Does exercise-induced muscle damage play a role in skeletal muscle hypertrophy?

Brad Schoenfeld, MSc, CSCS, NSCA-CPT

Department of Health Science

Lecturer in Exercise Science

Lehman College

Bronx, NY 10468

brad@workout911.com

Abstract

Exercise-induced muscle damage (EIMD) occurs primarily from the performance of unaccustomed exercise, and its severity is modulated by the type, intensity, and/or duration of training. Although concentric and isometric actions contribute to EIMD, the greatest damage to muscle tissue is seen with eccentric exercise, where muscles are forcibly lengthened. Damage can be specific to just a few macromolecules of tissue or result in large tears in the sarcolemma, basal lamina, and supportive connective tissue, as well as inducing injury to contractile elements and the cytoskeleton. Although EIMD can have detrimental short-term effects on markers of performance and pain, it has been hypothesized that the associated skeletal muscle inflammation and increased protein turnover are necessary for long-term hypertrophic adaptations. A theoretical basis for this belief has been proposed, whereby the structural changes associated with EIMD influence gene expression, resulting in a strengthening of the tissue and thus protection of the muscle against further injury. Other researchers, however, have questioned this hypothesis, noting that hypertrophy can occur in the relative absence of muscle damage. Therefore, the purpose f this paper will be twofold: 1) to extensively review the literature and attempt to determine what, if any, role EIMD plays in promoting skeletal muscle hypertrophy, and; 2) to make applicable recommendations for resistance training program design.

Introduction

Damage to skeletal muscle tissue arising from physical exercise has been well-documented in the literature (34, 42, 85). This phenomenon, commonly known as exercise-induced muscle damage (EIMD), occurs primarily from the performance of unaccustomed exercise, and its severity is modulated by the type, intensity, and/or duration of training (94). Damage can be specific to just a few macromolecules of tissue or result in large tears in the sarcolemma, basal lamina, and supportive connective tissue, as well as inducing injury to contractile elements and the cytoskeleton (160).

EIMD is heightened from the performance of eccentric exercise, where muscles are forcibly lengthened. Concentric and isometric exercise also contribute to EIMD, albeit to a lesser extent than eccentric training (32, 51). Fast twitch fibers are more vulnerable to eccentrically-induced damage than slow twitch fibers (161). Possible reasons include a reduced oxidative capacity, higher levels of tension generated during training, and/or structural differences between fiber phenotypes (122).

The damaging effects of eccentric exercise are believed to be related to mechanical disruption of the actomyosin bonds as opposed to ATP-dependent detachment, which places a higher degree of stress and strain on the involved structures compared to other muscle actions (44). Since the weakest sarcomeres are located at different regions of each myofibril, it is believed that the associated non-uniform lengthening causes a shearing of myofibrils. This deforms membranes, particularly T-tubules, leading to a disruption of calcium homeostasis that further degrades muscle by potentiating the release of calcium-activated neutral proteases (such as calpain) involved in damaging Z-line proteins (5, 14). A dose-response relationship has been noted, where a greater volume of exercise results in a greater magnitude of damage (112).

Symptoms of EIMD include a reduced ability to generate muscular force, increased stiffness and swelling, delayed onset muscle soreness (DOMS), and an increased physiological stress response characterized by greater lactate production and an elevated heart rate response to submaximal exercise (147).

EIMD is attenuated with subsequent bouts of the same exercise stimulus (98). This phenomenon, dubbed the "repeated bout effect," has been attributed to strengthening of connective tissue, increased efficiency in the recruitment of motor units, greater motor unit synchronization, a more even distribution of the workload among fibers, and/or a greater contribution of synergistic muscles (20, 147). Adaptations may last for up to several months, even if no eccentric training is performed during the interim. Interestingly, the arm muscles appear to be more predisposed to EIMD than the leg muscles, leading to the supposition that susceptibility may be mollified in muscles that are used more during activities of daily living (29).

Although EIMD can have detrimental short-term effects on markers of performance and pain, it has been hypothesized that the associated skeletal muscle inflammation and increased protein turnover are necessary for long-term hypertrophic adaptations (45, 163). A theoretical basis for this belief has been proposed, whereby the structural changes associated with EIMD influence gene expression, resulting in a strengthening of the tissue and thus protection of the muscle against further injury (10). Other researchers, however, have questioned this hypothesis, noting that hypertrophy can occur in the relative absence of muscle damage (20, 47, 87). Therefore, the purpose of this paper will be twofold: 1) to review the literature and attempt to determine what, if any, role EIMD plays in promoting skeletal muscle hypertrophy, and; 2) to

make applicable recommendations as how lifters may utilize this information to optimize a hypertrophic response.

