Mechanical load increases muscle IGF-I and androgen receptor mRNA concentrations in humans

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Bamman, Marcas M., James R. Shipp, Jie Jiang, Barbara A. Gower, Gary R. Hunter, Ashley Goodman, Charles L. McLafferty, Jr., and Randall J. Urban. Mechanical load increases muscle IGF-I and androgen receptor mRNA concentrations in humans. Am J Physiol Endocrinol Metab 280: E383–E390, 2001.—The mechanism(s) of load-induced muscle hypertrophy is as yet unclear, but increasing evidence suggests a role for locally expressed insulin-like growth factor I (IGF-I). We investigated the effects of concentric (CON) vs. eccentric (ECC) loading on muscle IGF-I mRNA concentration. We hypothesized a greater IGF-I response after ECC compared with CON. Ten healthy subjects (24.4 ± 0.7 yr, 174.5 ± 2.6 cm, 70.9 ± 4.3 kg) completed eight sets of eight CON or ECC squats separated by 6–10 days. IGF-I, IGF binding protein-4 (IGFBP-4), and androgen receptor (AR) mRNA concentrations were determined in vastus lateralis muscle by RT-PCR before and 48 h after ECC and CON. Serum total testosterone (TT) and IGF-I were measured serially across 48 h, and serum creatine kinase activity (CK), maximum voluntary contraction (MVC), and IGFBP-4 mRNA concentration de-
hormones. Whether ECC loading enhances local mechanism(s) in humans is largely unknown.

Increasing evidence indicates that modulation of muscle protein turnover is tightly regulated by a number of locally expressed tissue growth factors (1, 12, 13). Insulin-like growth factor I (IGF-I) is known to stimulate myoblast proliferation and differentiation in vitro (13) as well as muscle protein synthesis (22) and, as such, has received increasing attention in studies of muscle hypertrophy. Local expression of IGF-I in skeletal muscle appears to be load sensitive and acts independently of any change in serum GH or IGF-I (1). Furthermore, Yang et al. (37) recently identified two isoforms of IGF-I in skeletal muscle, one of which appears to be regulated exclusively by mechanical load. Some have proposed the name mechanogrowth factor (MGF) for this mechanically sensitive isoform (16). This local IGF-I (or MGF) is thought to induce myofiber hypertrophy by autocrine (i.e., direct stimulation of myofibrillar protein synthesis) and/or paracrine (i.e., satellite cell proliferation, differentiation, and fusion) action (1).

The efficacy of muscle IGF-I is dependent not only on its expression but also on its availability, which is regulated by a family of six IGF binding proteins (BPs) and by the abundance of the type 1 IGF receptor. For example, in muscle, IGFBP-4 has a high affinity for IGF-I and thus inhibits its myogenic effects, whereas IGFBP-5 may facilitate (13) or inhibit (21) IGF-I-stimulated differentiation under certain conditions. Additionally, IGFBP-1 has been shown to inhibit IGF-I-stimulated protein synthesis (14).

The increase of serum IGF-I with exogenous administration of GH or IGF-I does not appear to stimulate myofiber hypertrophy in the absence of mechanical load (4), nor does systemic GH treatment enhance the hypertrophic effect of resistance training (33, 38). However, induction of exogenous IGF-I directly into skeletal muscle does increase muscle mass (2), suggesting that any stimulus causing an increase in muscle IGF-I availability may lead to muscle growth. Urban et al. (34) have recently shown that exogenous testosterone administration in hypogonadal older men increases muscle strength and protein synthesis and is associated with increased muscle IGF-I mRNA concentration with a concomitant reduction in IGFBP-4 mRNA. Muscle IGF-I mRNA content is also increased in muscle after heavy exercise in humans and after stretch in animals (37). Taken together, these findings lead to the attractive speculation that mechanical load associated with resistance exercise may increase muscle IGF-I availability, which in turn may cause increased myofibrillar protein synthesis, satellite cell activation, and consequent myofiber hypertrophy. Because ECC loading appears to enhance the hypertrophic response to resistance training (17) and because stretch tension increases muscle IGF-I mRNA (37), it also seems plausible that ECC loading may enhance the local IGF-I response.

