THE MECHANISMS OF MUSCLE HYPERTROPHY AND THEIR APPLICATION TO RESISTANCE TRAINING

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ABSTRACT

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KEY WORDS muscle development, hypertrophic response, muscle growth, muscle tension, muscle damage, metabolic stress

INTRODUCTION

The quest to increase lean body mass is widely pursued by those who lift weights. Given the strong correlation between muscle cross-sectional area and muscular strength (111), increased muscle mass is a primary goal of athletes involved in strength and power sports such as football, rugby, and powerlifting. Muscle mass also is vital to the sport of bodybuilding, where competitors are judged on both the quantity and quality of their muscle development. On a more general level, muscle hypertrophy is also pursued by the many recreational lifters who aspire to develop their physiques to the fullest. Therefore, the maximization of muscle mass has far reaching implications to a variety of populations associated with sports and health.

In untrained subjects, muscle hypertrophy is virtually nonexistent during the initial stages of resistance training, with the majority of strength gains resulting from neural adaptations (124). Within a couple of months of training, however, hypertrophy begins to become the dominant factor, with the upper extremities shown to hypertrophy before the lower extremities (124,177). Genetic background, age, gender, and other factors have been shown to mediate the hypertrophic response to a training protocol, affecting both the rate and the total amount of gains in lean muscle mass (93). Further, it becomes progressively more difficult to increase lean muscle mass as one gains training experience, heightening the importance of proper routine design.

Although muscle hypertrophy can be attained through a wide range of resistance training programs, the principle of specificity dictates that some routines will promote greater hypertrophy than others (16). Research is lacking, however, as to the best approach for achieving this goal. Bodybuilders generally train with moderate loads and fairly short rest intervals that induce high amounts of metabolic stress. Powerlifters, on the other hand, routinely train with high-intensity loads and lengthy rest periods between sets. Although both groups are known to display impressive muscularity, it is not clear which method is best for maximizing hypertrophic gains (149) or whether other training methods may perhaps be superior. Therefore, the purpose of this paper is twofold: (a) to extensively review the literature as to the mechanisms of muscle hypertrophy and their application to resistance training variables and (b) to draw conclusions from the research and develop a hypertrophy-specific routine for maximizing muscle growth.

TYPES OF MUSCLE HYPERTROPHY

Muscle hypertrophy can be considered distinct and separate from muscle hyperplasia. During hypertrophy, contractile elements enlarge and the extracellular matrix expands to support growth (187). This is in contrast to hyperplasia, which results in an increase in the number of fibers within a muscle. Contractile hypertrophy can occur either by adding sarcomeres in series or in parallel.

The majority of exercise-induced hypertrophy subsequent to traditional resistance training programs results from an

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increase of sarcomeres and myofibrils added in parallel (135,179). When skeletal muscle is subjected to an overload stimulus, it causes perturbations in myofibers and the related extracellular matrix. This sets off a chain of myogenic events that ultimately leads to an increase in the size and amounts of the myofibrillar contractile proteins actin and myosin, and the total number of sarcomeres in parallel. This, in turn, augments the diameter of individual fibers and thereby results in an increase in muscle cross-sectional area (182).

A serial increase in sarcomeres results in a given muscle length corresponding to a shorter sarcomere length (182). In-series hypertrophy has been shown to occur when muscle is forced to adapt to a new functional length. This is seen with limbs that are placed in a cast, where immobilization of a joint at long muscle lengths results in an increased number of sarcomeres in series, whereas immobilization at shorter lengths causes a reduction (182). There is some evidence that certain types of exercise can affect the number of sarcomeres in series. Lynn and Morgan (107) showed that when rats climbed on a treadmill (i.e., incline), they had a lower sarcomere count in series than those who descended (i.e., decline). This suggests that repeated eccentric-only actions lead to a greater number of sarcomeres in series, whereas exercise consisting solely of concentric contractions results in a serial decrease in sarcomere length.

It is hypothesized that hypertrophy may be augmented by an increase in various noncontractile elements and fluid (108,205). This has been termed "sarcoplasmic hypertrophy," and may result in greater muscle bulk without concomitant increases in strength (154). Increases in sarcoplasmic hypertrophy are thought to be training specific, a belief perpetuated by studies showing that muscle hypertrophy is different in bodybuilders than in powerlifters (179). Specifically, bodybuilders tend to display a greater proliferation of fibrous endomysial connective tissue and a greater glycogen content compared to powerlifters (109,177), presumably because of differences in training methodology. Although sarcoplasmic hypertrophy is often described as nonfunctional, it is plausible that chronic adaptations associated with its effects on cell swelling may mediate subsequent increases in protein synthesis that lead to greater contractile growth.

Some researchers have put forth the possibility that increases in cross-sectional area may be at least partly because of an increase in fiber number (8). A meta-analysis by Kelley (84) found that hyperplasia occurs in certain animal species under experimental conditions as a result of mechanical overload. Increases in muscle fiber number were greatest among those groups that used an avian vs. a mammalian model, and stretch overload yielded larger increases in fiber count than exercise. However, subsequent research suggests that such observations may be erroneous, with results attributed to a miscounting of the intricate arrangements of elongating fibers as a greater fiber number (135). Evidence that hyperplasia occurs in human subjects is lacking and, if it does occur at all, the overall effects on muscle cross-sectional area would appear to be minimal (1,108).

Satellite Cells And Muscle Hypertrophy

Muscle is a postmitotic tissue, meaning that it does not undergo significant cell replacement throughout life. An efficient method for cell repair is therefore required to avoid apoptosis and maintain skeletal mass. This is carried out through the dynamic balance between muscle protein synthesis and degradation (69,182). Muscle hypertrophy occurs when protein synthesis exceeds protein breakdown.

Hypertrophy is thought to be mediated by the activity of satellite cells, which reside between the basal lamina and sarcolemma (66,146). These "myogenic stem cells" are normally quiescent but become active when a sufficient mechanical stimulus is imposed on skeletal muscle (187). Once aroused, satellite cells proliferate and ultimately fuse to existing cells or among themselves to create new myofibers, providing the precursors needed for repair and subsequent growth of new muscle tissue (182).

