ORIGINAL ARTICLE

Hypertrophy with unilateral resistance exercise occurs without increases in endogenous anabolic hormone concentration

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Abstract We aimed to gain insight into the role that the transitory increases in anabolic hormones play in muscle hypertrophy with unilateral resistance training. Ten healthy young male subjects (21.8 ± 0.4 years, 1.78 ± 0.04 m, 75.6 ± 2.9 kg; mean $\pm$ SE) engaged in unilateral resistance training for 8 week (3 days/week). Exercises were knee extension and leg press performed at 80–90% of the subject's single repetition maximum (1RM). Blood samples were collected in the acute period before and after the first training bout and following the last training bout and analyzed for total testosterone, free-testosterone, luteinizing hormone, sex hormone binding globulin, growth hormone, cortisol, and insulin-like growth factor-1. Thigh muscle cross sectional area (CSA) and muscle fibre CSA by biopsy (*vastus lateralis*) were measured pre- and post-training. Acutely, no changes in systemic hormone concentrations were observed in the 90 min period following exercise and there was no influence of training on these results. Training-induced increases were observed in type IIx and IIa muscle fibre CSA of 22 ± 3 and $13 \pm 2\%$ (both $P < 0.001$). No changes were observed in fibre CSA in the untrained leg (all $P > 0.5$). Whole muscle CSA increased by $5.4 \pm 0.9\%$ in the trained leg ($P < 0.001$) and remained unchanged in the untrained leg ($P = 0.76$). Isotonic 1RM increased in the trained leg for leg press and for knee extension ($P < 0.001$). No changes were seen in the untrained leg. In conclusion, unilateral training induced local muscle hypertrophy only in the exercised limb, which occurred in the absence of changes in systemic hormones that ostensibly play a role in muscle hypertrophy.

Keywords Testosterone · Growth hormone · Strength · Weightlifting

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Introduction

Muscle hypertrophy resulting from resistance training arises due to an accumulation of multiple post-exercise periods of positive protein balance (Phillips 2004; Phillips et al. 2005; Rennie et al. 2004; Rennie and Tipton 2000). Evidence showing that provision of exogenous anabolic hormones to humans, such as testosterone (in various forms) and growth hormone, is very strong insofar as testosterone's action as an anabolic agent is concerned (Bhasin et al. 1996; Sinha-Hikim et al. 2002, 2003b). What is also clear is that when supraphysiological doses of testosterone are administered that they synergistically interact with resistance exercise to promote lean mass and strength gains (Bhasin et al. 1996). Whether the same can be said of the rise in endogenous hormones is not clear. Versus testosterone, however, it is entirely equivocal as to whether growth hormone is a hypertrophy-promoting hormone (Lange et al. 2002; Rennie 2003). Various studies have also been conducted examining the endogenous concentration

changes in systemic hormones that are proposed to have an active role in skeletal muscle hypertrophy and potentially also in strength gains (Ahtiainen et al. 2003, 2005; Hakkinen et al. 1998, 2001; Kraemer et al. 1998, 2001; McCall et al. 1999; Nindl et al. 2001; Raastad et al. 2001, 2003). Ultimately, however, the causative role that acute and/or chronic changes in endogenous anabolic hormone concentrations, induced as a result of resistive exercise, play in hypertrophy is difficult to determine.

The unilateral model of resistance training in humans is one that has been used to show effects of various training protocols and examine strength gains as well as cross-education effects, (i.e, strength gains in a contralateral untrained limb) (Hakkinen et al. 1996; Hubal et al. 2005; Kim et al. 2005; McCurdy et al. 2005; Munn et al. 2005). The unilateral model is convenient in that it provides for an 'untrained' contralateral control limb for comparison that is a within-subject parameter insofar as statistical analysis in concerned. This within-person comparison provides a significant advantage from the standpoint of reducing variability, with the assumption that within-person variability is less than between person, and ultimately would allow more subtle differences in muscle and muscle fibre morphology as well as molecular events to be detected (Tarnopolsky et al. 2006). The unilateral model has been shown to result in hypertrophy (Hubal et al. 2005; Kim et al. 2005; Shepstone et al. 2005) of the trained arm with no significant change, or comparatively minor changes, in the contralateral limb. Using the unilateral design, detecting strength gains is a more complicated prospect due to the cross-education effect; see Munn et al. (2004) for a recent meta analysis of this phenomenon.

We chose that the unilateral model since one can induce local hypertrophy in the ipsilateral limb and examine strength changes due the combined action of neuromuscular and hypertrophic mechanisms. The contralateral limb serves as a 'control' not for strength gains, which are contaminated due to cross-education, but for any hypertrophy due to humoral mechanisms, (i.e., hormonal 'spillover' that might potentially affect gains in strength). Thus the purpose of this study was to use unilateral resistance training to examine hypertrophy in the trained limb along with changes in the contralateral untrained limb and measure changes in endogenous systemic hormones to determine whether these changes play a role in the hypertrophic response, in either the trained our untrained limb. Our working hypothesis was that unilateral training of the quadriceps femoris would not induce a significant change in endogenous hormone concentrations but that hypertrophy would occur in the trained limb nonetheless. We also hypothesized that the untrained limb would not exhibit hypertrophy and would show lesser strength gains compared to the trained limb.