In this study we investigated the separate effects of CON and ECC resistance exercise on muscle mRNA concentrations of IGF-I and IGFBP-4. We hypothesized that the local IGF-I response after a single bout of resistance exercise would be greater when heavy ECC muscle actions were performed as opposed to heavy CON muscle actions. Levels of IGF-I and IGFBP-4 mRNA in vastus lateralis muscle samples were determined before and 48 h after ECC and CON. We also measured muscle androgen receptor (AR) mRNA concentration and serum levels of testosterone and IGF-I to investigate possible interactions between serum anabolic factors and local tissue responses.

METHODS

Subjects. Ten healthy subjects (7 men, 3 women) >19 yr of age participated in this study. Each subject was screened for health history by means of a health status questionnaire and for level of activity by use of the Baecke Questionnaire of Habitual Physical Activity. Exclusion criteria included current lower-body resistance training or previous history of diagnosed condition or illness that would endanger the subject during strenuous resistance exercise. All subjects were given an oral and written briefing of the study before signing informed consent forms. The study was approved by the Institutional Review Board and was conducted in the General Clinical Research Center (GCRC) at the University of Alabama at Birmingham.

Familiarization sessions. Each subject completed three familiarization sessions on a Smith squat machine (York Barbell, Wright Exercise Equipment, Birmingham, AL) to learn proper execution of the exercise and to become familiar with heavy loads. The third familiarization was completed ≥5 days before the first exercise session in an effort to prevent residual effects of the familiarization routine. In familiarization 1, subjects warmed up with a light weight and performed one set of 10 biphasic (CON/ECC) repetitions with a comfortable submaximal load. In familiarization 2, which was 3 days later, subjects warmed up, completed a one-repetition maximum (1RM) strength test, and concluded the session with three sets of 10 repetitions at 60% of 1RM. Approximately 3-4 days later, subjects returned for the final familiarization, which consisted of a warm-up, a 1RM test, three sets of 10 repetitions at 70% of that day's 1RM, and two sets of 8 repetitions at 80% of 1RM.

Strength testing. As mentioned in the preceding section, each subject performed a 1RM squat strength test during the second and third familiarizations. After a sufficient warm-up period, sets of one repetition were executed with increasing load until two failed attempts occurred at a given weight. 1RM was recorded as the highest weight successfully lifted. Each attempt was separated by 2 min.

Isometric maximum voluntary contraction (MVC) strength was assessed unilaterally during knee extension. MVC was determined at a knee angle of 1.91 rad (110°) using a calibrated force transducer (Omega) interfaced with a desktop computer. Force output was recorded at 100 Hz, and the system provided visual numeric feedback for both subject and investigator. During each test, three MVCs (6 s duration) were performed separated by 1- to 2-min rest periods. The mean of the two highest peak forces (kg) obtained across the three trials was used for analysis. Subjects were instructed to contract as hard as possible and were verbally encouraged throughout each trial. MVC was assessed before the familiarization sessions and was repeated 48 h post-CON and post-ECC.
GCRC procedures. Each subject had two exercise days; one day, ECC-only resistance exercise was performed, and the other day, CON-only resistance exercise was performed. CON and ECC bouts were separated by 6–10 days, and order was randomly assigned. For CON, subjects performed eight sets of eight repetitions with resistance for the first set established at 85% of the 1RM achieved in the third familiarization. For ECC, subjects also performed eight sets of eight repetitions, but the resistance for the first set was established at 110% of the 1RM. The resistance was set at these levels to maintain relative workloads (because ECC strength is 20–50% greater than CON) and thus maximize motor unit recruitment in both CON and ECC modes. Resistance was decreased if a subject began to fatigue to the point that proper form, repetition number, and/or pace could not be maintained. If a subject reached volitional fatigue after six repetitions or fewer, the load was reduced 5–10 kg for the next set. Volitional fatigue during CON was defined as an inability to ascend without assistance. During ECC, fatigue was defined as a controlled descent faster than the 2-s minimum. Within subjects, a minimum squat depth was defined during familiarization sessions as a point in the range of motion at which the subject’s femur was horizontal (parallel with the floor). This minimum descent was used as a criterion for successful performance during both 1RM testing and the CON and ECC exercise bouts.

