

# Comments on Point:Counterpoint: IGF is/is not the major physiological regulator of muscle mass

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*J Appl Physiol* 108:1825-1831, 2010. doi:10.1152/jappphysiol.00312.2010

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This information is current as of January 18, 2011.

## Comments on Point:Counterpoint: IGF is/is not the major physiological regulator of muscle mass

### HYPERTROPHY WITHOUT IGF-I????

TO THE EDITOR: This is a timely Point:Counterpoint that addresses the role of IGF-I in the regulation of muscle mass. Clearly, IGF-I is critical for muscle development and postnatal muscle growth (2). However, its role in the area of load-induced muscle hypertrophy has been recently questioned (5). There are a few clarifications that should be made, in that the mice used in my study are not knockouts of the IGF-I receptor as implicated by Flück and Goldspink (6), but they are transgenic mice that contain a point mutation in the ATP binding domain resulting in abrogated IGF-I receptor function in a dominant negative fashion. Second, one of the key points of my findings was that it was possible for mechanical load to activate mTOR signaling independent of the IGF-I receptor. There are other critical pieces of evidence that must be considered as well. In response to acute loading, the increase in IGF-I production by the muscle occurs over a matter of days (1), while activation of the mTOR signaling is activated in a matter of minutes to hours (4). Furthermore, a major critical aspect of IGF-I signaling is Akt activation; however, the magnitude of phosphorylation and duration of activation of Akt in response to acute mechanical loading is substantially smaller compared to downstream components of mTOR (i.e. p70s6k) (4). Thus, unless IGF-I bypasses Akt to induce protein synthesis, it would suggest that mTOR is likely activated independent of Akt and IGF-I. Stewart and Pell (6) suggest that all muscle growth is dependent on satellite cell activation (6); however, mechanical load can induce smaller increases in muscle mass independent of satellite cell activation (3). Thus, if the major role of IGF-I is to affect satellite cell function and there are cases where we can get growth of muscle without satellite cell activation, then we must conclude IGF-I is not always necessary for muscle growth.

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### IN SEARCH OF THE SKELETAL MUSCLE GROWTH POTENTIAL OF “GROWTH” HORMONES

TO THE EDITOR: There would seem to be something intrinsically wrong when a hormone called growth hormone (GH) or insulin-like growth factor-1 (IGF-1) doesn't promote growth, but when it comes to adult humans they don't! Especially for GH where skeletal muscle is concerned, a number of studies have actually proven this point (6). Even when large doses of IGF-1 are given exogenously it has no effect on muscle, strength, or any other important metabolic parameter (2). Even “giants” who spend their lives awash in excesses of GH and IGF-1 have a skeletal muscle mass no different from controls (1). So where's the controversy? Quite simply, comparison of rodents or lagomorphs to humans yields the greatest discrepancy; however, even data from rodents indicate that circulating IGF-1 (3) and a functional IGF-1 receptor (4) are not requisites for load-induced hypertrophy. Hence, this Point:Counterpoint seems to be like a dog chasing its own tail, since from an adult human perspective the evidence suggesting that GH or IGF-1 plays any role in hypertrophy is quite fragile (5). As Flueck and Goldspink point out, local splice variants of IGF-1 may be important in autocrine/paracrine manner; however, we still lack evidence of the levels of the proteins encoded by these transcripts. Thus it seems that outside of the overexpressing or knockout mouse or a cell culture dish or an animal model of overload/stretch that the search for the true role of the “growth” potential for GH and IGF-1 in adult human hypertrophy is a vain one.

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# IGF IS A MAJOR PHYSIOLOGICAL REGULATOR, BUT NOT SOLELY RESPONSIBLE FOR MUSCLE MASS REGULATION

TO THE EDITOR: I read with interest the article by Stewart et al. (5) that debated whether IGF is the major physiological regulator of muscle mass. It is interesting to note that both sides of the argument agreed that IGF promotes muscle mass, but disputed its role in load-induced muscle mass changes. Although the Counterpoint side argued that load-induced muscle mass changes do not depend on IGF receptor signaling, they could not ignore the fundamental role IGF plays in muscle development (4) and hypertrophy (6). The Point side has strong evidence to support the argument, but it is still difficult to explain the fact that overexpression of IGF-I in skeletal muscle does not prevent unloading-induced muscle atrophy (2). Muscle is a tissue that is capable of undergoing alteration in mass under a variety of conditions such as altered nutrition, endocrine status, aging, mechanical stimuli, and some chronic diseases. The role of IGF cannot be ruled out in muscle mass changes under these conditions, but IGF is not solely responsible for these changes. For example, recent studies have shown that multiple signal transduction pathways are involved with aging-related muscle mass loss (3) and the myostatin pathway plays an important role in skeletal muscle wasting in cancer cachexia (1). Together, all these studies suggest that IGF is a major physiological regulator, but not solely responsible for muscle mass regulation.