Methods

Subjects

The study was approved by the Research Ethics Board of Hamilton Health Sciences and McMaster University and conformed to the regulations laid out in the declaration of Helsinki on the use of human subjects in research. All subjects gave their written consent to all procedures prior to participating. Subjects were ten young 21.8 ± 0.4 years (mean $\pm$ SE) males (1.78 ± 0.04 m, 75.6 ± 2.9 kg) who were deemed healthy based on their response to a general health questionnaire. Participants were all non-smokers and had no previous history of resistance training and participated in a minimal amount of physical activity (no more than 2 h/week).

Testing

At least 2 week prior to beginning the training protocol subjects reported to the Exercise Metabolism Research Laboratory for orientation to all procedures. At this time preliminary measures were made to estimate isotonic single repetition maximum (1RM) as well as isometric 1RM (Biodex-System 3, Biodex Medical Systems, Shirley, NY). Subjects were also familiarized with the guided motion training equipment for leg press and knee extension (Nautilus, Vancouver, WA).

To estimate isotonic 1RM for the knee extension subjects were seated with their hips at 90° and their back against a back rest that was at a 30° angle from horizontal (all tests were performed using a Nautilus guided motion machine; Tulsa, OK). The fulcrum of the machine was aligned with the lateral aspect of the midline of the subject's knee. The leg pad of the machine was positioned ∼5 cm above the subject's ankle and the rotation arm was positioned so that the subject's knee was bent to 90°. A full repetition was when the subject was able to move the weight through an arc of ∼80° (from 90° to ∼170°). The subjects 'settings' for pin placements for seating in the machine were recorded and kept constant throughout the study. Subjects warmed up using a light weight and performed 8–10 repetitions. Subjects then performed a single best effort at a weight estimated to be the subject's 1RM based on body weight and height by an

experienced trainer. If the subject could not lift the weight, the weight was lowered and if the subject could lift the weight then it was raised. Ultimately, a 1RM was determined in this way. This estimated 1RM was checked on two subsequent occasions by simply having the subject report to the lab and asking them to once more perform a 1RM at the previously determined weight. For a 'true' 1RM to be determined the coefficient of variation (CV) between two attempts had to be less than 5%. For no subject did it require more than three attempts to determine this 1RM.

Isometric 1RM was determined in two sessions using the Biodex dynamometer. Subjects were seated in the dynamometer with their hips at 90° and their shoulders strapped with harness straps that prevented any upper-body movement. The fulcrum of the rotation arm was positioned to align with the midline of the subject's knee. The subject's knee was bent to an angle of 120° and the pad of the rotation arm was positioned 5 cm above the subject's ankle. Isometric 1RM was determined by having the subject maintain a maximal effort for knee extension and hold that effort 5 s after which subjects were allowed to rest for 2 min before attempting a second and third 1RM. The single highest peak value of any one of the three efforts was taken as the isometric 1RM. Subjects reported back to the laboratory for repeat testing using the same procedures 3–4 days after the first 1RM estimate and if the CV for 1RM determined in these two sessions was greater than 5% the procedure was repeated a third time, which was necessary for only one subject.

Leg press 1RM (Nautilus, Tulsa, OK) was determined in a seated position with the subject positioned so that their back rested against the back rest at 30° from horizontal and the angle between their torso and their legs (at their hips) was ∼70°. Subjects had their knee bent at an angle of 90° and their foot placed on a foot plate so that a full 1RM resulted in full leg extension to 180°. The same procedure to determine 1RM as for the knee extension was followed for the leg press. A 'true' 1RM was determined for each subject within three visits to the lab, or less.

Training

Subjects had their legs randomly assigned to be trained in a counterbalanced manner so that five of ten subjects trained their dominant leg and the five their non-dominant leg, based on dominance from 1RM strength. Training was conducted 3 days/week (Monday, Wednesday, and Friday) for a total of 8 week. Each subject completed all training sessions. The intensity of the training was set at 80–90% of 1RM, which meant

that subjects usually reached voluntary fatigue within 6–10 repetitions per set. Subject's recovered for 3 min between sets. In the first 4 weeks of the training subjects complete 3 sets per training session and in weeks 5–8 they completed 3 sets of 8–10 repetitions and one set to voluntary fatigue (usually 5–10 repetitions). Training was progressive in nature with subjects' voluntary isotonic 1RM being retested every 2 weeks in the trained leg. Intensity was adjusted to ensure that subjects were always lifting loads between 80 and 90% of 1RM. The untrained leg was tested in the same manner for 1RM throughout the protocol.