Satellite cells are thought to facilitate muscle hypertrophy in several ways. For one, they donate extra nuclei to muscle fibers, increasing the capacity to synthesize new contractile proteins (123). Because a muscle's nuclear-content-to-fiber-mass ratio remains constant during hypertrophy, changes require an external source of mitotically active cells. Satellite cells retain mitotic capability and thus serve as the pool of a myonuclei to support muscle growth (15). 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. Given that muscles are comprised of multiple myonuclear domains, hypertrophy could conceivably occur as a result of either an increase in the number of domains (via an increase in myonuclear number) or an increase in the size of existing domains. Both are thought to occur in hypertrophy, with a significant contribution from satellite cells (182).

Moreover, satellite cells coexpress various myogenic regulatory factors (including Myf5, MyoD, myogenin, and MRF4) that aid in muscle repair, regeneration, and growth (27). These regulatory factors bind to sequence specific DNA elements present in the muscle gene promoter, with each playing distinct roles in myogenesis (148,155).

Myogenic Pathways

Exercise-induced muscle hypertrophy is facilitated by a number of signaling pathways, whereby the effects of mechano-stimulation are molecularly transduced to downstream targets that shift muscle protein balance to favor synthesis over degradation. Several primary anabolic signaling pathways have been identified including Akt/mammalian target of rapamycin (mTOR), mitogen-activated protein kinase (MAPK), and calcium-(Ca^{2+}) dependent pathways. The following is an overview of each of these pathways.

Akt/Mammalian Target of Rapamycin Pathway

The Akt/mTOR pathway is believed to act as a master network regulating skeletal muscle growth (18,77,181). Although the specific molecular mechanisms have not been fully elucidated, Akt is considered a molecular upstream nodal point that is both an effector of anabolic signaling and a dominant inhibitor of catabolic signals (126,182). When activated, Akt signals mTOR, which then exerts effects on various downstream targets that promote hypertrophy in muscle tissue.

Mitogen-Activated Protein-Kinase Pathway

Mitogen-activated protein kinase is considered a master regulator of gene expression, redox status, and metabolism (88). Specific to exercise-induced skeletal muscle hypertrophy, MAPK has been shown to link cellular stress with an adaptive response in myocytes, modulating growth and differentiation (147). Three distinct MAPK signaling modules are associated with exercise-induced muscle hypertrophy: extracellular signal-regulated kinases (ERK 1/2), p38 MAPK, and c-Jun NH_2–terminal kinase (JNK). Of these modules, JNK has shown to be the most responsive to mechanical tension and muscle damage, and it is particularly sensitive to eccentric exercise. Exercise-induced activation of JNK has been linked to a rapid rise in mRNA of transcription factors that modulate cell proliferation and DNA repair (9,10).

Calcium-Dependent Pathways

Various Ca^{2+}-dependent pathways have been implicated in the regulation of muscle hypertrophy. Calcineurin (Cn), a Ca^{2+}-regulated phosphatase, is believed to be a particularly critical regulator in the Ca^{2+} signaling cascade. Cn acts downstream in the Ca^{2+} pathway and mediates various hypertrophic effectors such as myocyte enhancing factor 2, GATA transcription factors, and nuclear factor of activated T cells (118). Cn-dependent signaling is linked to hypertrophy of all fiber types, and its inhibition has been shown to prevent muscle growth even in the presence of muscular overload (35,36).

Hormones And Cytokines

Hormones and cytokines play an integral role in the hypertrophic response, serving as upstream regulators of anabolic processes. Elevated anabolic hormone concentrations increase the likelihood of receptor interactions, facilitating protein metabolism and subsequent muscle growth (31). Many are also involved in satellite cell proliferation and differentiation and perhaps facilitate the binding of satellite cells to damaged fibers to aid in muscular repair (182,187).

The hormonal regulation of hypertrophy is complex, with many hormones and cytokines believed to contribute to the response. Hepato growth factor, Interleukin-5 (IL-5), Interleukin-6 (IL-6), fibroblast growth factor, and leukemia inhibitory factor, all have been shown to promote anabolism (162,182,187). Insulin also has been shown to possess anabolic properties, with greater effects on attenuating proteolysis rather than heightening protein synthesis. Insulin also is believed to induce mitosis and differentiation of satellite cells (187). Given that insulin levels are suppressed during exercise, however, it is not a modifiable aspect of an exercise regimen and thus will not be addressed further here.

Various types of exercise have been shown to cause acute, and in some cases chronic, hormonal alterations that appear to play a role in mediating hypertrophic signaling systems (119). The 3 most widely studied of these hormones are insulin-like growth factor (IGF-1), testosterone, and growth hormone (GH). Whether the acute hormonal response to exercise provides a significant anabolic stimulus has been questioned by some researchers (191,194), however with the inherent experimental limitations in these studies and a larger body of prevailing basic and applied evidence to the contrary, such an overt dismissal of the importance of hormonal signaling in the physiological adaptations resulting from resistance exercise over a training period is without context and premature.

Insulin-Like Growth Factor

Insulin-like growth factor is often referred to as the most important mammalian anabolic hormone. It is thought to provide the main anabolic response for the body as a whole and shows enhanced effects in response to mechanical loading (19,63). Structurally, IGF-1 is a peptide hormone, so named because of its structural similarities to insulin. Insulin-like growth factor receptors are found in activated satellite cells, adult myofibers, and Schwann cells (15). During exercise, muscles not only produce more systemic IGF-1 than the liver but also use more circulating IGF-1 (49). Availability of IGF-1 for muscle is controlled by IGF-1 binding proteins (IGFBPs), which either stimulate or inhibit the effects of IGF-1 after binding to a specific IGFBP (182).

Three distinct IGF-1 isoforms have been identified: the systemic forms IGF-1Ea and IGF-1Eb, and a splice variant, IGF-1Ec. Although all 3 isoforms are expressed in muscle tissue, only IGF-1Ec appears to be activated by mechanical signals (63,199). Because of its response to mechanical stimulation, IGF-1Ec is familiarly called mechano growth factor (MGF).

