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CLINICAL FEATURE
REVIEW

The role of hormones in muscle hypertrophy

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ABSTRACT

Anabolic-androgenic steroids (AAS) and other hormones such as growth hormone (GH) and insulin-like growth factor-1 (IGF-1) have been shown to increase muscle mass in patients suffering from various diseases related to muscle atrophy. Despite known side-effects associated with supraphysiologic doses of such drugs, their anabolic effects have led to their widespread use and abuse by bodybuilders and athletes such as strength athletes seeking to improve performance and muscle mass. On the other hand, resistance training (RT) has also been shown to induce significant endogenous hormonal (testosterone (T), GH, IGF-1) elevations. Therefore, some bodybuilders employ RT protocols designed to elevate hormonal levels in order to maximize anabolic responses. In this article, we reviewed current RT protocol outcomes with and without performance enhancing drug usage. Acute RT-induced hormonal elevations seem not to be directly correlated with muscle growth. On the other hand, supplementation with AAS and other hormones might lead to supraphysiological muscle hypertrophy, especially when different compounds are combined.

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Introduction

Although the anabolic effects of anabolic–androgenic steroids (AAS) are widely recognized, there has been considerable controversy about the hypertrophic effects of resistance training (RT)-induced endogenous hormonal elevations. Indeed, while a recent study found a significant correlation between RT-induced acute testosterone (T) elevations and long-term muscle hypertrophy [1], several others failed to observe any associations between these variables [2–4]. The theory supporting the anabolic effects of RT-induced hormonal elevations is based on the concept of elevated post-exercise anabolic hormones binding to hormone receptors and inducing upregulation of several intracellular anabolic pathways [1]. However, many studies only measured acute hormonal changes and research about responses several days after training is lacking. The exact anabolic mechanism of RT-induced hormonal elevations is not clear, but enhanced protein synthesis, decreased protein breakdown [5], satellite cell activation [6], Wnt signaling [7], and SHBG receptor binding [8] are speculated to be major factors. In addition, hormones might act via non-genomic pathways to increase intracellular calcium [9], thereby allowing for more force production [10] and ultimately leading to improved training intensity and muscular adaptations [1].

After the discovery and synthesis of T in the 1930s, AAS were developed for the treatment of various diseases, growth stimulation, and increase of muscle mass. By the 1970s, the anabolic and performance-enhancing effects of AAS were discovered by bodybuilders and some high-level athletes who began to abuse them. Furthermore, the cosmetic effects of increased muscle mass achieved with AAS led to the wide spread of AAS abuse among bodybuilders. It has been shown that supraphysiological levels of T increase muscle mass not only in elderly and hypogonadal men but also in healthy young men [11–13]. Previous research on the administration of T derivatives (AAS) also showed improved body composition after the treatment [14–16]. Indeed, AAS are synthetic substances derived from T with several different anabolic–androgenic ratios, often used by athletes for purposes such as bulking (increase of body mass in the off-season) or cutting (reduction of body fat while maintaining muscle mass pre-contest) cycles.

In addition to steroid hormones, naturally released peptide and protein hormones (PH) such as growth hormone (GH) and insulin-like growth factor 1 (IGF-1) have also been shown to increase after RT [4,17]. GH became popular as performance-enhancing drug in the early 1990s after the development of its improved recombinant form [18]. The difficulty to detect GH doping made this drug popular especially among bodybuilders. However, even though some studies have found a correlation between acute RT-induced GH increases and long-term muscle hypertrophy [17], other studies failed to support these findings [2,3]. It seems that GH improves body composition without direct effects on performance [19], making this drug especially notorious among bodybuilders. Indeed, GH increases serum IGF-1 concentrations [20] and might therefore have anabolic effects besides its well-recognized lipolytic effects.

