Post-exercise hypertrophic adaptations: A re-examination of the hormone hypothesis and its applicability to resistance training program design

Brad Schoenfeld
Department of Health Sciences
Program of Exercise Science
APEX Building, Room # 263
Lehman College, CUNY
250 Bedford Park Blvd West
Bronx, NY 10468
Email: brad@workout911.com

Abstract
It has been well-documented in the literature that resistance training can promote marked increases in skeletal muscle mass. Post-exercise hypertrophic adaptations are mediated by a complex enzymatic cascade whereby mechanical tension is molecularly transduced into anabolic and catabolic signals that ultimately leads to a compensatory response, shifting muscle protein balance to favor synthesis over degradation. Myocellular signaling is influenced, in part, by the endocrine system. Various hormones have been shown to alter the dynamic balance between anabolic and catabolic stimuli in muscle, helping to mediate an increase or decrease in muscle protein accretion. Resistance training can have an acute impact on the post-exercise secretion of several of these hormones including insulin-like growth factor (IGF)-1, testosterone, and growth hormone (GH). Studies show that hormonal spikes are magnified following hypertrophy-type exercise that involves training at moderate intensities with shortened rest intervals as compared to high-intensity strength-oriented training. The observed positive relationship between anabolic hormones and hypertrophy-type training has led to the hormone hypothesis, which postulates that acute post-exercise hormonal secretions mediate increases muscle size. Several researchers have suggested that these transient hormonal elevations may be more critical to hypertrophic adaptations than chronic changes in resting hormonal concentrations. Theoretically, high levels of circulating hormones increase the likelihood of interaction with receptors, which may have particular hypertrophic importance in the post-workout period when muscles are primed for anabolism. Moreover, hormonal spikes may enhance intracellular signaling so that post-exercise protein breakdown is rapidly attenuated and anabolic processes are heightened, thereby leading to a greater supercompensatory response. While the hormone hypothesis has received considerable support in the literature, however, several researchers have questioned its veracity, with some speculating that the purpose of post-exercise hormonal elevations is to mobilize fuel stores rather than promote tissue anabolism. Therefore, the purpose of this paper will be to critically and objectively review the current literature, and then draw relevant conclusions as to the potential role of acute systemic factors on muscle protein accretion.

It has been well-documented in the literature that resistance training can promote marked increases in skeletal muscle mass (68). Post-exercise hypertrophic adaptations are mediated by a complex enzymatic cascade whereby mechanical tension is molecularly transduced into anabolic and catabolic signals that ultimately lead to a compensatory response, shifting muscle protein balance to favor synthesis over degradation. A number of signaling pathways involved in post-exercise hypertrophic adaptations have been identified including phosphatidylinositol 3-kinase-protein kinase B-mammalian target of rapamycin (PI3K-Akt-mTOR), mitogen-activated protein kinase (MAPK), and various calcium- (Ca^{2+}) dependent pathways, amongst others. Although these pathways may overlap at key regulatory steps, there is evidence that they may be interactive rather than redundant (80).

Myocellular signaling is influenced, in part, by the endocrine system. Various hormones have been shown to alter the dynamic balance between anabolic and catabolic stimuli in muscle, helping to mediate an increase or decrease in muscle protein accretion (73). Resistance training can have an acute impact on the during- and post-exercise elevation of several of these hormones including insulin-like growth factor (IGF)-1, testosterone, and growth hormone (GH). Studies generally show that hormonal spikes are magnified following hypertrophy-type exercise that involves training at moderate intensities (~60 to 80% 1RM) with shortened rest intervals (~60 to 90 seconds between sets) and high volumes as compared to high-intensity strength-oriented training (39). It is believed that high metabolic stress associated with such routines potentiates post-exercise hormonal release. Although the exact mechanisms are not entirely clear, the accumulation of metabolites (lactate, Pi, etc), a reduction in pH, and/or the effects of hypoxia have been implicated as causative factors in the process. Studies involving restricted blood flow

3

exercise seem to support this view, as low intensity occlusion training produces significant increases in both metabolic stress and hormonal levels (18, 78, 79).

The observed positive relationship between anabolic hormones and hypertrophy-type training has led to the hormone hypothesis, which postulates that acute post-exercise hormonal elevations play a part in mediating increases in muscle size (22, 30). Several researchers have suggested that these transient hormonal elevations may be more critical to hypertrophic adaptations than chronic changes in resting hormonal concentrations because most studies have failed to show changes in resting hormonal concentrations with the exception of significant changes to the program or overtraining and detraining (39). High levels of circulating hormones increase the likelihood of interaction with receptors (15), which may have particular hypertrophic importance in the post-workout period when muscles are primed for anabolism. Moreover, hormonal spikes may enhance intracellular signaling so that post-exercise protein breakdown is rapidly attenuated and anabolic processes are heightened, thereby leading to a greater supercompensatory response.

Although the hormone hypothesis has received considerable support in the literature, several researchers have questioned its veracity (45, 61), with some speculating that the purpose of post-exercise hormonal elevations is to mobilize fuel stores rather than promote tissue anabolism (94). Therefore, the purpose of this paper will be to critically and objectively review the current literature, and then draw relevant conclusions as to the potential role of acute systemic factors on muscle protein accretion. To carry out this review, English-language literature searches of the PubMed, EBSCO, and Google Scholar databases were conducted for all time periods up to April 2012. Combinations of the following keywords were used as search terms: "skeletal muscle"; hypertrophy"; "muscle growth"; "cross sectional area"; "IGF-1";

4

"acute"; "transient"; "growth hormone"; "testosterone"; "anabolic hormone"; "metabolic stress";

"metabolite buildup"; metabolite accumulation"; "resistance training"; "resistance exercise";

"weight lifting"; and "bodybuilding". The reference lists of articles retrieved in the search were

then screened for any additional articles that had relevance to the topic. Given the broad scope of

the topic, a narrative approach was chosen as the best way to convey pertinent information and

inclusion criteria was based on applicability to the particular area of discussion.

Hormones and Muscle Growth

Studies have demonstrated that increases in muscle hypertrophy can occur in the relative

absence of post-exercise hormonal increases (93, 96). What remains equivocal is whether such

hormonal elevations can potentiate the hypertrophic response, thereby maximizing muscle

growth. A number of hormones have been shown to mediate anabolic signaling, with the

majority of studies focusing on IGF-1, testosterone and GH. What follows is an overview of each

of these hormones and their presumed roles in the growth process.

IGF-1

IGF-1 is a homologous peptide with structural similarities to insulin. Intracellular IGF-1

signaling is carried out through multiple pathways including PI3K-Akt-mTOR, MAPK-ERK,

and possibly Ca^{2+} -dependent calcineurin (24, 65, 70). These cascades exert both anabolic and

anti-catabolic effects, mediating hypertrophic adaptations (67). Cell culture studies have

repeatedly shown that IGF-1 acts to stimulate protein synthesis, suppress proteolysis, and

increase mean myotube diameter and the number of nuclei per myotube (31). Despite these

diverse anabolic actions, however, research indicates that a functional IGF-1 receptor is not

obligatory for compensatory muscle growth (75).