Although the exact mechanisms of IGF-1's mode of action have not been fully elucidated, it is believed that mechanostimulation causes the IGF-1 gene to be spliced toward MGF, which in turn "kick starts" muscle hypertrophy. Within a day or so, MGF then completely splices toward the systemic IGF-1 isoforms (IGF-1Ea and IGF-1Eb) (54,69). Levels of IGF-1 then remain elevated in muscle tissue for some time thereafter, with myogenic effects seen up to 72 hours postexercise (117). Although MGF has been shown to be particularly sensitive to muscle damage, it is not clear whether the isoform is upregulated by membrane damage or if membrane damage initiates MGF production (48).

Insulin-like growth factor has been shown to induce hypertrophy in both an autocrine and paracrine manner (34) and exerts its effects in multiple ways. For one, IGF-1 directly

promotes anabolism by increasing the rate of protein synthesis in differentiated myofibers (15,63). Moreover, locally expressed MGF has been shown to activate satellite cells and mediate their proliferation and differentiation (69,200). IGF-IEa, on the other hand, is thought to enhance fusion of satellite cells with muscle fibers, facilitating the donation of myonuclei and helping to maintain optimal DNA to protein ratios in muscle tissue (182).

Insulin-like growth factor also activates L-type calcium channel gene expression, resulting in an increased intracellular Ca^{2+} concentration (125). This leads to the activation of multiple anabolic Ca^{2+}-dependent pathways, including calcineurin and its numerous downstream signaling targets.

Testosterone

Testosterone is a cholesterol-derived hormone that has a considerable anabolic effect on muscle tissue (33,105). In addition to its effects on muscle, testosterone also can interact with receptors on neurons and thereby increase the amount of neurotransmitters released, regenerate nerves, and increase cell body size.

The majority of testosterone is synthesized and secreted by the Leydig cells of the testes via the hypothalamic–pituitary–gonadal axis, with small amounts derived from the ovaries and adrenals (22). In the blood, the great majority of testosterone is bound to either albumin (38%) or steroid hormone binding globulin (60%), with the remaining 2% circulating in an unbound state. Although only the unbound form is biologically active and available for use by tissues, weakly bound testosterone can become active by rapidly disassociating from albumin (105). Unbound testosterone binds to androgen receptors of target tissues, which are located in the cell's cytoplasm. This causes a conformational change that transports the testosterone to the cell nucleus where it interacts directly with chromosomal DNA.

Although the effects of testosterone on muscle are seen in the absence of exercise, its actions are magnified by mechanical loading, promoting anabolism both by increasing the protein synthetic rate and inhibiting protein breakdown (22). Testosterone may also contribute to protein accretion indirectly by stimulating the release of other anabolic hormones such as GH (31). Moreover, it has been shown to promote satellite cell replication and activation, resulting in an increase in the number of myogenically committed satellite cells (155). Suppression of testosterone has been shown to seriously compromise the response to resistance exercise (100).

Resistance training also has been shown to upregulate androgen receptor content in humans (13,80). In rodents, modulation of androgen receptor content appears to take place in a fiber-type specific manner, with increases specific to fast-twitch muscles (20). This would seem to enhance the potential for testosterone binding at the cellular level, and thus facilitate its uptake into target tissues.

Resistance exercise can have a substantial acute effect on testosterone secretion. Ahtiainen et al. (2) found significant correlations between training-induced elevations in testosterone and muscle cross-sectional area, suggesting that acute, exercise-induced elevations in testosterone may play an important role in muscle hypertrophy. However, acute responses are limited in women and the elderly, mitigating the hypertrophic potential in these populations (61,90,130).

The chronic effects of resistance training on bodily testosterone concentrations are not clear at this time. Although some studies show sustained increases as a result of regimented resistance exercise (60,93,163), others show little to no change (3,142). Further research is needed to enhance understanding on this topic.

Growth Hormone

Growth hormone is a polypeptide hormone considered to have both anabolic and catabolic properties. Specifically, GH acts as a repartitioning agent to induce fat metabolism toward mobilization of triglycerides, and stimulating cellular uptake and incorporation of amino acids into various proteins, including muscle (187). In the absence of mechanical loading, GH preferentially upregulates the mRNA of systemic IGF-1, and mediating nonhepatic IGF-1 gene expression in an autocrine/paracrine manner (63).

Growth hormone is secreted by the anterior pituitary gland and released in a pulsatile fashion, with the greatest nonexercise secretions occurring during sleep. More than 100 molecular isoforms of GH have been identified; however, most resistance training studies have focused solely on the 22-kDa isoform, limiting conclusions. Recent research suggests a preferential release of multiple GH isoforms with extended half-lives during exercise, allowing for sustained action on target tissues (131).

In addition to exerting effects on muscle tissue, GH also is involved in the regulation of immune function, bone modeling, and extracellular fluid volume. In total, GH is implicated as promoting over 450 actions in 84 cell types (190).

Growth hormone levels spike after the performance of various types of exercise (96). An exercise-induced increase in GH has been highly correlated with the magnitude of type I and type II muscle fiber hypertrophy (113). It is postulated that a transient GH increase may lead to an enhanced interaction with muscle cell receptors, facilitating fiber recovery and stimulating a hypertrophic response (134). Growth hormone is also thought to be involved in the training-induced increase of locally expressed IGF-1 (75). When combined with intense exercise, GH release is associated with marked upregulation of the IGF-1 gene in muscle so that more is spliced toward the MGF isoform (63).

Some researchers have questioned whether GH does, in fact, have a significant hypertrophic effect on muscle tissue (143). This view is based on the results of several studies that have failed to find significant increases in muscle mass when GH was administered as part of a resistance training protocol (101,201–203). However, these protocols did not replicate the large spikes in GH seen postexercise, nor did they take

into account the time course of GH elevation in conjunction with myotrauma. Thus, it is impossible to draw conclusions from these studies as to whether an exercise-induced GH response is associated with skeletal muscle anabolism. Much is still unclear about the anabolic actions of GH, and further research is needed to fully elucidate its role in muscular development.

