Short-term creatine supplementation does not alter the hormonal response to resistance training

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ABSTRACT

OP 'T EIJNDE, B., and P. HESPEL. Short-term creatine supplementation does not alter the hormonal response to resistance training. Med. Sci. Sports Exerc., Vol. 33, No. 3, 2001, pp. 449–453. Purpose: In this study, the effect of short-term creatine supplementation on the growth hormone, testosterone, and cortisol response to heavy resistance training was investigated. Methods: According to a double-blind crossover study design, 11 healthy young male volunteers underwent a 1-h standardized heavy resistance training session (3 series of 10RM; 12 exercises), both before (pretest) and after (posttest) 5 d of either placebo (P, maltodextrine) or creatine (CR; 20 g·d⁻¹, 5 d) supplementation. A 5-wk washout period separated the treatments. Thirty minutes before each training session, CR subjects ingested 10 g of creatine monohydrate (CR) while P subjects received placebo. Venous blood was sampled before, immediately after, and 30 and 60 min after the training session. Results: The exercise-induced increase (P < 0.05) of serum growth hormone was not altered by acute creatine intake and was similar in P and CR. The weight training session, either or not in conjunction with acute or chronic creatine intake, did not significantly impact on serum testosterone. However, serum cortisol during recovery tended to be higher in CR than in P. Conclusion: It is concluded that short-term creatine supplementation does not alter the responses of growth hormone, testosterone, and cortisol to a single bout of heavy resistance training. Key Words: MUSCLE HYPERTROPHY, EXERCISE, GROWTH HORMONE, TESTOSTERONE, CORTISOL

In the 1990s, creatine had become a very popular nutritional supplement to boost muscular performance in athletic populations. Strength and power athletes in particular, have “discovered” the potential of creatine supplementation to stimulate their training output and performance. Meanwhile, research aimed to elucidate the physiological mechanisms underlying the “ergogenic” impact of creatine supplementation has boomed. Interestingly, in this respect, it recently has been demonstrated that oral creatine supplementation can enhance muscle hypertrophy during resistance training (17,22). Thus, in long-term intervention studies on young female (23) as well as male volunteers (17,25), creatine intake significantly boosted the gain of fat free mass and muscle force and power, produced by a given volume and intensity of heavy resistance training. Furthermore, recent data indicate that creatine intake stimulates hypertrophy of both type I and type II muscle fibers during strength training (25). In addition, the “ergogenic” actions of creatine probably allow for greater training loads to be accomplished (22,25), which in turn again contributes to improved training output in terms of muscle volume, force, and power.

Although evidence is accumulating that oral creatine intake stimulates muscle fiber hypertrophy in humans, the physiological mechanisms underlying this “anabolic” action of creatine remain largely unexplained. From a theoretical point of view, creatine supplementation might stimulate net muscle protein synthesis by either a direct intracellular action on protein synthesis or degradation, or by shifting the hormonal signals impinging on the muscle cells to the “anabolic” pole. With regard to the possible hormonal pathway, it is well known that signals of growth hormone, testosterone, and cortisol play a pivotal role in generating muscle hypertrophy due to heavy resistance training (6,13,16). Thus, enhanced stimulation of growth hormone and testosterone secretion, versus decreased secretion of cortisol after bouts of heavy resistance training, might conceivably contribute to enhance the long-term hypertrophic response to resistance training. In one study (24), oral creatine loading (25 g·d⁻¹, 7 d) was found not to impact on the serum testosterone and cortisol concentrations during a bout of heavy resistance exercise. However, the study did not use a crossover design and growth hormone responses were not considered.

Therefore, the present double-blind placebo-controlled crossover study explored the effect of both acute and short-term creatine intake on growth hormone, testosterone, and cortisol responses to a single bout of heavy-resistance training.

MATERIALS AND METHODS

Subjects. Eleven healthy male physical education students with no specific background of high-resistance training...
(20.7 ± 0.5 yr, 76.1 ± 2.3 kg) gave their informed written consent in accordance with the Catholic University of Leuven ethical guidelines for use of human subjects. They were informed in detail of all experimental procedures to be undertaken and were asked to abstain from any medication during the period of the study and to avoid changes in their diet or level of physical activity. One week before the start of the study, the subjects came to the local fitness center to have their T0 repetition maximum (10RM) assessed for the weight exercises to be performed and to have their body weight measured.