Biopsies

Percutaneous muscle biopsies were obtained under local anesthesia (2% xylocaine) using a 5 mm Bergstrom biopsy needle custom modified for manual suction as detailed previously (Kim et al. 2005; Shepstone et al. 2005; Stewart et al. 2004; Yasuda et al. 2005). Muscle was mounted in optimal cutting temperature (OCT) medium (Sakura Finetechnical, Osaka, Japan) with fibres oriented in the plane perpendicular to which it was to be cut. Detailed methods and procedures yielding the descriptive variables for fibre size, type, percentage area, and myosin heavy chain composition have been described in detail previously elsewhere (Kim et al. 2005; Shepstone et al. 2005; Stewart et al. 2004; Yasuda et al. 2005).

Muscle computerized tomographic scans

Subjects had both their trained and untrained legs scanned both pre- and post-training. Pre-training the scans were performed at least 2 days after any exercise or testing procedures and the scans were performed on both legs simultaneously. A General Electric CTI Scanner (GE, Milwaukee, WI) was used to perform computerized tomographic (CT) scans at baseline and after cessation of training. A scout scan was taken of the lower limbs to determine the femur and tibia lengths, and 5 mm slices were taken at two sites: 60% of femur length, starting from the distal end and measuring proximally. The system parameters used were as follows: slice thickness 5 mm, pixel matrix 512 × 512, and exposure factors of 120 kV, 200 mA and standard reconstruction algorithm. CT scans were analyzed using a validated software program (BonAlyse 1.3, BonAlyse Oy, Jyvaskyla, Finland), according to the manufacturer's instructions. Thresholds −270 to −101 Hounsfield Units (HU) were used to identify fat, and thresholds −101 to 270 HU were used to identify muscle. BonAlyse was used to calculate muscle cross

sectional area (CSA) (mm^2). We have determined that muscle CSA obtained from CT scans using our scanner can be measured with a CV of less than 1% in repeat scans with the same person across several weeks.

Hormone measurements

Prior to the first training workout and the last training bout subjects had a venous catheter inserted into a dorsal hand vein. The hand was kept warm using a heating blanket to maintain an 'arterialized' sample of blood on which to measure hormone concentrations. Subjects had blood samples drawn immediately prior to performing the training bout (pre), immediately after the exercise bout (post), and then again at 30, 60, 90, and 120 min post-exercise. Blood was collected in heparinized tubes as well as additive-free tubes. All tubes were kept on ice briefly (never more than 5 min for plasma and 10 min for serum) before being spun in a refrigerated centrifuge (4°C, 4,500 rpm) for 10 min to isolate plasma (heparinized tubes) or serum (additive-free tubes). Plasma and serum was stored at −80°C prior to analysis.

Plasma total testosterone (T), free testosterone (T_f), luteinizing hormone (LH), sex-hormone binding globulin (SHBG), growth hormone (GH), and cortisol (C) were analyzed using commercially available radioimmunoassay kits (Diagnostics Products Corporation, Los Angeles, CA) and manufacturers instructions were closely followed. To minimize any intra-assay CV all pre- and post-training samples from each subject were analyzed in duplicate on the same day. A between sample CV (on pairs) of less than 5% was taken as good agreement and the values were averaged to yield a single concentration. On pooled plasma within-sample CVs ranged from as low as 0.3% to no higher than 4.8% on 6–8 replicates.

IGF-1 concentrations were measured in duplicate by immunoassay (Quantikine IGF-1 Immunoassay, R&D Systems, Minneapolis, MN); recombinant human IGF-1 was used to generate the standard curve. The mean intra-assay CV, determined by assaying the IGF-1 concentration in a number of samples analyzed as replicates was less than 3.0%. The mean minimal detectable concentration of IGF-1 in this assay is 0.026 ng/ml.

Blood metabolite

Whole blood lactate was determined by adding heparinized plasma to 0.6M perchloric acid to deproteinize the sample. The sample was then spun (15 min, 4,500 rpm, 4°C) to pellet the proteins and to the supernatant, which was kept on ice, was added 1.25M KHCO$_3$ to neutralize the sample. Again the resulting salt was spun (15 min, 4,500 rpm, 4°C) down and the resulting supernatant was collected and stored at −80°C until analysis. Analysis of whole blood lactate concentration was performed as described previously (Phillips et al. 1995).

Statistics

Data were analyzed using a two-way repeated measures analysis of variance with time on multiple levels as well as training status (trained vs untrained) of the leg as factors. Significant F ratios were further examined using Tukey's posthoc test to isolate the differences. Significance was set at $P < 0.05$. Data are presented and means ± SE.

Results

Strength

Isotonic 1RM increased as a result of training for the leg press and for knee extension (Table 1; both $P < 0.001$). In addition, a moderate cross-education effect was also observed for knee extension 1RM such that the contralateral untrained limb showed a 15 ± 3% increase ($P < 0.05$; Table 1).