Cell Swelling

Cellular hydration (i.e., cell swelling) serves as a physiological regulator of cell function (65). It is known to simulate anabolic processes, both through increases in protein synthesis and decreases in proteolysis (53,120,165). Although a physiological basis linking cell swelling with an anabolic drive is yet to be determined, it is conceivable that increased pressure against the 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.

A hydrated cell has been shown to initiate a process that involves activation of protein-kinase signaling pathways in muscle, and possibly mediating autocrine effects of growth factors in signaling the anabolic response to membrane stretch (106). Cell swelling induced membrane stretch may also have a direct effect on the amino acid transport systems mediated through an integrin-associated volume sensor. Phosphatidylinositol 3-kinase appears to be an important signaling component in modulating glutamine and alpha-(methyl)aminoisobutyric acid transport in muscle because of cell swelling (106).

Resistance exercise has been shown to induce alterations of intra- and extracellular water balance (156), the extent of which is dependent upon the type of exercise and intensity of training. Cell swelling is maximized by exercise that relies heavily on glycolysis, with the resultant lactate accumulation acting as the primary contributor to osmotic changes in skeletal muscle (41,157). Fast-twitch fibers are particularly sensitive to osmotic changes, presumably related to a high concentration of water transport channels called aquaporin-4. Aquaporin-4 has been shown to be strongly expressed in the sarcolemma of mammalian fast-twitch glycolytic and fast-twitch oxidative-glycolytic fibers, facilitating the influx of fluid into the cell. Given that fast-twitch fibers are most responsive to hypertrophy, it is conceivable that cellular hydration augments the hypertrophic response during resistance training that relies heavily on anaerobic glycolysis.

Exercise regimens that cause an increased glycogen storage capacity also have the potential to augment cell swelling. Given that glycogen attracts three grams of water for every gram of glycogen (25), this may reflect an increased capacity for protein synthesis in those who possess greater intramuscular glycogen stores.

Hypoxia

Hypoxia has been shown to contribute to increases in muscle hypertrophy, with effects seen even in the absence of exercise. Takarada et al. (172) found that 2 daily sessions of vascular occlusion significantly attenuated muscular atrophy in a group of patients confined to bed rest. Similar findings were observed by Kubota et al. (62,98), with occlusion conferring a protective effect on muscle strength and cross-sectional area during a 2-week period of leg immobilization.

When combined with exercise, hypoxia seems to have an additive effect on hypertrophy. This was demonstrated by Takarada et al. (173), who divided 24 older women into 3 subgroups: low-intensity elbow flexion exercise (~50% 1 repetition maimum [1RM]) with vascular occlusion, low-intensity elbow flexion exercise (~50% 1RM) without occlusion, and high- to medium-intensity elbow flexion exercise without occlusion (~80% 1RM). After 16 weeks, the group that performed low-intensity training with occlusion showed a significantly greater cross-sectional area of the elbow flexor muscles as compared to low-intensity exercise without occlusion. Moreover, the hypertrophic gains realized were similar to those experienced by the moderate- to high-intensity group.

There are several theories as to the potential hypertrophic benefits of muscle hypoxia. For one, hypoxia has been shown to cause an increased lactate accumulation and reduced acute lactate clearance rate (173). This may mediate increased cell swelling, which has been shown to upregulate protein synthesis. Moreover, the rise in lactate may mediate elevations in anabolic hormones and cytokines. Takarada et al. (172) noted a 290% increase in GH levels after low-intensity hypoxic training and an increase in the concentration of the myogenic cytokine IL-6, which was sustained for 24 hours postexercise.

Another potential mechanism of hypoxic-induced hypertrophy is its effect on the activity of reactive oxygen species (ROS). Reactive oxygen species production has been shown to promote growth in both smooth muscle and cardiac muscle (170), and it is theorized to have similar hypertrophic effects on skeletal muscle (171). Nitric oxide, an ROS produced during exercise, has been shown to mediate the proliferation of satellite cells, which would presumably lead to greater skeletal muscle growth (81,174). Reactive oxygen species generated during resistance training also has been shown to activate MAPK signaling in skeletal myoblasts (83), potentially modulating a hypertrophic response.

Hypoxia also may promote hypertrophic effects from reactive hyperemia (i.e., increased blood flow) after ischemic exercise (173). Hyperemia within damaged muscle would conceivably allow for the delivery of anabolic endocrine agents and growth factors to satellite cells, thereby regulating their proliferation and subsequent fusion into myotubes (187).

Initiation Of Exercise-Induced Muscle Hypertrophy

It is hypothesized that 3 primary factors are responsible for initiating the hypertrophic response to resistance exercise: mechanical tension, muscle damage, and metabolic stress (38,79,153,185). The following is an overview of each of these factors.

Mechanical Tension

Mechanically induced tension produced both by force generation and stretch is considered essential to muscle growth, and the combination of these stimuli appears to have a pronounced additive effect (48,72,185). More specifically, mechanical overload increases muscle mass while unloading results in atrophy (47). This process appears largely controlled by protein synthetic rate during the initiation of translation (11,87).

It is believed that tension associated with resistance training disturbs the integrity of skeletal muscle, causing mechanochemically transduced molecular and cellular responses in myofibers and satellite cells (182). Upstream signaling is thought to occur through a cascade of events that involve growth factors, cytokines, stretch-activated channels, and focal adhesion complexes (23,48,162). Evidence suggests that the downstream process is regulated via the AKT/mTOR pathway, either through direct interaction or by modulating production of phosphatidic acid (72,73). At this point, however, research has not provided a clear understanding of how these processes are carried out.

During eccentric contractions, passive muscular tension develops because of lengthening of extramyofibrillar elements, especially collagen content in extracellular matrix and titin (182). This augments the active tension developed by the contractile elements, enhancing the hypertrophic response. Both the amplitude and duration of excitation coupling is determined by motor unit (MU) firing frequency, the extent of which are believed to encode signals to various downstream pathways including Ca^{2+} calmodulin phosphatase calcineurin, CaMKII, and CAMKIV, and PKC (26). These pathways help to determine gene expression, coupling muscle excitation with transcription (182).

