Shortening of muscle relaxation time after creatine loading

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Van Leemputte, M., K. Vandenbergh, and P. Hespel. Shortening of muscle relaxation time after creatine loading. J. Appl. Physiol. 86(3): 840–844, 1999.—The effect of creatine (Cr) supplementation on muscle isometric torque generation and relaxation was investigated in healthy male volunteers. Maximal torque (Tmax), contraction time (CT) from 0.25 to 0.75 of Tmax, and relaxation time (RT) from 0.75 to 0.25 of Tmax were measured during 12 maximal isometric 3-s elbow flexions interspersed by 10-s rest intervals. Between the pretest and the posttest, subjects ingested Cr monohydrate (4 × 5 g/day; n = 8) or placebo (n = 8) for 5 days. Pretest Tmax, CT, and RT were similar in Cr and placebo groups. Also in the posttest, Tmax and CT were similar between groups. However, posttest RT was decreased consistently by ~20% (P < 0.05) in the Cr group from the first to the last of the 12 contractions. In addition, the mean decrease in RT after Cr loading was positively correlated with pretest RT (r = 0.82). It is concluded that Cr loading facilitates the rate of muscle relaxation during brief isometric muscle contractions without affecting torque production.

Over the last 5 years, it has been clearly established that high-dose creatine (Cr) intake for several days may markedly increase muscle Cr and phosphocreatine levels. Because this elevated Cr level has been shown to be associated with enhanced capacity to perform maximal high-intensity muscle contractions (13), Cr intake has become a popular ergogenic supplement in sports. However, the physiological mechanisms underlying the ergogenic action of Cr loading are poorly understood today. In this respect, the particular effectiveness of Cr to improve intermittent exercise performance (1, 4, 7, 15, 17, 28) has raised the logical assumption that facilitated postexercise muscle phosphocreatine resynthesis, by virtue of elevated intracellular Cr level, may be the first-line mechanism that causes the beneficial effects of Cr loading (14). However, recent findings indicate that accelerated postcontraction phosphocreatine resynthesis, although possibly contributing to improved muscle performance in individuals with low initial Cr levels (14), probably is not essential for Cr loading to exert its ergogenic action (K. Vandenbergh, unpublished observations; 26). Furthermore, it is clear that enhanced muscle power during the first bout of an intermittent series of rapid dynamic muscle contractions (28) occurs independently of enhanced muscle phosphocreatine resynthesis.

To explore further the physiological mechanisms underlying the ergogenic action of Cr, we investigated here the effect of Cr loading on the rate of torque generation and relaxation during intermittent maximal voluntary elbow flexions in humans. A recent study by Wakatsuki and co-workers (30) has shown that Cr feeding in rats not only raised muscle phosphocreatine level but at the same time shortened one-half relaxation time (RT50). Accordingly, phosphocreatine depletion by β-guanidinopropionic acid feeding was found to increase muscle relaxation time (RT; Refs. 22, 25, 30). Furthermore, relaxation processes account for an important fraction of total energy consumption in muscles during short, repeated muscle contractions (2, 18, 19). Thus, during high-intensity cyclic joint movements, facilitation of muscle relaxation might conceivably contribute to reduce total energy expenditure, both by diminishing the energy cost of relaxations and by reducing co-contraction activity. Finally, shortening of muscle RT may be expected to improve cross-bridge cycling efficiency during a series of rapid concentric muscle contractions, because recovery time after a concentric contraction is very critical to the amount of postshortening force decrease (9). Thus, during muscle activity involving fast, repetitive, short muscle contractions and relaxations, with no pauses in between, facilitated muscle relaxation may significantly contribute to improvement of muscle power output. In keeping with this line of reasoning, enhanced muscle power after short-term Cr loading has been reported exclusively for such type of muscle activity (1, 4, 7, 15, 17, 28).

The data presented in this paper demonstrate for the first time that oral Cr loading indeed facilitates muscle relaxation after maximal contraction. This finding may help to explain the reported ergogenic action of oral Cr supplementation in humans.

