

The Growth Hormone – IGF Axis and its Role in Muscular Hypertrophy

Researched and Composed by Jacob Wilson, BSc. (Hons), MSc. CSCS

Introduction

Growth Hormone (GH) is the primary pituitary hormone responsible for the regulation of somatic (whole body) growth (Florini, Ewton, and Coolican, 1996). Experimentation began 50 years ago to examine the growth promoting effects of GH (Murphy, Daughaday, and Hartnett, 1956). Specifically, it was found that rats with an attenuated ability to produce GH compromised growth in costal cartilage. However, in vitro (when a tissue is studied in isolation outside of the organism) GH administration to costal cartilage had minimal effect, suggesting that GH was acting indirectly on cartilage. This led to the Somatomedin Hypothesis which suggested that somatic growth by GH was controlled by a secondary substance (Daughaday, and Reeder, 1966). Daughaday et al. (1972) introduced the term Somatomedin to describe the growth promoting effects of this substance. Nearly 20 years following the original hypothesis, Rinderknecht and Humbel (1978) isolated Insulin Like Growth Factor 1 (IGF-1) and found it to be the Somatomedin substance regulated by GH.

Experimental evidence strongly supports the implication that GH and IGF-1 are two of the primary hormones involved in skeletal muscle growth (Palmer et al., 1994; Cuneo et al., Beshyah, 1995; Rodriguez-Arno et al., 1999; Whitehead et al., Perrone et al., 1995, Jennishe and Hansson, 1987, Jennishe, 1989, Edwall et al., 1989; Jurasinski and Veri, 1995). This was demonstrated by McCall et al. (1999) who found that acute GH increases after resistance training over 33 sessions in college age men had a 0.74 correlation with muscular hypertrophy! While several indicators of increased IGF-1 availability have been correlated to muscle mass (Eliakim et al., 1996, 2001). In this context, the purpose of this paper is to review the role of GH and IGF-1 in muscular hypertrophy. The paper is divided into three sections—one pertaining to mechanisms of muscular hypertrophy, a second to GH, and a third pertaining to IGF-1. Each section will review the evidence for these hormones effect on muscular hypertrophy, as well as the mechanisms for their actions. Special care was taken to review the effect of exercise choice, intensity, order, volume, and rest on GH and IGF-1.

Note: The effects of GH on lipolysis, interactions with other hormones, and nutrient partitioning have been reviewed in past articles in this journal ([Wilson and Wilson 2005](#); Knowlden, 2003, [a](#), [b](#), [c](#))

Overview of Muscular Hypertrophy

Muscular Hypertrophy can be defined as an enlargement of muscle tissue caused by an increase in myofibril content, non contractile protein accretion (i.e. mitochondria) number, an increase in non protein based substances such as glycogen, water, and

myoglobin, and the addition of myotubes to the periphery of a muscle cell. This article is concerned with direct myofibrillar protein synthesis as well as peripheral size additions to a muscle fiber.

The myofibril is a contractile unit comprised of numerous cylindrical contractile units known as sarcomeres. Each sarcomere is linked in a chain like fashion to form a myofibril. Finally, the sarcomere unit itself is comprised of various contractile proteins such as actin and myosin (for a review of the anatomy of a muscle see Wilson, 2001 – The Anatomy of a Muscle, and Wilson, 2003, Is The All or None Principles Applicable to a Single Muscle Fiber?). Net muscle protein accretion (hypertrophy) is the result of the difference between protein synthesis and protein degradation (see Wilson, 2005 - The Importance of Amino Acid Shooters). Typically studies examine overall muscular protein synthesis, or degradation increases, as well as the measurement of specific contractile filaments synthetic rates such as actin and myosin.