Passive tension produces a hypertrophic response that is fiber-type specific, with an effect seen in fast-twitch but not slow-twitch fibers. This was demonstrated by Prado et al. (139), who found that slow-twitch fibers in rabbits exhibited low passive tension in titin, but the tension was highly variable in fast-twitch fibers.

Although mechanical tension alone can produce muscle hypertrophy, it is unlikely to be solely responsible for hypertrophic gains associated with exercise (79). In fact, certain resistance training routines employing high degrees of muscle tension have been shown to largely induce neural adaptations without resultant hypertrophy (28,188).

Muscle Damage

Exercise training can result in localized damage to muscle tissue which, under certain conditions, is theorized to generate a hypertrophic response (38,69). 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, and induces injury to contractile elements and the cytoskeleton (187). Because the weakest sarcomeres are located at different regions of each myofibril, the nonuniform lengthening causes a shearing of myofibrils. This deforms membranes, particularly T-tubules, leading to a disruption of calcium homeostasis and consequently damage because of tearing of membranes and/or opening of stretch-activated channels (4).

The response to myotrauma has been likened to the acute inflammatory response to infection. Once damage is perceived by the body, neutrophils migrate to the area of microtrauma and agents are then released by damaged fibers that attract macrophages and lymphocytes. Macrophages remove cellular debris to help maintain the fiber's ultrastructure and produce cytokines that activate myoblasts, macrophages and lymphocytes. This is believed to lead to the release of various growth factors that regulate satellite cell proliferation and differentiation (182,187).

Furthermore, the area under the myoneural junction contains a high concentration of satellite cells, which have been shown to mediate muscle growth (69,155). This gives credence to the possibility that nerves impinging on damaged fibers might stimulate satellite cell activity, thereby promoting hypertrophy (187).

Metabolic Stress

Numerous studies support an anabolic role of exercise-induced metabolic stress (145,149,161) and some have speculated that metabolite accumulation may be more important than high force development in optimizing the hypertrophic response to training (153). Although metabolic stress does not seem to be an essential component of muscular growth (40), a large body of evidence shows that it can have a significant hypertrophic effect, either in a primary or secondary manner. This can be noted empirically by examining the moderate intensity training regimes adopted by many bodybuilders, which are intended to heighten metabolic stress while maintaining significant muscular tension.

Metabolic stress manifests as a result of exercise that relies on anaerobic glycolysis for ATP production, which results in the subsequent buildup of metabolites such as lactate, hydrogen ion, inorganic phosphate, creatine, and others (169,178). Muscle ischemia also has been shown to produce substantial metabolic stress, and potentially produces an additive hypertrophic effect when combined with glycolytic training (136,182). The stress-induced mechanisms theorized to mediate the hypertophic response include alterations in hormonal milieu, cell swelling, free-radical production, and increased activity of growth-oriented transcription factors (50,51,171). It also has been hypothesized that a greater acidic environment promoted by glycolytic training may lead to increased fiber degradation and greater stimulation of sympathetic nerve activity, thereby mediating an increased adaptive hypertrophic response (22).

Training Variables And Muscle Hypertrophy

Consistent with the principle of specificity, proper manipulation of training variables is essential for maximizing exercise-induced muscle hypertrophy. The following is

a review as to how each training variable impacts the hypertrophic response with respect to the physiological variables previously discussed.

Intensity

Intensity (i.e., load) has been shown to have a significant impact on muscle hypertrophy and is arguably the most important exercise variable for stimulating muscle growth (42). Intensity is customarily expressed as a percentage of 1RM and equates to the number of repetitions that can be performed with a given weight. Repetitions can be classified into 3 basic ranges: low (1–5), moderate (6–12), and high (15+). Each of these repetition ranges will involve the use of different energy systems and tax the neuromuscular system in different ways, impacting the extent of the hypertrophic response.

The use of high repetitions has generally proven to be inferior to moderate and lower repetition ranges in eliciting increases in muscle hypertrophy (24,71). In the absence of artificially induced ischemia (i.e., occlusion training), a load less than approximately 65% of 1RM is not considered sufficient to promote substantial hypertrophy (115). Although such high rep training can bring about significant metabolic stress, the load is inadequate to recruit and fatigue the highest threshold MUs.

Whether low reps or moderate reps evoke a greater hypertrophic response has been a matter of debate, and both produce significant gains in muscle growth (24). However, there is a prevailing belief that a moderate range of approximately 6–12 reps optimizes the hypertrophic response (86,89,205).

The anabolic superiority of moderate repetitions has been attributed to factors associated with metabolic stress. Although low repetition sets are carried out almost exclusively by the phosphocreatine system, moderate repetition schemes rely heavily on anaerobic glycolysis (144). This results in a significant buildup of metabolites. Studies of bodybuilding-style exercise routines performed with multiple sets of 6–12 reps show significant postexercise declines in ATP, creatine phosphate, and glycogen, along with marked increases in blood lactate, intramuscular lactate, glucose and glucose-6-phosphate (37,178). Buildup of these metabolites has been shown to have a significant impact on anabolic processes (96). It is therefore conceivable that there is a maximum threshold for tension-induced hypertrophy, above which metabolic factors become more important than additional increases in load.

Resultant to metabolic buildup, moderate repetition range training has been shown to maximize the acute anabolic hormonal response of exercise. Both testosterone and GH are acutely elevated to a greater degree from routines employing moderate rep sets as compared to those using lower repetitions (57,90,92,94,114), thereby increasing the potential for downstream cellular interactions that facilitate remodeling of muscle tissue.

