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Short-term growth hormone treatment does not increase muscle protein synthesis in experienced weight lifters

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YARASHESKI, KEVIN E., JEFFREY J. ZACHWIEJA, THEODORE J. ANGELOPOULOS, AND DENNIS M. BIER. *Short-term growth hormone treatment does not increase muscle protein synthesis in experienced weight lifters.* J. Appl. Physiol. 74(6): 3073–3076, 1993.—The purpose of this study was to determine whether recombinant human growth hormone (GH) administration enhances muscle protein anabolism in experienced weight lifters. The fractional rate of skeletal muscle protein synthesis and the whole body rate of protein breakdown were determined during a constant intravenous infusion of [^{13}C]leucine in 7 young (23 ± 2 yr; 86.2 ± 4.6 kg) healthy experienced male weight lifters before and at the end of 14 days of subcutaneous GH administration (40 $\mu g \cdot kg^{-1} \cdot day^{-1}$). GH administration increased fasting serum insulin-like growth factor-I (from 224 ± 20 to 589 ± 80 ng/ml, $P = 0.002$) but did not increase the fractional rate of muscle protein synthesis (from 0.034 ± 0.004 to 0.034 ± 0.002%/h) or reduce the rate of whole body protein breakdown (from 103 ± 4 to 108 ± 5 $\mu mol \cdot kg^{-1} \cdot h^{-1}$). These findings suggest that short-term GH treatment does not increase the rate of muscle protein synthesis or reduce the rate of whole body protein breakdown, metabolic alterations that would promote muscle protein anabolism in experienced weight lifters attempting to further increase muscle mass.

somatotropin; insulin-like growth factor-I; muscle hypertrophy; amino acid/protein metabolism; stable isotope tracers

PREVIOUSLY, WE REPORTED that when recombinant human growth hormone (GH) was administered (40 μg/kg, 5 days/wk) to healthy sedentary young men in conjunction with a 12-wk muscle-building exercise program, increments in muscle protein synthesis rate and muscle strength were similar to those achieved by young men doing an identical muscle-building exercise program but receiving placebo injections (13). However, this study did not exclude the possibility that GH administration might augment muscle protein synthesis during the early phase of treatment (6), because muscle protein synthesis was determined only before and after 3 mo of GH treatment.

Furthermore the previous study (13) did not consider the possibility that GH administration might enhance muscle protein synthesis in experienced weight lifters or body builders who, having already achieved a large muscle mass by use of heavy-resistance exercise training, might further increase muscle mass only by supplementation with another potential anabolic stimulus. When young highly conditioned (resistance- and aerobic-trained) men and women were given 6 wk of methionyl-GH treatment (30–50 μg/kg, 3 days/wk), fat-free mass increased (5), but whether this increment was the result of an accelerated rate of muscle protein synthesis and an accumulation of muscle tissue was not addressed. Finally, from a practical perspective, skilled weight lifters and body builders represent the most likely abusers of GH for muscle anabolism, if GH was generally available.

Therefore the purpose of this study was to determine whether short-term (14 days) GH administration to experienced weight lifters increases the rate of muscle protein synthesis or reduces the rate of whole body protein breakdown, prerequisite metabolic alterations that would promote muscle protein anabolism.

METHODS

Subjects. Seven healthy young men (23 ± 2 yr, 177 ± 2 cm, 86.2 ± 4.6 kg) volunteered for the study, which was approved by the Human Studies Review Board at Washington University School of Medicine. Informed consent was obtained after the purpose and procedures were described. Three subjects were college football players and were studied while weight training during the off-season, three were trained weight lifters/body builders and were studied during their regular training routine designed to increase muscle size, and one was a sprint cyclist using weight training to increase lower body muscle strength.

The subjects' weight-training routines varied but could be described generally as high-intensity (75–90% maximum strength) low-repetition (5–10 lifts) progressive-resistance exercise performed 3–6 days/wk for at least the prior 3 yr. Typically, free weights and weight-lifting machines were combined during a daily training session, which consisted of several exercises focused on training one or two particular muscle groups (e.g., chest, arms, shoulders, back, legs). Each training session was not rigidly controlled, because these young men were devoted to progressive-resistance exercise as a means of increasing

muscle mass and strength and had achieved a relatively large muscle mass that was only slowly increasing or stabilized because of some limit to how large their muscles could grow. We examined whether GH treatment would augment this slow rate of muscle growth by increasing the rate of muscle protein synthesis. The subjects maintained their exercise training during the study.

Three of the subjects agreed to consume a 3-day meat-free controlled-protein diet (1.5 g protein $\cdot$ kg^{-1} $\cdot$ day^{-1}) for the purpose of estimating muscle mass by use of 24-h urinary creatinine excretion (8) before the initial and final measures of protein metabolism (see below). This diet was prescribed by a research dietitian and prepared and provided by the Research Kitchen on the General Clinical Research Center. Muscle mass in these three subjects was calculated to be 47.0 ± 0.9 kg (49 ± 2% body wt).