**Study protocol.** A double-blind placebo-controlled crossover study was performed. Subjects were assigned in random order to two experimental protocols (placebo or creatine supplementation), each lasting 8 d and separated by a 5-wk washout period. It is well documented that the muscle creatine store after creatine loading returns to basal values within 4–5 wk after cessation of the creatine intake (5,18,22). On the evening before the experiments, the subjects received a standardized meal (855 kcal, 47% CHO, 25% fat, 28% proteins) between 7:30 and 9:00 p.m. and were instructed to consume water only thereafter. On the next morning, after a 12- to 14-h fast, they reported to the laboratory for the first experimental session. Upon arrival, the subjects were weighed and consumed a light standardized breakfast within 15 min (320 kcal, 65% CHO, 15% fat, 20% proteins), whereafter they were seated in a semisupine position in a comfortable chair. One hour later, subjects ingested 10 g of creatine monohydrate (CR) powder that was dissolved in 150 mL of weak tea or placebo (tea only). Thirty minutes later (t1), a 10-mL venous blood sample was taken from an antecubital vein into Li-heparinized tubes (Vacutainer®), one of which contained clot activator for separation of serum. Immediately after, the subjects drank 250 mL of natural water, before they started into a standardized and supervised high-resistance training session lasting 60 min. The training consisted of a series of 12 weight-lifting exercises (vertical traction, standing gluteus, shoulder press, abdomen, rhomboidei, leg extension, chest press, rotary torso, vertical row, leg curl, lateral machine, and horizontal leg press, in this order) to be performed in a fixed order. Workload was set at 10RM. Furthermore, given that the hormonal response to resistance training also depends on the duration of the rest intervals between exercise bouts (14,15), the exercise intensity was controlled by scheduling exactly 5 min for three series of 10 repetitions at each of the 12 exercise stations. Immediately at the end of the training session, subjects drank 250 mL of natural water and resumed the semisupine position, whereupon a second blood sample was taken from an antecubital vein (t20). The subjects remained seated for the next hour of recovery. Additional venous blood samples were taken after 30 min (t40) and 60 min (t120) of recovery. This measurement session is termed pretest throughout the manuscript. Two days later, the subjects started with a 5-d period of creatine/placebo supplementation. Half of the subjects ingested 5 g of creatine monohydrate four times per day. The creatine supplements were flavored by the addition of citrate (60 mg·g⁻¹ creatine) and maltodextrine (940 mg·g⁻¹ creatine). The other half of the subjects ingested matched placebo supplements (maltodextrine) containing citrate (40 mg·g⁻¹ maltodextrine). It is well established that such creatine supplementation regimen is effective to increase muscle total creatine concentration by 20% in young male volunteers (8,9,21). On the last day of creatine/placebo supplementation, between 7:30 and 9:00 p.m., the subjects consumed an identical meal as the week before. On the next morning, they returned fasting to the laboratory to undergo the experimental procedures identical to the week before. Throughout this manuscript, this measurement session will be referred to as posttest. After a 5-wk washout period (21), the entire experimental procedure was repeated with the treatment regimens being switched between the groups.

**Biochemical analyses.** Venous blood samples were centrifuged for separation of plasma and serum, which was stored at −80°C until being analyzed at a later date. Plasma creatine concentration was determined after extraction in 0.6 mol/L perchloric acid, using a standard enzymatic fluorometric assay (3). Serum growth hormone (GH) concentrations were determined by a radio-immunoassay, using a polyclonal antibody (4). The intra-assay coefficient of variation was 7.3% at 6.7 μg·L⁻¹ and 4.6% at 14.4 μg·L⁻¹. The detection limit was 1.1 μg·L⁻¹. Serum testosterone concentration was measured by a radio-immunoassay, after extraction with a mixture of cyclohexane and ethylacetate, and purification on Sephadex LH₂₀ columns (12). The intra-assay coefficient of variation was 3.5% at 29.3 nmol·L⁻¹. The detection limit was 0.35 nmol·L⁻¹. Serum cortisol concentration was measured by a radio-immunoassay after extraction of the serum with dichloromethane (20). The intra-assay coefficient of variation was 3.1% at 417 nmol·L⁻¹.