Potential Mechanisms of Action

There is a large body of evidence indicating the EIMD is associated with factors involved in the accretion of muscle proteins. Research shows that muscle regeneration and repair subsequent to damaging exercise is coordinated by novel transcriptional programs involving clusters of genes that regulate inflammatory processes, growth, stress response, and membrane biosynthesis (93). The following is an overview of these aspects as they relate to EIMD.

Signaling Via Inflammatory Cells

The response to myodamage has been likened to the acute inflammatory response to infection (133). Once damage is perceived by the body, neutrophils migrate to the area of trauma and agents are then released by damaged fibers that attract macrophages to the region of injury (97). These inflammatory cells consequently secrete other agents to damaged tissue to facilitate repair and regeneration. Inflammatory processes can have either a beneficial or detrimental effect on muscle function depending on the magnitude of the response, previous exposure to the applied stimulus, and injury-specific interactions between the muscle and inflammatory cells (151).

Neutrophils, often referred to as phagocytic cells, are the most abundant type of white blood cells in the human body. In addition to possessing phagocytic capabilities, neutrophils also secrete proteases that assist in degrading cellular debris produced by EIMD as well as releasing cytolytic and cytotoxic molecules that can increase damage to injured muscle and cause damage to healthy neighboring tissues (151). Thus, their primary role appears to be restricted to myolysis

and other aspects involved in the removal of cellular debris rather than promoting hypertrophic supercompensation of muscle tissue.

Although there is a lack of current evidence supporting a role for neutrophils in muscle growth, it is conceivable that they may be responsible for signaling other inflammatory cells necessary for muscle regeneration. One such possibility are reactive oxygen species (ROS) (158), which can function as key cellular signaling molecules in the response to exercise (54, 77, 78, 148). Neutrophils are capable of producing a variety of ROS including superoxide, hydrogen peroxide, hypochlorous acid, and hydroxyl radical (80). ROS have been shown to promote growth in both smooth muscle and cardiac muscle (143), and it is theorized to have similar hypertrophic effects on skeletal muscle (144). Transgenic mice with suppressed levels of selenoproteins, a class of proteins that function as potent antioxidants, display increased exercise-induced muscle growth, potentially indicating an ROS-mediated hypertrophic effect through redox sensitive signaling pathways (69).

Hypertrophic effects associated with ROS may be carried out through heightened MAPK signaling. In vitro analysis has shown that treatment of C2 myoblasts with an ROS variant increases MAPK activation, with the response of the various MAPK subfamilies (ERK 1/2, JNK, and p38-MAPK) differing over time (79). Eccentric actions have, in fact, been shown to increase MAPK activation to a greater extent than concentric or isometric actions (93, 95), suggesting a possible contribution from ROS activity. ROS also may modulate protein synthesis via enhanced IGF-1 signaling. In vitro analysis by Handayaningsih et al., (62) displayed that IGF-I-induced phosphorylation of the IGF-I receptor in C2C12 myocytes treated with ROS while this action was markedly blunted with treatment of antioxidants, suggesting that ROS have a critical function in the biological action of IGF-I.

On the other hand, ROS have been found to have a negative effect on various serine/threonine phosphatases, including calcineurin. ROS activity can interfere with calcineurin activation by blocking its calmodulin-binding domain (26). Calcineurin is purported to play a role in both muscle hypertrophy (41, 100) and fiber phenotype transformation (117), and thus its inhibition may have a negative impact on muscle growth. Furthermore, some researchers have failed to show that ROS are involved in muscle damage pursuant to resistance training (132). Ultimately, the effects of ROS on muscle development may be dependent on the mode of exercise (i.e. anaerobic versus aerobic), the species of ROS produced, and perhaps other factors. Further investigation is needed to elucidate their precise role in muscle development.

As opposed to neutrophils, there is a large body of evidence that suggests a role for macrophages in muscle regeneration and growth following EIMD (151), and some researchers have hypothesized that they are required for compensatory hypertrophy (80). Macrophages appear to mediate hypertrophy through the secretion of various anabolic agents, with cytokines emerging as a particularly important player in this process. Research suggests that cytokines synthesized within skeletal muscle (a.k.a. myokines) significantly contribute to the hypertrophic response (111, 123, 137). Numerous myokines have been identified in the literature including interleukin (IL)-6, IL-7, IL-8, IL-10, IL-13, IL-15, fibroblast growth factor (FGF), leukemia inhibitory factor (LIH), and tumour necrosis factor (TNF), amongst others. Each of these agents exerts its effects in an autocrine/paracrine fashion to bring about unique effects on skeletal muscle adaptation, and intense exercise appears to potentiate their response.