5

Three distinct IGF-1 isoforms have been identified in humans: IGF-1Ea, IGF-1Eb, and IGF-1Ec. Both IGF-1Ea and IGF-1EB are systemic isoforms whose production is primarily derived from the liver. Other tissues also express these isoforms, however, with the extent of non-hepatic production increasing in response to exercise. In fact, exercised muscles are the primary producers of systemic IGF-1 during intense physical training, and the majority of circulating IGF-1 is ultimately taken up by the working musculature (12, 19). Alternatively, IGF-1Ec is a splice variant of the IGF-1 gene exclusively expressed by muscle tissue in response to mechanical loading and then exerting its influence in an autocrine/paracrine fashion (19). The local actions of IGF-1Ec dictate that it is more accurately classified as a myokine rather than a hormone. Because this isoform is activated mechanically and has a different carboxy peptide sequence to systemic IGF-1, it has been termed mechano growth factor (MGF).

Current theory suggests that MGF is more relevant to compensatory muscle growth than the systemic IGF-1 isoforms (31). It has been proposed that MGF helps to "kick-start" the post-exercise adaptive process, resulting in enhanced muscle protein accretion and the local repair of damaged tissue (19). A recent cluster analysis provides compelling support for this view. Bamman et al. (7) categorized 66 subjects into extreme responders (mean myofiber hypertrophy of 58%), moderate responders (mean myofiber hypertrophy of 28%) and non-responders (no increase in myofiber hypertrophy) based on their hypertrophic response to a 16 week resistance training protocol for the knee extensors. Assessment by muscle biopsy found that MGF was differentially expressed across clusters: whereas extreme responders upregulated MGF by 126%, levels remained relatively unchanged in non-responders. These results strongly suggest that transient exercise-induced elevations in MGF gene expression are important hypertrophic cues.

6

MGF is believed to regulate muscle hypertrophy in several ways. For one, it acts directly on muscle fibers to influence protein synthesis, presumably by exerting downstream effects via PI3K-Akt-mTOR on p70 S6 kinase (2, 3, 55). MGF also may heighten protein synthesis by downregulating catabolic signaling processes involved in protein degradation. Specifically, there is evidence that local IGF-1 production suppresses FoxO nuclear localization and transcriptional activities, blocking downstream proteolytic actions (21). These combined actions can help to trigger greater post-exercise muscle protein accretion.

MGF also mediates compensatory hypertrophy by regulating satellite cell activity. Satellite cells are muscle stem cells that reside between the basal lamina and sarcolemma. In the resting state, these precursor cells remain in a dormant state. When muscle is subjected to mechanical overload, however, satellite cells enter the cell cycle and initiate muscular repair by first undergoing proliferation and then differentiating into myoblast-like cells (59). Differentiated myoblasts can then fuse to traumatized myofibers and donate their nuclei to increase the muscle's ability to synthesize new contractile proteins. Myoblasts also can fuse to each other to form new functional myofibers (59), although it remains questionable whether such hyperplasia occurs during traditional resistance training in humans (1). In addition, satellite cells co-express myogenic regulatory factors such as c-met myogenin, MyoD, Myf5 and MRF4 that mediate muscle growth (20). There is some controversy as to whether satellite cells are obligatory for muscle hypertrophy (52), but recent evidence suggests they may be vital for maximizing muscular development in humans (58). A complete discussion of the topic is beyond the scope of this paper, and interested readers are referred to the point/counterpoint articles by O'Connor and Pavlath (56) and McCarthy and Esser (51).

Locally expressed MGF has been shown to be involved primarily in the initial phase of satellite cell activity. This is consistent with studies showing that MGF mediates ERK1/2 signaling while systemic isoforms do not, as well as the fact that it is expressed earlier than hepatic-type IGF-1 in response to exercise (8, 20). Accordingly, there is evidence that MGF is critical for inducing satellite cell activation and proliferation (32, 98). In this way, MGF helps increase the number of myoblasts available for post-exercise repair as well as facilitating replenishment of the satellite cell pool.

The hypertrophic role of systemic IGF-1 is less clear and considerable debate exists as to whether it is in fact involved in exercise-induced skeletal muscle growth. An age-related decline of circulating IGF-1 levels has been found to correlate with losses of muscle mass and strength (29). This may indicate that there is a threshold for systemically produced IGF-1 below which muscle development is compromised. On the other hand, blood levels of IGF-1 do not always correlate with post-exercise increases in muscle protein synthesis (102). Moreover, compensatory hypertrophy is not blunted in liver IGF-1-deficient mice that display an ~80% reduction in circulating levels of IGF-1 (48). These conflicting data have yet to be reconciled and require further study.

There is speculation that IGF-1Ea may act in concert with MGF to mediate satellite cell activity. As noted, MGF is rapidly upregulated following mechanical loading while systemic IGF-1 production is delayed and lasts considerably longer (57). Thus, the primary hypertrophic role of systemic IGF-1 may be in later stage satellite cell regulation, stimulating differentiation and fusion following myotrauma and thereby facilitating the donation of myonuclei to muscle fibers so that optimal DNA-to-protein ratios are maintained (82, 86). Whether the systemic isoforms have additional hypertrophic actions following resistance training remains to be

8

elucidated. A complete discussion of the roles of the various IGF-1 isoforms is beyond the scope

of this paper. Those interested in further exploration of the topic are referred to recent reviews by

Velloso and Harridge (87) and Philippou et al. (60).

Growth Hormone

GH is a superfamily of polypeptide hormones secreted by the anterior pituitary gland and

released in a pulsatile fashion, with the greatest non-exercise secretions occurring during sleep.

GH has been shown to mediate both anabolic and catabolic processes (86). Specifically, it acts as

a repartitioning agent to induce fat metabolism toward mobilization of triglycerides, as well as

stimulating cellular uptake and incorporation of amino acids into various proteins, including

those in skeletal muscle (88). GH also plays a role in a wide array of other bodily actions

involving multiple organs and physiological systems. A total of more than 100 molecular

isoforms of GH are produced endogenously (54), and the precise functions of each have yet to be

determined.

With respect to muscle tissue, it is believed that GH primarily mediates hypertrophic

adaptations through the actions of IGF-1 (86). Murine studies indicate that the effects of GH on

muscle function and mass are dependent on an intact IGF-1 receptor (35). These findings are

supported by a wealth of research showing that circulating IGF-1 levels are increased following

GH administration (6, 28, 64). In addition to exerting effects on systemic IGF-1 isoforms,

evidence suggests that GH also can directly act on muscle-derived IGF-1. Klover and

Henninghausen (36) displayed that deletion of the genes for signal transducers and activators of

transcription (STAT), which are critical mediators of GH-induced transcription of the IGF-I

gene, resulted in a selective loss of STAT5 protein in skeletal muscle while liver expression

remained unaffected (36). This is consistent with *in vitro* research showing that murine myoblast

C1C12 cells exposed to recombinant GH displayed a direct and preferential increase in MGF expression prior to that of IGF-1Ea (34). Furthermore, exogenous GH administration in dwarf lit/lit mice significantly increased MGF, providing evidence that MGF mRNA is expressed in parallel with GH action (33). On the other hand, GH-independent expression of IGF-I Ea and MGF has been noted in hypophysectomized rats after compensatory overload (97), indicating that the effects of GH potentiate rather than control IGF-1 function. Interestingly, *in vivo* human studies show that while recombinant GH administration markedly enhances mRNA levels of MGF when combined with resistance exercise in elderly men (28), such effects are not observed in young adult men (6). The reasons for these inconsistent findings remain to be elucidated.