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## IGF IS NOT A MAJOR REGULATOR OF MUSCLE MASS

TO THE EDITOR: IGF-1 as an activator of Akt/mTOR signaling cascade is usually believed to cause muscle hypertrophy after eccentric exercise, passive stretch, etc. (5). Disuse decreases protein synthesis rate and causes skeletal muscle atrophy. We (4) and Adams et al. (1) showed the noticeable decrease in the serum IGF-1 level accompanied by the reduction of soleus fiber cross-sectional area and protein content loss after prolonged disuse. In rat soleus IGF-1 mRNA level decreased 70% after 3 days of unloading, then slightly increased to the 7th day. Fiber size decreased by the 3rd day and continued to fall further to the 14th day of unloading (3, 4). We also found no significant differences in rat soleus p70S6K content until the 14th day of disuse, when it is 24% diminished despite the 50% decrease in serum IGF-1. Ribosomal kinase phosphorylation rate and the rise in the protein synthesis were observed at the 3rd day of reloading of the disused soleus (6), when serum IGF-1 remained decreased (4). Soleus IGF-1 mRNA increased only at the 7th day of reloading after disuse. The experimental evidence indicates that IGF-1 is not the only, and probably, not

## THE STRANGE CASE OF IGF-1

TO THE EDITOR: Over the past few years, different factors have been proposed as modulators of muscle mass. Among these, IGF-1, is an important mediator of anabolic pathways in skeletal muscle (4). However, there is no consensus on whether or not IGF-1 is the major physiological regulator of muscle mass. Indeed, Stewart and Pell (6) discussed several experimental evidences in support of the role of IGF-1 in the induction of physiological muscle hypertrophy. In contrast, Flueck and Goldspink (2) deny the pivotal hypertrophic activ-

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the major regulator of mTOR activity and protein synthesis during muscle unloading and reloading, and thus, not the major regulator of muscle mass.

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## IRRELEVANT GROWTH FACTOR-I

TO THE EDITOR: There is experimental evidence to support a role for IGF-I in regulating muscle mass during development (6, 7). However, the primary physiological regulator of adult muscle mass is not hormonal but mechanical. During unloading atrophy, there is no decrease in IGF-I and genetic overexpression has no protective affect on muscle mass (4). Since decreasing mechanical input to a skeletal muscle results in IGF-I-independent decreases in muscle mass, it is possible that load-induced increases in muscle mass are also IGF-I-independent. The evidence of a role for IGF-I in load-induced growth is at best circumstantial. IGF-I mRNA increases in some models of hypertrophy (1), IGF-I overexpression can increase muscle size (3), and mTORC1 is activated by both insulin/IGF-I and resistance exercise (2). However, no one has shown that, as with IGF-I treatment, the IGF-I receptor and IRS1/2 become tyrosine phosphorylated, that PI3K is recruited to the receptor, that akt/PKB phosphorylation occurs prior to mTORC1 activation, or that TSC2 becomes phosphorylated by akt/PKB after resistance exercise. In fact, all of the concrete evidence argues that IGF-I plays a limited role in regulating adult muscle mass. IGF-I is neither required for signaling to mTORC1, nor growth in response to chronic overload (6). Furthermore, IGF-I pathway inhibitors do not block stretch activation of mTORC1 (5). Together with the absence of other evidence linking IGF-I to load-induced growth, this suggests that although IGF-I may play a role in remodeling of the vascular, neural, and connective tissues that support muscle, as for muscle size: load rules!

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## IS ANY FACTOR NECESSARY AND SUFFICIENT FOR MUSCLE MASS REGULATION?

