Androgenic Responses to Resistance Exercise: Effects of Feeding and L-Carnitine

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[1]*Human Performance Laboratory, Department of Kinesiology, University of Connecticut, Storrs, CT;* [2]*Department of Health and Exercise Science, The College of New Jersey, Ewing, NJ; and* [3]*Department of Kinesiology, The College of William and Mary, Williamsburg, VA*

ABSTRACT

KRAEMER, W. J., B. A. SPIERING, J. S. VOLEK, N. A. RATAMESS, M. J. SHARMAN, M. R. RUBIN, D. N. FRENCH, R. SILVESTRE, D. L. HATFIELD, J. L. VAN HEEST, J. L. VINGREN, D. A. JUDELSON, M. R. DESCHENES and C. M. MARESH. Androgenic Responses to Resistance Exercise: Effects of Feeding and L-Carnitine. *Med. Sci. Sports Exerc.*, Vol. 38, No. 7, pp. 1288–1296, 2006. **Purpose:** The purpose of this investigation was to determine the effects of 3 wk of L-carnitine L-tartrate (LCLT) supplementation and post–resistance-exercise (RE) feeding on hormonal and androgen receptor (AR) responses. **Methods:** Ten resistance-trained men (mean ± SD: age, 22 ± 1 yr; mass, 86.3 ± 15.3 kg; height, 181 ± 11 cm) supplemented with LCLT (equivalent to 2 g of L-carnitine per day) or placebo (PL) for 21 d, provided muscle biopsies for AR determinations, then performed two RE protocols: one followed by water intake, and one followed by feeding (8 kcal·kg^{-1} body mass, consisting of 56% carbohydrate, 16% protein, and 28% fat). RE protocols were randomized and included serial blood draws and a 1-h post-RE biopsy. After a 7-d washout period, subjects crossed over, and all experimental procedures were repeated. **Results:** LCLT supplementation upregulated ($P < 0.05$) preexercise AR content compared with PL (12.9 ± 5.9 vs 11.2 ± 4.0 au, respectively). RE increased ($P < 0.05$) AR content compared with pre-RE values in the PL trial only. Post-RE feeding significantly increased AR content compared with baseline and water trials for both LCLT and PL. Serum total testosterone concentrations were suppressed ($P < 0.05$) during feeding trials with respect to corresponding water and pre-RE values. Luteinizing hormone demonstrated subtle, yet significant changes in response to feeding and LCLT. **Conclusion:** In summary, these data demonstrated that: 1) feeding after RE increased AR content, which may result in increased testosterone uptake, and thus enhanced luteinizing hormone secretion via feedback mechanisms; and 2) LCLT supplementation upregulated AR content, which may promote recovery from RE. **Key Words:** ANDROGEN RECEPTOR, ENDOCRINE, SUPPLEMENTS, TESTOSTERONE, TROPHIC HORMONES

The acute testosterone (T) response to resistance exercise (RE) is characterized by a brief increase followed by a decline to resting (or even below resting) concentrations (5,6,15–17). Interestingly, post-RE food intake depresses T concentrations compared with placebo and pre-RE values (5,6,17). T values also consistently drop after acute feeding alone (without RE), and there is evidence that this is dependent on the composition of the meal, particularly the fat content (11,28). The mechanism for decreased T following feeding has not been elucidated; however, this decline in T (with or without RE) may be caused by decreased synthesis/secretion of T or by increased cellular uptake of T. Because post-RE feeding (35 g of sucrose, 6 g of essential amino acids) increases synthesis of muscle-specific proteins (22,27), it is possible that decreased circulating T concentrations following feeding reflect increased cellular uptake; however, no direct evidence is available to support this hypothesis.

The influence of T on skeletal muscle protein synthesis is mediated by the androgen receptor (AR). T binding converts the AR to a transcription factor; the complex then translocates to the nucleus and associates with DNA to regulate androgen-specific gene expression. The physiological importance of AR for muscle protein accretion has been demonstrated, as muscle hypertrophy is attenuated by AR blockade (13). Relatively few studies, however, have investigated AR responses following acute bouts of intense exercise. In rats, AR content increased 2 h after physical exercise (26). Alternately, Lee et al. (21) showed that plantaris AR content decreased after 1 d of surgically induced overload. Human studies have found that AR mRNA (2,32), but not AR protein (32), increased 48 h after acute RE in untrained subjects; however, no immediately post-RE data were obtained in these studies in humans. The

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only immediately (1 h) post-RE AR data in humans were recently published by our laboratory and showed that AR responses did not change following a single-set protocol, and decreased after a multiple-set protocol (23). It may well be that a series of states exist from stabilization, catabolism, and then anabolism of the protein, depending on the effectiveness of the exercise stimuli (23).

An attractive intervention with which to investigate androgenic responses following RE may be carnitine supplementation, which has been shown to influence the hypothalamic–pituitary–gonadal axis in animal models. In rats, carnitine supplementation increased growth and secretory activity of gonadotropin-releasing hormone (GnRH) cells *in vitro* (20) and stimulated hypothalamic–pituitary function *in vivo* (19), although hormonal concentrations and oscillations remained within natural physiological limits. Applying this information to exercise, Bidzinska et al. (4) exposed rats supplementing with carnitine or placebo to 10 d of chronic exercise stress. Rats receiving placebo demonstrated marked decreases in T concentrations and increases in GnRH; however, these responses were prevented in rats receiving carnitine supplementation (4). Preliminary work in humans failed to show an effect of L-carnitine on post-RE T concentrations (18); nonetheless, significantly reduced post-RE muscle damage led those authors to speculate that L-carnitine supplementation may have resulted in more intact hormonal receptors available for binding interactions. Thus, the study of carnitine's influence on the hypothalamic–pituitary–gonadal axis remains an attractive area of research.

Therefore, the purposes of this study were 1) to investigate acute responses of hormones, receptors, and binding proteins involved in the pituitary–gonadal axis to RE; and 2) to determine the influence of post-RE feeding and/or carnitine supplementation on these responses. We hypothesized that 1) AR content would decrease following RE (based on the results of our previous study (23)); 2) nutritional intake following RE would upregulate AR content, which, concomitant with a decrease in circulating T concentrations, would suggest increased cellular uptake of T following post-RE feeding; and 3) carnitine supplementation would enhance the anabolic hormonal response following RE.