METHODS

Subjects. Sixteen men, who were physical education students (ages 18–23 yr), gave their informed written consent to take part in the study. They were informed of the experimental procedures to be undertaken, and they were asked to abstain from any medication and caffeine (28) during the period of the study and to avoid changes in their usual level of physical activity.

Study design. A double-blind study was performed. Subjects participated over a period of 2 wk in three maximal, intermittent-exercise sessions to exercise the arm flexor muscles on an isokinetic dynamometer. The first session aimed to habituate the subjects to the exercise protocol. One week later, the subjects returned to the laboratory for the pretest. On their arrival, their body weight was measured, and they performed the elbow-flexion test as described below. Thereafter, one-half of the subjects were assigned to either a Cr-supplementation group (n = 8) or a placebo (Pl) group (n = 8). The groups were balanced for body weight and maximal isometric elbow-flexion torque, as measured during the pretest. Two days later, the Cr group started the intake of tablets containing 5 g of Cr monohydrate 4 times/day for a period of 5 days. This procedure has been previously proven to be
effective in raising muscle phosphocreatine level and improving intermittent exercise capacity in young men (12, 14, 16, 28). Meanwhile, the other subjects ingested PI (maltodextrin) tablets which were matched with the Cr tablets for taste and color. The next session, on the same day of the week and same time of the day as for the pretest, the subjects returned to the laboratory for the posttest, which was identical to the pretest. The results of the measurements were disclosed to neither the subjects nor the investigators until completion of the study.

Test protocol. Subjects were seated on a backward-inclined (30°) chair with the right upper arm supported horizontally at the level of the elbow. The shoulders were stabilized by using safety belts. An isokinetic dynamometer, instrumented with a torque transducer (Lebow 1605, 0.05% accuracy level) and connected with a rigid lever arm, was positioned lateral to the elbow, such that the dynamometer axis was aligned with the elbow joint axis. To avoid disturbance caused by wrist movements, the forearm was strapped to the lever arm of the system at the level of processus styloideus radii. The lever arm was rotated to an elbow angle of 110° (180° being full extension). The positions of elbow and shoulder fixations, and of the axis of the measuring device, were noted for each individual and were set to be identical for the pre- and posttest. Subjects were asked to generate, from full relaxation and as fast as possible, a 3-s maximal isometric elbow flexion and thereafter to relax as fast as possible. The start of contraction and relaxation was indicated by a beep signal generated by a personal computer. After a standardized 5-min period of warming up, subjects performed 12 consecutive maximal isometric elbow flexions interspersed with 10-s rest intervals. To control the state of total relaxation during the rest intervals and to verify the continuation of maximal effort during the contractions, the electromyogram (EMG) of biceps was continuously registered by using bipolar surface preamplifier-electrode units (Analog Device AD511K) that were placed longitudinally on the muscle belly. Electrodes were connected to a standard biological amplifier (frequency response, 4–1,000 Hz; input impedance, 10 MΩ). For each contraction, torque and EMG were digitized at 500 Hz for 4 s and stored to disk for later analysis.

Data analysis. As shown in Fig. 1, the torque from each contraction was characterized by three parameters: 1) maximal torque (Tmax, in Nm); 2) contraction time (CT, in ms), which was defined as the time needed to build up muscle torque from 0.25 to 0.75 of Tmax; and 3) RT (in ms), which was defined as the time needed to reduce torque from 0.75 to 0.25 of Tmax. The latter two parameters were chosen because intraday reliability (0.94 and 0.96 for CT and RT, respectively) and interday reliability (0.92 and 0.95 for CT and RT, respectively) were higher than for the conventional RT50 measurements used in in vitro electrical-stimulation studies. The use of 0.25 and 0.75 of Tmax as reference points in the contraction and relaxation slopes avoids the variation of neuromechanical reaction times which may interfere with voluntary contraction measurements. The digitized raw EMG signal from each contraction was differentiated, which causes the necessary amplification of high-frequency components, rectified and integrated (DEMG) (29). Finally, the DEMG was normalized with respect to the maximum value observed within each contraction. As shown in Fig. 1, muscle activation time (AT) and deactivation time (DAT) were derived from the DEMG by analogy with the torque parameters.