TO THE EDITOR: It is well established that IGF-I plays a critical role in skeletal muscle physiology regulating muscle growth, development, and adaptation (1, 6). However, whether IGF-I is the major physiological regulator of muscle mass remains a point of controversy (3, 6). The absence of IGF-I activity through loss of the growth factor or its receptor leads to small muscle size (2, 4, 6) and supports a necessary role for IGF-I in regulating muscle mass, yet it is an oversimplification to claim that IGF works independently of the multiple mass regulators found in muscle and that it, alone, is sufficient to regulate muscle mass. We consider IGF-I to be an amplifier, as opposed to an instigator, for muscle growth, where the integration of mechanical muscle loading (3, 5), injury, other growth factors (FGF, HGF, or myostatin), and the nuances arising from peptides produced through alternative splicing of the *igf1* gene (1), ultimately drive hypertrophy or atrophy. Inhibition of IGF-I activity does not eliminate increased muscle mass through mechanical load, but driving IGF-I enhances the effects of load (3). Repair after injury can be resolved in the absence of IGF-I, but healing is accelerated when there is a boost in IGF-I levels (6). So, load can certainly determine muscle mass, but IGF-I can still regulate it.

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#### IGF-I AND ADULT MUSCLE MASS

TO THE EDITOR: Stewart and Pell (5) state that IGF-I is a major regulator of the development, recovery after injury, and adult maintenance of muscle mass. Normal muscle development in mice with liver-specific IGF-I knockout indicates a role of muscle-derived IGF-I rather than circulating IGF-I in myogenesis (4). Flueck and Goldspink (2) acknowledge the role of IGF-I in muscle development and regeneration but suggest that IGF-I is not required for load-induced muscle hypertrophy. IGF-I is of major importance for muscle development and early muscle growth in mice and humans (5). Postpubertally, after achievement of maximal muscle mass, the role of IGF-I is more controversial. Growth hormone treatment in elderly humans has minor effect on muscle strength (6), which could be due to small effect on local IGF-I levels in muscle. In mice, overexpression of IGF-I in skeletal muscle sustained hypertrophy and regeneration also in the senescent muscle (3), showing that muscle-derived IGF-I has the capacity to affect adult muscle hypertrophy. However, lack of protection from unloading-induced atrophy in mice overexpressing IGF-I in skeletal muscle (1) and improved muscle strength by resistance training in elderly humans without affected IGF-I expression in muscle (6) suggest that muscle-derived IGF-I is not the only regulator of adult muscle function. IGF-I has so far been selectively inactivated in the liver, pancreas, chondrocytes, and osteoblasts (4). The development of mouse models with selective IGF-I inactivation locally in muscle could further clarify the role of IGF-I in muscle physiology including load-induced muscle hypertrophy.

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#### IT'S ALL IN THE TIMING

TO THE EDITOR: As with most discussions there is merit in both sides of the debate with each outlining different but valid interpretations of what is meant by “the major physiological regulator of muscle mass.” Stewart and Pell (6) rightly describe the role of the IGFs in contributing to the establishment of muscle fiber number during prenatal development as a factor defining the limits of muscle mass postnatally. Flueck and Goldspink (4) are also probably correct to assert that IGF-1 plays no major role in the acute adaptive responses to mechanical stimuli. However the quoted study by Deldicque et al. (3) does not add strength to this argument as although Akt is not upregulated immediately following exercise, protein synthesis is also probably not. A number of studies have shown that short-term changes in Akt/mTOR signaling do not always correlate with the expected changes in protein synthesis (1). Furthermore IGF-1 not only stimulates Akt but also the MAPKs. In fact in rats hypertrophy induced by local administration of IGF-1 can be prevented by inhibition of ERK (5).

IGF-1 may not play a role in acute responses to load or nutrients but could be crucial for long-term adaptive remodeling to a continually altering mechanical environment (in part through satellite cells). The role of IGF-1 in chronic muscle remodeling may also be age dependent. Disuse atrophy in old rats is not reversed by reloading of the muscle unless combined with locally elevated IGF-1 levels (2).