Muscle and whole body protein metabolism. Before and at the end of 14 days of subcutaneous recombinant human GH administration (40 μg $\cdot$ kg^{-1} $\cdot$ day^{-1}; Genentech) and within 4 h of the final GH injection, each subject was admitted to the General Clinical Research Center where, during an overnight fast (1900–0800 h), a primed (7.58 μmol/kg) constant intravenous infusion (7.58 μmol $\cdot$ kg^{-1} $\cdot$ h^{-1}) of [1-^{13}C]leucine or [1,2-$^{13}C_2$]leucine (Tracer Technologies, Somerville, MA) was used to estimate the fasting rate of whole body protein breakdown (systemic leucine rate of appearance) by use of the reciprocal pool approach (1) and to determine the fractional rate of muscle protein synthesis (2, 14). In blood samples taken before and at 30-min intervals during the last 4 h of the infusion, plasma α-[^{13}C]ketoisocaproic acid enrichment (atom %excess) was determined as previously described (11) and used to calculate the rate of whole body protein breakdown (1) and as the precursor pool enrichment for the calculation of the rate of muscle protein synthesis (2, 10, 12). Muscle [^{13}C]leucine content was measured in one muscle sample (~15–30 mg wet wt) removed from the vastus lateralis 1.5–2 h after the [^{13}C]leucine infusion began and in a second muscle sample removed from the contralateral vastus lateralis at the end of the infusion (0800 h) (2, 10, 13, 14). All infusions were done 24–30 h after the last exercise session, except in one subject where they were done 48 h after the last exercise session and another subject where they were done within 4 h of the last exercise session. Although not controlled among subjects, this was controlled within each subject.

Circulating hormone levels. During the initial and final tracer infusion studies, fasting serum insulin-like growth factor-I (IGF-I) concentration was measured in the morning (0800 h) blood sample (7).

Statistical analysis. The initial and final measures of muscle protein synthesis rate, whole body protein breakdown rate, and serum IGF-I concentration were evaluated with a paired *t* test. Means ± SE are reported.

RESULTS

Despite a significant increase in fasting serum IGF-I levels from 224 ± 20 to 589 ± 80 ng/ml (P = 0.002; Fig. 1*A*), the fractional rate of vastus lateralis muscle protein synthesis measured in these resistance-trained men after 2 wk of daily GH injections was 0.034 ± 0.002%/h and was identical to the muscle protein synthesis rate (0.034 ± 0.004%/h) measured before GH treatment (Fig. 1*B*). In addition, the initial whole body protein breakdown rate (103 ± 4 μmol $\cdot$ kg^{-1} $\cdot$ h^{-1}) in these young men was not different from that (108 ± 5 μmol $\cdot$ kg^{-1} $\cdot$ h^{-1}) measured at the conclusion of GH treatment (Fig. 1*C*). Finally, the muscle protein synthetic and whole body proteolytic responses of the three subjects receiving the controlled diet and the two subjects not tested within 24–30 h of their last exercise session were not different from the responses of the other subjects.

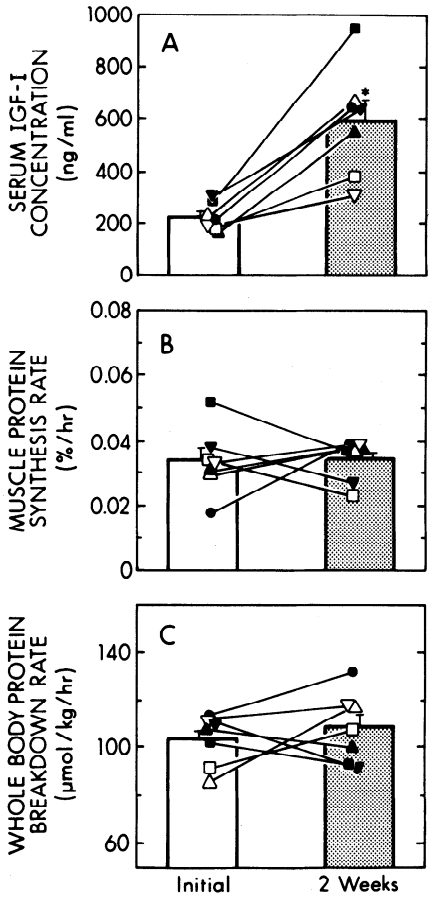

FIG. 1. Serum insulin-like growth factor-I (IGF-I) levels (*A*), fractional rate of vastus lateralis muscle protein synthesis (*B*), and estimated rate of whole body protein breakdown [systemic leucine rate of appearance (1); *C*] in experienced weight lifters before and after 2 wk of daily growth hormone administration (40 μg $\cdot$ kg^{-1} $\cdot$ day^{-1}). * P = 0.002 vs. Initial.