On each of the two exercise days, subjects reported to the GCRC in a fasted state between 0700 and 0800, and a catheter was placed in an antecubital vein shortly after arrival. The subjects lay quietly for 30–40 min before a baseline blood draw. This was immediately followed by the prescribed exercise bout. Subjects remained in the GCRC for 8 h after exercise for serial blood sampling and dietary control. Postexercise blood samples (5 ml) were withdrawn at 0.5, 1, 2, 4, and 8 h. A mixed diet was prescribed by the GCRC dietetics staff. The diet was designed to be isocaloric based on the subject’s body weight, and the same three meals were given on each of the two exercise days. The three meals were then subjected to PCR in the presence of the appropriate primers (Table 1). PCR began with 1 cycle (2 min) at 94°C followed by amplification cycles consisting of 1 min at 94°C, 1 min at 55°C, and 1 min at 72°C. The optimum number of amplification cycles was predetermined in control experiments and consisted of 25 cycles for AR and 25 cycles for both IGF-I and IGFBP-4.

The products of the PCR were run on Southern gel, and amplified DNA products were sized by DNA ladder. Within subjects, samples from the three time points were run in adjacent lanes. Southern blots were then made and hybridized to oligonucleotides of the DNA fragment (Table 1). Band densities on the Southern blots were quantified by densitometry. For standardization, optical density of each band was corrected for background, and the band density for glyceraldehyde phosphate dehydrogenase was used as the adjusting factor.

Serum IGF-I and total testosterone. Total IGF-I and total testosterone were determined in serum samples withdrawn before exercise and at 0.5, 1, 2, 4, 8, 24, and 48 h after CON and ECC bouts. Total IGF-I was determined by immunoradiometric assay (Diagnostic Systems Laboratories, Inc.) using 125I. Total testosterone was determined by solid-phase radioimmunoassay (Diagnostic Products, Los Angeles, CA) using 125I. All samples within subjects for a given hormone were assayed in random order during a single run. Mean intra-assay coefficients of variation (CVs) ranged from 2 to 7%, and mean interassay CVs ranged from 3 to 10%.

Serum creatine kinase. Total creatine kinase (CK) activity was determined in serum samples immediately before exercise and at 24 and 48 h after CON and ECC. CK assays of all samples were performed in random order by means of a

### Table 1. PCR primers and hybridization oligonucleotides used

<table>
<thead>
<tr>
<th>Oligonucleotide</th>
<th>Forward Primer</th>
<th>Reverse Primer</th>
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<tbody>
<tr>
<td>IGF-I sense</td>
<td>5'-AAATCACGAGTCTTGGAAACC-3'</td>
<td>5'-CTTCTGGTCTGGGCAATG-3'</td>
</tr>
<tr>
<td>IGF-I antisense</td>
<td>5'-CAGGGCGTTTTATCTACACAGA-3'</td>
<td>5'-GATGCTCTACTCTGCCCTCCATG-3'</td>
</tr>
<tr>
<td>IGFBP-4 sense</td>
<td>5'-CCACGAAATAGATCTTGCATG-3'</td>
<td>5'-CTGGGTTGGAAATGTAAGTG-3'</td>
</tr>
<tr>
<td>IGFBP-4 antisense</td>
<td>5'-CCATCCAGAAGACCTGCA-3'</td>
<td>5'-GTGATGGGATTTCCATTGAT-3'</td>
</tr>
<tr>
<td>GAP, 206 bp sense</td>
<td>5'-GGAGTCAACGGATTTGGGT-3'</td>
<td>5'-GTGATGGGATTTCCATTGTATG-3'</td>
</tr>
<tr>
<td>GAP, 206 bp antisense</td>
<td>5'-CTACCTGATGCTTCCACATA-3'</td>
<td>5'-TGGAAGTTGCCGTTGGGAT-3'</td>
</tr>
<tr>
<td>GAP, 473 bp sense</td>
<td>5'-CAGGTCGCCGTGCAAGACC-3'</td>
<td>5'-TGGAAGTTGCCGTTGGGAT-3'</td>
</tr>
<tr>
<td>GAP, 473 bp antisense</td>
<td>5'-GGAGTCAACGGATTTGGGT-3'</td>
<td>5'-CTACCTGATGCTTCCACATA-3'</td>
</tr>
</tbody>
</table>

IGF-I, insulin-like growth factor I; AR, androgen receptor; GAP, glyceraldehyde phosphate dehydrogenase.
SynchroN LX System (Beckman Coulter, Fullerton, CA) following manufacturer’s instructions. By use of this system, the within- and between-run CVs for serum in our laboratory are 2.1 and 1.2%, respectively.