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Since the anabolic effects of GH are mainly expressed via the conversion to IGF-1, doping with IGF-1 has gained in popularity; however, pharmaceutical grade IGF-1 has only been recognized for human treatment recently and is not widely available, giving rise to an increasing illicit production and trade market. IGF-1 is sought for its anabolic properties such as the ability to increase muscle fiber volume via activation of surrounding satellite cells [21].

Even though direct anabolic properties have not been recognized, the use of insulin is also widespread among bodybuilders and strength athletes seeking to increase muscle mass [22]. Insulin has preventive properties with regard to protein degradation [22] and insulin is a powerful transporter hormone often used after or pre workout, despite the risk of hypoglycemia, in order to transport as much nutrients as possible to the damaged muscle cells. Insulin is also used by some bodybuilders throughout the day in order to increase nutrient uptake.

In view of the anabolic effects of AAS and PH on muscle mass and performance, some bodybuilders and strength athletes started to attempt to increase their natural levels of T, GH, and IGF-1 via RT. However, the degree and duration of RT-induced systemic hormonal increases might not lead to similar effects as seen with exogenous administration of AAS or PH, often used at doses leading to levels way above physiological levels for long periods of time. The purpose of this review is to elucidate the degree of RT-induced acute hormonal elevations and if they can, to a certain degree, induce similar anabolic pathways as compared to the exogenous administration of AAS and PH.

Hypertrophic effects of RT-induced endogenous hormonal elevations

The effects of RT on hormonal responses have been widely investigated for several decades [23–25]. Even though broad guidelines exist regarding which type of RT protocols maximize the post-exercise hormonal response [26], the effects of these acute RT-induced hormonal elevations on long-term muscle hypertrophy are not currently clear.

Typical bodybuilding-type training protocols that include large muscle groups with moderate intensity, high volume, and relatively short rest periods are generally effective in inducing acute T responses [26]. A positive correlation (r = 0.76) between acute RT-induced T increases and muscle cross-sectional area (CSA) has been previously observed [1,27]. However, acute elevations of T after RT last only for about 60 min and the average peak generally does not exceed 650 ng/dL [28], whereas an average dose of testosterone replacement therapy (TRT) (200 mg of bi-weekly T-enanthate supplementation), which would be considered a very low dose among AAS abusers, leads to a sustained average of 815 ng/dL [29]. Indeed, healthy males produce between 2.1 and 11.0 mg of T per day [30]. TRT generally consists of a weekly administration of 75–100 mg of T or 150–200 mg every 2 weeks [31] to restore T within mid-normal physiological ranges (400–700 ng/dL) [32]. As a survey in the bodybuilding community showed, more than 50% of AAS users use more than 1000 mg of AAS weekly [33], which is 10 times more than natural T synthesis or TRT doses, and leads to chronic serum T levels several times higher than acute endogenous RT-induced T elevations. From these numbers, we can extrapolate that minor T raises occurring in response to RT cannot mimic the effects of large amounts of exogenous AAS administration. Besides, the various anabolic effects of AAS are much more pronounced as compared to endogenous T due to the numerous chemical structures of different AAS.

Endogenous GH release seems also to respond to smaller muscle groups with low to medium intensity and short rest periods [3], peaking between the period immediately after and 15 min after RT, coming back to baseline values around 60 min post-RT [3,23,34]. Depending on the muscle group trained, RT-induced GH responses can reach around 24 ug/L for large muscle mass (whole body) [23] and around 12 ug/L for small muscle mass (biceps and triceps) [3]. Studies supporting an association between acute hormonal responses and long-term muscle hypertrophy have either found a strong positive correlation between GH and muscle fiber type I (r = 0.74) and II (r = 0.71) [17] or a weak positive correlation (fiber type I (r = 0.36) and II (r = 0.28)) [17,35]. Normal GH levels in healthy males are <5 ug/L and GH-deficient adults are generally prescribed around 0.25–0.5 U/kg weekly in order to restore healthy GH levels [36], that is, between 25 and 50 U weekly for a 100 kg individual. However, many bodybuilders seem to add 2 to more than 15 U daily on top of their natural production spread over the day divided in several injections in order to constantly maintain elevated GH levels. Similar to T, acute RT-induced elevations in GH may not be large and long enough to induce similar effects to exogenous recombinant GH administration.