Early evidence showed that the production of myokines was related to myodamage (21, 120). This seems logical given that cytokines are known to be involved in the response to inflammation manifesting from EIMD. However, the results of subsequent research suggest that

myokine production may be largely independent of damage to muscle tissue. In a study of 20 young and elderly participants, Toft et al., (153) found that 60 minutes of eccentric cycle ergometry produced only modest increases in IL-6 relative to increases in creatine kinase (CK) levels, indicating a only a weak correlation between muscle damage and IL-6 production. Other studies have shown that the time course of CK and IL-6 are not well correlated (36), leading to speculation that the release of this myokine is primarily related to contraction of muscle fibers, perhaps as a means to mobilize substrate from fuel depots so that glucose homeostasis is maintained during intense exercise (46).

It should be noted, however, that only IL-6 and IL-8 appear to be released from muscle in the absence of damaging exercise (28). Conversely, systemic IL-15 levels and IL-15 mRNA in skeletal muscle are substantially increased following eccentric resistance exercise, not concentric exercise, and these elevations are believed to be dependent on the manifestation of tissue damage (22, 124). This is important because IL-15 has been shown to be a potent mediator of muscle mass, acting directly on differentiated myotubes to increase muscle protein synthesis and reduce protein degradation (111, 123). Furthermore, studies show that eccentric exercise preferentially upregulates FGF activity. FGFs are powerful proliferative agents that are involved in inducing myofiber hypertrophy as well as regulating satellite cell function (164, 165). FGF has been shown to be released directly from damaged fibers (30) and the time-course of its release parallels an increase in CK levels associated with EIMD (31). These findings seem to suggest that myodamage does in fact contribute to the growth process.

Satellite Cell Activity

Another possible means by which EIMD may augment muscle hypertrophy is via an increase in satellite cell activity. Satellite cells, which reside between the basal lamina and

sarcolemma of muscle fibers, are believed to play a critical role in the regulation of muscular growth (65, 127). In a cluster analysis following a 16-week resistance training protocol, Petrella et al. (121) demonstrated that subjects who experienced extreme increases in mean myofiber cross sectional area of the vastus lateralis (>50%) possessed a much greater ability to expand the satellite cell pool compared to those who experienced moderate or negligible increases in hypertrophy. These results are consistent with studies showing that muscle hypertrophy is significantly limited when satellite cells are obliterated by gamma-irradiation (127, 159).

Satellite cells remain quiescent until being aroused by a mechanical stimulus imposed on skeletal muscle (160). Once activated, they generate precursor cells (myoblasts) that proliferate and ultimately fuse to existing cells, providing agents needed for repair and subsequent growth of new muscle tissue (154, 168). This may involve the co-expression of various myogenic regulatory factors such as Myf5, MyoD, myogenin, and MRF4 (35), which bind to sequence specific DNA elements present in the promoter of muscle genes, aiding in the hypertrophic process (130, 139).

Satellite cells also help to retain the mitotic capability of muscles by donating their nuclei to existing muscle fibers, thereby increasing the capacity to synthesize new contractile proteins (12, 105). Since a muscle's nuclear-content-to-fiber-mass ratio remains constant during hypertrophy, the satellite cell-derived addition of new myonuclei is believed to be essential for realizing long-term increases in muscle mass (152). This is consistent with the concept of myonuclear domain, which proposes that the myonucleus regulates mRNA production for a finite sarcoplasmic volume and any increases in fiber size must be accompanied by a proportional increase in myonuclei (121).

The interplay between muscle damage and satellite cell activity has been well established in the literature (39, 129, 134). Damaged fibers must quickly obtain additional myonuclei to facilitate reparation; if not, they would face cell death and thus compromise the body's functional ability. Thus, when exercised fibers sustain damage, satellite cells proliferate and adhere to the damaged fiber as a means to initiate repair. Given that area under the myoneural junction contains a high population of satellite cells (67, 139), it is theorized that neurons innervating damaged fibers might further help to stimulate satellite cell activity, enhancing the regenerative response (160). Some researchers have proposed that a threshold of myodamage may exist beyond which stimulated satellite cells fuse to each other to form new myofibers (11), although this remains speculative.

The initial signal for damage-induced satellite cell activation is believed to originate from muscle-derived nitric oxide, possibly in conjunction with hepatocyte growth factor secretion (3, 146, 151). The process is thought to be regulated, at least in part, by the cyclooxygenase (COX)-2 pathway, which has been deemed as necessary to achieve maximal skeletal muscle hypertrophy in response to functional overload (140). COX-2 exerts its effects by mediating the synthesis of various prostaglandins known to stimulate satellite cell proliferation, differentiation, and fusion (17). The inflammatory response to EIMD is believed to play a crucial role in this regenerative response, as myogenesis has been shown to be enhanced when inflammatory cells are abundant and impaired in their absence (17). The hypertrophic importance of exercise-induced inflammation is further supported by research showing that non-steroidal anti-inflammatory drugs (NSAIDs), which inhibit COX-2 production, blunt the satellite cell response (9). Most (17, 18, 92, 101), but not all (119), studies have found significant decreases in satellite cell activity

when NSAIDs were administered in response to muscle damage, thereby potentially limiting long-term load-induced increases in muscle hypertrophy.