Data analysis. Results are reported as means ± SE. Muscle biopsy and isometric strength performance data were analyzed by one-way repeated-measures ANOVA with three time points, defined as preexercise baseline, 48 h post-CON, and 48 h post-ECC. A priori planned comparisons were analyzed between the baseline value and each of the two 48-h postexercise values.

Serum hormone and CK data were analyzed using a new baseline blood draw for each exercise day. The new baseline was established to prevent any residual effect of previous exercise on the postexercise values after the second exercise session. Hormone levels were evaluated by repeated-measures ANOVA with two repeat factors: exercise (CON and ECC) and mode (CON and ECC) eight time points (baseline and 0.5, 1, 2, 4, 8, 24, and 48 h postexercise). Total testosterone data for three female subjects were excluded from the testosterone analysis, because several values were below the detectable range of the assay. CK levels were tested by repeated-measures ANOVA in similar fashion but with three time points (baseline, 24 h postexercise, and 48 h postexercise). The least squares difference (LSD) test was employed for post hoc testing. Scores on the subjective soreness rating 48 h after CON and ECC were compared using the Wilcoxon matched pairs test. Significance for all tests was accepted at \( P < 0.05 \).

RESULTS

Subject characteristics are shown in Table 2. The mean repetitions and mean loads for CON and ECC were computed from each subject’s average across eight sets. As described in METHODS, the target repetition number was eight per set. Every effort was made to achieve an equivalent number of repetitions on CON and ECC days; thus individual loads were adjusted slightly for each set based on performance in the previous set (see METHODS for details). As shown in Table 2, the method of load adjustment resulted in nearly identical numbers of repetitions during CON and ECC. Moreover, the average loads for CON (82%) and ECC (102%) approximated the target loads of 85 and 110% 1RM for CON and ECC, respectively. ECC loading elicits a blunted metabolic response and activates fewer motor units than CON at the same absolute workload (3, 28). Loads were 20–30% higher during ECC loading in an effort to match relative intensity and thus maximize motor unit activity in both modes of exercise.

Measurements used to assess relative muscle damage after CON and ECC are presented in Table 3. Isometric MVC was unchanged 48 h after CON but was depressed 10% 48 h after ECC \((P < 0.05)\). Total CK was not different from baseline 24 and 48 h after CON. CK activity was elevated 183% 48 h after ECC \((P < 0.05)\). The average rating on the 11-point soreness scale was significantly higher \((P < 0.01)\) 48 h after ECC compared with CON.

RT-PCR results for IGF-I, IGFBP-4, and androgen receptor mRNAs are shown in Fig. 1. Repeated-measures ANOVA revealed significant time effects \((P < 0.05)\) for IGFBP-4 and AR mRNA concentrations but not for IGF-I mRNA concentration \((P = 0.21)\). Results for IGF-I mRNA concentration were highly variable between subjects and across time. A priori planned comparisons between the baseline value and 48 h post-CON and between baseline and 48 h post-ECC for IGF-I mRNA concentration showed a 62% increase and a 54% increase, respectively.

Table 2. Descriptive characteristics of all subjects

| Age, yr | 24.4 ± 0.7 |
| Height, cm | 174.5 ± 2.6 |
| Weight, kg | 70.9 ± 4.3 |
| 1RM squat, kg | 136.1 ± 10.3 |
| Average repetitions per set | CON 7.9 ± 0.1 | ECC 7.7 ± 0.1 |
| Average load per set, kg | CON 111.6 ± 7.6 | ECC 139.2 ± 11.8 |

Values are means ± SE; \( n = 10 \) subjects. 1RM, one-repetition maximum; CON, concentric exercise; ECC, eccentric exercise.