Table 1 Maximal isotonic strength for both the leg press and knee extension exercises in both the control and trained leg

	Pre	3	5	7	Post
Leg press 1RM (kg)					
Control	143 ± 21[a]	142 ± 26[a]	145 ± 26[a]	143 ± 27[a]	147 ± 25[a]
Trained	141 ± 26[a]	149 ± 26[b]*	159 ± 30[c]*	161 ± 27[c†]	166 ± 25[d†]
Knee extension 1RM (kg)					
Control	47 ± 8[a]	50 ± 9[a]	51 ± 9[a]	52 ± 9[b]	54 ± 8[b]
Trained	47 ± 7[a]	52 ± 7[ab]	59 ± 8[b]*	63 ± 11[c†]	68 ± 12[d†]

Values are means ± SE (N = 10). *1RM* single repetition maximum, *kg* kilogram. Means with different letters are significantly different
*Significantly different from control at the same time point ($P < 0.01$), [†] $P < 0.001$. Means with different letters are significantly different from each other ($P < 0.05$)

Isometric 1RM increased by $12 \pm 2\%$ in the trained leg (PRE = 256 ± 46 N m, POST = 286 ± 29 N m; $P < 0.01$) but remained unchanged (PRE = 242 ± 38 N m, POST = 248 ± 28 N m; $P = 0.58$) in the untrained leg.

Muscle and muscle fibre cross-sectional area

Muscle CSA from CT showed an increase of $5.4 \pm 0.9\%$ in the CSA of the trained leg (PRE = 157.5 ± 5.5 cm^2, POST = 165.9 ± 5.4 cm^2; $P < 0.001$; Fig. 1), but no change in the CSA of the untrained leg $0.0 \pm 0.5\%$ (PRE = 157.8 ± 6.5 cm^2, POST = 157.7 ± 6.4 cm^2; $P = 0.76$; Fig. 1).

Type I muscle fibre CSA remained unchanged from PRE = $4,184 \pm 426$ μm^2 to POST = $4,567 \pm 503$ μm^2 ($P = 0.06$) in the trained leg, and was also unchanged (PRE = $4,291 \pm 400$ μm^2, POST = $4,205 \pm 399$ μm^2; Fig. 2a) in the untrained leg. Type IIa fibre CSA increased by $13 \pm 2\%$ (PRE = $6,153 \pm 530$ μm^2, POST = $6,952 \pm 463$; $P < 0.001$, Fig. 2b) in the trained leg and remained unchanged in the untrained leg (PRE = $6,269 \pm 500$, POST = $6,144 \pm 466$). Type IIx fibre CSA increased by $22 \pm 3\%$ (PRE = $4,740 \pm 411$, POST = $5,769 \pm 444$; $P < 0.001$, Fig. 2c) in the trained leg and remained unchanged in the untrained leg (PRE = $4,988 \pm 511$, POST = $5,014 \pm 526$).

Muscle fibre percentage and percent area were calculated as previously described (Kim et al. 2005; Shepstone et al. 2005; Stewart et al. 2004; Yasuda et al. 2005) and are presented in Table 2. The percentage and percentage area of type IIa fibres was greater in the trained leg post- versus pre-training (Table 2; $P < 0.05$). The shift in type IIa fibre percentage was due
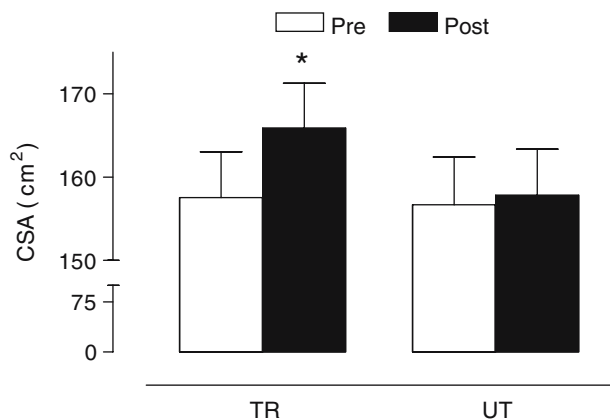
to a significant decline in the percentage of fibres that are type IIx, which was accompanied by a corresponding decline in the percentage of fibres that were type IIx (Table 2; $P < 0.05$).