METHODS

Experimental procedures. A balanced, randomized, double-blind, placebo-controlled crossover design was used to determine the effects of 3 wk of L-carnitine L-tartrate (LCLT) supplementation and post-RE feeding on hormones, receptors, and binding proteins involved in the pituitary–gonadal axis. Subjects were matched according to age, body size, and training experience and placed in either a LCLT treatment or placebo (PL) control group (Fig. 1). The experimental protocol required that each subject complete a total of four RE trials: two trials during the LCLT condition and two trials during the PL condition. Briefly, baseline muscle biopsies were obtained after subjects adhered to a 21-d supplementation period and a 12-h overnight fast. Subjects reported to the laboratory 48–72 h later, having fasting overnight for 12 h, for the first of two RE challenges and associated blood draws. Upon completion of the first RE challenge, a postexercise drink (either a caloric beverage or water) and corresponding supplemental dose were provided. One hour after subjects ingested the drink and the supplement, a post-RE biopsy was obtained. Subjects continued supplementing for an additional 48 h, then performed the second exercise challenge (followed by ingestion of caloric beverage or water, a supplemental dose, and another post-RE muscle biopsy). After a 7-d washout period, subjects crossed over (into either the LCLT or PL group), and experimental procedures were repeated.

Subjects. Ten healthy, recreationally resistance-trained men (mean ± SD: age, 22 ± 1 yr; mass, 86.3 ± 15.3 kg; height, 181 ± 11 cm) volunteered to participate. Participation

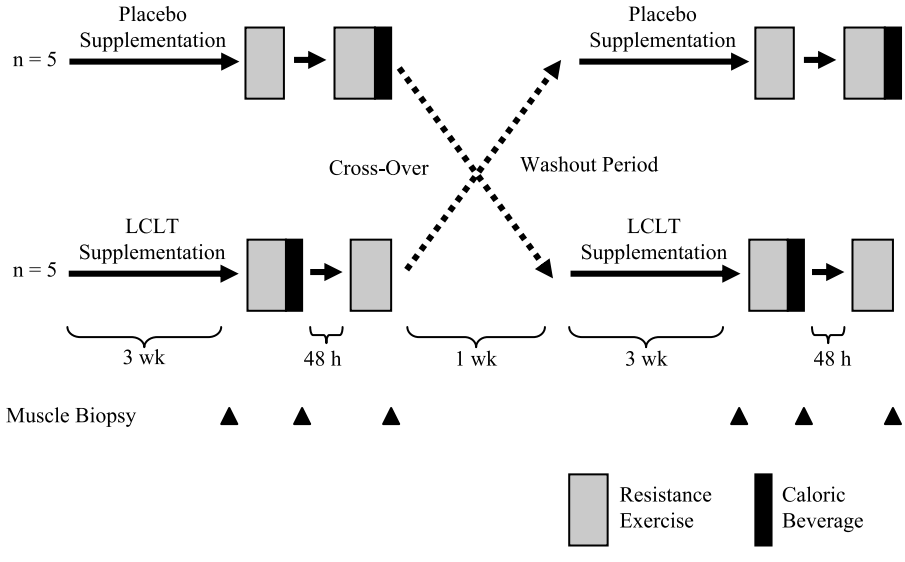

FIGURE 1—Experimental design.

required at least 1 yr of resistance training experience that included the squat exercise. Subjects were asked to maintain their normal physical training throughout the duration of the study to ensure completion of the exercise challenge without induction of severe muscle damage. Subjects completed a health screening questionnaire to exclude medical and endocrine disorders. Screening also ensured that no subjects were smokers or taking any medications or anabolic drugs. Participants supplementing with creatine 12 wk prior to participation were excluded. To ensure weight maintenance during the course of the study, subjects received nutritional counseling from a dietician, completed 3-d diet records, and were weighed pre- and poststudy. All subjects gave written informed consent as approved by the University of Connecticut's institutional review board for use of human subjects.

Supplementation protocol. Subjects were supplied with ingestible capsules of either L-CARNIPURE® LCLT (Lonza Inc., Allendale, NJ) containing 736 mg of LCLT (500 mg of L-carnitine and 236 mg of L-tartrate) or identical-looking PL (powdered cellulose). L-tartrate was added to help stabilize L-carnitine. LCLT readily dissociates into L-carnitine and L-tartaric acid in the gastrointestinal tract. There are no known biological effects of tartaric acid. Participants were instructed to consume two capsules with breakfast and two capsules with lunch for a total dose of 2 $g \cdot d^{-1}$ of L-carnitine. This dose of L-carnitine has been used in previous studies in our laboratory (18,24,29) and has been shown to maximize plasma carnitine concentrations without exceeding the renal threshold for carnitine (24). Supplementation began 21 d prior to baseline muscle biopsies and continued throughout completion of the two RE protocols. After a 7-d washout period, subjects crossed over (into either the LCLT or PL group), and experimental procedures were repeated.

RE protocol. The RE protocol was performed on a plyometric power system (PPS, Lismore, Australia) previously described in detail (33). Briefly, linear bearings attached to either side of the bar allow the bar to slide vertically along steel shafts with minimal friction. One week before beginning supplementation, each participant's one-repetition maximum (1RM) for the back squat, bench press, bent-over row, and shoulder press was determined using standard procedures (10). The RE protocol was a whole-body, heavy RE protocol designed to recruit all major muscle groups, and proceeded as follows: after a standardized warm-up (5-min submaximal cycling), participants performed four sets of 10 repetitions each for the squat, bench press, bent-over row, and shoulder press, comprising a total of 16 sets. Two minutes of rest were allowed between each set. Eighty percent of individual 1RM was selected as the starting load for each exercise. If a participant was unable to complete 10 repetitions on a particular set during the RE protocol, the load was decreased on subsequent sets to allow completion of all 10 repetitions. All RE protocols were performed in the morning (0800–1000 h), and the time of day was standardized for each participant throughout the entire investigation.

Postexercise supplementation. Immediately following the completion of the exercise challenge, participants were provided with a caloric drink during the "feeding" protocol or an equal volume of water. Additionally, a corresponding dose of either LCLT or PL was given. The caloric drink (Ensure Plus, Ross Products Division, Abbott Laboratories, Columbus, OH) contained 8 $kcal \cdot kg^{-1}$ body mass with a distribution of carbohydrate (1.1 $g \cdot kg^{-1}$), protein (total protein with all of the amino acids, 0.3 $g \cdot kg^{-1}$), and fat (0.25 $g \cdot kg^{-1}$). We previously showed that ingestion of a beverage of similar nutrient composition after RE depressed circulating T concentration more than water (17).