Some researchers dispute the claim that GH is solely reliant on IGF-1 to mediate skeletal muscle growth, and propose the hypertrophic effects of the 2 agents are in fact additive (74, 86). The IGF-1-independent action of GH is implied by the fact that IGF-I knockout mice display less growth retardation than in those lacking both an IGF-I and GH receptor (46). Moreover, a decrease in myofiber size has been noted in skeletal muscle lacking functional GH receptors (74). It is believed that these effects are carried out, at least in part, by later-stage GH-mediated cell fusion, thereby increasing the number of nuclei per myotube (74). GH also appears to have a permissive, or perhaps even a synergistic, effect on testosterone-mediated protein synthesis (89). Whether these autonomous effects are associated with transient endogenous post-exercise GH spikes is not clear at this time and requires further study. The actions of the GH superfamily are highly diverse and complex, and a complete discussion of the topic is beyond the scope of this paper. Those interested in further reading are referred to recent reviews by Ehrnborg and Rosen (17) and Kraemer et al. (40).

Several researchers have dismissed the anabolic role of GH primarily based on research showing that administration of recombinant GH has minimal effects on muscle growth in humans *in vivo* (61, 63, 94). Indeed, studies on both young and older men have failed to show significant increases in skeletal muscle mass when GH was administered exogenously in combination with resistance training compared to placebo (43, 99, 100). Moreover, while whole body protein synthesis was found to be increased in those taking supplemental GH, no increases in skeletal muscle protein synthesis were noted (99). These studies have led to the supposition that GH does not mediate hypertrophic adaptations and that its anabolic effects are limited to synthesis of non-contractile tissue (i.e. collagen) (63).

While these studies justifiably cast doubt on the hypertrophic benefits of supplemental GH, several mitigating factors must be taken into account when extrapolating conclusions to acute post-exercise hormonal elevations. For one, recombinant GH is almost exclusively comprised of the 22-kDa isoform (17). As previously noted, a wide spectrum of GH isoforms are produced endogenously (54) and these isoforms may possess greater anabolic properties than the 22-kDa isoform or perhaps even work in combination with one another to potentiate hypertrophic effects on skeletal muscle. This may have particular relevance to resistance training protocols given that supraphysiological doses of GH have been found to suppress exercise-induced stimulation of endogenous circulating isoforms of GH for up to 4 days in trained men (91). Furthermore, exogenous GH administration does not mimic the *in vivo* response to exercise-induced GH secretions either temporally or in magnitude. Considering that the anabolic milieu is primed during the post-workout period, it is conceivable that the large GH spikes seen following resistance exercise may facilitate muscular repair and remodeling. The implications of

11

these factors are not clear at this time and additional research is needed to further our understanding of the topic.

Testosterone

Testosterone is a steroid hormone synthesized from cholesterol in the Leydig cells of the testes via the hypothalamic-pituitary-gonadal axis, with small amounts derived from the ovaries and adrenals (13). Circulating testosterone levels are approximately tenfold higher in men compared to women, and this is believed to be a primary reason why men display substantially greater post-pubescent muscle bulk (31). The vast majority of circulating testosterone is bound to either albumin (38%) or steroid hormone binding globulin (60%), with the remaining 2% circulating in an unbound state. While only the unbound form is biologically active and available for use by tissues, weakly bound testosterone can become active by its rapid disassociation from albumin (44). Unbound testosterone binds to androgen receptors (AR) of target tissues located in the cell's cytoplasm. This results in a conformational change that transports the testosterone/AR complex to the cell nucleus where it mediates gene transcription (89).

Evidence supporting the anabolic functions of testosterone is inconvertible. Numerous studies have shown that exogenous testosterone administration can promote marked increases in skeletal muscle hypertrophy (9, 11, 71), and these effects are magnified when combined with resistance exercise (10). Older women with low basal testosterone levels display blunted increases in maximal strength and hypertrophy compared to those with higher testosterone concentrations (26, 27). Kvorning et al. (41) demonstrated that suppressing testosterone production via administration of a gonadotropin-releasing hormone analogue (goserelin) significantly blunted hypertrophic adaptations in young men following an 8 week resistance training program. Follow-up work by this group showed that blunting of muscular adaptations

resultant to acute testosterone suppression were seen despite no changes in acute mRNA expression of myoD, myogenin, myostatin, IGF-IEa, IGF-IEb, IGF-IEc and AR, implying that that the testosterone response may regulate intracellular signaling downstream from these factors (42). In this study, total and free testosterone levels in the placebo group increased by ~15% immediately after resistance training while those in the goserelin group showed a decrease in testosterone and free testosterone 15 minutes post-exercise. These results suggest a potential hypertrophic effect from acute testosterone elevations.

The growth-related effects of testosterone on muscle are believed to be carried out in part by increasing myofibrillar protein synthesis and attenuating protein breakdown (84, 101). Testosterone may also contribute indirectly to muscle protein accretion by potentiating the release of other anabolic factors such such as GH (85) and IGF-1/MGF (69), while reducing mRNA concentrations of the IGF-1 inhibitor IGFBP-4 (84). Moreover, the combination of increased testosterone and GH has been shown to confer a synergistic effect on muscle IGF-1 production (89). In addition, ARs have been identified in myoblasts and there is emerging evidence that testosterone production has a dose-dependent effect on satellite cell proliferation and differentiation, with higher levels increasing the number of myogenically committed cells (31, 71).

The role of ARs in post-exercise adaptations is purported to be of particular importance to post-exercise hypertrophic adaptations (5). There is evidence that AR concentration is reduced in the immediate post-workout period but then becomes upregulated several hours after resistance exercise (89). Interestingly, this upregulation has been shown to be present only when the training bout results in a substantial post-exercise elevation in testosterone levels (76). Thus, acutely increasing testosterone levels may have the dual effect of mediating adaptations to

13

resistance training both directly as well as through its effects on ARs. A complete discussion of this topic is beyond the scope of the present paper and interested readers are referred to the recent review article by Vingren et al. (89).

Binding of testosterone to membrane receptors can cause rapid (within seconds) activation of second messengers associated with downstream protein kinase signaling (16), suggesting that transient post-exercise elevations may enhance protein synthesis. However, while the majority of research shows substantial increases in IGF-1 and GH immediately after resistance exercise, studies on acute testosterone release have been somewhat inconsistent. Some trials have reported that testosterone was elevated to a greater extent following hypertrophy-oriented resistance training compared with strength-type routines (13, 23, 25, 53, 72), but others have failed to find significant differences (37, 62, 77). It should be noted that factors such as gender, age, and training status profoundly influence testosterone release (39), and these factors may account for discrepancies between studies. Further investigation into the topic is needed to clarify discrepancies.

Indirect Research Investigating the Hormonal Hypothesis

Several researchers have sought to quantify the strength of the relationship, if any, between the post-exercise endocrine response and muscle morphology (see Table 1). McCall et al. (50) studied the hypertrophic response of 11 college-aged men with recreational resistance training experience to 12 weeks of high-volume resistance training. Strong correlations were noted between acute elevations of GH and the degree of both type I ($r = 0.74$) and type II ($r = 0.71$) fiber hypertrophy. Similarly, Ahtiainen et al. (4) studied the effects of post-exercise hormonal fluctuations on muscle growth in 16 young men (8 strength athletes and 8 physically active individuals) over the course of a 21 week heavy resistance training program. Results

14

showed that acute elevations in testosterone production were strongly correlated with increases in quadriceps femoris muscle CSA (r = 0.76). Both of these studies had small sample sizes, however, thereby limiting conclusions. Recently, West and Phillips (95) conducted a larger trial (n = 56) where young untrained men performed intense resistance exercise for 12 weeks. Analysis revealed a weak positive correlation between acute elevations of GH and increases in type II fiber area (r = 0.28). These elevations were determined to explain approximately 8% of the variance in hypertrophic adaptations. No correlations were found between the acute response testosterone response and muscle hypertrophy. An interesting adjunct to the study was an evaluation of hormonal differences between hypertrophic "responders" and "non-responders" (those in the top and bottom ~16%), with results showing a strong trend for an association between increased IGF-1 levels and gains in lean body mass (p = 0.053). While the results of the aforementioned studies are intriguing, caution must be taken in drawing definitive conclusions as correlation is not necessarily indicative of causation.