Acutely, neither the first bout of training nor the final bout of training had any affect on serum T, T_f, LH, or SHBG (Fig. 3). Cortisol and the cortisol to T_f ratio were also unaffected by exercise or by training (Fig. 3). IGF-1 concentration was unaffected by exercise (Fig. 4). GH concentration showed a moderate but
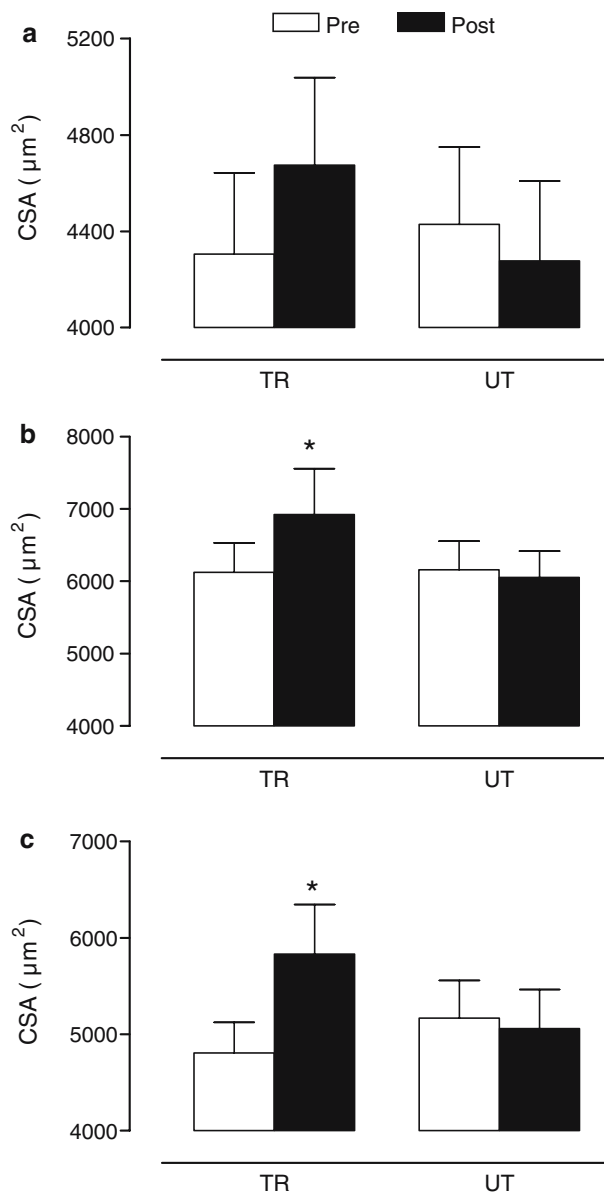
Fig. 2 Muscle (vastus lateralis) fibre cross-sectional area in both legs pre- and post-training for type I fibres (**a**), type IIa fibres (**b**), and type IIx fibres (**c**). TR trained leg, UT untrained leg. *Significantly different from Pre ($P < 0.001$). Note that the scales on each graph are different to show differences within each fibre type. Values are means $\pm$ SE ($N = 10$)

Fig. 1 Mid-thigh muscle cross-sectional area (CSA) by computerized tomography in both legs pre- and post-training; Pre and Post, respectively. TR trained leg, UT untrained leg. *Significantly different from Pre ($P < 0.001$). Values are means $\pm$ SE ($N = 10$)

Table 2 Muscle fibre type percentage and percentage area from vastus lateralis biopsies from both legs pre- and post-training

	Pre		Post	
	UT	T	UT	T
Fibre (%)				
I	34 ± 4	39 ± 4	36 ± 5	39 ± 3
IIa	39 ± 3	35 ± 4	39 ± 4	41 ± 2*
IIx	26 ± 2	26 ± 2	25 ± 3	20 ± 2*
Area (%)				
I	30 ± 4	34 ± 5	31 ± 3	33 ± 2
IIa	45 ± 2	42 ± 6	46 ± 4	48 ± 3*
IIx	25 ± 4	24 ± 2	23 ± 3	19 ± 5*

Values are means ± SE ($N = 10$)

*Significantly different from pre, within the same leg ($P < 0.05$)

statistically non-signifcant rise at 30 min post-exercise and a significant decline in concentration at 60 and 90 min post-exercise both pre- and post-training. Whole-blood lactate concentration was moderately elevated post-exercise in both the pre-trained and post-trained conditions, but only at 30 min post-exercise (Fig. 4).