Several studies have found the correlation between RT-induced endogenous hormonal increases and muscle hypertrophy as trivial to weak [2,3,34,37]. Differences in measurement methods and statistical analyses might contribute to the discrepancies observed among studies. Indeed, studies reporting a correlation between GH and muscle hypertrophy have measured muscle fiber CSA [17,35] and not total muscle CSA. On the other hand, one study reporting anabolic effects of acute T increases measured the correlation between differences in T responses before and after a 21-week training period and changes in muscle CSA [27]. The other study supporting a correlation between RT-induced acute T elevations and muscle hypertrophy used partial least squares regression structural equation modeling in order to analyze the relationships between endogenous responses to RT and muscle hypertrophy [1]. From the results above and the large body of evidence showing a lack of correlation between RT-induced endocrine responses and muscle hypertrophy, it appears that even if an association between RT-induced acute hormonal elevations and long-term muscle hypertrophy exists, the correlation might be so weak that it is undetectable depending on the study design.

Attempts have been made to determine causality between acute hormonal fluctuations and hypertrophy by carrying out longitudinal research on the topic. West et al. employed a within-subject design whereby 12 untrained young men

performed unilateral arm curl exercise under two different hormonal environments on separate days for 15 weeks [34]. One condition involved performance of 3–4 sets of elbow flexion alone, thereby minimizing the post-exercise hormonal response while the other condition involved the contralateral arm carrying out the same elbow flexion protocol, which was then followed immediately by performance of 5 sets of 10 repetitions of leg press and 3 sets of 12 repetitions of leg extension/leg curl supersets to induce a high post-exercise hormonal response. Results showed similar increases in muscle girth between conditions, indicating that the acute systemic response does not impact muscle growth. Subsequently, Ronnestad et al. employed a similar design to that of West et al., the primary difference being that the lower body exercise was carried out prior to elbow flexion in the high hormone condition [38]. Contrary to the findings of West et al., muscle CSAs of the elbow flexors were greater in the high hormone condition in the middle aspect of the muscle, suggesting a beneficial hypertrophic effect of acute systemic elevations. As we can see from the studies above, it is difficult to make comparisons between studies due to the differences in study design and measurement methods, especially for highly fluctuating data such as endocrine hormones (Table 1).

Hypertrophic effects of hormonal elevations induced via exogenous administration of AAS

Initially developed for medical purposes, AAS have spread to strength athletes and bodybuilders seeking supraphysiological strength, endurance and muscle mass while taking serious risks due to severe side effects [40]. A survey of 500 AAS users showed that more than 75% of respondents were non-competitive bodybuilders and non-athletes [33]. Furthermore, more than half of the respondents acknowledged the use of more than 1000 mg of T or similar AAS weekly, 25% reported the use of GH and insulin, and more than 99% admitted suffering from side effects related to AAS [33].

The administration of supraphysiological doses of T (600 mg/week) has been shown to improve muscle mass and strength with or without concomitant RT in healthy men compared to individuals without T supplementation [41], leaving no doubt of the anabolic effects of supraphysiological levels of T. Studies on other AAS such as trenbolone, stanozolol, or nandrolone have also shown improved body composition and/or performance in human or rodent studies [42–44]. Even though many AAS have been developed, only a few are for human consumption. Steroids like trenbolone are used as growth promoters in cattle [45]. Several animal studies [42,46,47] showed the potency of this compound making it notorious among bodybuilders seeking trenbolone even though it is not approved for human use. Moreover, the combined use of AAS and PH has shown the possibility of even larger improvements in fat-free mass as compared to the single use of either compound [48], indicating synergistic effects of AAS and PH. Especially the combination of GH with insulin and AAS is believed to induce muscle mass gains going far beyond the use of AAS only. Indeed, muscle gene IGF-1 expression tends to increase with the combination of T and GH [48] while insulin reduces proteolysis [49].