Training in a moderate repetition range also maximizes acute cellular hydration. During moderate rep training, the veins taking blood out of working muscles are compressed while arteries continue to deliver blood into the working muscles, thereby creating an increased concentration of intramuscular blood plasma. This causes plasma to seep out of the capillaries and into the interstitial spaces. The buildup of fluid in the interstitial spaces causes an extracellular pressure gradient, which causes a flow of plasma back into the muscle causing the phenomenon commonly referred to as a "pump." This is augmented by the accumulation of metabolic byproducts, which function as osmolytes, drawing fluid into the cell (157). Whether acute exercise-induced cell swelling mediates muscle hypertrophy is not known, but it seems plausible given the known role of hydration in regulating cell function.

Moreover, the extra time under tension associated with a moderate repetition scheme as compared to a lower rep scheme would theoretically enhance the potential for microtrauma and fatigueability across the full spectrum of muscle fibers. This would seem to have greatest applicability for hypertrophy of slow-twitch fibers, which have greater endurance capacity than fast-twitch fibers and thus would benefit by increased time under tension. Although slow-twitch fibers are not as responsive to growth as fast-twitch fibers, they nevertheless do display hypertrophy when subjected to an overload stimulus. Given that the majority of whole muscles exhibit significant slow-twitch profiles (55,102), this can potentially help to maximize whole muscle girth.

Some researchers have postulated that muscles containing a greater percentage of slow-twitch fibers might have the greatest hypertrophic response to a higher repetition range, whereas fast-twitch muscles would respond best to lower repetitions (138,192). Although this concept is intriguing, a fiber-type prescription with respect to repetition range has not been borne out by research. Moreover, given the variability of fiber-type composition between individuals, it would be difficult to impossible to determine fiber-type ratios without muscle biopsy, thus making application impractical for the vast majority of people.

Volume

A set can be defined as the number of repetitions performed consecutively without rest, whereas exercise volume can be defined as the product of total repetitions, sets, and load performed in a training session. Higher-volume, multiple-set protocols have consistently proven superior over single set protocols with respect to increased muscle hypertrophy (97,197).

It is not clear whether the hypertrophic superiority of higher-volume workloads is the product of greater total muscle tension, muscle damage, metabolic stress, or some combination of these factors. Higher-volume, body-building-style programs that generate significant glycolytic activity have been consistently proven to elevate acute testosterone

levels to a greater extent than low-volume routines (92,94). Schwab et al. (150) showed that testosterone did not significantly increase during squat performance until after completion of the fourth set, indicating a clear benefit of multiple-set routines in this regard.

Higher-volume programs also have been shown to mediate the acute release of GH, particularly in routines designed to heighten metabolic stress (70). A large body of research shows multiple-set protocols elicit greater GH responses than single set protocols (29,124). Smilios et al. (158) compared the GH response of a maximum strength (MS) routine consisting of 5 reps at 88% of 1RM, 3 minutes rest with a maximal hypertrophy (MH) routine consisting of 10 reps at 75% of 1RM, 2 minutes rest in young men. Post-exercise GH was measured after 2, 4, and 6 sets. GH levels were significantly greater after the 4-set compared to the 2-set sessions in MH but not in MS, indicating a superiority of higher-volume routines that generate metabolite buildup.

A split body routine where multiple exercises are performed for a specific muscle group in a session may help to maximize the hypertrophic response (86). Compared to full body routines, a split routine allows total weekly training volume to be maintained with fewer sets performed per training session and greater recovery afforded between sessions (85). This may enable the use of heavier daily training loads and thus generate greater muscular tension. Moreover, split routines can serve to increase muscular metabolic stress by prolonging the training stimulus within a given muscle group, potentially heightening acute anabolic hormonal secretions, cell swelling, and muscle ischemia.

To maximize hypertrophy, evidence exists that volume should be progressively increased over a given periodized cycle, culminating in a brief period of overreaching. Overreaching can be defined as a planned, short-term increase in volume and/or intensity intended to improve performance. Improvements are thought to be obtained by initiating a "rebound effect" where an initial decrease in anabolic drive causes the body to supercompensate by significantly increasing accretion of body proteins (42,189). Training status has been shown to affect the overreaching response, with reduced detrimental effects to the endocrine system seen in those with 1-plus years of experience (44). To ensure optimal supercompensation, the period of overreaching should be followed by a brief taper or cessation from training (99).

Prolonged periods of overreaching, however, can rapidly lead to an overtrained state (62). Overtraining has catabolic effects on muscle tissue, and is characterized by chronically decreased concentrations of testosterone and luteinizing hormone, and increased cortisol levels (43,58,140). The cytokine hypothesis of overtraining states that primary cause of overtraining syndrome is repetitive trauma to the musculoskeletal system resulting from high-intensity and high-volume training (159,160). However, studies seem to show that overtraining is more a result of excessive volume than intensity (43,59). Given that recuperative abilities are highly variable between individuals, it is essential to be cognizant of an athlete's training status and adjust volume accordingly to avoid a negative effect on protein accretion.

Furthermore, the quest to train with a high volume must be balanced with performance decrements arising from lengthy exercise sessions. Long workouts tend to be associated with reduced intensity of effort, decreased motivation, and alterations in immune response (92). Accordingly, it has been proposed that intense workouts should not last longer than one hour to ensure maximal training capacity throughout the session (205).

Exercise Selection

It is a well-accepted fitness tenet that varying exercise parameters (i.e., angle of pull, position of extremities, etc.) can cause different activation patterns within muscle compartments, and making synergists more active or less active (17). This is particularly important in a hypertrophy-oriented protocol, where promoting uniform growth of muscle tissue is essential for maximizing overall muscle girth.

Muscles can have different attachment sites that provide greater leverage for varying actions. The trapezius, for example, is subdivided so that the upper aspect elevates the scapula, the middle aspect abducts the scapula and the lower portion depresses the scapula (103). With respect to the pectoralis major, the sternal head is significantly more active than the clavicular head in the decline bench press (46). Further, the clavicular head of the pectoralis major and long head of the triceps have been shown to be more active in the narrow grip bench press vs. the wide grip variation, with anterior deltoid activity increasing in conjunction with increases in the degree of trunk inclination (14).