Discussion

Skeletal muscle hypertrophy as a result of resistance training in humans is due to an expansion of protein content of a pre-existing muscle fibre. This expansion occurs because of the synergistic interaction of feeding and resistance exercise (Phillips 2004; Phillips et al. 2005; Rennie et al. 2004; Rennie and Tipton 2000). The greater protein content is observed as a fibre with an increased cross-sectional area, but ultimately one with a constant nuclear to cytoplasmic ratio implying that new nuclei have been added to the fibre. The metabolic and molecular sequence of events that lead to hypertrophy are complex; however, one theory that has been put forward is that the endogenous rise in concentrations of anabolic hormones such as T, GH, and/or IGF-1
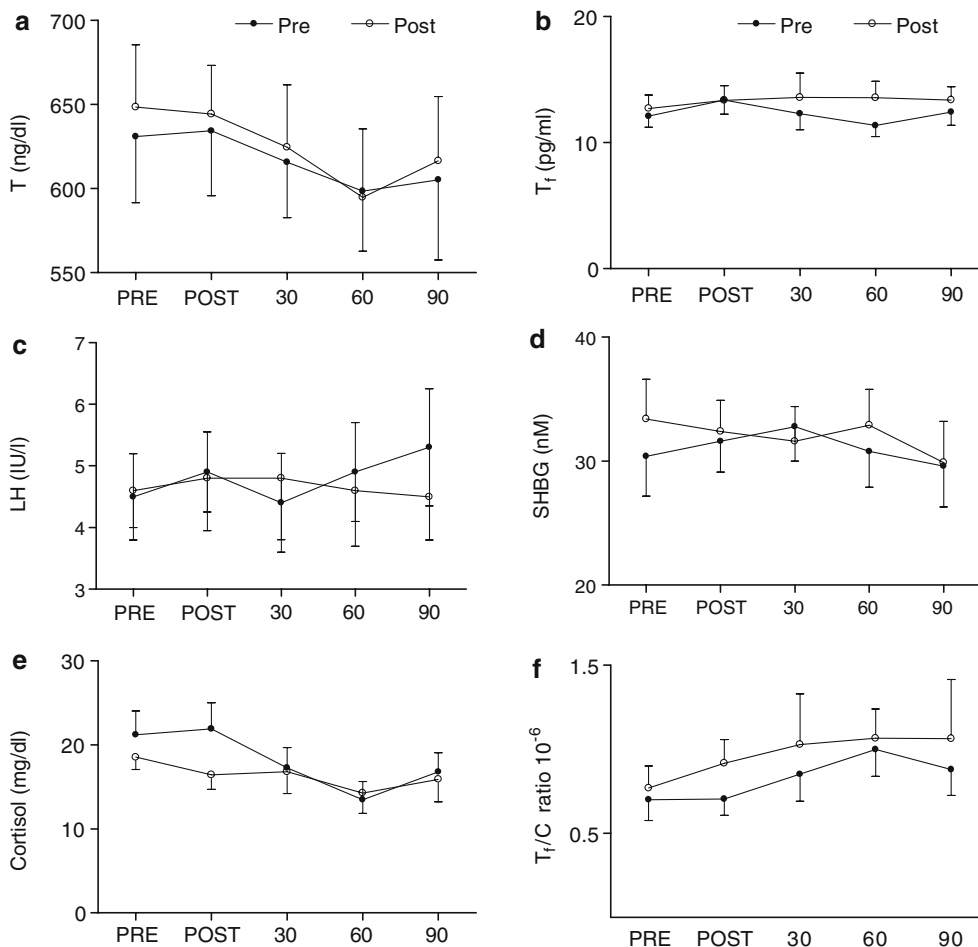

Fig. 3 Acute concentration changes in **a** Testosterone (T), **b** Free testosterone (T_f), **c** Luteinizing hormone (LH), **d** sex-hormone binding globulin (SHBG), **e** cortisol (C), and **f** the free testoster-one to cortisol ratio (T_f/C), following a single isolated bout of resistance exercise both pre- and post-training. Values are means ± SE ($N = 10$)
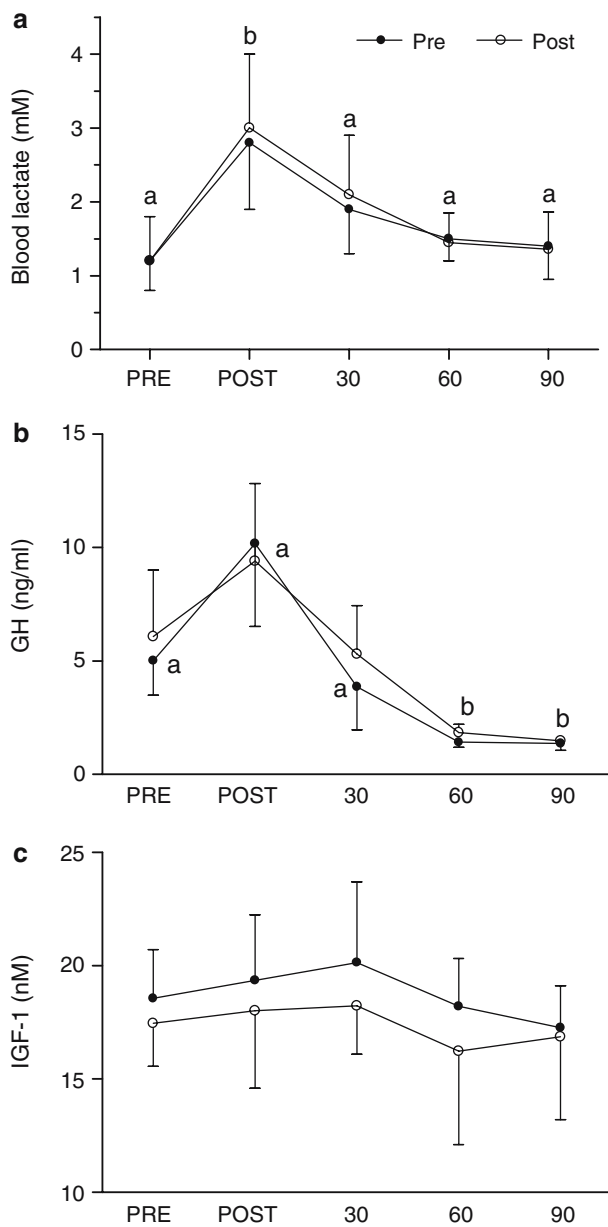
Fig. 4 Acute concentration changes in plasma lactate (**a**), growth hormone (**b**), and insulin-like growth factor following a single iso-lated bout of resistance exercise both pre- and post-training. Means with different letters are significantly different from each other ($P < 0.05$). Values are means ± SE ($N = 10$)