In an effort to better determine a causal relationship between acute hormonal concentrations and hypertrophy, West et al. (92) investigated the anabolic response to exercise with high post-exercise hormonal levels versus low hormonal levels. Subjects were 8 young men with no previous resistance training experience. A within-subject design was employed where participants completed 2 separate trials of unilateral elbow flexion. In one trial, only the elbow flexors were trained (LH) while in the other trial high-volume lower body training was added to elicit an increased hormonal response (HH). The trials were randomized and counterbalanced to account for arm-dominance and trial order. Results showed that despite a marked increase in acute hormonal concentrations in HH, both trials elevated myofibrillar protein synthesis to a similar extent. Furthermore, JAK2, STAT3, and p70^{S6k} phosphorylation were similar between

15

groups, indicating that anabolic signaling was also unaffected by post-exercise hormonal elevations. It is important to note that protein synthesis measured following an acute bout of exercise does not always occur in parallel with chronic upregulation of causative myogenic signals (14) and is not necessarily predictive of long-term hypertrophic responses to regular resistance training (81). The implications of these findings are therefore limited in scope.

Direct Research Investigating the Hormonal Hypothesis

Several studies have attempted to directly investigate the hormone hypothesis (see Table 2). Hansen et al. (30) was the first to do so. Sixteen young, untrained men were divided into 1 of 2 groups: an arm-only training group (A) and an arm plus leg training group (LA) designed to induce greater acute hormonal secretions. Both groups performed unilateral resistance exercise of the elbow flexors twice a week (8 sets of standing and seated biceps curls for 8-12 repetitions per set with 90 second rest intervals), but LA performed an additional 8 sets of the leg press. After 9 weeks, strength increased ~9% in A versus ~37% in LA. These findings correlated with post-exercise levels of testosterone and GH, which were significantly elevated in LA compared to A. The study was flawed, however, in that initial strength levels were ~20 to 25% lower in the LA group thereby indicating results were likely confounded by selection bias. Moreover, researchers did not evaluate changes in muscle mass. Thus, if any actual strength differences did indeed exist between groups post-testing, it remains speculative as to whether they were related to muscular or neural mechanisms.

Subsequently, Madarame et al. (47) expanded on the Hansen et al. (30) model by using lower extremity restricted blood flow training (Kaatsu) to examine the impact of post-exercise hormonal elevations on muscle morphology. Fifteen untrained young men were randomly divided into either a normal training group (NOR) or an occlusion group (OCC). Both groups

16

performed 3 sets of 10 repetitions of unilateral dumbbell curls at 50% 1RM with 3 minutes rest

between sets. After performance of the arm exercise, OCC performed restricted blood flow

exercise for the legs (1 set of 30 repetitions followed by 2 sets of 15 repetitions of knee

extensions and knee curls at 30% 1RM with 30 second rest intervals); NOR performed the same

lower body protocol without blood flow restriction. Training was carried out twice a week for 10

weeks. Results showed a significantly greater increase in muscle cross sectional area for the

upper arm in OCC compared to NOR. However, although OCC training showed a trend toward

greater GH increases versus NOR, the extent of these differences did not rise to statistical

significance. The authors attributed this null finding to a lack of statistical power (small sample

size and large inter-individual variation) and theorized that systemic factors may have in fact

played a role in muscular adaptations. No significant elevations were noted in post-exercise

testosterone levels.

     Employing a within-subject repeated measures design, West et al. (93) conducted an

experimental study on the topic. Twelve untrained young men performed unilateral elbow

flexion exercise on separate days under 2 different hormonal environments: a low hormone (LH)

condition where one arm performed arm curl exercise only (3 to 4 sets of 8 to 12 repetitions) and

a high hormone (HH) condition where the contralateral arm performed the same arm curl

exercise followed immediately by a bout of leg resistance exercises (5 sets of 10 repetitions of

leg press and 3 sets of 12 repetitions of leg extension/leg curl supersets). Training was carried

out over the course of 15 weeks. During the first 6 weeks, subjects trained 3 times every 2 weeks

with 72 hours between sessions; for the final 9 weeks, subjects trained twice a week with the

timing of between-trial sessions reduced to 48 hours. As expected, significant post-exercise

increases in anabolic hormones (GH, IGF-1, and total and free testosterone) were seen in the HH

group whereas hormonal levels were mostly unchanged in LA. Muscle girth of the upper arms increased similarly in LH and HH, with no significant differences noted between groups. These findings indicate that acute hormonal elevations are not involved in hypertrophic adaptations. It should be noted that the extra session in the final 9 weeks reduced recovery between arms to ~24 hours, which may have positively impacted protein synthesis in the untrained arm during the recuperative period.

Most recently, Ronnestad et al. (66) employed a similar within-subject protocol to that of West et al. (93), except that leg exercise was performed before the arm curl in the HH group. Subjects were 11 young men without resistance training experience. Exercise consisted of four weekly training sessions; 2 each for LH and HH with at least 48 hours recovery afforded between trials for the same arm. Study length spanned 11 weeks. In contrast to the findings of West et al. (93), greater increases in muscle CSA of the elbow flexors were seen in the HH group, implying that elevated hormones were responsible for hypertrophic gains. Differences were specific to distinct regions of elbow flexors, with increases in CSA seen only at the 2 middle sections where muscle girth was largest. While this may seem counterintuitive, it has been well-demonstrated that muscles often develop in non-uniform manner (4, 27, 49), seemingly caused by the regional-specific muscle activation associated with a given exercise (90). The reasons for the discrepancies between results in this study compared to West et al. (93) are not clear. The authors postulated that spiking hormonal levels prior to arm training may have played a role in morphological adaptations. Another possibility is that differences may be related to the volume of training for the arms. Subjects in the study by West et al. (93) performed 3 to 4 sets of arm curl exercise while those in Ronnestad et al. (66) performed a total of 6 sets (2 sets each of biceps curl, hammer curl, and reverse curl). It is conceivable that the effects of post-

18

exercise hormonal elevations are magnified by an increased myotrauma from a higher training volume. Further study is needed to reconcile these hypotheses. It also should be noted that the overall magnitude of differences in CSA were relatively small, raising question as to the practical application of results.

Conclusions

Research is contradictory as to whether or not the post-exercise anabolic hormonal response associated with metabolic stress plays a role in skeletal muscle hypertrophy. Given the inconsistencies between studies, any attempts to draw definitive conclusions on the subject would be premature at this time. Based on limited cellular signaling data, it is conceivable that the primary effect of post-exercise hormonal elevations is to increase satellite cell activity as opposed to mediating acute increases in muscle protein synthesis. If so, this could favor greater long-term increases in muscle hypertrophy without significantly impacting short-term gains. This hypothesis requires further study.

What seems relatively clear from the literature is that if a relationship does in fact exist between acute systemic factors and muscle growth, the overall magnitude of the effect would be fairly modest. The ~8% figure reported by West and Phillips (95) would seem to be a reasonable upper estimate as to a potential contribution from transient hormonal elevations, but further research is required to quantify any potential impact. Whether such modest effects are meaningful is a separate issue and would be dependent on individual goals and needs. For the recreational gym participant, slight increases in muscle mass might not have much practical importance. However, for the athlete or bodybuilder, it could mean the difference between winning and losing a competition. There also may be practical implications for the elderly, where even small morphological improvements could lead to an enhanced functional capacity.