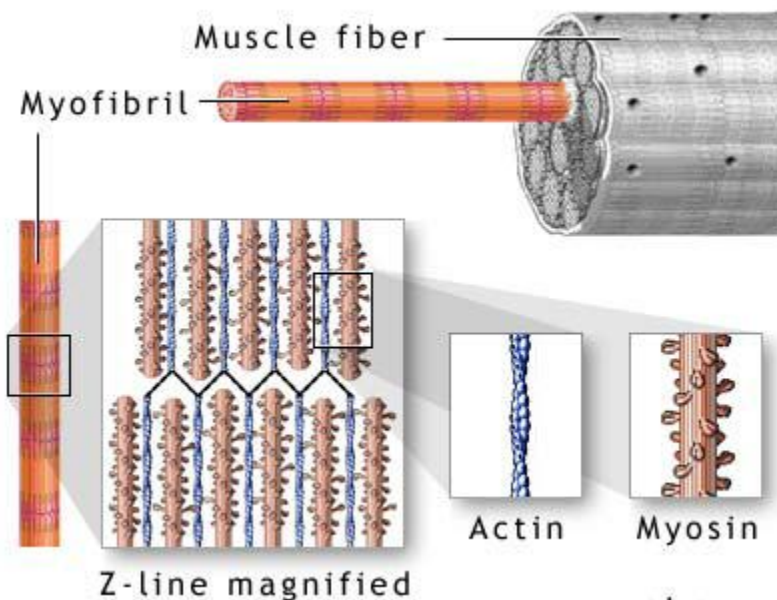


Figure 1 Muscle Fiber Diagram

Figure 1 graphically depicts a microscopic viewpoint of a muscle fiber. The Myofibril is represented as a long cylindrical unit, and as depicted is made of repeating subunits known as sarcomeres.

If a substance or hormone can increase protein synthesis, decrease protein degradation, or both, a more favorable environment will occur towards protein accretion (build up).

The enlargement of a muscle fiber appears to be attenuated (stopped) without the fusion of myotubes to the periphery of the muscle fiber (Allen et al, 1999; Hawke et al., 2001; Rosenblatt et al., 1994). The muscle fiber is a multinucleated cell (contains many nuclei). The nucleus is the control center of a cell, and contains the instructions for the various proteins which make up the cell's structure. It appears

that as a muscle fiber grows, the ratio of nuclei to cell size must remain constant (Fleck and Kraemer, 2004), this may be for the reason that the larger muscle fibers must be able to respond to various instructional stimuli (i.e. endocrine messengers, and mechanical stimuli) at a greater amplitude in order to maintain its newly enlarged structure.

Mature skeletal muscle cells are post mitotic and terminally differentiated (Hawke and Garry, 2001), meaning that they generally cannot divide (evidence does suggest that they may be able to split), or add new nuclei. In response to this dilemma Katz (1961) discovered a class of cell, with a high nuclei to cytoplasm ratio (the cytoplasm or intracellular environment is relatively small, and thus the nucleus comprises much of the size of the cell) on the periphery of the muscle fiber. Due to its location Maru (1961) coined the term satellite cell.

Satellite cells are quiescent (dormant). However, when activated through endocrine or mechanical stimuli they enter into two stages necessary for muscle growth. The first is known as the proliferative stage when Satellite cells begin to replicate (Hawke et al., 2001). Stimuli which induce this are known as mitogenic stimuli (Chen et al., 2005). An activated satellite cell is known as a myoblast, which is committed to muscle tissue. The myoblast begins to differentiate or change its structure such that its nucleus grows, as well as its cytoplasm. At its full growth it is elongated and known as a myotube, which can either fuse to an existing muscle fiber (hypertrophy), or fuse with other myotubes to form a new muscle fiber (hyperplasia).

To show the importance of these events, Adams (2002) investigated the effect of inhibiting satellite cell proliferation in response to skeletal muscular damage, and found that repair and hypertrophy were eliminated!

In summary, muscular hypertrophy can occur through an increase in specific contractile (or other) proteins, as well as addition of myotubes to the periphery of the fiber. This occurs through an increase in protein synthesis of specific proteins, or a decrease in protein degradation. Finally, enlargement of the muscle fiber cannot occur without addition of additional nuclei to the muscle fiber itself. Addition of myonuclei occurs through the replication, and finally fusion of satellite cells to the muscle fiber itself. In the end, the size to nuclei ratio of a muscle fiber must remain relatively constant. When this process is hindered, muscular hypertrophy is attenuated.

Growth Hormone Overview

Over 100 isoforms (variants) of GH have been identified (King, 2003). Of these, the most frequently occurring is the 22kDa isoform (Fleck and Kraemer, 2004). 22kDa GH is a peptide hormone that is 191 amino acids in length and comprises 21 % of total serum GH. Its concentration makes it the most frequently studied isoform to infer the effect of exercise on GH. However, recently other isoforms have been utilized and vastly expanded the understanding of training induced GH bursts (Gosselink et al., 1998).

GH is regulated by two hormones secreted by the hypothalamus – Growth Hormone Releasing Hormone (GHRH) and Somatostatin (SS), which increase and depress GH, respectively. Both of these hormones are released into a portal system, which allows

direct communication between the hypothalamus and the anterior pituitary gland. GH is released in a pulsatile fashion throughout the day and peaks dramatically at night

(Knowlden, 2003, [a](#), [b](#), [c](#) for a review of the relation between GH and sleep). Its peak at night is thought to be involved in various repair mechanisms of the body (Knowlden, 2003, [a](#), [b](#), [c](#)).

