animals are of great relevance, from the application in studies of muscular strengthening and hypertrophy to possible applications in therapies and treatments. In addition, regular exercise training is associated with lower risk of diseases, infections and increased activity of antioxidant enzymes, crucial to exercise-induced adaptation. Although studies have been growing in this sense, much research is still necessary to determine the full extent and mode of action of these factors.

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Conflict of interest

Author declares there is no conflict of interest.

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