Blood collections. Participants reported to the laboratory on the morning of the exercise protocols following a 12-h overnight fast and abstinence from caffeine and alcohol for at least 48 h. An intravenous catheter (Travenol, 22 g, 32 mm) was then inserted into an antecubital forearm vein, secured with adhesive bandaging, and kept patent using a saline lock throughout the exercise protocol. The catheter was positioned such that it had little interference with elbow flexion/extension during the exercise protocol.

A resting, preexercise (PRE) blood sample was collected following a 10-min equilibration period while participants were in a seated position. After finishing the exercise protocol, subjects were again placed in a seated position, and an immediate postexercise (IP) blood sample was collected. Following the IP blood draw, subjects were transferred to a quiet, temperature-controlled room to sit and rest. During this time, and within 10 min of completing the RE protocol, subjects ingested the drink (caloric beverage or water) and corresponding supplemental dose (LCLT or PL). Blood samples were then collected immediately (0 min) and at 10, 20, 30, 40, 50, and 60 min after consuming the post-RE drink and supplement.

Blood samples for serum analysis were allowed to clot at room temperature and then centrifuged at 3200 rpm (4°C) for 20 min. Resultant serum was removed and stored at −80°C until subsequent analysis. Blood collection procedures for all exercise challenges (including duration, timing and number of blood draws, and time of day) were identical.

Muscle biopsy procedures. A total of six muscle biopsy samples of the *vastus lateralis* were obtained from each participant using the percutaneous needle biopsy technique of Bergstrom (3) as modified by Evans et al. (8). Two separate series of three biopsies were obtained during each of the experimental conditions (LCLT and PL). An initial pre-RE biopsy was obtained following 21 d of supplementation. Post-RE biopsies were sampled at 60 min following the completion of each RE protocol. Tissue samples were obtained from adjacent sites 1.5 cm apart, one third the distance from the proximal lateral edge of the patella to the anterior superior iliac spine. The skeletal muscle sample was appropriately removed, mounted, placed in isopentane cooled in liquid nitrogen, snap frozen in liquid nitrogen, and stored at −80°C for later analysis.

Biochemical analyses. Serum total T and cortisol were determined in duplicate using ^{125}I solid phase

radioimmunoassays (RIA) (Diagnostic systems Laboratories, Webster, TX). Serum luteinizing hormone (LH) was determined in duplicate using a noncompetitive "sandwich-type" ^{125}I immunoradiometric assay (IRMA) (Diagnostic systems Laboratories, Webster, TX). Immunoreactivity values were determined using a gamma counter and online data reduction system (Cobra II, Packard Instruments Co., Meriden, CT). Serum adrenocorticotrophic hormone (ACTH) and follicle-stimulating hormone (FSH) were analyzed in duplicate using an enzyme-linked immunosorbent assay (ELISA) (Diagnostic systems Laboratories, Webster, TX). Sex-hormone binding globulin (SHBG) was measured using a double antibody radioimmunoassay (Diagnostic systems Laboratories, Webster, TX). To eliminate inter-assay variance, all samples for a particular assay were analyzed in the same run. In all cases, intraassay variances were < 10%. The minimum RIA and IRMA detection limits for T, cortisol, and LH were 0.28 $nmol \cdot L^{-1}$, 13.8 $nmol \cdot L^{-1}$, and 0.12 $mIU \cdot mL^{-1}$, respectively. Assay sensitivity for SHBG was 10 $nmol \cdot L^{-1}$. Minimum ELISA detection limits for ACTH and FSH were 0.264 $pmol \cdot L^{-1}$ and 0.1 $mIU \cdot mL^{-1}$, \respectively. Plasma glucose and lactate concentrations were determined using an automated glucose/lactate analyzer (2300 Stat glucose/L-lactate analyzer, YSI, Inc., Yellow Springs, OH). Serum carnitine was assessed in the presence of acetyl–CoA by measuring the CoASH set free during acetyl transfer to carnitine by the enzyme carnitine acetyltransferase. The CoASH was trapped with 5,5-dithiobis-(2-nitrobenzoic acid) and measured spectrophotometrically at 412 nm (30). For all procedures, samples were thawed only once before analysis.

Western blot analysis. Protein isolated from muscle biopsy samples was thawed in lysis buffer containing protease inhibitors (300 μL of RIPA buffer, 30 μL of aprotinin, 30 μL of phenylmethylsulfonyl fluoride, and 10 μL of sodium orthovanadate). Tissues were manually homogenized and centrifuged at 15,000 $\times$ *g* for 10 min. Resulting supernatant was removed for subsequent protein analysis and electrophoresis.

Total protein concentration was determined in triplicate using the Bradford protein assay and a Versa Max Microplate Reader (Molecular Devices, Sunnyvale, CA). One hundred fifty micrograms of homogenate protein was loaded into each gel well, and SDS-PAGE was performed using 4–15% gradient gels (Bio-Rad Laboratories, Hercules, CA) and a running buffer containing 0.1% SDS, 50 mM tris, and 196 mM glycine at 25°C for 1 h at 150 V. Samples were then transferred to a nitrocellulose membrane at 30 V at room temperature for 12 h in a buffer containing 192 mM glycine, 25 mM Tris, and 20% (vol/vol) methanol. Sequentially, membranes were incubated in 1) nonfat dry milk blocker (Bio-Rad Laboratories, Hercules, CA); 2) rabbit polyclonal primary antibody (Santa Cruz Biotechnology, Santa Cruz, CA) with a working solution concentration of 1:500 for 2 h at room temperature; 3) goat antirabbit horseradish peroxidase conjugated secondary antibody (Bio-Rad Laboratories, Inc., Hercules, CA) with a working solution of 1:1000 for 1 h; and 4) Opti-4CN dilutent/substrate for colorimetric detection (Bio-Rad Laboratories, Hercules, CA) for 45 min. AR protein was quantified using the Kodak Image System and Kodak 1D Image Software (Kodak Scientific Imaging Systems, New Haven, CT).