Many AAS share the following effects on performance and muscle mass:

- Increase in satellite cell and myonuclear number leading to larger mitochondrial areas and lower nuclear-to-cytoplasmic ratio [6] which might lead to increased maximal aerobic capacity (VO_{2max}) [50]
- Increased protein synthesis [30]
- Decreased protein breakdown [30]
- Nitrogen retention [30]
- Increase in red blood cells and the following increase of oxygen delivery to the muscles [51,52]

After the discovery of T in the 1930s, researchers tried to find new chemical structures minimizing side effects and maximizing anabolic effects. In many cases this means increasing anabolic while decreasing androgenic effects. In order to classify the muscle-building potency of AAS, an anabolic to androgenic ratio chart is often used by athletes. However, this ratio is based on the growth rate of the levator ani muscle versus the prostate in rodents after treatment with several AAS [53]. Nevertheless, even though this ratio based on a specific muscle of rodents can hardly be replicated to humans, it seems that many AAS abusers still consider it when choosing their performance-enhancing compound.

The major AAS used by athletes can be divided into three groups [30]:

(1) Testosterone derivatives (T, Methyltestosterone, Methandrostenolone, Chlorodehydromethyltestosterone, Fluoxymesterone, Boldenone): The compounds in this group are known to induce fast strength and muscle gains but show a high rate of aromatization. Due to the high water retention caused by aromatization, they are mainly used in bulking cycles for quick mass gains.
(2) Dihydrotestosterone derivatives (Stanozolol, Oxandrolone, Oxymetholone, Mesterolone, Methenolone, Drostanolone): Even though most of these compounds are highly androgenic, they have a high binding affinity to the androgen receptor and are potent strength and muscle mass builders. Due to the DHT structure, these compounds cannot aromatize to estrogen. Therefore, these compounds are often used for cutting cycles and pre-contest.
(3) Nandrolone derivatives (Nandrolone, Trenbolone): Compounds in this group show the highest anabolic to androgenic ratio and have strong muscle building effects. However, administration of nandrolone derivatives can result in elevated progestogenic activity. The use of this group of AAS is versatile and is used for both bulking and cutting cycles.

Cellular memory can lengthen the effects of AAS even after discontinuation of use. Indeed, a rodent study showed that the increase in myonuclei is largely increased by AAS and persists for several months after discontinuation [54]. Furthermore, these AAS-treated rodents' muscle fiber CSA

Table 1. Previous research about the correlation between resistance training (RT)-induced hormonal increases and muscle hypertrophy.