DISCUSSION

These observations suggest that short-term GH administration did not *1*) increase the fractional rate of skeletal muscle protein synthesis or *2*) reduce the rate of whole body protein breakdown in young experienced weight lifters, despite an increase in circulating IGF-I. Because an increase in the rate of synthesis and/or a decrease in the rate of breakdown are requisite events for enhancing muscle protein anabolism and the direct determination

of amino acid incorporation into skeletal muscle protein was not increased by the short-term high-dose GH treatment regimen utilized in these experienced weight lifters, it is doubtful that prolonged GH administration would result in additional muscle protein accretion.

These findings are in agreement with our previous study, in which chronic GH administration did not further enhance the rate of muscle protein synthesis or reduce the rate of whole body protein breakdown [determined with ^{13}C and ^{15}N amino acid tracers and confirmed by others (9)] in young untrained men during a resistance-exercise program (13). These findings reemphasize that GH supplementation that increases serum IGF-I levels during muscle-building exercise does not provide an additional anabolic stimulus to skeletal muscle, even in young men with a substantial muscle mass who are progressively increasing their training intensity but are not experiencing notable increments in muscle mass. Perhaps the skeletal muscles of young resistance-trained men (novice or experienced) respond to the potent muscle-building stimulus of resistance exercise and are unable to respond to the potential anabolic actions of additional GH/IGF-I.

It has recently been reported that resistive exercise acutely increases the fractional rate of biceps muscle protein synthesis in young weight-trained men 4 and 24 h after the exercise session (3). Most of our measurements were made within this time interval, yet the initial rates of muscle protein synthesis in the present study were not above normal. This is not surprising, because our subjects were training 3–6 days/wk, whereas the subjects in the recent report (3) refrained from weight-lifting exercise for 3 days before the experiment. Furthermore our experienced weight lifters would not be expected to have high initial rates of muscle protein synthesis, because, as recently suggested (3), the acute increment in muscle protein synthesis in response to resistive exercise diminishes as the muscle adapts to the protein anabolic effects of years of resistance training and, as a result, the rate of increase in muscle mass stabilizes. We examined whether another potential anabolic stimulus (GH) enhances muscle protein synthesis in experienced weight lifters with a large but slowly growing muscle mass and found no evidence that GH treatment increased the rate of muscle protein synthesis.

Measuring arteriovenous differences of amino acids across the forearm tissues of normal volunteers, Fryburg et al. (6) demonstrated that an acute intra-arterial infusion of GH (14 $ng \cdot kg^{-1} \cdot min^{-1}$) resulted in a more positive forearm amino acid balance. It is important to note that these observations were accompanied by an increase in forearm blood flow and no change in local (forearm) or systemic IGF-I levels and reflect the increased uptake of amino acids by all tissues in the forearm, not just skeletal muscle (i.e., fat and connective tissue), conditions vastly different from those of the present study. The authors' implication that this uptake should result in an increase in forearm muscle protein synthesis was not confirmed directly.

In the present study, we directly determined the amount of stable labeled amino acid incorporated into vastus lateralis muscle protein and did not observe an increased fractional rate of leucine incorporation into this muscle. Furthermore our subjects were doing resistance exercise in combination with GH treatment, received a different dose of GH by a different route of administration, and received this dose for a longer period of time than the subjects studied previously (6). Taken together, these findings support the notion that GH treatment that results in supraphysiological levels of circulating GH and IGF-I, when combined with muscle-building exercise, does not stimulate the rate of skeletal muscle protein synthesis. Therefore GH administration does not appear to enhance muscle protein anabolism in novice or in experienced weight lifters. Finally, as mentioned previously (13) but now confirmed in a group of experienced weight lifters, *1*) baseline fasted IGF-I levels were not increased with chronic weight-lifting exercise and *2*) 2 wk of exogenous GH treatment that doubled the circulating IGF-I levels did not further enhance muscle protein synthesis in experienced weight lifters. Thus, circulating IGF-I seems to play a minor role in inducing muscle growth during resistance exercise. This lack of an effect may be related to an as yet undefined interaction among GH, IGF-I, their serum binding proteins, and their receptors in exercising muscle (4).

The measurements of muscle protein synthesis reported here [0.034 ± 0.004%/h (SE) range 0.020–0.052%/h] were made in the overnight fasted condition and were, as expected, lower than previously reported values measured in the fed condition (3, 13). Our conclusion is therefore limited to the effects of GH administration on the fractional rate of skeletal muscle protein synthesis measured after an overnight fast in a group of well-trained weight lifters whose increments in muscle mass had stabilized. However, it seems unlikely, on the basis of our previous observations (13), that our conclusions would be different had the rate of muscle protein synthesis been determined in the fed condition.

In summary, 2 wk of recombinant human GH administration did not increase the fractional rate of skeletal muscle protein synthesis or reduce the rate of whole body protein breakdown, conditions that would favor muscle protein accumulation in this group of experienced weight lifters. This suggests that GH supplementation does not enhance the rate of muscle protein synthesis in experienced weight lifters attempting to further increase muscle mass.

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