Statistics. The results are given as means ± SE. A 2 × 2 × 12 [group (Cr, PI) × test (pre, post) × contraction (12 successive contractions)] repeated-measures (on test and contraction) ANOVA was used to analyze the dependent variables of torque (Tmax, CT, RT) and EMG (AT, DAT). Tukey’s test was used as a post hoc test to locate differences among means. The reliability of measurements of torque and time was evaluated by means of intraclass correlation. The relationship between variables was evaluated by using Pearson’s correlation coefficient. The level of statistical significance was set at P ≤ 0.05. All statistical procedures were performed by using Statistica software (Statsoft, Tulsa, OK).

RESULTS

Isometric elbow-flexion torque. Isometric torque production by the elbow flexor muscles was measured at an elbow angle of 110° during 12 maximal contractions interrupted by 10-s rest intervals. In the PI group, during the pretest, Tmax production was 57.0 ± 6.9 Nm for the first contraction and decreased to 50.0 ± 5.7 Nm at the last contraction. Corresponding values during the posttest were 58.1 ± 6.7 and 50.2 ± 5.6 Nm, respectively. In the Cr group, during both pre- and posttest, initial torque production as well as the time course of fatigue were similar to values in the PI group. Thus, during the pretest, elbow-flexion torque initially was 57.5 ± 6.3 Nm and decreased to 47.2 ± 4.4 Nm at the last contraction. During the posttest, initial and final torques were 57.9 ± 5.4 and 45.8 ± 4.3 Nm, respectively. In the total group of subjects, pre- and posttest mean torques were highly correlated (r = 0.98).
Subjects were asked to produce for each contraction a Tmax in the shortest possible time. CT was then defined as the time needed to raise torque from 0.25 to 0.75 of Tmax. Pre- and posttest values were similar in Pl (pretest, 81.7 ± 6.8 ms; posttest, 78.0 ± 9.8 ms) and Cr (pretest, 85.8 ± 7.8 ms; posttest, 80.8 ± 5.9 ms). Furthermore, CT was not affected by fatigue in either group.

RT. RT was calculated as the time course of isometric torque decay from 0.75 to 0.25 of Tmax. In the Pl group, a very high intraclass correlation ($r = 0.95$) existed between pre- and posttest RT measurements; this proves the high reproducibility of the RT measurements. As shown in Fig. 2, during the pretest, muscle RTs were similar for Pl and Cr. Mean RT over the 12 contractions was 98.3 ± 7.5 ms for Pl vs. 103.0 ± 7.0 ms for Cr. With increasing numbers of contractions, RT increased ($F_{\text{contraction}} = 23.7; P < 0.05$) to the same degree in both groups ($F_{\text{group} \times \text{contraction}} = 0.3; \text{not significant}$). However, compared with Pl intake, Cr loading resulted in faster muscle relaxation ($F_{\text{test} \times \text{group}} = 9.95; P < 0.05$; see Fig. 2, inset). Thus, during the posttest, mean RT over the 12 contractions was ~20% shorter in Cr (82.9 ± 4.0 ms) than in Pl (96.7 ± 8.6 ms). Furthermore, in the Cr group, as shown in Fig. 3, a high positive correlation ($r = 0.82$) was found between initial RT (mean of the 12 contractions) and the decrease in RT (pretest – posttest RT) produced by Cr intake.

AT and DAT. AT and DAT were derived from the quantified EMG. Both parameters were constant during the exercise test. During the pretest, overall AT (Pl, 62.2 ± 3.9 ms; Cr, 61.5 ± 3.8 ms) and DAT (Pl, 83.9 ± 3.1 ms; Cr, 82.1 ± 2.4 ms) were similar in both groups. Accordingly, during the posttest, mean AT was 60.6 ± 5.6 ms for Pl vs. 59.8 ± 3.7 ms for Cr. Mean DAT was 84.9 ± 2.9 ms and 83.9 ± 2.3 ms in Pl and Cr, respectively.