The actions of GH are transmitted to specific tissues after GH binds to a Growth Hormone Receptor (GHR). The GHR is a transmembrane protein, which means it has a binding portion on the outside of a cell, and an aspect which faces the intracellular environment. Binding of GH to a GHR activates a receptor associated tyrosine kinase. This is a molecule which when activated rapidly adds phosphate groups to other molecules, leading to a signaling cascade which ultimately activates several specific genes.

The Effect of Growth Hormone on Muscular Hypertrophy

GH is the primary pituitary hormone responsible for the regulation of muscular growth (Florini, Ewton, and Coolican, 1996). A great deal of evidence supporting this has come from studies in which GH was inhibited. Palmer et al. (1994) injected polyclonal antiserum (anti-rGH) which inhibits GH to rats and found that it markedly reduced the weight, total protein and RNA content of muscles of the hind limb. However administration of GH to the rats prevented these effects. In a second experiment anti-rGH was administered to rats for 8 weeks. A 58 % decrease in total bodyweight was found, while muscle mass decreased by 64%, 65% and 61% for the plantaris, soleus and gastrocnemius respectively. These results have generalized to humans. Cuneo et al. (1990) found that GH deficient adults compared to a control group had reduced cross-sectional area of thigh muscle/body weight, reduced quadriceps force/weight, and reduced quadriceps force/muscle area, suggesting that lowered GH levels are associated with lower skeletal muscle mass and force production capability. In a second investigation Cuneo et al. (1991) found that administration of GH to deficient participants reversed these muscle wasting effects, a result which has been replicated in numerous studies (Beshyah, 1995; Rodriguez-Arnao et al., 1999; Whitehead et al, 1992, Cuneo, 1998).

To assess the specific effects of GH on muscle growth Fryburg, Gelfand, and Barrett (1991) administered GH to healthy males in the brachial artery (artery which services the arm) such that GH concentrations increased in the brachial region, without other systemic increases. A rapid increase in forearm muscular protein synthesis was found. In a similar experiment Fong et al. (1989) found that exogenous GH led to an increase in myosin heavy chain (MHC) mRNA. Myosin is a critical contractile protein in the musculature, while a rise in mRNA reflects an increased capacity to synthesize this protein. Studies have shown that GH increases muscle RNA content (the capacity for a muscle to produce proteins) (Pell and Bates, 1991), the rate of protein synthesis per unit of RNA (Florini, Weton, and Coolican, 1996), as well as muscle cell amino acid uptake and transport (Cameron et al., 1988).

Growth Hormone's Mechanisms of Action

The direct effects of GH are typically measured through in vitro studies, in which skeletal muscle is studied outside of the body in isolation. Such a procedure reduces

the uncertainty of indirect effects. Allen et al. (1983, 1986) investigated the effect of GH administration twice on satellite cells in vitro in a rising dose fashion and found that they were not stimulated to proliferate (a step necessary for muscular hypertrophy). In other experiments both Harper (1987) and Roe et al. (1989) investigated the effect of GH on protein synthesis of muscle cells in vitro and found that protein synthesis was not increased. However it was found that protein synthesis did increase when IGF-1 was administered. These effects and others important in muscular hypertrophy have been replicated in numerous studies (see Florini et al., 1996 for a review).

The above evidence suggests that GH works indirectly through IGF-1 to facilitate muscular hypertrophy. This is known as the Somatomedin Hypothesis (Roith et al. 2001). It is well established that GH stimulates the release of IGF-1 from the liver (Florini et al., 1996). In one study Bichell et al. (1992) administered GH to hypophysectomized rats and found a dramatic rise in hepatic (from the liver) IGF-1 mRNA within two hours, with peak values of more than 15-fold above untreated animals by 4 hours! These results have generalized greatly (Florini et al., 1996) including through in vitro studies on isolated hepatocytes (Tollet et al., 1990) (liver cells).

A subject of great debate however is the effect of GH on muscular IGF-1 expression. This is due to a great number of difficulties in locating GH receptors on muscle tissue (Kelly et al., 1995). However in a break through study, Martini et al. (1995) found mRNA for Growth Hormone Receptors in skeletal muscle tissue, providing strong evidence for GH interaction. The effect of GH administration on muscle IGF-1 mRNA has been studied extensively. Within muscle tissue there have been three isoforms of IGF-1 found, with two receiving the most study (Eliakim, Nemet, and Cooper, 2005). The first is IGF-1a and is similar to the IGF-1 released from liver tissue, while the second is sensitive to mechanical stimuli and is denoted Mechano Growth Factor (MGF). In a recent study the effect of GH on IGF-1a and MGF in resistance trained and non resistance trained participants was investigated (Kramer and Rogol, 2005). After five weeks of GH administration without exercise, IGF-1a mRNA increased 237 %, while MGF did not increase. A third group performed exercise without GH administration and found a 163 % increase in MGF. Finally the group which exercised and had GH administration increased MGF by 456 %! This suggests that GH has a potent effect on non exercise induced stimulation of IGF-1 as well as the capacity to potentiate the effect of exercise on MGF mRNA expression.