**Statistical analyses.** Statistical analyses of the data was done by three-way analyses of variance (2 × 2 × 4), using Statistica® software (Statsoft Inc., Tulsa, OK). When appropriate, Tukey's post hoc tests were applied. All data are presented as means ± SEM. A probability level of P < 0.05 was chosen as the threshold for acceptance of statistical significance.

**RESULTS**

**Body weight and side effects.** During placebo treatment (P), body weight was 75.5 ± 2.5 kg at the pretest and was similar for the posttest (75.7 ± 2.5 kg). Corresponding values during creatine treatment (CR) were 75.6 ± 2.3 kg and 76.0 ± 2.5 kg. Thus, compared with P, CR treatment did not significantly impact on body weight. Two subjects complained of nausea during the pretest training session. No side effects were reported during either the CR or P supplementation period or during the posttest.

**Effect of acute creatine intake.** The effects of acute creatine intake on serum growth hormone, testosterone, and cortisol were evaluated by comparing the pretest data between the P and CR condition. During P, plasma creatine concentration was similar before (90 ± 32 μmol·L⁻¹) and after (50 ± 22 μmol·L⁻¹) the training session. In CR, administration of 10-g creatine 30 min before the training
session increased ($P < 0.05$) plasma creatine concentration to 662 ± 78 μmol·L$^{-1}$ at the onset ($t_0$), and further to 1250 ± 81 μmol·L$^{-1}$ by the end ($t_{60}$) of the resistance exercise session.

During the pretest, baseline ($t_0$) concentrations of growth hormone (Fig. 1), testosterone (Fig. 2) and cortisol (Fig. 3) were similar during P and CR. In both P and CR the heavy-resistance training session increased ($P < 0.05$) serum growth hormone about four- to five-fold, where after values returned to baseline within the 60 min recovery period. Serum testosterone and cortisol concentrations were not significantly altered by either the weight training per se or by the intake of creatine. Serum testosterone and cortisol concentrations did not significantly change due to either training or recovery, or as a result of creatine administration before the training session.

**Effect of creatine loading.** The effect of chronic creatine administration on serum hormones was evaluated by comparing the pre- and posttest responses between P and CR. Baseline ($t_0$) plasma creatine concentrations during the posttest were similar to pretest values (see above) in both P (66 ± 26 μmol·L$^{-1}$) and CR (738 ± 67 μmol·L$^{-1}$). Furthermore, at the end of the training session ($t_{60}$), compared with the pretest, plasma creatine was similar in P (76 ± 47 μmol·L$^{-1}$) but was significantly higher in CR (1650 ± 65 μmol·L$^{-1}$).

Baseline ($t_0$) serum growth hormone, testosterone, and cortisol concentrations were similar in the pretest and the posttest in either experimental condition. Figure 1 shows that the increase of plasma growth hormone concentration caused by the training was similar in the pre- and post-test for both P and CR. Accordingly, the responses of serum testosterone (Fig. 2) to heavy resistance training were independent of prior creatine loading. Although training per se did not significantly impact on serum cortisol, cortisol concentrations (Fig. 3) during recovery ($t_{60}$ and $t_{120}$) were slightly higher in CR than in P ($P < 0.05$).

**DISCUSSION**

Resistance training activates a number of neuromuscular adaptations that eventually lead to increased muscle force and power production. Although neural mechanisms account for the major fraction of this increment during the initial weeks of a resistance training program, thereafter muscle fiber hypertrophy becomes the primary physiological mechanism by which muscle strength is further enhanced (14). In this respect, it has recently been shown that oral creatine supplementation can augment muscle fiber...
hypertrophy during heavy resistance training (22). It is well established that endocrine factors play a pivotal role to initiate the structural adaptations of skeletal muscle to resistance training. Therefore, in this paper we explored the impact of acute creatine intake, alone or in combination with 5 d of prior high dose creatine loading, on the responses of growth hormone (GH), testosterone, and cortisol to a single bout of heavy-resistance training.