Statistical analyses. Two-way analysis of variance with repeated measures was used to examine pairwise differences. Appropriate *post hoc* tests (i.e., Tukey) were used when a significant *F* score resulted. All linear assumptions were tested and, when appropriate, Log_{10} transformations were utilized and the data were reanalyzed. Regression analysis was used to examine bivariate relationships where appropriate. Using nQuery Advisor® software (Statistical Solutions, Saugus, MA), the statistical power for the *n* size was calculated for each variable and ranged from 0.80 to 0.90. Significance in this study was set at $P \leq 0.05$. Post-exercise integrated area under the curve (AUC) concentrations were calculated for all hormonal variables using standard trapezoidal methods. Free androgen index (FAI) was calculated:

$$FAI = \text{total T } (nmol \cdot L^{-1}) \cdot \text{SHBG } (nmol \cdot L)^{-1}$$

RESULTS

Androgen receptor. Twenty-one days of LCLT supplementation significantly ($P < 0.05$) increased pre-exercise *vastus lateralis* AR content compared with PL (Fig. 2). When RE was followed by water intake, AR content increased compared with PRE for PL only. Feeding following RE significantly increased AR content compared with pre-RE values for both LCLT and PL trials. In addition, for the LCLT trial, feeding significantly increased post-RE AR content compared with water intake.

Testosterone. RE increased serum total T at IP and 0 min during all trials (Table 1). Nutrient intake following RE depressed T below PRE values after 20 min and remained depressed through 60 min of recovery. LCLT supplementation increased post-RE T concentrations at 0, 30, 40, 50, and 60 min during the water trial and prevented the postexercise decline in T compared with PL plus water. AUC analysis showed that T concentrations were significantly greater following water intake than nutrient ingestion. T AUC demonstrated the following order (from highest to lowest) ($P < 0.05$): 1) LCLT plus water; 2) PL plus water; 3) PL plus feeding and LCLT plus feeding. T AUC demonstrated a significant inverse correlation with AR content ($r = -0.74$).

Luteinizing hormone. LH responses are shown in Table 2. LH concentrations were suppressed below PRE at all time points after water intake. Following feeding, there was an interaction of LCLT supplementation; LCLT plus feeding showed no change or an increase from PRE, whereas PL plus feeding showed significant decreases from PRE. LH AUC analysis revealed the following order ($P < 0.05$): 1) LCLT plus feeding; 2) PL plus feeding and PL plus water (no difference between these two trials; 3) LCLT plus water.

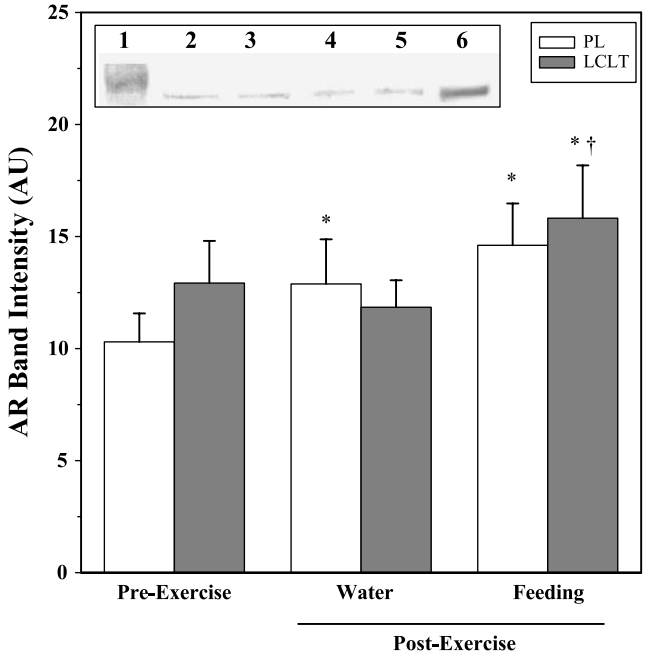

FIGURE 2—Androgen receptor (AR) content before and after resistance exercise. Figure shows values for each of the preexercise time points (following 3 wk of either placebo and LCLT supplementation) and following each of the four postexercise interventions. Values are means ± SE; AU, arbitrary units. *$P < 0.05$ from corresponding preexercise values; †$P < 0.05$ from corresponding water value; ‡$P < 0.05$ from corresponding placebo value. A representative immunoblot is shown in the upper portion of the figure. Lane 1: molecular weight standard (β-galactosidase, 128 kDa); lane 2: postexercise PL plus water; lane 3: postexercise LCLT plus water; lane 4: postexercise PL plus feeding; lane 5: postexercise LCLT plus feeding; lane 6: rat prostate positive control.

Follicle-stimulating hormone. FSH data are presented in Table 3. There were no significant differences at any time point between trials.

SHBG. LCLT supplementation significantly increased SHBG concentrations at all time points compared with PL (Table 4). RE invoked increases in SHBG concentrations during all trials at IP, with LCLT trials remaining greater than PL trials. Feeding had a minimal impact on SHBG concentrations. SHBG AUC was significantly greater during LCLT than PL trials; there were no differences between feeding and water trials.

TABLE 1. Total testosterone (nmol·L^{-1}) responses to resistance exercise.

	PL: Water	PL: Feeding	LCLT: Water	LCLT: Feeding
PRE	17.42 ± 4.21	17.93 ± 3.33	18.24 ± 5.89	18.52 ± 4.39
IP	22.31 ± 5.10*	24.04 ± 5.86*	24.60 ± 6.92*	24.11 ± 6.56*
0	21.01 ± 6.22*	21.82 ± 5.60*	23.55 ± 4.48*‡	20.88 ± 6.03*
10	19.84 ± 6.40*	19.01 ± 5.11	20.02 ± 3.80*	17.81 ± 4.14
20	17.72 ± 5.15	15.67 ± 3.09*†	17.89 ± 3.89	15.16 ± 3.97*†
30	16.52 ± 4.56	15.50 ± 3.61*	18.53 ± 4.12‡	13.40 ± 3.11*†
40	16.63 ± 5.27	14.31 ± 3.39*	17.54 ± 3.55‡	14.24 ± 2.93*
50	15.92 ± 5.61	13.87 ± 3.59*	18.12 ± 3.01‡	14.56 ± 3.92*
60	16.41 ± 4.64	13.04 ± 3.35*	18.40 ± 4.26‡	14.12 ± 3.44*
AUC	146.37 ± 40.83^{b}	137.25 ± 30.43^{c}	158.65 ± 30.55^{a}	134.28 ± 29.07^{c}

Values are means ± SD. * $P < 0.05$ from corresponding preexercise values; †$P < 0.05$ from corresponding water value; ‡$P < 0.05$ from corresponding placebo value; dissimilar superscripts denote significant ($P < 0.05$) differences in AUC values.