Table 3. Indexes of muscle soreness and/or damage

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>48 h Post-CON</th>
<th>48 h Post-ECC</th>
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</thead>
<tbody>
<tr>
<td>MVC, (^*) kg</td>
<td>72.4 ± 4.6</td>
<td>77.6 ± 4.2</td>
<td>65.3 ± 3.9‡†</td>
</tr>
<tr>
<td>Soreness, ordinal scale, 0–10</td>
<td>0(0–3)</td>
<td>6(2–8)‡†</td>
<td></td>
</tr>
<tr>
<td>Creatine kinase, U/l</td>
<td>Baseline</td>
<td>24 h postexercise</td>
<td>48 h postexercise</td>
</tr>
<tr>
<td>CON</td>
<td>345.2 ± 67.0</td>
<td>326.0 ± 71.5</td>
<td>264.6 ± 65.1</td>
</tr>
<tr>
<td>ECC</td>
<td>224.6 ± 47.0</td>
<td>449.4 ± 89.0</td>
<td>636.3 ± 244.6†</td>
</tr>
</tbody>
</table>

Ordinal soreness data are shown as median (range). All other values are means ± SE. MVC, maximum voluntary isometric knee extension contraction. Baseline MVC was tested only once (before any exercise). \(^*\)Main time effect, \( P < 0.05 \); †different from baseline, \( P < 0.05 \); ‡different from 48 h post-CON, \( P < 0.01 \).
after ECC ($P < 0.05$) with a similar trend after CON ($P = 0.12$). Planned comparisons identified a 57% reduction in IGFBP-4 mRNA after ECC ($P < 0.01$) and a strong trend toward decreased IGFBP-4 after CON ($P = 0.06$). AR mRNA concentration was elevated ($P < 0.05$) 102 and 63% after CON and ECC, respectively. Southern blot results for IGF-I, IGFBP-4, and AR mRNAs are shown in Fig. 2.

Serum levels of total testosterone and IGF-I are shown in Table 4. Because testosterone was not within the detectable range for several samples among the three women, testosterone data are presented only for men. Main time effects were found for testosterone after both CON ($P < 0.001$) and ECC ($P = 0.026$) loading. After both exercise bouts, total testosterone levels tended to fall. Testosterone was depressed after CON at 1, 2, 4, and 8 h after exercise ($P < 0.05$). After ECC, testosterone was lower than baseline for all time points beyond 0.5 h postexercise ($P < 0.05$) except at 24 h. A time effect was noted for serum IGF-I ($n = 10$) after CON ($P = 0.005$). IGF-I was elevated 48 h after CON ($P = 0.006$), but no changes were found after ECC loading.

### DISCUSSION

Based on previous work linking muscle hypertrophy with local availability of IGF-I (2) or with ECC loading (17), the primary objective of this study was to determine whether ECC loading was associated with increased availability of local IGF-I in the working muscles. We noted a high degree of variability in IGF-I mRNA concentrations between subjects and across time. As a result, no main time effect was found in the ANOVA model. However, mean IGF-I mRNA levels trended upward 48 h after both CON and ECC loading, with the increase after ECC being significant as determined by planned comparison. To our knowledge, this is the first evidence in humans of muscle IGF-I transcriptional modulation after a single bout of heavy resistance exercise. Using immunohistochemistry, two recent investigations report increased IGF-I staining in human muscle after several bouts of high-intensity exercise (18, 31). Hellsten et al. (18) found an increased number of IGF-I immunoreactive capillaries and satellite cells in vastus lateralis muscle after 7 days of intense military training including 150 km of terrain marching with a 30-kg overload (i.e., gear). The increased IGF-I staining was accompanied by a sixfold increase in serum CK activity. Singh et al. (31) found a marked 491% increase in IGF-I staining in vastus lateralis of frail elderly after 10 wk of leg resistance training. Greater IGF-I staining at baseline was predictive of the magnitude of muscle hypertrophy ($r = 0.70$). It should be noted that both of these exercise protocols included both CON and ECC loading. IGF-I immunoreactivity within myofibers has also been shown to rise 4 days after 5 days of successive electrically stimulated ECC loading in the rat tibialis anterior (36). Others have reported increases in muscle IGF-I peptide with no concomitant increase in IGF-I gene expression after 5 days of endurance training in rats (11).