It should be noted that mechanical stimuli alone can initiate satellite cell proliferation and differentiation without subsequent damage to muscle tissue (110, 162). Therefore, it remains to be determined whether the effects of EIMD are additive or redundant in terms of maximizing one's hypertrophic potential.

IGF-1 Signaling

Insulin-like growth factor (IGF-1) is an anabolic hormone that, as the name implies, has similar structural properties to insulin. A clear cause and effect relationship has been established between IGF-1 and skeletal muscle hypertrophy, with both mitogenic and anabolic effects seen in muscle tissue (60). Although IGF-1 plays a general role in anabolism under normal physiological conditions, its anabolic effects on muscle are thought to be enhanced in response to mechanical loading (19, 61). Some consider it to be the major extracellular mediator of skeletal muscle growth (131), and there is evidence that it may be necessary for compensatory hypertrophy (60).

Several IGF-1 isoforms have been identified including the systemic forms IGF-1Ea and IGF-1Eb, and the muscle-specific IGF-1Ec, which has been termed mechano growth factor (MGF) and is believed to be the isoform principally responsible for compensatory hypertrophy (115). These isoforms are involved in the transduction of multiple anabolic signaling pathways. For one, IGF-1 is involved in mitogen-activated protein kinase (MAPK) signaling, particularly via the extracellular signal-regulated kinase (ERK) cascade. Haddad and Adams (60) demonstrated that co-infusion of a MAPK/ERK inhibitor prevented an increase in IGF-1-mediated protein synthesis, apparently via reduced S6K1 phosphorylation. These results

highlight the importance of the IGF-1/MAPK/ERK signaling cascade in the regulation of muscle growth. As discussed, MAPK signaling has been shown to be highly active during eccentric exercise. Whether this is mediated by the IGF-1 system is not entirely clear at this time.

IGF-1 also has been implicated in various Ca^{2+} -dependent pathways shown to stimulate L-type calcium channel gene expression, leading to an increased intracellular Ca^{2+} concentration (106). This in turn instigates the activation of calcineurin, a Ca^{2+}-sensitive phosphatase that plays an important regulatory role in muscle adaptation via the expression of various downstream signaling targets including nuclear factor of activated T-cells and GATA-2 (136, 150). Levels of the striated muscle activator of Rhos signaling (STARS) gene, a muscle specific transducer for intracellular signaling sensitive to calcineurin, are increased 10-fold following EIMD suggesting that STARS may be an important downstream target in the early signaling for skeletal muscle remodeling (93). The precise effects of calcineurin in muscle development remains in question. Although some studies suggest that calcineurin has a significant effect on muscular growth (41, 100), others indicate its primary role is in the regulation of fiber phenotype, i.e. type I, IIA, or IIX (117). Recent research suggests that calcineurin may have a selective hypertrophic effect on slow-twitch muscle fibers (13, 131), raising uncertainty over its role in regeneration following EIMD.

In addition, IGF-1 is known to influence the mTOR pathway. This is important because mTOR is widely considered a master network for controlling skeletal muscle growth (16, 55, 76, 149). IGF-1 mediates mTOR activity via phosphatidylinositol 3-kinase (PI3K)/Akt, an upstream molecular nodal point that both facilitates anabolic signaling and inhibits catabolic signals (107, 154). The binding of IGF-1 to its receptor triggers the activation of PI3K, leading to the phosphorylation of Akt. Akt, in turn, signals mTOR, which then exerts effects on various

downstream targets including $p70^{S6k}$ to promote muscle protein synthesis through increases in translation initiation and elongation (16). It should be noted that recent research suggests that resistance exercise can activate mTOR independently of PI3K/Akt, presumably under the control of phosphatidic acid and/or the ERK/TSC2 pathway (70, 71, 103, 114). With respect to EIMD, some studies have found that phosphorylation of Akt is significantly greater in eccentric contractions compared to isometric contractions (128) while others show it remains unaffected regardless of contraction type (43). It therefore remains unclear what, if any, role this pathway has in regeneration following EIMD.

Another means by which IGF-1 promotes anabolism is by increasing the protein synthetic rate in differentiated myofibers (12, 61). Locally expressed MGF has been shown to activate satellite cells and mediate their proliferation and differentiation (68, 166). Systemically produced IGF-IEa, on the other hand, has been shown to upregulate fusion of satellite cells with existing muscle fibers, facilitating the donation of myonuclei and helping to maintain optimal DNA-to-protein ratios in muscle tissue (154, 159).