TABLE 2. Luteinizing hormone (mIU·L^{-1}) responses to resistance exercise.

	PL: Water	PL: Feeding	LCLT: Water	LCLT: Feeding
PRE	4.77 ± 1.81	4.15 ± 0.78	4.55 ± 1.27	4.30 ± 1.50
IP	4.80 ± 1.29	4.76 ± 1.38*	3.97 ± 1.09*†‡	5.02 ± 0.90*
0	4.26 ± 0.99*	4.42 ± 1.67	3.53 ± 1.01*†‡	4.47 ± 0.9
10	3.77 ± 0.87*	4.03 ± 1.38	3.76 ± 1.07*	4.59 ± 1.48†‡
20	3.69 ± 1.23*	3.90 ± 1.13	3.81 ± 1.45*	4.27 ± 1.22†‡
30	3.73 ± 1.39*	3.68 ± 1.21*	3.98 ± 1.36*	4.63 ± 1.52*†‡
40	3.78 ± 1.40*	3.57 ± 1.48*	3.69 ± 1.26*	4.25 ± 1.27†‡
50	3.51 ± 1.31*	3.50 ± 1.11*	3.58± 1.04*	4.18 ± 1.37†‡
60	3.96 ± 1.20*	3.64 ± 1.44*	3.43 ± 1.01*	4.12 ± 1.23
AUC	31.49 ± 8.20^{b}	31.51 ± 9.46^{b}	29.75 ± 7.25^{c}	35.54 ± 8.16^{a}

Values are means ± SD; * $P < 0.05$ from corresponding preexercise values; †$P < 0.05$ from corresponding water value; ‡$P < 0.05$ from corresponding placebo value; dissimilar superscripts denote significant ($P < 0.05$) differences in AUC values.

Free androgen index. Free androgen index values are presented in Table 5. FAI was significantly increased at IP and 0 min compared with PRE during the LCLT plus water trial only. In general, water intake had no effect on FAI, whereas feeding ingestion depressed FAI at 20–60 min. The only difference between LCLT and PL was a significant decrease at 30 min during feeding trials. FAI AUC was depressed compared with other trials during LCLT plus feeding.

Adrenocorticotrophic hormone. RE evoked significant increases in ACTH in all trials from IP to 20 min (Table 6). ACTH values for LCLT plus feeding were significantly less than corresponding water and PL plus feeding values at IP and 0 min. PL plus water was less than LCLT plus water at 0 min. Values for PL plus feeding were significantly greater than corresponding water values at 0 min. ACTH AUC for PL plus feeding and LCLT plus water was significantly greater than PL plus water and LCLT plus feeding.

Cortisol. In general, cortisol was elevated following RE in all trials (Table 7). Cortisol values for LCLT plus feeding were significantly less than corresponding water and PL plus feeding trials at IP, 0 min, and 50 min. Values for PL plus water were significantly less than corresponding feeding and LCLT trials at 0 and 50 min. Cortisol AUC revealed the following order ($P < 0.05$): 1) LCLT plus water and PL plus feeding; 2) PL plus water; 3) LCLT plus feeding.

Lactate and glucose. Plasma lactate values are presented in Table 8. RE increased lactate concentrations at all time points for all trials. Peak lactate concentrations

TABLE 3. Follicle-stimulating hormone (IU·L^{-1}) responses to resistance exercise.

	PL: Water	PL: Feeding	LCLT: Water	LCLT: Feeding
PRE	2.27 ± 1.59	2.17 ± 1.17	2.00 ± 1.15	2.42 ± 1.29
IP	1.93 ± 1.14	2.18 ± 1.13	2.15 ± 1.18	2.27 ± 1.28
0	1.86 ± 1.12	2.09 ± 1.15	2.04 ± 1.04	2.20 ± 1.20
10	1.81 ± 0.99	2.00 ± 1.20	2.09 ± 1.07	2.24 ± 1.21
20	1.89 ± 0.98	1.95 ± 1.08	2.13 ± 0.97	2.20 ± 1.20
30	1.91 ± 1.06	2.00 ± 1.15	2.16 ± 0.98	2.09 ± 1.05
40	1.93 ± 1.12	2.04 ± 1.13	1.96 ± 1.03	2.24 ± 1.21
50	1.93 ± 1.31	2.04 ± 1.19	2.00 ± 1.07	2.06 ± 1.09
60	2.03 ± 1.19	1.98 ± 1.14	2.08 ± 1.06	2.09 ± 1.16
AUC	15.30 ± 8.75	16.26 ± 9.06	16.59 ± 8.30	17.17 ± 9.06

Values are means ± SD.

TABLE 4. Sex-hormone binding globulin (nmol·L^{-1}) responses to resistance exercise.

	PL: Water	PL: Feeding	LCLT: Water	LCLT: Feeding
PRE	54.65 ± 9.52	56.78 ± 12.33	62.86 ± 13.50‡	64.97 ± 18.84‡
IP	66.09 ± 15.95*	69.81 ± 16.10*	76.70 ± 19.59*‡	75.29 ± 15.06*‡
0	60.70 ± 13.05	62.89 ± 14.14*	69.34 ± 15.03*‡	67.48 ± 14.70‡
10	59.44 ± 12.29	59.82 ± 12.07	68.00 ± 17.56‡	66.75 ± 13.68‡
20	56.45 ± 11.40	56.84 ± 11.28	65.70 ± 16.17‡	67.05 ± 15.13‡
30	54.91 ± 11.14	58.37 ± 11.47	63.17 ± 14.38‡	69.26 ± 16.41‡
40	55.59 ± 12.52	58.60 ± 14.32	66.45 ± 16.52‡	64.02 ± 13.98‡
50	54.31 ± 11.20	57.51 ± 11.18	66.94 ± 17.74‡	65.69 ± 14.85‡
60	54.74 ± 10.14	57.05 ± 12.11	68.17 ± 17.01‡	65.62 ± 14.36‡
AUC	462.24 ± 90.67[b]	475.03 ± 104.86[b]	544.46 ± 130.23[a]	527.70 ± 103.49[a]

Values are means ± SD; * $P < 0.05$ from corresponding preexercise values; ‡$P < 0.05$ from corresponding placebo value; dissimilar superscripts denote significant ($P < 0.05$) differences in AUC values.