It should be noted that a second explanation which is gaining acceptance is the 'Dual Effector Theory' proposed by Green et al (1985) which posits that GH has both direct and indirect effects on peripheral tissues. Evidence for this was found in the Fryburg, et al. (1991), Barrett (1991), and Fong et al. (1989) studies mentioned previously. They found that direct infusion of GH into the brachial arteries increased both protein synthesis and MHC mRNA in the forearm musculature. However, because the GH was administered in vivo, the indirect effect of GH on muscle tissue through IGF-1 cannot be dismissed.

In summary GH is suggested to increase circulating IGF-1 levels through stimulating their production and secretion from the liver. It is also suggested to increase IGF-1 in muscle tissue, as well as potentiate mechanically stimulated MGF increase. Finally Greene et al (1985) proposes that GH may have direct effects on skeletal muscle. However, direct evidence for this has been sparse (Florini et al, 1996).

The Effect of Acute Training Variables on Growth Hormone

A high correlation between acute GH release in response to exercise and muscular hypertrophy exists (McCall et al., 1999). In this context the effect of exercise choice, intensity, order, volume, and rest on GH will be reviewed.

1. Exercise Choice – This variable is related to compound vs. isolation exercises, as well as the size of the muscle groups being trained. In a recent review on GH, Fleck and Kramer (2004) provided evidence that GH is released to a greater extent with compound vs. isolation exercises, and in exercises that involve larger rather than smaller muscle groups. Compound exercises involve movements at more than one joint. In this context, when all other variables are held constant a bench press which involves movement at both the elbow and glenohumeral joints would have a greater effect than the dumbbell fly at stimulating a GH response. Further, when comparing squats to bench presses, the squat which involves larger muscle groups such as the gluteals, quadriceps, and hamstrings would elicit a greater GH response than the bench press, which mainly stimulates the pectorals and triceps. The theoretical rationale is the fast twitch fiber feedback hypothesis and lactate concentration hypothesis, explained under exercise intensity.

2. Exercise Intensity – There appears to be a threshold intensity required to stimulate an acute GH burst (Felsing et al., 1992). Pyka et al. (1992) investigated the effect of exercise intensity on GH response in seven young (27 years old) individuals. Intensities consisted of 60 %, 70 % and 85 % of participants' 1-RM for a total of three sets on each of 12 different exercises. No significant increase in GH was found during the 60 % intensity condition. However, GH rose and increased progressively at 70% and 85% of 1RM. In another study Vanhelder et al. (1984) equated work and volume, while varying intensity. In condition one participants performed at 85 % of their max in leg lifts for 7 repetitions over 7 sets. In condition 2 they performed 1/3rd of this intensity for 21 repetitions for seven sets. It was found that session one increased GH, while session two had no significant increase in GH. What was significant about this study was that the authors found an incredibly strong 0.99 correlation between the amount of lactic acid produced during condition one and the amount of GH secreted.

The above evidence lays the basis for the lactate concentration hypothesis, which suggests that an exercise protocol will stimulate the secretion of GH proportionally to the amount of lactate produced during the exercise protocol (Wilson and Wilson, 2005). This hypothesis was supported by Felsing et al. (1992) who investigated the GH response in ten healthy male volunteers (18-35 yr) performing a ramp-type progressive cycle-ergometer exercise for either 1, 5, or 10 minutes. In each case intensity was varied such that participants performed either under or over their lactate threshold (LT). It was found that GH did not increase until participants performed over their lactate threshold and exercised for 10 minutes (note: the 10 minutes suggests that a volume threshold may also exist – see below). "It has been postulated that lactic acid indirectly stimulates GH when it disassociates into lactate (its salt) and h⁺ (its acid) effectively decreasing pH. Thus, pH may be a potent mediator of GH secretion (Wilson and Wilson, 2005 – Slow Acting Hormones and Their Role in Exercise)." This was supported by Gordon et al. (1994) who found that the effect of intensity on GH was lowered when a buffer was added to increase the pH of the blood (alkalinity group). Gordon et al. (1994) postulates that a drop in pH elicits a general stress response by the hypothalamus which increases GHRH and

subsequent GH release. A second explanation was provided by Sethumadhavan et al. (1991) who found that a pH of 5.0 optimally facilitated GHRH binding to the anterior pituitary gland.