The optimum time point for an acute postexercise elevation in muscle IGF-I content is unknown. Increased myofiber IGF-I mRNA has been detected by in situ hybridization immediately after 6 days of continuous stretch in rabbits (37). We elected to biopsy the vastus lateralis muscle 48 h after the loading bouts to

**Table 4. Serum hormone levels before and after CON and ECC loading**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>0.5 h</th>
<th>1 h</th>
<th>2 h</th>
<th>4 h</th>
<th>8 h</th>
<th>24 h</th>
<th>48 h</th>
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<tbody>
<tr>
<td><strong>Testosterone</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CON†</td>
<td>621 ± 63</td>
<td>555 ± 62</td>
<td>504 ± 50$\dagger$</td>
<td>417 ± 45$\dagger$</td>
<td>416 ± 44$\dagger$</td>
<td>451 ± 48$\dagger$</td>
<td>586 ± 67</td>
<td>542 ± 40</td>
</tr>
<tr>
<td>ECC†</td>
<td>589 ± 60</td>
<td>580 ± 77</td>
<td>486 ± 65$\dagger$</td>
<td>447 ± 63$\dagger$</td>
<td>444 ± 46$\dagger$</td>
<td>451 ± 36$\dagger$</td>
<td>496 ± 73</td>
<td>472 ± 46$\dagger$</td>
</tr>
<tr>
<td><strong>IGF-I</strong> (ng/ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CON†</td>
<td>349 ± 37</td>
<td>317 ± 22</td>
<td>345 ± 36</td>
<td>358 ± 32</td>
<td>352 ± 44</td>
<td>372 ± 49</td>
<td>385 ± 35</td>
<td>416 ± 49$\dagger$</td>
</tr>
<tr>
<td>ECC</td>
<td>412 ± 70</td>
<td>361 ± 43</td>
<td>371 ± 45</td>
<td>361 ± 47</td>
<td>350 ± 34</td>
<td>373 ± 35</td>
<td>379 ± 41</td>
<td>386 ± 34</td>
</tr>
</tbody>
</table>

Values are means ± SE. *Testosterone data for men only ($n = 7$). †Main time effect, $P < 0.05$; $\dagger$different from baseline, $P < 0.05$.  

Fig. 2. Sample Southern blot results for IGF-I, IGFBP-4, and AR mRNAs before loading (PRE), 48 h after concentric loading (CON), and 48 h after eccentric loading (ECC). Samples from each subject were run in adjacent lanes as depicted here. A: ECC performed 6–10 days before CON; B and C: CON performed 6–10 days before ECC. GAP, glyceraldehyde phosphate dehydrogenase.
make the sample time coincide with previous reports of 1) increased mixed muscle protein synthesis after an acute bout of heavy resistance exercise (29) and 2) drops in isometric force and increases in myofibrillar disruption after ECC loading (19). Although a direct link is not apparent, our data indicate that important changes in the local IGF-I system occur during the acute phase of tissue repair and regeneration after mechanical loading. Singh et al. (31) and Yan et al. (36) studied muscle 4–6 days after exercise and found large increases in immunoreactivity for IGF-I peptide, suggesting that the posttranscriptional effect continues for at least a few days.

The biological activity of IGF-I is regulated by a family of six IGFBPs in serum and in extravascular tissues. In skeletal muscle, the myogenic effects of IGF-I are inhibited by IGFBP-4, which appears to exert a strong affinity for IGF-I, thereby reducing the level of free IGF-I (9, 34). In cultured myoblasts, both proliferation and differentiation are inhibited by overexpression of IGFBP-4 (9). We report a 56% drop in IGFBP-4 mRNA after ECC loading and a 31% (nonsignificant) decrease after CON. Additional components of the IGF-I system not measured in this study (including other IGFBPs and the type 1 IGF receptor) can certainly modulate the availability of IGF-I in muscle. Because, however, IGFBP-4 has been consistently shown to inhibit IGF-I action in muscle cells, we suggest that the decrease in IGFBP-4 mRNA concentration coupled with the increase in IGF-I mRNA found in this study would promote an increase in IGF-I availability within the muscle after mechanical loading. These changes occurred in the absence of any increase in serum IGF-I. This is not surprising. Several others have reported that muscle IGF-I activity is independent of changes in serum IGF-I (1). Further, this is not the first report of unchanging serum IGF-I after a single bout of heavy resistance exercise (25).