TABLE 6. Adrenocorticotrophic hormone (pmol·L^{-1}) responses to resistance exercise.

	PL: Water	PL: Feeding	LCLT: Water	LCLT: Feeding
PRE	8.11 ± 4.77	7.17 ± 3.95	8.05 ± 2.35	6.66 ± 4.94
IP	21.06 ± 18.42*	22.99 ± 14.37*	23.15 ± 27.04*	17.59 ± 10.98*†‡
0	15.27 ± 12.85*	22.10 ± 13.00*†	19.99 ± 20.56*‡	14.97 ± 8.26*†‡
10	13.36 ± 14.09*	14.01 ± 8.17*	14.95 ± 15.88*	12.58 ± 6.98*
20	8.59 ± 4.50*	12.52 ± 7.37*	12.39 ± 12.47*	10.21 ± 6.22*
30	7.67 ± 4.78	10.14 ± 6.18	9.75 ± 8.05	8.46 ± 4.97
40	7.02 ± 4.08	8.28 ± 4.67	8.13 ± 5.12	7.99 ± 5.42
50	6.94 ± 4.29	7.75 ± 5.33	7.79 ± 4.43	5.92 ± 2.84
60	7.01 ± 4.39	6.82 ± 3.90	7.10 ± 3.04	6.37 ± 3.29
AUC	86.92 ± 57.64[b]	104.60 ± 56.13[a]	103.26 ± 90.86[a]	84.07 ± 42.77[b]

Values are means ± SD; * $P < 0.05$ from corresponding preexercise values; † $P < 0.05$ from corresponding water value; ‡$P < 0.05$ from corresponding placebo value; dissimilar superscripts denote significant ($P < 0.05$) differences in AUC values.

were > 14.00 mmol·L^{-1} in all trials. There were no significant differences between LCLT and PL or feeding and water. Plasma glucose concentrations increased following RE from IP to 20 min in all trials, and to 50 min in feeding trials. Glucose values during feeding trials were greater than water values from 10 to 40 min. There were no differences between LCLT and PL at any time point (Table 9).

Carnitine. As in our prior work, total serum carnitine values were examined at each of the time points to validate the supplementation protocol (28). As expected, compared with PL, serum total carnitine concentrations were significantly higher during supplementation at all time points measured. In addition, serum total carnitine was significantly elevated over preexercise concentrations at each of the time points measured, which was consistent with our prior work (28). Because there were no differences between water and feeding trials, results were pooled. Serum total carnitine concentrations (μM·L^{-1}) at PL treatment condition were: pre: 60.5 ± 2.4, 0: 65 ± 2.2, 10: 66.2 ± 3.3; 20: 64.4 ± 5.9; 30: 66 ± 9.2; 40: 63 ± 3.2; 50: 64.1 ± 5.2; 60: 65.3 ± 4.2; and at LCLT treatment condition were: pre: 96.5 ± 5.4; 0: 110 ± 4.2; 10: 111.2 ± 4.6; 20: 112.2 ± 8.9; 30: 125 ± 10.2; 40: 119 ± 8.2; 50: 119.1 ± 8.2; 60: 115.3 ± 7.2.

DISCUSSION

The primary findings of this investigation were: 1) exercise stimulated an increase in AR content during the PL plus water trial, and postexercise AR content was greater following feeding compared with water and resting conditions; and 2) 21 d of LCLT supplementation upregulated resting AR content. The increased AR content concomitant with decreased T concentrations after post-RE feeding suggests increased cellular uptake of T and provides a mechanism for increased protein synthesis found in other studies (22,27) following post-RE food intake. These data provide novel insights on AR responses immediately (within 1 h) after an acute bout of RE exercise in humans. Studies in rats have shown conflicting results, with one study (26) showing an increase in AR 2 h after exercise and another (21) showing downregulation in AR 1 d after surgically induced muscular overload. Our previous investigation showed that AR content did not change following a single-set squat protocol and decreased following a multiple-set squat protocol (23). Therefore, the current study provides novel information regarding AR responses to acute RE.

Increased AR content following RE in three of the four postexercise conditions sharply opposes the results of our previous study, in which AR content either decreased or did not change following RE (23). This is surprising because the two protocols used similar subjects, and both biopsied the *vastus lateralis* 1 h post-RE. However, an important difference between the two protocols may have been the duration of the RE intervention. During the current study, the exercise session lasted approximately 46 min, whereas during our previous study (23) the multiple-set squat session lasted approximately 16 min. This difference may be important because research indicates that T exposure upregulates skeletal muscle AR content *in vitro* (7) and *in vivo* (1,9). Therefore, it is possible that AR content is downregulated immediately post-RE due to protein degradation in the absence of nutritional intake (22) and subsequently upregulated due to T stimulation. However, it is clear that further research is necessary to fully elucidate the exact temporal nature of AR responses to RE.

The second major finding of this investigation (increased resting AR content following 21 d of LCLT supplementation) was also original. Although studies in rats have shown that carnitine supplementation affects the hypothalamic–pituitary–gonadal axis (4,19,20), no studies have investigated potential modifications in target tissue to accompany these central adaptations. RE-trained humans have been shown to have significantly less muscle damage

TABLE 5. Free androgen index (total testosterone – SHBG) responses to resistance exercise.

	PL: Water	PL: Feeding	LCLT: Water	LCLT: Feeding
PRE	0.33 ± 0.09	0.33 ± 0.10	0.32 ± 0.17	0.31 ± 0.12
IP	0.36 ± 0.13	0.37 ± 0.15	0.36 ± 0.19*	0.34 ± 0.13
0	0.35 ± 0.11	0.37 ± 0.14	0.37 ± 0.15*	0.32 ± 0.11
10	0.34 ± 0.10	0.34 ± 0.15	0.32 ± 0.13	0.28 ± 0.10
20	0.32 ± 0.10	0.29 ± 0.08*†	0.30 ± 0.13	0.24 ± 0.09*†
30	0.31 ± 0.10	0.28 ± 0.09†	0.31 ± 0.11	0.21 ± 0.08*†‡
40	0.31 ± 0.10	0.26 ± 0.10*†	0.29 ± 0.13	0.24 ± 0.08*†
50	0.30 ± 0.12	0.25 ± 0.10*†	0.29 ± 0.11	0.23 ± 0.09*†
60	0.31 ± 0.10	0.24 ± 0.09*†	0.30 ± 0.15	0.22 ± 0.06*†
AUC	2.60 ± 0.79[a]	2.40 ± 0.86[a]	2.53 ± 1.07[a]	2.07 ± 0.70[b]

Values are means ± SD; * $P < 0.05$ from corresponding preexercise values; †$P < 0.05$ from corresponding water value; ‡$P < 0.05$ from corresponding placebo value; dissimilar superscripts denote significant ($P < 0.05$) differences in AUC values.