Another possibility to consider is that genetic factors may influence a person's response to post-exercise hormonal elevations. It has been estimated that genetic differences can account for approximately half of the variation in athletic performance (16). This is consistent with studies showing that the hypertrophic response to resistance training displays tremendous variance between individuals (7, 58). It is therefore conceivable that acute hormonal responses may be more relevant to certain lifters as opposed to others. There is some evidence to support this contention as a strong trend for a significant association has been shown between IGF-1 and those who respond favorably to hypertrophy-type training (95).

Finally and importantly, studies in trained individuals on the topic are lacking and it remains to be determined whether training status influences the morphological response to acute exercise-induced hormonal elevations. Some researchers have proposed that post-exercise hormonal fluctuations may be permissive for untrained individuals but follow a dose-response relationship in those with considerable training experience. Indeed, hormonal levels following resistance exercise were shown to be significantly more pronounced in strength athletes compared to endurance athletes and sedentary individuals (83), suggesting that such elevations may play a greater role in hypertrophic adaptations as one gains resistance training experience (38). This hypothesis warrants further investigation.

Table 1: Summary of Indirect Studies Investigating the Hormone Hypothesis

Study	Subjects	Study Length	Results
McCall et al. (50)	11 young recreationally trained men	12 weeks	Strong correlation between acute elevations of GH and fiber hypertrophy
Ahtiainen et al. (4)	16 young men (8 strength-trained athletes and 8 physically active individuals)	21 weeks	Strong correlation between acute elevations of testosterone and fiber hypertrophy
West and Phillips (95)	56 young untrained men	12 weeks	Weak correlation between acute elevations of GH and the type II fiber hypertrophy; no correlation between acute testosterone elevations and fiber hypertrophy
West et al. (92)	8 young untrained men	2 separate trials	No additive effects from acute hormonal elevations on myofibrillar protein synthesis or intracellular signaling

Table 2: Summary of Direct Studies Investigating the Hormone Hypothesis

Study	Subjects	Study Length	Results
Hansen et al. (30)	16 young untrained men	9 weeks	Significant increases in muscle strength as a result of acute hormonal elevations
Madarame et al. (47)	15 young untrained men	10 weeks	Significant increases in fiber hypertrophy as a result of acute hormonal elevations
West et al. (93)	12 young untrained men	15 weeks	No additive effects from acute hormonal elevations on fiber hypertrophy
Ronnestad et al. (66)	11 young untrained men	11 weeks	Significant increase in fiber hypertrophy as a result of acute hormonal elevations

References

1. Abernethy, PJ, Jurimae, J, Logan, PA, Taylor, AW, and Thayer, RE. Acute and chronic response of skeletal muscle to resistance exercise. *Sports Med.* 17: 22-38, 1994.

2. Adams, GR, and McCue, SA. Localized infusion of IGF-I results in skeletal muscle hypertrophy in rats. *J. Appl. Physiol.* 84: 1716-1722, 1998.

3. Adams, GR. Invited Review: Autocrine/paracrine IGF-I and skeletal muscle adaptation. *J. Appl. Physiol.* 93: 1159-1167, 2002.

4. Ahtiainen, JP, Pakarinen, A, Alen, M, Kraemer, WJ, and Hakkinen, K. Muscle hypertrophy, hormonal adaptations and strength development during strength training in strength-trained and untrained men. *Eur. J. Appl. Physiol.* 89: 555-563, 2003.

5. Ahtiainen, JP, Hulmi, JJ, Kraemer, WJ, Lehti, M, Nyman, K, Selanne, H, Alen, M, Pakarinen, A, Komulainen, J, Kovanen, V, Mero, AA, and Hakkinen, K. Heavy resistance exercise training and skeletal muscle androgen receptor expression in younger and older men. *Steroids* 76: 183-192, 2011.

6. Aperghis, M, Velloso, CP, Hameed, M, Brothwood, T, Bradley, L, Bouloux, PM, Harridge, SD, and Goldspink, G. Serum IGF-I levels and IGF-I gene splicing in muscle of healthy young males receiving rhGH. *Growth Horm. IGF Res.* 19: 61-67, 2009.

7. Bamman, MM, Petrella, JK, Kim, JS, Mayhew, DL, and Cross, JM. Cluster analysis tests the importance of myogenic gene expression during myofiber hypertrophy in humans. *J. Appl. Physiol.* 102: 2232-2239, 2007.

8. Barton, ER. Viral expression of insulin-like growth factor-I isoforms promotes different responses in skeletal muscle. *J. Appl. Physiol.* 100: 1778-1784, 2006.

9. Bhasin, S, Storer, TW, Berman, N, Callegari, C, Clevenger, B, Phillips, J, Bunnell, TJ, Tricker, R, Shirazi, A, and Casaburi, R. The effects of supraphysiologic doses of testosterone on muscle size and strength in normal men. *N. Engl. J. Med.* 335: 1-7, 1996.

10. Bhasin, S, Woodhouse, L, and Storer, TW. Proof of the effect of testosterone on skeletal muscle. *J. Endocrinol.* 170: 27-38, 2001.

11. Bhasin, S, Woodhouse, L, Casaburi, R, Singh, AB, Mac, RP, Lee, M, Yarasheski, KE, Sinha-Hikim, I, Dzekov, C, Dzekov, J, Magliano, L, and Storer, TW. Older men are as responsive as young men to the anabolic effects of graded doses of testosterone on the skeletal muscle. *J. Clin. Endocrinol. Metab.* 90: 678-688, 2005.

12. Brahm, H, Piehl-Aulin, K, Saltin, B, and Ljunghall, S. Net fluxes over working thigh of hormones, growth factors and biomarkers of bone metabolism during short lasting dynamic exercise. *Calcif. Tissue Int.* 60: 175-180, 1997.

13. Buresh, R, Berg, K, and French, J. The effect of resistive exercise rest interval on hormonal response, strength, and hypertrophy with training. *J Strength Cond Res* 23: 62-71, 2009.

14. Coffey, VG, Shield, A, Canny, BJ, Carey, KA, Cameron-Smith, D, and Hawley, JA. Interaction of contractile activity and training history on mRNA abundance in skeletal muscle from trained athletes. *Am. J. Physiol. Endocrinol. Metab.* 290: E849-55, 2006.

15. Crewther, B, Keogh, J, Cronin, J, and Cook, C. Possible stimuli for strength and power adaptation: acute hormonal responses. *Sports Med.* 36: 215-238, 2006.

16. Crewther, BT, Cook, C, Cardinale, M, Weatherby, RP, and Lowe, T. Two emerging concepts for elite athletes: the short-term effects of testosterone and cortisol on the neuromuscular system and the dose-response training role of these endogenous hormones. *Sports Med.* 41: 103-123, 2011.

17. Ehrnborg, C, and Rosen, T. Physiological and pharmacological basis for the ergogenic effects of growth hormone in elite sports. *Asian J. Androl.* 10: 373-383, 2008.

18. Fujita, S, Abe, T, Drummond, MJ, Cadenas, JG, Dreyer, HC, Sato, Y, Volpi, E, and Rasmussen, BB. Blood flow restriction during low-intensity resistance exercise increases S6K1 phosphorylation and muscle protein synthesis. *J. Appl. Physiol.* 103: 903-910, 2007.

