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

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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
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 speculate 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";
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"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).
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.
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
elicited. 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-1 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-1Ea 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
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 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 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
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
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 p70S6k phosphorylation were similar between
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
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-
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

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Study Length</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>McCall et al. (50)</td>
<td>11 young recreationally trained men</td>
<td>12 weeks</td>
<td>Strong correlation between acute elevations of GH and fiber hypertrophy</td>
</tr>
<tr>
<td>Ahtiainen et al. (4)</td>
<td>16 young men (8 strength-trained athletes and 8 physically active individuals)</td>
<td>21 weeks</td>
<td>Strong correlation between acute elevations of testosterone and fiber hypertrophy</td>
</tr>
<tr>
<td>West and Phillips (95)</td>
<td>56 young untrained men</td>
<td>12 weeks</td>
<td>Weak correlation between acute elevations of GH and the type II fiber hypertrophy; no correlation between acute testosterone elevations and fiber hypertrophy</td>
</tr>
<tr>
<td>West et al. (92)</td>
<td>8 young untrained men</td>
<td>2 separate trials</td>
<td>No additive effects from acute hormonal elevations on myofibrillar protein synthesis or intracellular signaling</td>
</tr>
</tbody>
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## Table 2: Summary of Direct Studies Investigating the Hormone Hypothesis

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

### References