TABLE 7. Cortisol (nmol·L^{-1}) responses to resistance exercise.

	PL: Water	PL: Feeding	LCLT: Water	LCLT: Feeding
PRE	643.60 ± 149.16	585.24 ± 200.55	622.40 ± 192.02	531.82 ± 132.09
IP	926.08 ± 265.60*	905.63 ± 234.35*	980.50 ± 277.79*	718.72 ± 186.30*†‡
0	809.23 ± 245.74*	932.95 ± 195.51*†	983.88 ± 314.12*‡	775.88 ± 219.02*†‡
10	820.53 ± 322.44*	912.11 ± 161.00*	943.07 ± 378.09*	767.91 ± 252.46*
20	812.82 ± 320.68*	865.87 ± 201.24*	928.94 ± 342.99*	757.10 ± 303.26*
30	701.09 ± 269.81	801.43 ± 153.03*	857.19 ± 333.73*	693.18 ± 299.40*
40	679.98 ± 227.95	757.73 ± 189.53*	800.37 ± 321.56*	673.70 ± 291.41*
50	622.67 ± 203.59	713.60 ± 175.16*†	760.11 ± 325.91*‡	593.69 ± 271.88†‡
60	593.76 ± 193.20	616.85 ± 161.16	707.26 ± 309.42*	560.78 ± 209.17
AUC	5966.16 ± 1922.21[b]	6506.16 ± 1274.67[a]	6961.31 ± 2457.67[a]	5540.96 ± 1901.74[c]

Values are means ± SD; * $P < 0.05$ from corresponding preexercise values; † $P < 0.05$ from corresponding water value; ‡ $P < 0.05$ from corresponding placebo value; dissimilar superscripts denote significant ($P < 0.05$) differences in AUC values.

following an acute bout of RE following LCLT supplementation (18). These investigators suggested that less muscle damage may have resulted in more intact hormonal receptors available for binding interaction with anabolic hormones, which may explain the reduced progression of muscle damage (as measured by magnetic resonance imaging) in the days following RE in those studies (18,29). Although muscle damage was not measured during the current investigation, carnitine ingestion during the 21-d supplementation period, which was concomitant with the participants' habitual RE regimen, may have reduced the muscle damage associated with RE training and attenuated catabolism of muscle-specific proteins (perhaps including AR content). However, due to the crossover design used in this study, we have controlled for the influence of habitual RE training on AR content. Therefore, we hypothesize that the mechanism of LCLT action is enhanced T uptake via less muscle damage and increased availability of AR, and not due to direct stimulation of T secretion (i.e., LCLT is not a T-enhancing supplement). Additionally, all of these effects could be mediated by a blood flow difference at the level of the muscle tissue as originally hypothesized in our earlier work on LCLT, yet to be established due to technological demands of such techniques in muscle (29).

Similar to previous investigations (5,6,17), this study showed that post-RE nutrient intake depressed T concentrations below nonfeeding and preexercise values. Reduced T concentrations compared with water trials were noted at 20 and 30 min post-RE and in the integrated post-RE AUC; differences compared with preexercise values during the feeding trials were noted at multiple time points (i.e., 20–60 min) and in AUC analysis. Because AR content increased following nutrient ingestion, depressed T concentrations following post-RE feeding may potentially reflect increased cellular uptake of T; this hypothesis is supported by research that demonstrates that T exposure upregulates skeletal muscle AR content *in vitro* (7) and *in vivo* (1,9) and is indirectly supported in the current study by an inverse correlation ($r = -0.74$) between AUC T concentrations and AR receptor content.

T responses to RE may have also been influenced by LCLT supplementation. During water trials, post-RE T concentrations were greater for LCLT than PL trials at 30–60 min; similarly, T AUC was greater for LCLT plus water than PL plus water. This is the first investigation to show that LCLT may have an influence on T responses to RE in humans. Kraemer et al. (18) showed no differences in post-RE T concentrations between LCLT and PL trials; however, the RE protocol used in the Kraemer et al. (18) study was a "hypoxic RE challenge" (i.e., five sets of 20 repetitions of back squat at 50% 1RM), which was different from the whole-body RE protocol used in the current investigation. Based on the study design, however, it is not possible to determine whether the T responses to LCLT supplementation in this study were due to a different RE protocol or driven by the changes in AR content seen between trials (which may affect circulating T concentrations). However, it should be noted that feeding negated any influence of LCLT on postexercise T concentrations.

In general, LH values declined below resting values following RE. Interestingly, though, in the LCLT trials, LH values were higher at specific time points during feeding than water trials. Furthermore, LH AUC during LCLT plus feeding was greater than all other conditions. These findings are in contrast to those of Chandler et al. (6), who found no significant differences in LH after RE or RE plus

TABLE 8. Plasma lactate (mmol·L^{-1}) responses to resistance exercise.

	PL: Water	PL: Feeding	LCLT: Water	LCLT: Feeding
PRE	1.75 ± 0.40	1.63 ± 0.58	1.86 ± 0.46	1.36 ± 0.25
IP	14.22 ± 2.40*	14.99 ± 3.50*	14.07 ± 2.86*	14.56 ± 3.25*
0	10.42 ± 2.51*	11.06 ± 3.35*	10.99 ± 1.98*	10.06 ± 1.54*
10	7.38 ± 1.95*	7.82 ± 2.79*	7.60 ± 2.21*	7.23 ± 1.59*
20	5.44 ± 1.39*	6.39 ± 2.81*	5.63 ± 1.73*	5.63 ± 1.30*
30	4.51 ± 1.13*	5.45 ± 2.30*	4.82 ± 1.26*	4.61 ± 1.02*
40	3.79 ± 0.78*	4.80 ± 1.53*	4.06 ± 1.06*	4.01 ± 0.85*
50	3.35 ± 0.66*	4.29 ± 1.33*	3.44 ± 1.16*	3.68 ± 0.83*
60	3.07 ± 0.59*	3.75 ± 1.04*	3.04 ± 0.89*	3.37 ± 0.76*

Values are means ± SD; * $P < 0.05$ from corresponding preexercise values.