may be playing a role in the hypertrophic process (Ahtiainen et al. 2003, 2005; Hakkinen et al. 1998; Hansen et al. 2001; Kraemer et al. 1998, 2001; McCall et al. 1999; Nindl et al. 2001; Raastad et al. 2001, 2003). Ultimately, much of the evidence to support this the-sis comes from longitudinal studies in which changes in concentrations of hormones such as testosterone are retrospectively correlated with hypertrophy (Ahtiainen et al. 2003; Hakkinen et al. 2001; McCall et al. 1999). Hansen et al. (2001) used arm only versus

arm preceded by leg exercise to test whether endoge-nous hormonal increases, which were observed to be greater in arm plus leg exercise group, affected strength gains in each, respective, arm. Strength gains in the arm only training group were lower than the arm plus leg group, however, the change was not statistically sig-nificant. Due to differences in the mean initial strength of the groups (higher in the arm only), however, it is difficult to interpret these findings (Hansen et al. 2001). In addition, no measures of muscle cross-sectional area, lean mass, or fibre size were made by Hansen et al. (2001) so it is difficult to ascribe the higher endogenous hormonal changes seen in the arm plus leg group as truly causative in the strength gains let alone whether greater hypertrophy occurred. Currently, to the authors' best knowledge, an investigation that highlights a causative role that exercise-induced rises in endogenous anabolic hormones play in hypertrophy does not exist.

There is little question that exogenous administra-tion of testosterone to supraphysiological levels results in hypertrophy when given to non-exercising persons, and also augments exercise-induced hypertrophy when combined with resistance exercise (Bhasin et al. 1996; Sinha-Hikim et al. 2002, 2003b). Good evidence exists to show that testosterone administration enhances mus-cle protein synthesis (Ferrando et al. 1998) and increases satellite cell number (Sinha-Hikim et al. 2003a); hence it is with good basis that exogenous tes-tosterone would enhance resistance exercise-induced muscle hypertrophy and strength gains (Bhasin et al. 1996). By comparison, changes in endogenous testoster-one that occur with resistance exercise (Ahtiainen et al. 2003, 2005; Hakkinen et al. 1998; Hansen et al. 2001; Kraemer et al. 1998, 2001; McCall et al. 1999; Nindl et al. 2001; Raastad et al. 2001, 2003) are orders of magnitude less than those seen with exogenous testos-terone administration (Bhasin et al. 1996; Sinha-Hikim et al. 2002, 2003a) and are often within the normal daily diurnal variability in testosterone [for review see Byrne and Nieschlag 2003]. In addition, the changes in testos-terone concentration that are seen with resistance exer-cise are transient, normally not lasting any longer than 60–90 min after exercise (Ahtiainen et al. 2003, 2005; Hakkinen et al. 1998; Hansen et al. 2001; Kraemer et al. 1998, 2001; McCall et al. 1999; Nindl et al. 2001; Raas-tad et al. 2001, 2003). Furthermore, theses changes in testosterone have been shown to track changes blood hematocrit implying that it is not, in fact, an increase in endogenous testosterone production that occurs with resistance training, but simply a hemoconcentration. In the current study we observed no change in either total or free testosterone or in the free testosterone to corti-sol ratio either acutely or with training.

Changes in growth hormone concentration following resistance exercise have been shown to be due to varying isoforms of the hormone (Nindl et al. 2000) and a very consistent response to heavy resistance and high intensity anaerobic exercise [for review see Kraemer and Ratamess (2005)]. A number of clinical trials with human growth hormone administration have been performed in young and old men and women and evidence for a true anabolic effect is difficult to discern (Lange et al. 2002; Rennie 2003). We observed no elevation in growth hormone, but instead observed a significant reduction in concentration, admittedly only the 22 kDa isoform was measured by the immunoassay we utilized (see Methods for details). This finding is most likely due to the relatively small muscle mass utilized for the resistance exercise with an accompanying small rise in blood lactate (Fig. 4); activation of large muscle masses with accompanying lactate responses, via either high intensity aerobic or resistive exercise, result in substantial increases in plasma GH (Kraemer and Ratamess 2005).