A number of studies have reported that EIMD potentiates IGF-1 production and thereby enhances the hypertrophic response to exercise. For example, Bamman et al., (8) showed that eccentric exercise increased IGF-1 mRNA concentrations by 62% while decreasing levels of IGFBP-4 mRNA--a strong inhibitor of IGF-1--by 57%. Concentric exercise produced negligible changes in these markers, indicating that structural damage to the muscle was responsible for activation of the IGF-1 system.

McCay et al., (99) studied the in vivo response of all 3 IGF-1 isoforms to a protocol specifically designed to bring about damage in human skeletal muscle. Eight healthy males performed a series of 300 lengthening contractions of the knee extensors. MGF mRNA increased

significantly 24 h after the intervention, while the expression of both IGF-1Ea and IGF-1Eb mRNA were not elevated until 72 hours post-intervention. Because MGF expression was found to occur earlier than other IGF-1 splice variants, researchers speculated that this isoform may have a distinct role in the reparation process subsequent to EIMD.

Not all studies have found an association between IGF-1 production and EIMD, however. Garma et al., (50) evaluated the acute effects of eccentric, concentric, and isometric actions on anabolic signaling in rodents. The protocol was designed so that volume of accumulated force was equated between exercise conditions. Nearly identical results were found in the anabolic response of the three modes of contraction, including no differences in IGF-1 mRNA levels. The reason for discrepancies between studies is not readily apparent and requires further investigation.

Cell Swelling

A novel theory by which EIMD may contribute to muscle hypertrophy is via an increase in intracellular water content. This phenomenon, known as cell swelling, serves as a physiological regulator of cell function (64), stimulating anabolic processes both by increasing protein synthesis and decreasing protein breakdown (57, 102, 142). It has been proposed that increased pressure against the cytoskeleton and/or cell membrane is perceived as a threat to cellular integrity, which in turn causes the cell to initiate a signaling response that ultimately leads to reinforcement of its ultrastructure (86, 133).

The exact mechanisms by which cellular swelling promotes anabolism have not been fully elucidated. There is evidence that integrin-associated volume sensors located within cells are involved in the process (88). When the membrane is subjected to swelling-induced stretch, these sensors activate anabolic protein-kinase transduction pathways in muscle, possibly

mediated by autocrine effects of growth factors (30). This may also have a direct effect on amino acid transport systems. PI3K appears to be an important signaling component in modulating glutamine and methylaminoisobutyric acid transport in muscle due to increased cellular hydration (88). In addition, the stimulus associated with cell swelling may trigger proliferation of satellite cells and facilitate their fusion to hypertrophying myofibers (37).

The inflammatory response following EIMD is characterized by an accumulation of fluid and plasma proteins within the affected tissue to an extent whereby this buildup exceeds the capacity of lymphatic drainage resulting in swelling (59, 97, 122). Associated damage to capillaries may augment the degree of edema (34). Howell et al., (73) found that an acute bout of eccentric exercise for the elbow flexors in untrained subjects led to a swelling-induced increase in arm circumference of as much as 9%, with values remaining elevated for as long as 9 days. Using a similar protocol, Nosaka and Clarkson (113) reported up to a 4.3 cm increase in arm circumference attributed to edema, with swelling conspicuous in all subjects by 3 days post-exercise. Although these effects are attenuated with regimented exercise via the repeated bout effect, significant swelling nevertheless persists even in trained subjects with increases in muscle girth seen 48 hours post-workout (72).

To date, no study has directly evaluated the effects of EIMD-mediated cell swelling on muscle growth. NSAID administration, which reduces the inflammatory response and thus diminishes cell swelling, has been shown in several studies to impair the increase in muscle protein synthesis normally associated with resistance exercise (116, 125, 155). It is possible that these negative hypertrophic effects may be attributable to a reduction in cellular hydration. However, a cause-effect relationship between inflammatory-derived cell swelling and protein accretion cannot be established based on this data, and results conceivably could be related to

confounding factors such as reduced satellite cell and/or macrophage activity. Further study is needed to investigate this theory.

Research Examining the Relationship Between EIMD and Hypertrophy

Despite the apparently sound theoretical rationale, a direct cause-effect relationship has yet to be established between EIMD and increased muscle growth. The following section will discuss what is known from the literature based on studies evaluating the hypertrophic effects of protocols designed to induce myodamage.