TABLE 9. Plasma glucose (mmol·L^{-1}) responses to resistance exercise.

	PL: Water	PL: Feeding	LCLT: Water	LCLT: Feeding
PRE	4.96 ± 0.45	4.98 ± 0.43	5.21 ± 0.38	5.14 ± 0.51
IP	6.22 ± 1.17*	5.89 ± 1.13*	6.00 ± 0.78*	6.14 ± 1.04*
0	6.08 ± 1.26*	6.23 ± 1.43*	6.13 ± 1.09*	5.89 ± 0.69*
10	5.76 ± 1.37*	7.42 ± 1.09*†	6.12 ± 1.28*	6.74 ± 1.07*†
20	5.43 ± 1.21*	7.94 ± 1.12*†	5.77 ± 1.43*	7.80 ± 1.08*†
30	5.02 ± 0.85	7.73 ± 1.42*†	5.62 ± 1.47	7.48 ± 1.36*†
40	4.56 ± 0.59	6.77 ± 1.52*†	5.57 ± 1.44	6.48 ± 1.64*†
50	4.62 ± 0.41	6.06 ± 1.65*	5.52 ± 1.23	5.88 ± 1.46*
60	4.65 ± 0.45	5.26 ± 1.71	5.47 ± 1.11	5.25 ± 1.36

Values are means ± SD; * $P < 0.05$ from corresponding preexercise values; † $P < 0.05$ from corresponding water value.

nutrient intake (ingestion of carbohydrate, protein, or carbohydrate/protein). However, during that study (6), subtle differences in LH concentrations between feeding and PL trials may have been undetectable due to the large time intervals between post-RE blood samples (1 h).

The AR, T, and LH results from this study imply that the pituitary–gonadal axis works in a negative feedback loop following RE. Thus, our paradigm indicates that changes in AR content following RE (which is affected by feeding and LCLT supplementation) drives changes in the hypothalamic–pituitary–gonadal axis. Increased AR content may result in enhanced tissue uptake of T, thus depressing circulating T concentrations. Reduction in T concentrations (due to enhanced cellular uptake) is monitored by the hypothalamus, which releases GnRH to stimulate LH secretion; LH then stimulates T synthesis/secretion. Although GnRH concentrations were not measured in this study, the responses of AR, T, and LH to the four RE protocols support this paradigm. Examining our results, it is clear that T and LH concentrations are decreased below resting values during the 60 min after exercise. However, the highest LH AUC is associated with the lowest T AUC. Therefore, although RE may decrease T and LH concentrations, it seems that low T concentrations are being detected by the hypothalamus, which adjusts concentrations of LH. Ultimately, these results indicate that feeding and LCLT supplementation may affect androgenic responses to exercise (both singularly and synergistically), which may enhance recovery following RE.

FAI (calculated as total $T \cdot SHBG^{-1}$) is an indirect marker of the fraction of total T that is available to bind to the AR, because binding to SHBG effectively inhibits T's bioactivity. Although SHBG concentrations were significantly greater during LCLT trials, this response appears to have little impact on the FAI (Table 5). The primary difference between LCLT and PL trials was that LCLT plus feeding had a significantly lower FAI AUC. This effect was influenced by low T concentrations (perhaps secondary to increased cellular T uptake); therefore, FAI changes following LCLT supplementation were due to changes in both SHBG and total T.

Changes in FAI following post-RE feeding is another novel finding of this study. The FAI was significantly less during feeding than water trials at 20–60 min; these time points were significantly less than PRE values as well. Kraemer et al. (17) found no change in FAI in response to RE or post-RE feeding. Because the RE protocol and the feeding beverage used in both studies were similar, it is difficult to ascertain the discrepancy between the findings of this investigation and those of Kraemer et al. (17); however, subjects in the current investigation displayed greater relative falls in T concentrations, which likely influenced the FAI.

ACTH and cortisol were ancillary variables used to further describe the influence of LCLT and feeding on endocrine responses to RE. In all trials, RE induced significant increases in ACTH and cortisol through 20 min. During PL trials, ACTH and cortisol AUC were significantly greater following feeding than water ingestion. Kraemer et al. (17) found similar results, as cortisol was greater following post-RE feeding. Others have shown that carbohydrate or carbohydrate combined with protein before and after RE does not alter the cortisol response compared with PL (5,14,31). However, one study showed that carbohydrate intake during RE significantly blunted the cortisol response, which was shown to be significantly related to increases in muscle fiber hypertrophy (25). Thus, the interaction of feeding on cortisol responses to RE are mixed, and the specific parameters that impact this hormone's response are unclear. The influence of LCLT on ACTH and cortisol are difficult to interpret because this is the first investigation of the influence of LCLT on the pituitary–adrenal axis.

Due to the design of the study, it is not possible to ascertain whether the effects of LCLT were attributable to the chronic (3 wk) or the acute (immediately postexercise) ingestion of 2 g of LCLT. The purpose of the acute dose of LCLT was to ensure that the concentration of L-carnitine remained elevated throughout the postexercise period. However, research has shown that absorption of L-carnitine is a relatively slow process, with peak plasma concentrations occurring approximately 2–4 h after oral ingestion (12). Because all post-RE blood draws and biopsies in the present study were taken within 1 h after the last supplemental dose, it seems likely that the effects of LCLT supplementation observed in this study were due to the 3-wk supplementation protocol; however, it cannot be ruled out that the acute dose of LCLT had some influence on the results.

In summary, post-RE feeding has a significant impact on the pituitary–gonadal axis. It appears that feeding stimulates increases in AR content, which may stimulate cellular uptake of T. Cellular T uptake decreases circulating T concentrations, which then incites LH secretion via negative feedback. In addition, it seems that LCLT supplementation may also influence exercise-induced responses in the pituitary–gonadal axis, although hormonal concentrations remained within normal physiological limits. LCLT's primary means of action, however, appears to be an upregulation in AR content following 21 d of supplementation. Finally, based on the results of the present study, LCLT and feeding may independently and synergistically enhance the hormonal environment following RE and promote recovery.

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