The second theoretical rationale is the fast twitch motor neuron feedback hypothesis, which posits that afferent feedback from the activation of fast twitch motor neurons, or

feedback generated from fast twitch muscular contraction itself is carried back to the hypothalamus or anterior pituitary gland resulting in an increase in GH secretion. In this context, Gosselink et al. (1998) investigated the effect of electrically stimulating slow twitch nerve fibers for 15 minutes of distal hind limbs of rats on bioassailable Growth Hormone (bGH), which is a distinct isoform of GH. 15 minutes of stimulation of slow nerve fibers produced no increase in bGH. In contrast, stimulation of fast twitch nerve fibers stimulated a 250 % increase in bGH, and this rise began at 5 minutes after stimulation! Further, there was a subsequent decrease in pituitary GH concentration.

Intensity appears to be optimized in a moderate (70-85%) intensity zone. Hakkinen et al. (1993) compared the effect of 20 sets of squats using participants' 1 repetition maximum (1-RM) to 10 sets of participants' 10-RM. It was found that the 1-RM condition did not produce a significant rise in GH, whereas the 10-RM condition produced a dramatic rise in GH. The theoretical rationale is that moderate intensity exercise primarily relies on glycolysis which is responsible for the production of lactic acid. However extremely high intensity exercise (100 % 1RM) primarily depends on the phosphagen system. The phosphagen system liberates energy from creatine phosphate to synthesize ATP. This process does not result in lactic acid production (See Wilson and Wilson, 2004 – Energetic Transference in The Biosphere 1-3 for a review). The second theoretical rationale is the effect of volume on GH. The 10-RM condition resulted in more total work (volume) than the 1-RM condition (discussed in greater detail below).

3. Rest Periods – Practice distribution is a critical element in designing resistance training programs. Wilson and Wilson (2005, Specificity – Practice Distribution) in an analysis found that increased rest periods over numerous studies results in greater 1-RM gains in a criterion task. However, hypertrophy may be optimized with shorter rest periods. Kraemer et al (1990, 1991, 1993) in a series of studies examined the effect of five RM sets vs. 10 RM sets as well as 1 vs. 3 minutes of rest in each protocol, resulting in 5/1, 5/3 and 10/1, 10/3 combinations. The results demonstrated the dramatic effect rest periods have on blood lactate concentrations. Short rest periods significantly elevated blood lactate concentrations compared to longer rest periods. Further, comparison of 10-RM conditions to 5 RM conditions found that the 10 RM conditions resulted in higher blood lactate concentrations.

This suggests that moderate intensity exercise with shorter rest periods have the greatest effect on the acute GH response to exercise.

4. Volume – Volume is determined by the amount of sets, repetitions, and weight lifted in a given training session. The Kraemer et al. (1990, 1991, 1993) and Hakkinen et al. (1993) studies found that moderate intensity exercise (10 Xs 10 RM vs. 20 Xs 1 and 10 vs. 5 RM) resulted in a greater GH stimulus than lower volume workouts. Gotshalk et al. (1997) investigated the effect of a single vs. three set

workout on serum GH response. It was found that serum GH increased to a greater extent in the three set vs. single set condition. In a similar study Mulligan et al. (1996) investigated a two condition paradigm in which participants performed either eight exercises, with one set per exercise (8 set condition), or the same eight exercises, with three sets per exercise (24 set condition). The intensity was standardized at participants' 10 RM, while rest was standardized at 1 minute between sets and exercises. Growth Hormone was measured at 0, 15, and 30 minutes post exercise. Comparison of 8 sets to 24 sets found that GH increased significantly in the 24 set condition at 0, 15, and 30 minutes post exercise. However, GH only increased after 15 minutes above resting in the 8 set condition, and this increase was much lower than the 24 set condition at this same time frame.

The above evidence suggests that volume is a powerful factor in GH response. Moderate intensity exercise may facilitate volume due to the greater amount of work that can be performed in a given set as compared to a very high intensity protocol. Further, studies found increases in GH from 1 to 3 sets, and from 8 to 24 sets. This suggests that, when intensity is held constant, that volume may increase GH in a dose dependent manner. However more studies need to be conducted to see how far reaching this relationship is.

5. Exercise Order – Compound exercises with larger muscle groups elicit the greatest GH response. In this context, performing larger muscle group exercises first may facilitate a more anabolic response for the remainder of the training session. Evidence suggests that GH peaks 25 minutes after a high intensity exercise (Kramer and Olig, 2005). There are several practical implications for this. For example, typically after a leg workout athletes leave the weight room. However, if an athlete is prioritizing a smaller body part, they may benefit by training it after the workout to promote GH enriched blood flow to the muscle group. This also has implications in full body workouts. When such workouts occur, it would suggest that larger muscle groups should be trained before smaller to facilitate a more anabolic hormone environment throughout the duration of the session.