19. Goldspink, G. Mechanical signals, IGF-I gene splicing, and muscle adaptation. *Physiology (Bethesda)* 20: 232-238, 2005.

20. Goldspink, G. Impairment of IGF-I gene splicing and MGF expression associated with muscle wasting. *Int. J. Biochem. Cell Biol.* 38: 481-489, 2006.

21. Goodman, CA, Mayhew, DL, and Hornberger, TA. Recent progress toward understanding the molecular mechanisms that regulate skeletal muscle mass. *Cell. Signal.* 23: 1896-1906, 2011.

22. Goto, K, Ishii, N, Kizuka, T, and Takamatsu, K. The impact of metabolic stress on hormonal responses and muscular adaptations. *Med. Sci. Sports Exerc.* 37: 955-963, 2005.

23. Gotshalk, LA, Loebel, CC, Nindl, BC, Putukian, M, Sebastianelli, WJ, Newton, RU, Hakkinen, K, and Kraemer, WJ. Hormonal responses of multiset versus single-set heavy-resistance exercise protocols. *Can. J. Appl. Physiol.* 22: 244-255, 1997.

24. Haddad, F, and Adams, GR. Inhibition of MAP/ERK kinase prevents IGF-I-induced hypertrophy in rat muscles. *J. Appl. Physiol.* 96: 203-210, 2004.

25. Hakkinen, K, and Pakarinen, A. Acute hormonal responses to two different fatiguing heavy-resistance protocols in male athletes. *J. Appl. Physiol.* 74: 882-887, 1993.

26. Hakkinen, K, Pakarinen, A, Kraemer, WJ, Newton, RU, and Alen, M. Basal concentrations and acute responses of serum hormones and strength development during heavy resistance training in middle-aged and elderly men and women. *J. Gerontol. A Biol. Sci. Med. Sci.* 55: B95-105, 2000.

27. Hakkinen, K, Pakarinen, A, Kraemer, WJ, Hakkinen, A, Valkeinen, H, and Alen, M. Selective muscle hypertrophy, changes in EMG and force, and serum hormones during strength training in older women. *J. Appl. Physiol.* 91: 569-580, 2001.

28. Hameed, M, Lange, KH, Andersen, JL, Schjerling, P, Kjaer, M, Harridge, SD, and Goldspink, G. The effect of recombinant human growth hormone and resistance training on IGF-I mRNA expression in the muscles of elderly men. *J. Physiol.* 555: 231-240, 2004.

29. Hand, BD, Kostek, MC, Ferrell, RE, Delmonico, MJ, Douglass, LW, Roth, SM, Hagberg, JM, and Hurley, BF. Influence of promoter region variants of insulin-like growth factor pathway genes on the strength-training response of muscle phenotypes in older adults. *J. Appl. Physiol.* 103: 1678-1687, 2007.

30. Hansen, S, Kvorning, T, Kjaer, M, and Sjogaard, G. The effect of short-term strength training on human skeletal muscle: the importance of physiologically elevated hormone levels. *Scand. J. Med. Sci. Sports* 11: 347-354, 2001.

31. Harridge, SD. Plasticity of human skeletal muscle: gene expression to in vivo function. *Exp. Physiol.* 92: 783-797, 2007.

32. Hill, M, Wernig, A, and Goldspink, G. Muscle satellite (stem) cell activation during local tissue injury and repair. *J. Anat.* 203: 89-99, 2003.

33. Iida, K, Itoh, E, Kim, DS, del Rincon, JP, Coschigano, KT, Kopchick, JJ, and Thorner, MO. Muscle mechano growth factor is preferentially induced by growth hormone in growth hormone-deficient lit/lit mice. *J. Physiol.* 560: 341-349, 2004.

34. Imanaka, M, Iida, K, Murawaki, A, Nishizawa, H, Fukuoka, H, Takeno, R, Takahashi, Y, Okimura, Y, Kaji, H, and Chihara, K. Growth hormone stimulates mechano growth factor expression and activates myoblast transformation in C2C12 cells. *Kobe J. Med. Sci.* 54: E46-54, 2008.

35. Kim, H, Barton, E, Muja, N, Yakar, S, Pennisi, P, and Leroith, D. Intact insulin and insulin-like growth factor-I receptor signaling is required for growth hormone effects on skeletal muscle growth and function in vivo. *Endocrinology* 146: 1772-1779, 2005.

36. Klover, P, and Hennighausen, L. Postnatal body growth is dependent on the transcription factors signal transducers and activators of transcription 5a/b in muscle: a role for autocrine/paracrine insulin-like growth factor I. *Endocrinology* 148: 1489-1497, 2007.

37. Kraemer, WJ, Marchitelli, L, Gordon, SE, Harman, E, Dziados, JE, Mello, R, Frykman, P, McCurry, D, and Fleck, SJ. Hormonal and growth factor responses to heavy resistance exercise protocols. *J. Appl. Physiol.* 69: 1442-1450, 1990.

38. Kraemer, WJ, Fry, AC, Warren, BJ, Stone, MH, Fleck, SJ, Kearney, JT, Conroy, BP, Maresh, CM, Weseman, CA, and Triplett, NT. Acute hormonal responses in elite junior weightlifters. *Int. J. Sports Med.* 13: 103-109, 1992.

39. Kraemer, WJ, and Ratamess, NA. Hormonal responses and adaptations to resistance exercise and training. *Sports Med.* 35: 339-361, 2005.

40. Kraemer, WJ, Dunn-Lewis, C, Comstock, BA, Thomas, GA, Clark, JE, and Nindl, BC. Growth hormone, exercise, and athletic performance: a continued evolution of complexity. *Curr. Sports Med. Rep.* 9: 242-252, 2010.

41. Kvorning, T, Andersen, M, Brixen, K, and Madsen, K. Suppression of endogenous testosterone production attenuates the response to strength training: a randomized, placebo-controlled, and blinded intervention study. *Am. J. Physiol. Endocrinol. Metab.* 291: E1325-32, 2006.

42. Kvorning, T, Andersen, M, Brixen, K, Schjerling, P, Suetta, C, and Madsen, K. Suppression of testosterone does not blunt mRNA expression of myoD, myogenin, IGF, myostatin or androgen receptor post strength training in humans. *J. Physiol.* 578: 579-593, 2007.

43. Lange, KH, Andersen, JL, Beyer, N, Isaksson, F, Larsson, B, Rasmussen, MH, Juul, A, Bulow, J, and Kjaer, M. GH administration changes myosin heavy chain isoforms in skeletal muscle but does not augment muscle strength or hypertrophy, either alone or combined with resistance exercise training in healthy elderly men. *J. Clin. Endocrinol. Metab.* 87: 513-523, 2002.

44. Loebel, C, and Kraemer, W. A brief review: Testosterone and resistance exercise in men. *J. Strength and Conditioning Research* 12: 57-63, 1998.

45. Loenneke, JP, Fahs, CA, Wilson, JM, and Bemben, MG. Blood flow restriction: the metabolite/volume threshold theory. *Med. Hypotheses* 77: 748-752, 2011.

46. Lupu, F, Terwilliger, JD, Lee, K, Segre, GV, and Efstratiadis, A. Roles of growth hormone and insulin-like growth factor 1 in mouse postnatal growth. *Dev. Biol.* 229: 141-162, 2001.

47. Madarame, H, Neya, M, Ochi, E, Nakazato, K, Sato, Y, and Ishii, N. Cross-transfer effects of resistance training with blood flow restriction. *Med. Sci. Sports Exerc.* 40: 258-263, 2008.