Regional differences within various muscles can impact their response to exercise choice. For example, slow and fast MUs are often scattered across muscle, so that a slow-twitch fiber can be activated while an adjacent fast-twitch fiber is inactive and vice versa (7). Moreover, muscles are sometimes divided into neuromuscular components–distinct regions of muscle each of which is innervated by its own nerve branch–suggesting that portions of a muscle can be called into play depending on the activity (7). For example, the sartorius, gracilis, biceps femoris, and semitendinosus are all subdivided by one or more fibrous bands or inscriptions, with each compartment innervated by separate nerve branches (193,198). Further, the gracilis and sartorius are composed of relatively short, in series fibers that terminate intrafascicularly, refuting the supposition that muscle fibers always span the entire origin to insertion (67).

The effects of muscle partitioning on mechanical activity are seen in the biceps brachii, where both the long and short heads have architectural compartments that are innervated by private branches of the primary neurons (151). Studies investigating muscle activity of the long head of the biceps brachii show that MUs in the lateral aspect are recruited for elbow flexion, MUs in the medial aspect are recruited for

supination, and centrally located MUs are recruited for nonlinear combinations of flexion and supination (175,176,184). Further, the short head appears to be more active in the latter part of an arm curl (i.e., greater elbow flexion), whereas the long head is more active in the early phase (21).

These architectural variances of muscle give support for the need to adopt a multiplanar, multiangled approach to hypertrophy training using a variety of different exercises. Moreover, given the need to fully stimulate all fibers within a muscle, it would seem that a frequent exercise rotation is warranted to maximize the hypertrophic response.

There is evidence to support the inclusion of both multijoint and single-joint exercises in a hypertrophy-specific routine. Multijoint exercises recruit large amounts of muscle mass to carry out work. This has an impact on the anabolic hormonal response to training. Specifically, the magnitude of postexercise hormonal elevations has been shown to be related to the extent of muscle mass involved, with multijoint movements producing larger increases in both testosterone and GH levels compared to single-joint exercises (64,91).

Moreover, multijoint movements tend to require significant stabilization of the entire body, thereby involving numerous muscles that otherwise might not be stimulated in the performance of single-joint movements. The squat, for example, dynamically recruits not only the quadriceps femoris and hip extensors but also most of the other lower body muscles including the hip adductors, hip abductors, and triceps surae (132). In addition, significant isometric activity is required by a wide range of supporting muscles (including the abdominals, erector spinae, trapezius, rhomboids, and many others) to facilitate postural stabilization of the trunk. In all, it is estimated that over 200 muscles are activated during squat performance (167). To achieve a comparable degree of muscular coverage would necessitate the performance of dozens of single-joint movements–a strategy that is both inefficient and impractical.

On the other hand, single-joint exercises allow for a greater focus on individual muscles compared to multijoint movements. During performance of multijoint movements, certain prime movers may take precedence over others, creating a hypertrophic imbalance between muscles. The use of single-joint exercises can selectively target underdeveloped muscles, improving muscular symmetry. Moreover, the unique architecture of individual muscles suggests employing single-joint movements can elicit differing neuromuscular activation patterns that heighten overall muscular development (7).

The use of unstable surfaces in a hypertrophy-oriented routine is generally not supported by research. Resistance exercise on an unstable surface requires extensive activation of the core musculature to carry out performance (6,110). This, in turn, results in significant decreases in force output to the prime muscle movers. Anderson and Behm (5) found that force output was 59.6% lower when performing a chest press on an unstable surface compared to a stable surface. Similarly, McBride et al. (112) demonstrated significant reductions in peak force and rate of force development (by 45.6 and 40.5%, respectively) when performing a squat on an unstable vs. stable surface. Such large reductions in force output diminish dynamic tension to the target muscles, mitigating the hypertrophic response.

An exception to the use of unstable surfaces in a hypertrophy-oriented routine involves exercises for the core musculature. Sternlicht et al. (164) found that crunches performed on a stability ball elicited significantly greater muscle activity in both the upper and lower rectus abdominus than crunches performed under stable conditions. Similar results were shown by Vera-Garcia et al. (186), who displayed significantly increased activity of both the rectus abdominis and the external obliques when performing curl ups on an unstable surface compared to a stable surface. These results suggest a role for unstable surface training in developing the abdominals.

Rest Interval

The time taken between sets is referred to as the rest interval. Rest intervals can be classified into 3 broad categories: short (30 seconds or less), moderate (60–90 seconds), and long (3 minutes or more). The use of each of these categories has distinct effects on strength capacity and metabolite buildup, thereby impacting the hypertrophic response (195).

Short rest intervals tend to generate significant metabolic stress, thereby heightening anabolic processes associated with metabolite buildup (52). However, limiting rest to 30 seconds or less does not allow sufficient time for an athlete to regain muscular strength, significantly impairing muscular performance in subsequent sets (137,141). Thus, the hypertrophic benefits associated with greater metabolic stress are seemingly counterbalanced by a decreased strength capacity, making short rest intervals suboptimal for maximizing hypertrophic gains.

Long rest intervals afford full recovery of strength between sets, facilitating the ability to train with maximum force capacity (121). de Salles et al. (32) displayed that rest intervals of 3–5 minutes allowed for greater repetitions over multiple sets when training with loads between 50 and 90% of 1RM. However, although mechanical tension is maximized by long rest periods, metabolic stress is compromised (92,94). This may blunt anabolic drive, attenuating a maximal hypertrophic response.

Moderate rest intervals appear to provide a satisfactory compromise between long and short rest periods for maximizing the muscle hypertrophy. Research indicates that a majority of an athlete's strength capacity is recovered within the first minute after cessation of a set (168). Moreover, consistently training with shorter rest intervals leads to adaptations that ultimately allow a lifter to sustain a significantly higher mean percentage of 1RM during training (95). These adaptations include increased capillary and mitochondrial density and an improved capacity to buffer H+ and shuttle it out of muscle, thereby minimizing performance decrements.