Chronic Adaptations of Growth Hormone to Exercise

Typically chronic (long term) changes in GH are inferred through measuring resting concentrations of serum GH in trained vs. untrained individuals. Training in a number of studies has not been found to effect resting concentrations of 22kdGH (Kraemer et al., 1999). As an illustration, McCall et al. (1999) investigated chronic GH responses to resistance training in 11 college men who completed 12 weeks (33 sessions) of high volume resistance training. No differences in resting concentrations of growth hormone (GH) were found before or after the 12 sessions.

However other methods of testing have shown differences in the acute response of GH to trained vs. untrained individuals. In one study Craig et al. (1989) investigated the effect of 12 weeks of resistance training in young and elderly women. Comparison of pre and post training conditions found that GH increased in response to exercise to a greater extent after 12 weeks of training. The theoretical rationale is that trained individuals possess a greater overall capacity to elicit a necessary stimulus for increased serum GH responses to exercise (i.e. greater volume, and lactate concentrations). Studies also suggest that chronic training may be able to increase overnight GH amplitude. For example Eliakim et al (1996) found a strong

correlation between thigh muscle volume, maximal O₂ uptake and circulating components of the GH in females 15-17 years of age. Further, Kelley et al. (1990) found a significant correlation between V_{O₂ max and GH and IGF-1 in pre and post menopausal women. Further, it was found that even when age was analyzed that V_{O₂ max was the only independent predictor to significantly correlate with circulating IGF-1 levels. This suggests that GH and IGF-1 may be effected by chronic training in some capacity, and that elderly individuals can prevent decreases in circulating anabolic hormones through maintaining a high level of activity.}}

Insulin Like Growth Factor

IGF-1 is peptide hormone synthesized in the liver, a process which takes 8-28 hours after GH stimulation (Kraemer et al., 2005). Its structure is similar to insulin. The similarity allows IGF-1 to bind to insulin receptors, but only at pharmacological doses. Similarly insulin can bind to IGF-1 receptors, but with 100 times less affinity (binding capacity) than IGF-1 itself can bind (Kraemer et al., 2005). This peptide hormone acts mainly through IGF-I receptors. Similar to GH, the binding of IGF-1 to an IGF-1 receptor activates a tyrosine kinase which sets in motion a series of phosphorylations which lead to activation of various genes, such as those coding for myofibrillar proteins. Finally, there are six IGF binding proteins (IGF-BP), which IGF-1 is transported in when circulating in the blood. The dominant binding protein is IGF-BP-3 (Adams., 2003).

The Effect of Insulin Like Growth Factor-1 on Muscular Hypertrophy

In a classic study Vandeburgh et al. (1979) found that mechanical stimuli such as the stretching of skeletal muscle in vitro led to increased amino acid accumulation, and increased incorporation of amino acids into general cellular proteins and myosin heavy chains. Findings such as this led Tidball (2005) to suggest that " there may be mechanisms within muscle cells through which mechanical signals can be converted to chemical signals that generate numerous, specific downstream events that determine muscle's form and function " This postulation is supported by the observation that IGF-1 content and mRNA increase in response to various forms of mechanical stimuli such as stretch, eccentric contractions, and injury (Perrone et al., 1995, Jennishe and Hansson, 1987, Jennishe, 1989, Edwall et al., 1989).

As discussed previously muscle tissue hypertrophy can occur through an increase in protein accretion (the difference between protein synthesis and degradation) and the addition of myotubes to the periphery of a muscle cell.

IGF-1 is a potent stimulator of muscle protein accretion processes. Jurasinski and Veri (1995) investigated the effect of an infusion of IGF-1 on the gastrocnemius of septic rats and found a 2.5 fold increase in the rate of protein synthesis. While Hong et al. (1994) found that IGF-1 administration decreased protein degradation in muscle fibers by 14 percent, with a subsequent decrease in proteases. One of the largest stimuli for protein degradation is found in burn victims. However Fang et al. (1997) and Jurasinski et al. (1995) found that IGF-1 administration both lowered protein degradation and increased protein synthesis in burn victims. Further Vandeburgh et al (1991) found that in vitro IGF-I administration was associated with a tremendous accumulation of myosin heavy chain proteins with a subsequent increase in hypertrophy of myofibrils. This was due to both a decrease in various.

What is also of interest is that numerous studies have shown IGF-1 to stimulate both proliferative (mitogenic) and myogenic (differentiation leading to fusion of myotubes to muscle cells) processes in satellite cells (Coolican et al., 1997, Florini et al., 1997, Robertson et al., 1992).