48. Matheny, RW, Merritt, E, Zannikos, SV, Farrar, RP, and Adamo, ML. Serum IGF-I-deficiency does not prevent compensatory skeletal muscle hypertrophy in resistance exercise. *Exp. Biol. Med. (Maywood)* 234: 164-170, 2009.

49. Matta, T, Simao, R, de Salles, BF, Spineti, J, and Oliveira, LF. Strength training's chronic effects on muscle architecture parameters of different arm sites. *J. Strength Cond Res.* 25: 1711-1717, 2011.

50. McCall, GE, Byrnes, WC, Fleck, SJ, Dickinson, A, and Kraemer, WJ. Acute and chronic hormonal responses to resistance training designed to promote muscle hypertrophy. *Can. J. Appl. Physiol.* 24: 96-107, 1999.

51. McCarthy, JJ, and Esser, KA. Counterpoint: Satellite cell addition is not obligatory for skeletal muscle hypertrophy. *J Appl Physiol* 103: 1100-1102, 2007.

52. McCarthy, JJ, Mula, J, Miyazaki, M, Erfani, R, Garrison, K, Farooqui, AB, Srikuea, R, Lawson, BA, Grimes, B, Keller, C, Van Zant, G, Campbell, KS, Esser, KA, Dupont-Versteegden, EE, and Peterson, CA. Effective fiber hypertrophy in satellite cell-depleted skeletal muscle. *Development* 138: 3657-3666, 2011.

53. McCaulley, GO, McBride, JM, Cormie, P, Hudson, MB, Nuzzo, JL, Quindry, JC, and Travis Triplett, N. Acute hormonal and neuromuscular responses to hypertrophy, strength and power type resistance exercise. *Eur. J. Appl. Physiol.* 105: 695-704, 2009.

54. Nindl, BC, Hymer, WC, Deaver, DR, and Kraemer, WJ. Growth hormone pulsatility profile characteristics following acute heavy resistance exercise. *J. Appl. Physiol.* 91: 163-172, 2001.

55. Ochi, E, Ishii, N, and Nakazato, K. Time course change of IGF1/Akt/mTOR/p70s6k pathway activation in rat gastrocnemius muscle during repeated bouts of eccentric exercise. *JSSM* 9: 170-175, 2010.

56. O'Connor, RS, and Pavlath, GK. Point:Counterpoint: Satellite cell addition is/is not obligatory for skeletal muscle hypertrophy. *J. Appl. Physiol.* 103: 1099-1100, 2007.

57. Petrella, JK, Kim, JS, Cross, JM, Kosek, DJ, and Bamman, MM. Efficacy of myonuclear addition may explain differential myofiber growth among resistance-trained young and older men and women. *Am. J. Physiol. Endocrinol. Metab.* 291: E937-46, 2006.

58. Petrella, JK, Kim, J, Mayhew, DL, Cross, JM, and Bamman, MM. Potent myofiber hypertrophy during resistance training in humans is associated with satellite cell-mediated myonuclear addition: a cluster analysis. *J. Appl. Physiol.* 104: 1736-1742, 2008.

59. Philippou, A, Halapas, A, Maridaki, M, and Koutsilieris, M. Type I insulin-like growth factor receptor signaling in skeletal muscle regeneration and hypertrophy. *J. Musculoskelet. Neuronal Interact.* 7: 208-218, 2007.

60. Philippou, A, Maridaki, M, Halapas, A, and Koutsilieris, M. The role of the insulin-like growth factor 1 (IGF-1) in skeletal muscle physiology. *In Vivo* 21: 45-54, 2007.

61. Phillips, SM. Physiologic and molecular bases of muscle hypertrophy and atrophy: impact of resistance exercise on human skeletal muscle (protein and exercise dose effects). *Appl. Physiol. Nutr. Metab.* 34: 403-410, 2009.

62. Reeves, GV, Kraemer, RR, Hollander, DB, Clavier, J, Thomas, C, Francois, M, and Castracane, VD. Comparison of hormone responses following light resistance exercise with partial vascular occlusion and moderately difficult resistance exercise without occlusion. *J. Appl. Physiol.* 101: 1616-1622, 2006.

63. Rennie, MJ. Claims for the anabolic effects of growth hormone: a case of the emperor's new clothes? *Br. J. Sports Med.* 37: 100-105, 2003.

26

64. Rigamonti, AE, Locatelli, L, Cella, SG, Bonomo, SM, Giunta, M, Molinari, F, Sartorio, A, and Muller, EE. Muscle expressions of MGF, IGF-IEa, and myostatin in intact and hypophysectomized rats: effects of rhGH and testosterone alone or combined. *Horm. Metab. Res.* 41: 23-29, 2009.

65. Rommel, C, Bodine, SC, Clarke, BA, Rossman, R, Nunez, L, Stitt, TN, Yancopoulos, GD, and Glass, DJ. Mediation of IGF-1-induced skeletal myotube hypertrophy by PI(3)K/Akt/mTOR and PI(3)K/Akt/GSK3 pathways. *Nat. Cell Biol.* 3: 1009-1013, 2001.

66. Ronnestad, BR, Nygaard, H, and Raastad, T. Physiological elevation of endogenous hormones results in superior strength training adaptation. *Eur. J. Appl. Physiol.* 111: 2249-2259, 2011.

67. Sandri, M. Signaling in muscle atrophy and hypertrophy. *Physiology (Bethesda)* 23: 160-170, 2008.

68. Schoenfeld, BJ. The mechanisms of muscle hypertrophy and their application to resistance training. *J. Strength Cond Res.* 24: 2857-2872, 2010.

69. Sculthorpe, N, Solomon, AM, Sinanan, AC, Bouloux, PM, Grace, F, and Lewis, MP. Androgens Affect Myogenesis In Vitro and Increase Local IGF-1 Expression. *Med. Sci. Sports Exerc.* 44: 610-615, 2012.

70. Semsarian, C, Wu, MJ, Ju, YK, Marciniec, T, Yeoh, T, Allen, DG, Harvey, RP, and Graham, RM. Skeletal muscle hypertrophy is mediated by a Ca2+-dependent calcineurin signalling pathway. *Nature* 400: 576-581, 1999.

71. Sinha-Hikim, I, Cornford, M, Gaytan, H, Lee, ML, and Bhasin, S. Effects of testosterone supplementation on skeletal muscle fiber hypertrophy and satellite cells in community-dwelling older men. *J. Clin. Endocrinol. Metab.* 91: 3024-3033, 2006.

72. Smilios, I, Pilianidis, T, Karamouzis, M, and Tokmakidis, SP. Hormonal responses after various resistance exercise protocols. *Med. Sci. Sports Exerc.* 35: 644-654, 2003.

73. Solomon, AM, and Bouloux, PM. Modifying muscle mass - the endocrine perspective. *J. Endocrinol.* 191: 349-360, 2006.

74. Sotiropoulos, A, Ohanna, M, Kedzia, C, Menon, RK, Kopchick, JJ, Kelly, PA, and Pende, M. Growth hormone promotes skeletal muscle cell fusion independent of insulin-like growth factor 1 up-regulation. *Proc. Natl. Acad. Sci. U. S. A.* 103: 7315-7320, 2006.

75. Spangenburg, EE, Le Roith, D, Ward, CW, and Bodine, SC. A functional insulin-like growth factor receptor is not necessary for load-induced skeletal muscle hypertrophy. *J. Physiol.* 586: 283-291, 2008.