Moderate rest intervals also help to enhance the body's anabolic environment to a greater extent than longer rest intervals. For one, moderate rest induces greater hypoxia, heightening the potential for increased muscular growth (182). Moderate rest also is associated with a greater metabolic buildup, mediating a large spike in anabolic hormonal concentrations after exercise (94). However, there is some evidence that this hormonal advantage is not sustained over time. Buresh et al. (22) compared the anabolic hormonal response to routines with rest intervals of 1 vs. 2.5 minutes. Although the shorter rest intervals had a significantly greater impact on elevating GH levels in the early stages of the protocol, the difference in hormonal response was not significant between routines by end of the fifth week and was nonexistent by week 10. This suggests a postadaptive response by the muscles to reduced rest intervals, lending support to the need for periodization in a hypertrophy-oriented resistance training program.

Muscular Failure

Muscular failure can be defined as the point during a set when muscles can no longer produce necessary force to concentrically lift a given load. Although the merits of training to failure are still a matter of debate, it is commonly believed that training to muscular failure is necessary to maximize the hypertrophic response (196). Several theories have been proposed in support of this contention.

For one, training to failure is hypothesized to activate a greater number of MUs (196). When a lifter becomes fatigued, a progressively greater number of MUs are recruited to continue activity, providing an additional stimulus for hypertrophy (145). In this way, failure may provide increased stimulation to the highest threshold MUs when moderate repetition ranges are employed.

Training to failure also may enhance exercise-induced metabolic stress, thereby potentiating a hypertrophic response. Continuing to train under conditions of anaerobic glycolysis heightens the buildup of metabolites, which in turn enhances the anabolic hormonal milieu. Linnamo et al. (104) displayed that performing sets at 10RM to failure caused a significantly greater postexercise elevation in GH secretion compared to the same load not performed to failure.

Although training to failure does appear to confer hypertrophic benefits, there is evidence that it also increases the potential for overtraining and psychological burnout (43). Izquierdo et al. (76) found that training to failure caused reductions in resting IGF-1 concentrations and a blunting of resting testosterone levels over a 16-week protocol, suggesting that subjects may have been overtrained. Thus, although it seems prudent to include sets performed to failure in a hypertrophy-oriented program, its use should be periodized and/or limited to avoid an overtrained state.

Repetition Speed

The speed with which a lifter performs repetitions can impact the hypertrophic response. Despite limitations both in the quantity of research and aspects of study design, some conclusions can be drawn on the topic.

With respect to concentric repetitions, there is some evidence that faster repetitions are beneficial for hypertrophy. Nogueira et al. (133) found that performing concentric actions at 1-second cadence instead of three seconds had greater impact on both upper and lower limb muscle thickness in elderly men. This may be attributed to an increased recruitment and corresponding fatigue of high-threshold MUs. Other studies, however, suggest that training at moderate speeds has greater effects on hypertrophy (56), perhaps through a heightened metabolic demand (12). Maintaining continuous muscle tension at moderate repetition speeds also has been shown to enhance muscle ischemia and hypoxia, thereby augmenting the hypertrophic response (174). Training at very slow velocities (i.e., superslow training) has generally been shown to be suboptimal for the development of strength and hypertrophy (82,129), and therefore should not be employed when the goal is to maximize muscle growth.

From a hypertrophy standpoint, speed of movement may have greater importance on the eccentric component of a repetition. Although concentric and isometric contractions have been shown to produce a hypertrophic response, a majority of studies seem to show that eccentric actions have the greatest effect on muscle development. Specifically, lengthening exercise is associated with a more rapid rise in protein synthesis (122) and greater increases in IGF-1 mRNA expression (152) compared to shortening exercise. Moreover, isotonic and isokinetic training that does not include eccentric contractions result in less hypertrophy than those that include lengthening contractions (39,68,74).

The hypertrophic superiority of eccentric exercise is largely attributed to a greater muscular tension under load. It is theorized that this is because of a reversal of the size principle of recruitment, which results in fast-twitch fibers being selectively recruited (152,173). This was demonstrated by Nardone and Schieppati (128), who showed derecruitment of the slow-twitch soleus muscle and a corresponding increase in activity of the gastroc during eccentric plantar flexion contractions. There is also evidence that eccentric contractions result in additional recruitment of previously inactive MUs (116,127).

As a result of the excessive stress on a small number of active fibers, eccentric exercise also is associated with greater muscle damage when compared to concentric and isometric contractions (116). This manifests as Z-line streaming, which current research suggests is indicative of myofibrillar remodeling (30,204). It has been shown that MyoD mRNA expression is specifically upregulated by eccentric contractions (78).

Shepstone et al. (152) found that fast (3.66 rads·s^{-1}) eccentric repetitions resulted in significantly greater hypertrophy of type II fibers compared to slow (0.35 rad·s^{-1}) repetitions. This is consistent with the lengthening portion of the force–velocity curve, which shows greater muscle forces are

generated at higher velocities. However, findings of this study are limited because subjects trained on an isokinetic dynamometer, which provides a resistive force against the agonist muscle and is not gravity dependent. Traditional dynamic constant resistance exercise (i.e., free weights, cable pulleys, etc.) does not confer such an advantage. Rather, eccentric contractions are aided by the pull of gravitational force, requiring the lifter to resist gravity to sustain muscular tension. Thus, a slower speed of movement is necessary to maximize the training response (45).

Practical Applications

Current research suggests that maximum gains in muscle hypertrophy are achieved by training regimens that produce significant metabolic stress while maintaining a moderate degree of muscle tension. A hypertrophy-oriented program should employ a repetition range of 6–12 reps per set with rest intervals of 60–90 seconds between sets. Exercises should be varied in a multiplanar, multiangled fashion to ensure maximal stimulation of all muscle fibers. Multiple sets should be employed in the context of a split training routine to heighten the anabolic milieu. At least some of the sets should be carried out to the point of concentric muscular failure, perhaps alternating microcycles of sets to failure with those not performed to failure to minimize the potential for overtraining. Concentric repetitions should be performed at fast to moderate speeds (1–3 seconds) while eccentric repetitions should be performed at slightly slower speeds (2–4 seconds). Training should be periodized so that the hypertrophy phase culminates in a brief period of higher-volume overreaching followed by a taper to allow for optimal supercompensation of muscle tissue.

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