The Response of IGF-I to Training induced Stimuli

One of the fascinating aspects of IGF-1 regulation by exercise is that this hormone can increase through both GH dependent and independent pathways. Serum IGF-1 changes are in large part mediated by GH stimulation of the liver to both increase IGF-1 synthesis and secretion (Florini et al., 1996). However, in muscle tissue mechanical stimuli can trigger IGF-1 increases (see above) and stimulate hypertrophy independent of GH. This was first found in a classic study conducted by Goldberg (1967) who investigated the compensatory hypertrophy response in hypophysectomized rats. Compensatory hypertrophy was stimulated by cutting the tendon of the gastrocnemius, therefore placing greater workload on the soleus. A significant amount of hypertrophy was found in the soleus in only two weeks time, which to Goldberg (1967) "was striking and had not been anticipated." This is in large part mediated by autocrine, mechanical stimulation of IGF-1 isoforms such as Mechanogrowth factor in muscle tissue (Kraemer and Rogol, 2005). Evidence suggests that mechanical stimuli serve as the mediators of muscle growth expression of MGF, and that circulating GH concentrations augment this process greatly (Kraemer and Rogol, 2005).

Conflicting Effects of Exercise and IGF-1 Expression

In cases several paradoxes have been found in the acute response of circulating IGF-1 concentrations. For example, IGF-1 concentrations can peak in as little as 10 minutes, while GH peaks in 30 minutes (Kraemer and Rogol, 2005). This is conflicting as increases in serum concentrations of IGF-1 occur hours after GH administration. However, a closer look explains the situation nicely. For example exercise stimulates fluid shifts from organs which can degrade circulating IGF-1 levels toward working musculature. Flem (1990) found that exercise decreased blood volume in the kidneys and liver by 24 and 18 % respectively. This is known as blood shunting. Exercise is also known to stimulate the release of blood from the spleen which has a high hormone concentration (Flem, 1990). Further, exercise can cause dehydration (Wilson, 2003 -Myofibrillar Hydration) which would naturally increase the concentration of various hormones. Therefore the immediate increases seen in IGF-1 have been found in studies, even when the intensity was below lactate threshold, but these increases are thought to be transient and due to fluid shifts, dehydration, release of concentrated blood from the spleen and blood shunting.

Biphasic Response of Circulating IGF-1 concentrations to Exercise

Muscular IGF-1 expression increases immediately to various forms of mechanical stimuli (Perrone et al., 1995, Jennische and Hansson, 1987, Jennische, 1989, Edwall et al., 1989). However, circulating concentrations of IGF-1 appear to respond to exercise in a biphasic manner (Eliakim, Nemet, Cooper, 2005). Circulating IGF-1 levels have been found to decrease in brief exercise periods in a number of studies and increase in more chronic periods of exercise (Sheet et al, 2002, Eliaking et al. 1996, 1998b; Eliakim et al., 2001). As an illustration Raastad et al. (2001) found that during a strength training program that IGF-1 was decreased after eight days of

training. While Borst et al. (2001) found that circulating IGF-1 had increased after 13 weeks on a 25 week resistance training program. A rapid increase in lifting capacity in the tasks used were correlated with this rise. A second way to examine IGF-1 adaptations are through cross sectional studies, in which individuals who have trained for long periods of time are compared to untrained individuals. In this context IGF-1 has been found to be positively correlated to several fitness indexes such as cross sectional area and VO2 max (Eliakim et al., 1996, 2001, Borer et al. 1986) again suggesting that increases in fitness are linked in part by adaptations in the GH-IGF-Axis.

From the above evidence it appears that the first phase of circulating IGF-1 response to training is a decrease followed by an anabolic rebound. This may explain some of the observations observed in various resistance training programs in which the majority of adaptations are neural early in training programs, while latter changes (>10 weeks) have a much higher contribution of structural changes such as muscular hypertrophy (Fleck and Kraemer, 2004, Sale, 1992).

Explanations for Biphasic Phase

There are two explanations for the Biphasic phase of IGF-1 response to exercise. The first explanation is the inflammatory hypotheses (Sheet et al., 2002). Sheet et al. (2002) suggests that the beginning phases of an exercise program leads to a tremendous increase in serum concentrations of various cytokines which increase inflammation. This was seen in a study in which he had participants play 1.5 hours of intense soccer. Proinflammatory cytokines such as tumor necrosis factor increased, and with their increase IGF-1 decreased. Eliakim, Nemet, and Cooper (2005) suggest that as training progresses participants make successful adaptations to the training load, with a subsequent lowering of pro inflammatory cytokines. As they lower the authors suggest that it produces an 'anabolic rebound' as IGF-1 levels increase. It should also be understood that IGF-1 receptors up regulate when in lower concentrations (Lee et al., 2000) which further augments this response.