76. Spiering, BA, Kraemer, WJ, Vingren, JL, Ratamess, NA, Anderson, JM, Armstrong, LE, Nindl, BC, Volek, JS, Hakkinen, K, and Maresh, CM. Elevated endogenous testosterone concentrations potentiate muscle androgen receptor responses to resistance exercise. *J. Steroid Biochem. Mol. Biol.* 114: 195-199, 2009.

77. Suga, T, Okita, K, Morita, N, Yokota, T, Hirabayashi, K, Horiuchi, M, Takada, S, Omokawa, M, Kinugawa, S, and Tsutsui, H. Dose effect on intramuscular metabolic stress during low-intensity resistance exercise with blood flow restriction. *J. Appl. Physiol.* 108: 1563-1567, 2010.

78. Takano, H, Morita, T, Iida, H, Asada, K, Kato, M, Uno, K, Hirose, K, Matsumoto, A, Takenaka, K, Hirata, Y, Eto, F, Nagai, R, Sato, Y, and Nakajima, T. Hemodynamic and hormonal responses to a short-term low-intensity resistance exercise with the reduction of muscle blood flow. *Eur. J. Appl. Physiol.* 95: 65-73, 2005.

79. Takarada, Y, Nakamura, Y, Aruga, S, Onda, T, Miyazaki, S, and Ishii, N. Rapid increase in plasma growth hormone after low-intensity resistance exercise with vascular occlusion. *J. Appl. Physiol.* 88: 61-65, 2000.

80. Tidball, JG. Mechanical signal transduction in skeletal muscle growth and adaptation. *J. Appl. Physiol.* 98: 1900-1908, 2005.

81. Timmons, JA. Variability in training-induced skeletal muscle adaptation. *J. Appl. Physiol.* 110: 846-853, 2011.

82. Toigo, M, and Boutellier, U. New fundamental resistance exercise determinants of molecular and cellular muscle adaptations. *Eur. J. Appl. Physiol.* 97: 643-663, 2006.

83. Tremblay, MS, Copeland, JL, and Van Helder, W. Effect of training status and exercise mode on endogenous steroid hormones in men. *J. Appl. Physiol.* 96: 531-539, 2004.

84. Urban, RJ, Bodenburg, YH, Gilkison, C, Foxworth, J, Coggan, AR, Wolfe, RR, and Ferrando, A. Testosterone administration to elderly men increases skeletal muscle strength and protein synthesis. *Am. J. Physiol.* 269: E820-6, 1995.

85. Veldhuis, JD, Keenan, DM, Mielke, K, Miles, JM, and Bowers, CY. Testosterone supplementation in healthy older men drives GH and IGF-I secretion without potentiating peptidyl secretagogue efficacy. *Eur. J. Endocrinol.* 153: 577-586, 2005.

86. Velloso, CP. Regulation of muscle mass by growth hormone and IGF-I. *Br. J. Pharmacol.* 154: 557-568, 2008.

87. Velloso, CP, and Harridge, SD. Insulin-like growth factor-I E peptides: implications for aging skeletal muscle. *Scand. J. Med. Sci. Sports* 20: 20-27, 2010.

88. Vierck, J, O'Reilly, B, Hossner, K, Antonio, J, Byrne, K, Bucci, L, and Dodson, M. Satellite cell regulation following myotrauma caused by resistance exercise. *Cell Biol. Int.* 24: 263-272, 2000.

89. Vingren, JL, Kraemer, WJ, Ratamess, NA, Anderson, JM, Volek, JS, and Maresh, CM. Testosterone physiology in resistance exercise and training: the up-stream regulatory elements. *Sports Med.* 40: 1037-1053, 2010.

90. Wakahara, T, Miyamoto, N, Sugisaki, N, Murata, K, Kanehisa, H, Kawakami, Y, Fukunaga, T, and Yanai, T. Association between regional differences in muscle activation in one session of resistance exercise and in muscle hypertrophy after resistance training. *Eur. J. Appl. Physiol.* 112: 1569-1576, 2012.

91. Wallace, JD, Cuneo, RC, Bidlingmaier, M, Lundberg, PA, Carlsson, L, Boguszewski, CL, Hay, J, Boroujerdi, M, Cittadini, A, Dall, R, Rosen, T, and Strasburger, CJ. Changes in non-22-kilodalton (kDa) isoforms of growth hormone (GH) after administration of 22-kDa recombinant human GH in trained adult males. *J. Clin. Endocrinol. Metab.* 86: 1731-1737, 2001.

92. West, DW, Kujbida, GW, Moore, DR, Atherton, P, Burd, NA, Padzik, JP, De Lisio, M, Tang, JE, Parise, G, Rennie, MJ, Baker, SK, and Phillips, SM. Resistance exercise-induced increases in putative anabolic hormones do not enhance muscle protein synthesis or intracellular signalling in young men. *J. Physiol.* 587: 5239-5247, 2009.

93. West, DW, Burd, NA, Tang, JE, Moore, DR, Staples, AW, Holwerda, AM, Baker, SK, and Phillips, SM. Elevations in ostensibly anabolic hormones with resistance exercise enhance neither training-induced muscle hypertrophy nor strength of the elbow flexors. *J. Appl. Physiol.* 108: 60-67, 2010.

94. West, DW, and Phillips, SM. Anabolic processes in human skeletal muscle: restoring the identities of growth hormone and testosterone. *Phys. Sportsmed* 38: 97-104, 2010.

95. West, DW, and Phillips, SM. Associations of exercise-induced hormone profiles and gains in strength and hypertrophy in a large cohort after weight training. *Eur. J. Appl. Physiol.* 112: 2693-2702, 2012.

96. Wilkinson, SB, Tarnopolsky, MA, Grant, EJ, Correia, CE, and Phillips, SM. Hypertrophy with unilateral resistance exercise occurs without increases in endogenous anabolic hormone concentration. *Eur. J. Appl. Physiol.* 98: 546-555, 2006.

97. Yamaguchi, A, Fujikawa, T, Shimada, S, Kanbayashi, I, Tateoka, M, Soya, H, Takeda, H, Morita, I, Matsubara, K, and Hirai, T. Muscle IGF-I Ea, MGF, and myostatin mRNA expressions after compensatory overload in hypophysectomized rats. *Pflugers Arch.* 453: 203-210, 2006.

98. Yang, SY, and Goldspink, G. Different roles of the IGF-I Ec peptide (MGF) and mature IGF-I in myoblast proliferation and differentiation. *FEBS Lett.* 522: 156-160, 2002.

99. Yarasheski, KE, Campbell, JA, Smith, K, Rennie, MJ, Holloszy, JO, and Bier, DM. Effect of growth hormone and resistance exercise on muscle growth in young men. *Am. J. Physiol.* 262: E261-7, 1992.

100. Yarasheski, KE, Zachwieja, JJ, Campbell, JA, and Bier, DM. Effect of growth hormone and resistance exercise on muscle growth and strength in older men. *Am. J. Physiol.* 268: E268-76, 1995.

101. Zhao, W, Pan, J, Zhao, Z, Wu, Y, Bauman, WA, and Cardozo, CP. Testosterone protects against dexamethasone-induced muscle atrophy, protein degradation and MAFbx upregulation. *J. Steroid Biochem. Mol. Biol.* 110: 125-129, 2008.

102. Zou, K, Meador, BM, Johnson, B, Huntsman, HD, Mahmassani, Z, Valero, MC, Huey, KA, and Boppart, MD. The alpha(7)beta(1)-integrin increases muscle hypertrophy following multiple bouts of eccentric exercise. *J. Appl. Physiol.* 111: 1134-1141, 2011.