Along with no change in GH concentration we, not surprisingly, saw no change in plasma IGF-I concentration. Insofar as supplemental IGF-I treatment is concerned, the longest trial to date saw no significant effect of IGF-I treatment in elderly women on lean or bone mass after 1 year (Friedlander et al. 2001). While there is no question that IGF-I does play a role in the hypertrophic response of skeletal muscle that is synergistic with resistance exercise (Lee et al. 2004), the effects of this hormone are more likely autocrine or paracrine in nature (Adams 2002; Lee et al. 2004) and the changes in circulating IGF-I may not accurately reflect the local-acting hormonal concentration.

Our results show that a single leg, (i.e., unilateral) model of resistance training results in hypertrophy in the absence of changes in systemic hormones that are proposed to play a role in the hypertrophic process (Ahtiainen et al. 2003, 2005; Hakkinen et al. 1998; Hansen et al. 2001; Kraemer et al. 1998, 2001; McCall et al. 1999; Nindl et al. 2001; Raastad et al. 2001, 2003). As such, the unilateral training model we describe here appears to be a good model for induction of local fibre hypertrophy that does not induce any measurable change in muscle or fibre phenotype in the contralateral limb, at least not as far as we could detect. Recently, Hubal et al. (2005) reported that unilateral limb training of the arm did result in hypertrophy of the contralateral untrained arm of $1.4 \pm 0.3\%$, this increase in size, while statistically significant, represented a hypertrophy of only ~7% of that seen in the trained arm. Clearly, such a small gain in size could only be detected when a large sample size was examined as it was by Hubal et al. [(2005); $N = 585$ total]. Such small changes in hypertrophy of the contralateral limb would, however, suggest that it could still serve as a valid internal control for most measures.

The degree of hypertrophy we observed ($5.4 \pm 0.9\%$ increase in mid thigh CSA; Fig. 1) with only 8 weeks of resistance training (24 total sessions) is comparable to that seen with other unilateral training studies of 4–7% varying in duration from 8 to 10 weeks (Higbie et al. 1996; Housh et al. 1992; Kim et al. 2005), but is markedly less than that seen with a longer duration unilateral training (24 weeks) study in which an increase in thigh muscle CSA of 13% was observed (Narici et al. 1996). As such, our results represent relatively early events in the hypertrophic process. Nonetheless, we also observed a hallmark fibre type change in the trained limb; that is a reduction in type IIx fibre type at the expense of an increase in type IIa fibre type (Staron et al. 1989, 1994; Williamson et al. 2001). Hence, from a model perspective we propose that this unilateral resistance training regime induces 'typical' hypertrophic changes in the trained limb.

We observed the expected results in terms of strength gains with the unilateral resistance training model (Munn et al. 2004). Namely, we observed comparatively minor changes in strength in the contralateral limb compared to the trained limb (Table 1). The 15% relative change in isotonic knee extension strength of the contralateral limb is in the upper end of the range of that reported by Munn et al. (2004) in their meta-analysis. We propose that this increased contralateral leg strength may be larger due to the relative frequency of 1RM testing we employed in the contralateral untrained leg, which may itself have enhanced neuromuscular strength changes. When leg press isotonic 1RM was examined, however, we observed no change in strength in the contralateral limb (Table 1). However, strength was a secondary outcome in this study and is used here only as a variable that illustrates the greater hypertrophy seen in the trained limb. Moreover, as an argument that gains in strength seen in the untrained limb were neurologically mediated we observed no change in maximal isometric torque, a non-specific mode of strength testing in comparison to the mode of training, in this limb compared to trained limb.

Our interpretation of the current data is that a minimal testosterone concentration is required for basal functioning of the regulatory processes underlying hypertrophy, (i.e., protein synthesis, gene expression changes, and satellite cell activation), as demonstrated by the reduced lean mass seen in hypogondal men (Ferrando et al. 2002). However, hypertrophy can occur in the absence of changes in endogenous

testosterone as our results demonstrate. Our results do not rule out the possibility that exercise-induced increases in endogenous testosterone concentration, known to occur with large muscle mass and/or whole-body resistance exercise, may augment hypertrophy, as is clearly seen with large supraphysiological doses of exogenous testosterone (Bhasin et al. 1996). In summary, the evidence we present here suggests that as little as 8 weeks of unilateral limb training involving knee extension and leg press induces local hypertrophy, greater strength changes, and hallmark fibre type shifts only in the trained limb whereas, the contralateral untrained limb appears to be a valid control for the trained limb, at least from a phenotypic perspective. All of these changes occurred in the absence of changes in systemic anabolic hormones meaning that the unilateral model is one of hypertrophy that is not augmented by systemic hormones.

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