It is well known that heavy-resistance exercise is a potent stimulus for GH secretion (15,16). Increased circulating GH, by enhancing the action of insulin-like growth factor I on muscle protein synthesis, is important to muscle fiber hypertrophy resulting from resistance training (1). In the current study, serum growth hormone was augmented four- to five-fold immediately at the end of the 1-h heavy-resistance training session. Thereafter, it returned to normal within 60 min of recovery. Acute ingestion of a 10-g creatine dosage, either or not preceded by 5 d of high-dose creatine intake, increased plasma creatine about 10-fold. However, the time course of serum growth hormone concentration during exercise and recovery was unchanged. Thus, short-term creatine loading clearly does not alter the acute growth hormone response to a single bout of heavy-resistance training.

A bout of heavy resistance training in young male subjects typically increases serum testosterone. However, the response among and even within individuals is very variable (15). Accordingly, the weight training session in all experimental conditions tended to increase serum testosterone concentration, yet the changes were not statistically significant. By analogy with testosterone, also the cortisol response to resistance exercise exhibits a high degree of variability (13). In the current study, postexercise (t0) serum cortisol was not different from the corresponding pre-exercise value, in any experimental condition. During recovery, cortisol exhibited the expected decrease to below baseline levels, yet the time window considered (60 min) probably was too short for the decrease to become significant. However, neither serum testosterone nor cortisol was altered by creatine supplementation, either before or after exercise. By analogy, Volek and his co-workers previously have found similar testosterone and cortisol responses to high-intensity resistance exercise before and after short-term (7 d) creatine supplementation (24). The slightly higher serum cortisol concentrations measured during recovery after 5 d of high-dose creatine loading are difficult to explain but presumably reflect the normal diurnal variations of this hormone. Thus, the present findings together with previous observations (16) clearly indicate that short-term creatine intake does not alter the testosterone and cortisol responses to a single bout of weight training. In spite of similar circulating plasma hormone levels, the hormonal signals transmitted to the muscle cells might still differ because of regulatory mechanisms occurring at the site of receptor binding or expression, and/or the intracellular signal transmission. It is also important to emphasize that the current study has specifically addressed the impact of short-term creatine supplementation on the acute hormonal responses to a given volume and intensity of heavy resistance exercise. However, it has been well established that creatine supplementation (2,8,17,22,25) can enhance the ability to perform resistance training workouts. This "ergogenic" action of creatine intake conceivably may enhance the acute hormonal responses to heavy resistance training and thereby facilitate the resulting physiological adaptations. Furthermore, it remains to be investigated whether long-term creatine supplementation, in contrast to the short-term supplementation used in the current study, may alter the responses of growth hormone, testosterone, and cortisol to weight training.

The present study has explored a potential hormonal pathway to explain the "anabolic" action of creatine supplementation. However, possible direct actions of creatine within the muscle cells to stimulate net protein synthesis must also be considered. In this respect, some early observations on muscle cell cultures have suggested that creatine may directly stimulate the rate of muscle protein synthesis (10,11,19). However, this preliminary evidence was discredited thereafter (7). The possible impact of creatine intake on the intracellular signaling pathways involved in the regulation of muscle protein synthesis and breakdown, needs to be addressed in future studies.

In conclusion, our current findings demonstrate that acute creatine intake, either before or after short-term creatine loading, does not alter the growth hormone, testosterone, and cortisol responses to a given volume and intensity of heavy resistance exercise. Thus, other mechanisms must be considered to explain the potential of creatine supplementation to augment muscle volume and muscle force gains resulting from resistance training.

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REFERENCES


5. Ferraedt, M., T. R. Flanagan, R. J. Snow, S. Zhao, and M. F. Carey. Effect of creatine supplementation on intramuscular TCr, metabolism and performance during intermittent, supra-