Study	Sample size and population	Acute changes in hormones	Correlation between endogenous hormonal increases and muscle size
Ahtiainen et al. [25]	*n* = 16 Age = 26.8 ± 3.5 yr Recreational RT experience	FT, GH, T increased during RT	Correlation between the difference in acute T responses pre and post a 21-week training period and changes in muscle CSA
Fink et al. [3]	*n* = 14 Age = 20.2 ± 0.3 yr Athletes not involved in RT for at least 2 years	GH increased immediately after RT and stayed elevated for 30 min post-RT IGF-1 increased immediately after RT T did not significantly increase	No correlation between hormonal increases and CSA
Fink et al. [4]	*n* = 20 Age = 19.9 ± 1.0 and 19.6 ± 1.0 yr Athletes with experience in RT	GH increased immediately after RT	No correlation between hormonal increases and CSA
McCall et al. [17]	*n* = 11 Age = 18–25 yr Recreational RT	GH and IGF-1 increased mid- and post-RT T did not significantly increase	No correlation between GH and CSA but a correlation between GH and type I and II muscle fibers
Mitchell et al. [39]	*n* = 23 Age = 24 ± 3 yr Men recreationally active but without RT for at least 1 year	N/A	No correlation between FT, GH or IGF-1 and muscle fiber hypertrophy
Mangine et al. [1]	*n* = 33 Men with at least 2 years of RT experience	N/A	Correlation between T and muscle size
Morton et al. [2]	*n* = 49 Age = 23 ± 1 yr RT for at least the past 2 years	N/A	No correlation between acute anabolic hormonal elevations and long-term muscle fiber hypertrophy
Rønnestad et al. [38]	*n* = 11 Age = 20–34 yr Untrained men	GH and T increased in the leg + arm RT No changes in arm only RT	Greater CSA increases in a high hormone condition as compared to low hormone condition
West et al. [37]	*n* = 8 Age = 20.0 ± 1.1 yr Recreationally active men with no RT activity over the past year	GH IGF-1 and T increased immediately after RT and stayed elevated for 30 min post-RT in the arm + leg RT protocol No changes in arm only RT	No improvement in anabolic signaling or acute post-exercise muscle protein synthesis response in a high hormone condition
West et al. [34]	*n* = 12 Age = 21.8 ± 0.4 yr Recreationally active men with no RT experience	GH, T, free T, and IGF-1 increased immediately after RT and peaked at 15 min post-RT in the arm + leg RT protocol No changes in arm only RT	No improvements in total CSA or muscle fiber size in a high hormone condition
West and Phillips [35]	*n* = 56 Young men recreationally active with no RT activity over the past 8 months	N/A	Weak correlation between C and fiber area and between GH and fiber area

C: Cortisol; CSA: cross-sectional area, FT, free testosterone, gh growth hormone, I: insulin, IGF-1: insulin-like growth factor 1, T: Testosterone.

grew more than 30% within 6 days in response to overload after 3 months of discontinuation of AAS treatment [54].

New discoveries in this field do not remain unnoticed by AAS abusers seeking supraphysiological enhancement. Indeed, combinations of several performance-enhancing compounds might lead to synergistic effects. The main anabolic effects of GH are believed to be indirect via conversion of GH to IGF-1 in the liver triggering the IGF-1-Akt-mTOR pathway [55–57]. However, GH administration might induce insulin resistance believed to be the main cause for cardiovascular risks of increased GH levels [58–62]. The administration of insulin might restore normal skeletal muscle glucose transport [63] and revert the effects of elevated GH. Therefore, many AAS abusers using GH are thought to combine insulin in order to avoid the negative side effects on insulin sensitivity induced by GH. Further, besides its anabolic effects, T administration also has been shown to improve insulin resistance [64,65]. Moreover, since both insulin and IGF-1 receptors are members of the superfamily of receptor tyrosine kinase (RTKs) [66], some athletes using GH seem to add insulin in order to increase serum IGF-1 levels by preventing large amounts of IGF-1 binding to the insulin receptors [67].

Conclusion

In conclusion, acute RT-induced hormonal elevations may have at best minor effects on muscle hypertrophy. Acute hormonal responses might give us an indication on the intensity and the following mechanical and metabolic stress of a given RT protocol but should not be used as causative evidence for a hypertrophic response to exercise.

On the other hand, high doses of AAS and PH have profound effects on body composition by sustaining supraphysiological levels of anabolic hormones increasing protein synthesis, satellite cell, and Wnt pathway activation while preventing protein breakdown. The combination of AAS with GH, IGF-1, and insulin might lead to supraphysiological levels of muscle fiber growth (hypertrophy) and increase hyperplasia. However, high doses of AAS and PH might cause severe side effects. The fact that many of these compounds are only available with prescription or are not even produced by pharmaceutical companies nourishes illegal black markets where products of questionable quality are sold to unaware athletes seeking supraphysiological muscle gains. Furthermore, studies of direct effects of AAS and PH combined with RT on muscle

mass and performance are lacking. This lack of knowledge might be one reason for the ongoing abuse of illicit drugs among bodybuilders and strength athletes. This field needs more research in order to prevent AAS and PH abuse among individuals endangering themselves by using drugs with effects they are not aware of.

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