Direct Studies

To date, few experimental studies have directly attempted to determine if a causal relationship exists between EIMD and muscle hypertrophy. Komulainen et al., (81) investigated the hypothesis that severe exercise-induced damage results in greater muscle hypertrophy compared to minor damage. Wistar rats were subjected to repeated shortening (S) or lengthening (L) contractions of the tibialis anterior muscles. After 8 days post-exercise, the rats in the L group displayed a 7.1-fold increase in muscle damage (measured by beta-glucuronidase activity) compared to a 2.6-fold increase in the S group. At the conclusion of the study, increases in muscle cross sectional area were similar between groups. These results appear to indicate that a threshold exists beyond which damage does not have any further effect on hypertrophy. A drawback to the study is that varying degrees of damage were not studied, making it impossible to know whether a dose-response relationship may exist at more moderate levels of EIMD. Moreover, these results are only applicable to early stage training adaptations, as the repeated bout effect would preclude excessive muscle damage in well-trained individuals.

Recently, Flann et al., (47) sought to determine whether muscle damage enhanced muscle hypertrophy in untrained human subjects. Participants were divided into two groups: 1) a naïve

group (NA) performed eccentric exercise on an ergometer at a "somewhat hard" level (as determined by a rating of perceived exertion scale). Training was carried out 3 times a week for 20 minutes over an 8 week period, and ; 2) a pre-trained group (PT) performed the identical protocol to NA, except training for these subjects included a "ramp up" period lasting 3 weeks that employed low intensity exercise to gradually acclimate their muscles to the protocol. At the end of the study period, no statistically significant differences in muscle girth were noted between groups.

Although these results are intriguing, several methodological limitations make it difficult to draw relevant conclusions on the topic. First, the PT group trained for a total of 11 weeks compared to only 8 weeks for the NA group. The authors stated that this issue was addressed by adjusting workload so that subjects in both groups performed the same cumulative training over the course of the study. The hypertrophic effects of packing more exercise into a shorter time period in untrained subjects is not clear, however, and it is difficult to assess whether this may have impacted results.

Second, both groups performed eccentric exercise throughout the protocol making it likely that the PT group actually experienced some degree of muscle damage from the training. CK analysis did in fact show evidence of EIMD in the PT group, although it was significantly lower than that experienced by those in the NA group. Thus, it may be that the amount of damage sustained by the PT group was sufficient for eliciting a maximal hypertrophic response or perhaps that the damage sustained by the NA group was excessive and ultimately attenuated gains by reducing their ability to train with sufficient intensity and/or delaying supercompensatory adaptations.

Third, the study was underpowered, thereby raising the possibility of a Type II error. A hypertrophic advantage was actually noted for the NA group compared to the PT group (7.5% versus 6.5%, respectively), but the results did not reach statistical significance. Whether these results would have been significant with an adequately powered study is not clear. The possibility also exists that had the study lasted longer, the difference may have become statistically significant.

Finally, participants had no prior training experience, limiting generalizability to untrained individuals. It is possible that the stimulus for hypertrophy is different between trained and untrained individuals, and that adaptive responses related to EIMD may become more important as one gains training experience. Further research is warranted to address these limitations and provide more definitive evidence as to whether EIMD contributes to muscle hypertrophy in various populations.

Indirect Studies

A recent meta-analysis indicates that eccentric exercise is superior for inducing gains muscle mass compared to concentric exercise. Roig et al., (126) evaluated 3 studies encompassing 73 subjects and found that eccentric exercise produced statistically significant greater increases in muscle girth compared to concentric exercise. Moreover, the researchers noted that 2 of the 3 studies not included in the analysis underscored the superiority of eccentric exercise in maximizing hypertrophy. In support of these findings, it has been proposed that optimal exercise-induced muscle growth is not attained unless eccentric muscle actions are performed (63).

That said, several studies have failed to show any hypertrophic benefit associated with eccentric actions (4, 104) and there is even some research indicating that concentric training may

in fact promote greater muscle growth (96). These inconsistencies may be due at least in part to methodological differences between studies, and the possibility remains that the hypertrophic advantage of eccentric exercise is nullified when protocols equate for volume-load. When the body of literature is considered, however, eccentric resistance training does appear to elicit greater hypertrophic gains compared to other muscle actions.

There is evidence that eccentrically-induced hypertrophy may include sarcomerogenesis, as several studies have reported a serial increase in sarcomeres associated with lengthening actions. Lynn et al., (90) showed that rats exposed to downhill running had an increase in sarcomere count compared to a group that ran uphill. The downhill group displayed a smaller shift in the optimal torque angle, potentially indicative of reduced muscle damage. Similar findings have been noted by other researchers in both rodent and human subjects (24, 89, 167). These results are believed to be a protective response whereby the average sarcomere length is decreased at a given muscle length so that less of the muscle's working range includes the region of instability during future eccentric actions (122). Research seems to indicate, however, that sarcomerogenesis is limited to the first few weeks of exercise and ceases to occur thereafter (15, 138).