The second explanation involves the response of IGF-1 to states of catabolism. Smith et al. (1995) investigated the effect of a 50 % calorie restrictive diet on 8 children and 8 adults on circulating IGF-1 concentration for 6 days followed by 6 days of normal dieting. It was found that IGF-1 concentrations decreased in both groups. These results were also found in a protein restricted diet. Further, IGF-1 levels returned to baseline after return to a normal diet. This result has generalized over a number of studies (Katz et al., 2002, Ross et al., 2000). Eliakim et al. (2005) suggests that the common link between the findings of Smith et al. (1995) and exercise interventions which show decreased IGF-1 levels is a state of catabolism induced by either energy restriction, or exercise induced increases in energy expenditure above caloric intake. To examine this hypothesis Nemet et al. (2004) had participants perform a 7 day strenuous exercise program in which young men were divided into two groups. One group was a positive energy balance group in which calories consumed were greater than energy expenditure, and a negative energy group. At the end of the seven days the negative energy balance group lost weight (confirming a catabolic state) and experienced a significant decrease in circulating IGF-1 levels. However, the overfed condition gained weight and experienced no change in circulating IGF-1 levels. It should also be noted that statistical analysis in the above study suggested that in an isoenergetic state (calories in = calories out) IGF-1 levels would slightly decrease. This suggests that

the Biphasic phase is both nutrient and Cytokine dependent, and that overfeeding can attenuate the lowering response of IGF-1 during heavy training or the start of a new training regimen.

In summary, during catabolic states, when muscles are taxed the body adapts by lowering IGF-1 levels, while local IGF-1 levels in the trained musculature increase. This creates systemic catabolism, while maintaining the possibility for local anabolism. Theintz (1993) suggests that this attenuates somatic growth while maintaining muscular adaptation during states of caloric restriction. These hormonal adaptations have been seen in both female gymnasts and wrestlers who enter states of catabolism during weight loss periods, while still maintaining or adding musculature in the trained regions (Jahreis et al., 1991, Roemmich and Sinning, 1997, Elokim et al., 2005). Finally, it also explains partially why periods of overfeeding facilitate a more whole body anabolic environment conducive to size increases.

The Effect of Contraction Type of Local IGF-1 Response to Training

IGF-1 appears to be sensitive to the type of contraction elicited to a muscle group. In one study Bamman et al. (2001) found a significant increase (62 %) in IGF-1 mRNA concentration 48 hours after an acute bout of eccentric but not concentric contractions! This may be due to the reason that eccentric contractions elicit greater myofibrillar damage than concentric contractions. This may be why studies have found less muscle growth when eccentric activity was inhibited during a resistance training protocol.

This suggests that techniques which emphasize the eccentric component of a repetition may augment the hypertrophy process.

Summary

Growth Hormone and IGF-1 are primary mediators of muscular hypertrophy. The Somatomedin hypothesis suggests that GH indirectly controls growth through the stimulation of IGF-1 from the liver and muscle tissue. Growth Hormone is greatly correlated to muscular hypertrophy. For this reason athletes will want to seek to maximize this hormone when training for this adaptation. GH is maximized when intensity is moderate (75-85 %), and rest periods are short (1 minute). This may be due to the reliance on glycolysis and subsequent production of lactic acid, which has shown to sensitize the anterior pituitary hormone to GHRH. Further, the stimulation of fast twitch fibers have also been shown to stimulate GH secretion. In terms of volume, studies have shown that GH increases from 1-3 and 8-24 sets, however more studies need to be conducted to see at what point this relationship is maximized. Finally, exercises which recruit more total muscle mass, such as bench press and squats elicit a greater GH response than isolation exercises. In this context, it may be valuable to perform compound before isolation exercises, as well as train small body parts after large body parts so as to expose them to a physiologically high concentration of GH.

IGF-1 is stimulated locally in both energy deprived and energy enriched environments. However, circulating IGF-1 levels appear to respond to training in a biphasic manner, with a decrease at the beginning of a training program (1st few weeks) and an increase thereafter (> 12 weeks and perhaps less). This increase is

coordinated to rapid increases in muscle mass. Further, a diet which provides a caloric surplus attenuates the decrease found, suggesting that it may be related to a greater increase in energy expenditure. This provides validation for periods of overfeeding, however it also demonstrates that during periods of caloric restriction, if protein intake is sufficient, particularly in essential amino acids (see Amino Acid Shooter Breakdown) that adaptations in muscle can occur. Finally, IGF-1 is sensitive to contraction types, with eccentric contractions eliciting the greatest stimulus for IGF-1 muscular concentrations. This may be attributed to the greater myofibrillar disruption elicited by eccentric contractions.

Jacob Wilson jwilson@abcbodybuilding.com

President, Abcbodybuilding.com
Co Editor - The Journal of HYPERplasia Research

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