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#### IGF-I—AN ENIGMA DISGUISED AS GROWTH FACTOR

TO THE EDITOR: This Point:Counterpoint (2, 7) serves to highlight the diversity of situations in which muscle mass is regulated: growth, hypertrophy, repair, disuse atrophy, cachexia, sarcopenia, etc. Given this diversity, it is not surprising

that there is no single regulator. The fact that IGF-I can act in a systemic, autocrine, and a paracrine manner, is regulated by multiple binding proteins, and as alternative splicing can result in human muscle expressing transcripts for three different C terminal E-peptides (3), suggest complex and subtle roles for this growth factor. Obvious effects of IGF-I are missing, as evidenced by the inability of elevated systemic levels of IGF-I (induced by growth hormone administration) to promote muscle growth. Furthermore, experiments that have blocked the IGF-I receptor, but not the hypertrophic response to overload (6), provide strong evidence that exercise-induced hypertrophy is not regulated by IGF-I. That said, if there is no role for IGF-I, why does enhanced local IGF-I expression (through gene transfer) act synergistically with mechanical overload (5)?

The most convincing evidence for a positive action of IGF-I on skeletal muscle seems to be its influence on satellite cell behavior. When a muscle is damaged, repair requires the activation of satellite cells and the proliferation and fusion of resulting myoblasts. Cell culture studies suggest that the mature IGF-I peptide is unique in stimulating both of these effects (1, 4). Thus it makes sense to hypothesize that IGF-I might only be involved in hypertrophy when satellite cell activation and differentiation are required. Whether this is a necessity is another debate.

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#### IGF-1 IS A MAJOR REGULATOR OF MUSCLE MASS DURING GROWTH BUT NOT FOR ADULT MYOFIBER HYPERTROPHY

TO THE EDITOR: We consider that IGF-1 is a (not “the”) major regulator of muscle mass during growth, but probably not for adult muscle. Genetically modified animal models support the role for IGF-1 during muscle development (5). In particular, mice where IGF-1 receptor signaling is completely abolished and insulin receptor signaling is reduced by ~85%, have 30% less muscle mass at 3 wk of age; however, there is a gradual decrease in this muscle mass deficiency as they mature into adults (1). Furthermore, we have recently shown in vivo that

transgenic elevation of IGF-1 promotes myofiber hypertrophy in growing, but not adult mice (3). Young muscles respond to elevated IGF-1 by elevated signaling downstream from the IGF-1 receptor and increased myofiber growth rate, while adult muscles do not (3). While IGF-1 is critical during muscle growth, other molecules are also major regulators of muscle mass during development.

In adults, where muscles hypertrophy in response to mechanical loading (e.g., resistance exercise), evidence for a critical role for IGF-1 is lacking (2). Instead, the mechanical loading appears to increase protein synthesis via signaling that is independent of IGF-1 receptor activation (4), as does high protein enhancement of the hypertrophic response. However, if damage and regeneration does occur in adult muscles, IGF-1 will act on the growing new myofibers (3). In conclusion, IGF-1 is not the major regulator for muscle mass in all situations, although it is certainly important during growth.

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TO THE EDITOR: Both reviews from Stewart and Pell (2) and from Flueck and Goldspink (6) recognize IGF as a critical regulator of muscle mass, but while Stewart and Pell suggest an obligatory function for IGF in the regulation of muscle mass, Flueck and Goldspink stress the importance of adaptive mechanisms occurring during postnatal growth that rely mainly on mechanical stress signals, and not on hormonal signals such as IGFs (2, 6). The view of Stewart and Pell is supported by our work showing that locally synthesized IGF-1 propeptide is a major physiological regulator of muscle mass in the absence of injury; in mice, muscle-specific overexpression of transgenic IGF-1Ea propeptide results in increased muscle mass, strength, and resistance to atrophy without changing serum IGF-1 levels (1, 3, 5), whereas improved regeneration after injury in these animals is achieved through a variety of downstream factors, including modulation of the inflammatory response (4). The relevance of these findings in humans is supported by the production of IGF-1 propeptides containing either Ea or Ec C-terminal peptides in the muscle upon injury and mechanical stretch. The effects of local IGF-1 on muscle mass likely require a growing or regenerating muscle (such as during postnatal developmental or in response to endogenous necrosis) with an active population of satellite cells, as Flueck and Goldspink suggest. However they further comment that IGF-1 may not be relevant “in physiological situations where mass

gains are achieved with minimal injury (i.e. mild exercise), where considerable increases in protein synthesis are apparent, and satellite cell activation is possibly not essential." We note that human studies performed in young or elderly patients are discordant on this issue: whether elevated IGF-1 in the muscle bed has an additional effect on exercise-induced muscle hypertrophy has not been conclusively tested, thus warranting further future investigation.