Nosaka et al., (112) proposed that EIMD promotes muscle hyperplasia rather than muscle hypertrophy. Although this is an intriguing hypothesis, studies reporting evidence of hyperplasia in animal models have been called into question, with results attributed to a miscounting of the intricate arrangements of elongating fibers as a greater fiber number (118). Evidence that hyperplasia occurs in human subjects is lacking at this time (2, 91). Further research is needed to determine if damage to tissue can, in fact, promote splitting of myofibers and thus an increase in the number of fibers within a muscle.

Is There a Causal Link Between EIMD, Eccentric Exercise, and Hypertrophy?

Given that eccentric exercise causes EIMD, a logical assumption is that the damage to tissue may be responsible for its additional growth promoting effects. Although this presents an enticing hypothesis, the underlying logic has been challenged by a number of researchers. The following section will detail potential issues with the EIMD hypothesis and discuss proposed alternative hypotheses that attempt to explain the hypertrophic advantages of eccentric exercise.

Challenges to the EIMD Hypothesis

Some researchers have questioned the validity of the EIMD hypothesis based on the fact that muscles become increasingly less susceptible to damage with repeated exercise (112). As discussed, a repeated bout effect has been consistently reported whereby EIMD is attenuated after a single bout of exercise and becomes increasingly less prevalent thereafter. This observation would suggest that damage does not contribute to training-induced muscle hypertrophy. A problem with this theory, however, is that EIMD persists even in well-trained subjects, albeit to a lesser degree than in novice trainees. Gibala et al., (52) studied the response of 6 strength trained males to the performance of 8 sets of 8 repetitions at a load equivalent to 80% of their concentric 1-repetition maximum. Training was carried out unilaterally so that one arm performed only concentric actions while the other arm performed only eccentric actions. Muscle biopsy obtained 21 hours post-exercise revealed a significantly greater fiber disruption in the eccentrically-trained arm compared to the concentrically-trained armed. These results highlight the fact that the repeated bout effect only attenuates the extent of myodamage rather than preventing its occurrence. Thus, the possibility that damage may in fact play a role in the hypertrophic response cannot be ruled out based solely on the repeated bout effect.

Another claim made to refute a potential role for EIMD in muscle hypertrophy is that low-intensity occlusion training produces marked hypertrophy with apparently minimal damage to muscle (1, 144). This method of exercise, called Kaatsu, employs light loads (20 to 50% of 1RM) using a pressure cuff to create a hypoxic environment. After several months of training, hypertrophic gains have been reported to be approximately equal to those seen with traditional "hypertrophy" loads of 70 to 80% 1RM. Given that the very light loading employed in Kaatsu training would seemingly minimize disruption of myofibers, this would suggest the lack of a cause-effect relationship. It should be noted, however, that muscle damage is a known consequence of reperfusion subsequent to ischemia (48, 58). Takarada et al., (144) found that while markers of muscle damage were indeed lower following Kaatsu training, there nevertheless was evidence of fine microdamage within muscle tissue. Thus, the potential exists that damage may have contributed to results. Perhaps more importantly, it is not clear whether hypertrophy would have been more pronounced had an even greater amount of EIMD been present in the Kaatsu group. Future protocols should seek to address these issues.

Finally, some researchers question whether a correlation exists between EIMD and hypertrophy based on findings that aerobic exercise such as downhill running can cause significant damage to muscle tissue without corresponding growth (20). This observation, however, fails to account for the fact that aerobic exercise and resistance exercise elicit unique molecular responses, activating and/or suppressing a distinctly different subset of genes and cellular signaling pathways (66). Atherton et al., (6) found that the body has an "AMPK-PKB switch" whereby signaling is switched to either a catabolic AMPK/PGC-1α- or anabolic PKB-TSC2-mTOR-dominated state depending on whether the imposed demand is endurance- or resistance-based. Specifically, aerobic training is associated with activation of AMPK and its

various downstream targets including PGC-1α, which have been shown to mediate mitochondrial biogenesis and progression toward a slower muscle phenotype while impairing contractile protein synthesis (7, 141). The catabolic effects of this signaling cascade remain well into the post-exercise period, suppressing phosphorylation of PKB or other downstream targets associated with protein synthesis (38, 53, 157). Resistance training, on the other hand, promotes anabolism through a variety of signaling pathways. Although AMPK is activated during the performance of resistance exercise, these effects are reversed immediately post-workout, with signaling rapidly switched to bring about a highly anabolic state (40). Thus, one can infer that muscle damage by itself is not sufficient to override catabolic signaling and, if EIMD does in fact play a role in hypertrophic remodeling, it can only do so in the presence of resistance-based mechanical overload.