Although evidence linking local IGF-I availability to growth potentiation in muscle is mounting (1), the mechanism by which mechanical load modulates IGF-I expression is not clear. In his comprehensive review, Adams (1) proposes that this load-sensitive IGF-I in muscle works by paracrine or autocrine action to induce satellite cell proliferation and differentiation, followed by fusion of differentiated myoblasts to hypertrophy myofibers. The process of myoblast fusion is thought to maintain myonuclear domain size and thus the capacity for muscle protein synthesis. Indeed, myonuclear domain is maintained during mechanical load-induced myofiber hypertrophy (27). The model proposed by Adams (1) is well supported; however, the direct link between high-intensity mechanical load and muscle IGF-I modulation requires further investigation. Goldspink (16) has proposed a mechanotransduction mechanism involving cytoskeletal proteins during stretch. By this proposed mechanism, stretch tension on the basement membrane (e.g., laminin) physically activates intracellular signaling via a membrane-bound signaling molecule on the plasmalemma.

Based on the CK and soreness data after ECC loading, we suggest that myofibrillar disruption and/or sarcolemma damage may play a role in activating the muscle IGF-I system. We have previously shown an increase in serum levels of acidic fibroblast growth factor (aFGF) after resistance exercise with an ECC component (7). The FGF response paralleled an increase in serum CK activity. FGFs are powerful proliferative agents in myoblast cultures (12) and have been shown to induce myotube hypertrophy (8). Additionally, FGFs are known to be released directly from mechanically wounded muscle cells (8). Because we report increased IGF-I mRNA after 48 h and others have shown increased IGF-I peptide after 4–6 days (31, 36), it is possible that the IGF-I response is activated by an earlier local release of FGF or some other factor(s). Based on these data, we suggest that IGF-I activity is somehow linked to mechanisms involved in tissue regeneration after mechanical damage. One problem with this hypothesis, however, is the fact that ECC exercise-induced muscle damage does not necessarily result in hypertrophy. Marked muscle damage follows unaccustomed endurance exercise with a large ECC component (e.g., downhill running) (32); however, endurance exercise is not a potent hypertrophic stimulus (23). The ECC damage associated with high-tension contractions during resistance exercise is somehow uniquely different. This is an attractive area for further study.

Another possible mechanism for increasing muscle IGF-I availability is via androgen activation. Increased muscle protein synthesis after testosterone therapy in older men has been shown to be associated with increased IGF-I mRNA concentration and a concomitant reduction in IGFBP-4 mRNA concentration (34). Furthermore, inducing androgen deficiency in young men decreases muscle IGF-I mRNA concentration and causes muscle atrophy (26). These data suggest that IGF-I action in muscle is secondary to androgen activity. In the seven men in the present study, serum total testosterone was not increased but fell after both CON and ECC loading. The testosterone response to resistance exercise is highly variable (24). The fall in serum testosterone across time in the present study most likely reflects diurnal variation, as testosterone levels are highest in the morning and decrease into the evening hours. In support of this, testosterone values were not different from the initial morning levels 24 h after both exercise bouts. However, we found a substantial increase in AR mRNA concentration after both CON and ECC loading. To our knowledge, this is the first report of such an increase in humans after an acute exercise bout. AR content has been shown to increase in type II muscle after resistance training in rats (10). Also in rats, gastrocnemius hypertrophy by electrical stimulation has been associated with an increased number of muscle ARs (20). Our data indicate both AR and IGF-I mRNA concentrations are upregulated by heavy mechanical load. Although the mechanism is not clear, muscle androgen and IGF-I activities may be related.
We report for the first time changes in muscle mRNAs associated with tissue growth and repair after a single bout of resistance exercise in humans. The novel approach of studying high-intensity CON and ECC loading separately enabled us to test the influence of ECC action on the IGF-I and AR responses to mechanical load. The results indicate that high-intensity lengthening and shortening contractions both induce muscle IGF-I and AR gene transcription. Moreover, the enhanced IGF-I activation after ECC loading supports the concept that IGF-I is somehow involved in tissue regeneration after mechanical load-induced damage.

We thank the participants for their tolerance and tireless effort. We thank Leo Wright of Wright Exercise Equipment in Birmingham, Alabama, for providing the exercise equipment used in this study. This work was funded by a University of Alabama at Birmingham Provost’s Faculty Development Award (M. M. Bamman), National Institutes of Health R01-AG/AR-11000. Provost’s Faculty Development Award (M. M. Bamman), National Institutes of Health R01-AG/AR-11000.

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