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#### IGF-1 IS NOT KEY FOR ADULT SKELETAL MUSCLE HYPERTROPHY

TO THE EDITOR: Stewart and Pell (6) argue that IGFs are critical for the developmental growth of skeletal muscle while Flueck and Goldspink (2) focus on the physiological regulation of adult muscle mass. Thus a salient point regarding the current debate is that the fundamental contribution of IGFs to skeletal muscle mass is very context dependent. In weighing both parties' arguments we agree that IGFs are a regulator of muscle mass during development and maturation but we support the contention that IGFs are not the major physiological regulator of adult muscle mass. As presented by Flueck and Goldspink, a deficiency of circulating IGF-1, resulting from the liver-specific inactivation of IGF-1 gene expression, did not prevent compensatory hypertrophy of skeletal muscle (4). Consistent with this finding, expression of a muscle-specific dominant negative IGF-I receptor revealed that mechanical load-induced muscle hypertrophy did not require functional IGF-1 receptor signaling (5). These studies demonstrate that regardless of the source, IGF-1 is not necessary for adult skeletal muscle hypertrophy.

Alternatively, mTOR signaling, which is a well-described pathway downstream of IGF-1/PI3K, has been shown to be critical for adult skeletal muscle hypertrophy (1). While mTOR can be activated by IGF-1, mechanical strain is also capable of activating mTOR independent of PI3K signaling (3). Thus we

concur with Flueck and Goldspink and support a model whereby mechanical loading is a fundamental upstream regulator of muscle mass that may, in fact, function independently of IGFs.

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#### IGF-1 PLAYS A UNIQUE ROLE IN MUSCLE REGENERATION

TO THE EDITOR: IGF-1 is involved in muscle regenerative processes by modulating the inflammatory process, inhibiting apoptosis, maintaining muscle mass, activating satellite cells (2) and enhancing the recruitment of bone marrow-derived cells (5). Stem cell recruitment and activation are initiated in response to secretion of inflammatory cytokines and growth factors such as leukemia inhibitory factor, IGF-1, basic fibroblast growth factor, platelet-derived growth factors, hepatocyte growth factor, and nerve growth factor. The initial and transient inflammatory response is an important step for muscle regeneration, whereas prolonged and excessive inflammation is detrimental. It has been shown that enhanced regenerative capacity of MLC/mIGF-1 mice correlates with a dampening of the later stages of inflammation while the early phases of the inflammatory response are not affected by mIGF-1 expression (4). It is also noteworthy that IGF-1 is one of the few myogenic regulators that stimulate both satellite cell proliferation and differentiation (3), which are usually considered to be mutually exclusive events. The mitogenic and myogenic effects of IGF-I render it useful for muscle regeneration in response to injury and the adaptation of muscle to increased loading. IGF-1 infusion also induce muscle hypertrophy in the absence of changes in loading state (1). In summary, IGF-1 is an important regulator of muscle mass (6).

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#### IGF—A KEY REGULATOR OF MUSCLE MASS AND FUNCTION IN CHRONICALLY ACTIVE MUSCLE?

TO THE EDITOR: The consideration of arguments put forth, regarding whether IGF is or is not the major physiological regulator of muscle mass (3), brings one to a conclusion that both points can be correct, and necessarily synergistic. Given that muscle is a complex biochemical protein machine with a major function of moving or countering loads (there are others, e.g., heat generation, insulation, and organ/bone protection), it makes sense that a combination of humoral and physical regulators are necessary to achieve muscle mass regulation in its most optimized state of responsiveness, because, in fact, the ability of muscle to perform most of its physical functions (with the exception of shortening) is directly related to its mass. The arguments put forth mainly focus on limb skeletal

muscle as the attendant example; however, a case in point where the combination of humoral and physical stimulatory factors are constantly in play is that of the respiratory muscles, e.g., the diaphragm and accessory muscles within the thorax. For example, rat models of significant muscle mass reduction through dietary restriction, followed by dietary repletion with addition of growth hormone (GH), indicate that the most effective restoration of diaphragm mass and function occurs with addition of GH (1, 2), suggesting the necessity of growth factors as a key optimizer/amplifier in the presence of chronic repetitive activity. This is particularly true for the contribution of the force or load component to diaphragm power capacity, which tracks with humoral-dependent alterations in muscle mass (2). Therefore, the relative contributions of IGF and physical activity to muscle mass are likely dependent on the muscle and its function.

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