Interestingly, the damage induced by aerobic exercise manifests differently from that of anaerobic training. CK activity has been shown to peak approximately 12-24 hours post-exercise following downhill running while that associated with resistance training does not manifest until after about 48 hours and can peak 4 to 6 days post-exercise (135). Moreover, peak CK levels associated with downhill running range from 100 to 600 IU while resistance training produces levels ranging from 2000 to 10,000 IU (33). The implications of these discrepancies have yet to be elucidated. It also should be noted that CK levels do not necessarily reflect the degree or time course of muscle damage (34)

Alternative Theories

If muscle damage is not responsible for the increased hypertrophy associated with eccentric resistance exercise, the question then arises as to what mechanisms account for these effects. A common hypothesis posits that results may be a function of a selective recruitment of

fast-twitch muscle fibers, whereby a greater amount of tension is assumed by a reduced number of fibers. Several EMG studies have indicated a reversal of the Henneman's size principle of recruitment during eccentric training, whereby the larger fast-twitch fibers are preferentially accessed to carry out exercise performance (74, 108, 109). This seems to be consistent with research showing that lengthening actions increase $p70^{S6k}$ in fast twitch fibers but not in slow twitch fibers (145). Given that fast-twitch fibers have a significantly greater potential for growth (82, 156), it is feasible that this could potentially account for the greater protein accretion seen in eccentric protocols. Other studies, however, seem to refute whether a reversal of the size principle actually does occur. An extensive review of literature by Chalmers (27) concluded that the preponderance of evidence does not support selective recruitment of fast-twitch fibers during eccentric contractions. These results held constant in 9 out of 10 studies deemed suitable to address the topic and were applicable over a wide range of efforts and speeds.

Another alternative hypothesis proposes that hypertrophic benefits associated with eccentric exercise may be due to a greater imposed mechanical stress compared to concentric or isometric actions (112). Indeed, muscles are capable of generating greater absolute force when contracting eccentrically versus concentrically (126). Despite this fact, however, muscle activation during maximal eccentric actions is generally less compared to those performed concentrically. This paradox was demonstrated by Grabiner et al., (56), who found that the maximum EMG of the vastus lateralis during eccentric knee extension was only 84 ± 41% of that obtained concentrically. Hence, while the potential to exert peak force is greater with eccentric exercise, most find it extremely difficult to achieve the maximum force during eccentric actions, ultimately resulting in an incomplete activation of the spectrum of motor neurons for a given working muscle (44).

Perhaps more importantly, the use of absolute maximal loads is not necessarily paramount for optimal muscle growth. Although mechanical force appears to be the primary stimulus for eliciting hypertrophic gains, there is evidence that a threshold may exist beyond which other factors predominate (133). Hypertrophy-oriented routines traditionally employ submaximal intensities, with loads in the range of 65 to 85% 1RM (25, 75, 83). Fry et al., (49) determined that the optimum load for muscle growth was in the upper range of these values--a figure still well below concentric maximum. Further support for this stance can be found in studies showing that protocols using submaximal loads produce increases in anabolic signaling and protein synthesis greater than or equal to protocols that employ high-intensity loads of >90% 1RM (23, 75). Thus, the theory that the hypertrophic superiority of eccentric actions is solely a function of higher force output remains speculative at this time.

Practical Applications

There is a sound theoretical rationale supporting a potential role for EIMD in the hypertrophic response. While it appears that muscle growth can occur in the relative absence of muscle damage, potential mechanisms exist whereby EIMD may enhance the accretion of muscle proteins including the release of inflammatory agents, activation of satellite cells, and upregulation of the IGF-1 system, or at least set in motion the signaling pathways that lead to hypertrophy. Although research suggests that eccentric exercise has greater hypertophic effects compared to other types of actions, however, a cause-effect relationship directly linking these gains to EIMD has yet to be established. Moreover, if such a relationship does in fact exist, it is not clear what extent of damage is optimal for inducing maximum muscle growth.

Evidence does seem to show that a threshold exists beyond which damage does not further augment muscle remodeling and may in fact interfere with the process. Given that a high

degree of EIMD causes a reduction in the force-producing ability of the affected muscle, excessive damage can impair an individual's ability to train, which necessarily would have a detrimental effect on muscle growth. Moreover, while training in the early recovery phase of EIMD does not seem to exacerbate muscle damage, it may interfere with the recovery process (84, 112). Thus, current research indicates that a protocol that elicits a moderate amount of damage would be most appropriate for maximizing the hypertrophic response.

Future research should seek to clarify whether a causal relationship exists between EIMD and muscle hypertrophy and, if so, evaluate optimal levels of damage to maximize the response. Furthermore, the vast majority of studies have been carried out on untrained subjects. Considering that a ceiling effect slows the rate of muscle growth as one gains training experience, it is possible that myodamage may become an increasingly important mediator of hypertrophy in highly trained individuals. Elucidating these issues will help to increase our understanding of the mechanisms of muscle development and allow for the optimization hypertrophy-oriented training programs.

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