**DISCUSSION**

In 1992, Harris and co-workers (16) showed for the first time that short-term, high-dose Cr intake may markedly increase muscle Cr pool and improve one's capacity to perform rapid intermittent muscle contractions (17). However, to date, the precise physiological mechanisms underlying this ergogenic action remain poorly understood. Because facilitation of muscle relaxation may conceivably contribute to generate the ergogenic action of Cr loading during intermittent muscle contractions, we investigated here the effect of Cr supplementation on muscle relaxation rate during voluntary muscle contractions in humans. It is well documented that, compared with sustained muscle contraction, the excess energy expenditure during intermittent muscle contractions is at least partly accounted for by the energy cost of muscle relaxations (2, 18, 19). Furthermore, a recent study by Wakatsuki and co-workers (30) on rat soleus muscles stimulated to contract in vitro has indicated a beneficial effect of Cr intake on muscle relaxation rate. In their study, Cr supplementation (10 days, 0.2 g/day) was found to increase muscle phosphocreatine level to the same
degree as has been recently observed in humans (12, 14, 16, 28). Interestingly, this procedure was found also to shorten muscle RT, whereas the rate and level of force production during stimulation were unchanged.

In keeping with these in vitro data, the present findings on healthy volunteers during voluntary, maximal isometric contractions of biceps clearly demonstrate that Cr loading facilitates muscle relaxation. First, as shown in Fig. 2, after each of 12 intermittent, maximal isometric muscle contractions, RT was consistently shortened (~20%) after 5 days of Cr ingestion. This effect was not caused by different contraction power output or fatigue, because both the rate and level of torque production were not changed by Cr intake. Furthermore, altered neuromotor drive was not involved either, because the EMG activity (DEMG) was identical during Cr and PI administration. Second, in contrast with PI and as shown in Fig. 3, the shortening of muscle RT occurred in all subjects who were administered Cr. Moreover, the longer the initial RT, the better was the response to Cr intake. Accordingly, it has been demonstrated previously that subjects with low initial muscle Cr levels exhibit greater increment of muscle Cr store and improvement of muscle power during intermittent muscle contractions after Cr supplementation (7, 16, 28). This might indicate that persons with low initial muscle Cr levels exhibit a greater increment of muscle Cr store on Cr intake (7, 16, 28) which, in turn, may result in a more pronounced shortening of muscle RT. Furthermore, it must also be considered that persons with a higher percentage of slow-twitch muscle fibers may conceivably have lower mixed muscle Cr content (7, 27) and slower muscle relaxation (8, 11), hence responding better to Cr loading. In keeping with this line of reasoning, we recently have found Cr supplementation in rats to cause a greater rise of Cr content in slow-oxidative muscle fibers than in their fast-glycolytic counterparts (B. Op’t Eynde, unpublished observations).

The rate of cross-bridge detachment and the decay of cytoplasmic Ca$^{2+}$ by sarcoplasmic Ca$^{2+}$-ATPase activity are the major determinants of human skeletal muscle relaxation rate (8, 11). However, in regard to the action of Cr supplementation on muscle relaxation, sarcoplasmic Ca$^{2+}$-ATPase is likely to be the primary site of regulation. A very tight structural and functional coupling exists between Cr-kinase and Ca$^{2+}$-ATPase activity in the fast-twitch muscle fibers. In a more pronounced regulation of Cr kinase serves to optimize free energy of ATP hydrolysis by maintaining a low concentration of free ADP, which is very critical to Cr$^{2+}$-ATPase pump efficacy (11, 20, 21, 31). In this particular context, the current findings might indicate that the biochemical adaptations induced by Cr loading at the level of the sarcoplasmic reticulum, presumably the rise in local phosphocreatine concentration (12, 13, 16, 28), may allow sarcoplasmic Ca$^{2+}$-ATPase to operate at a higher thermodynamic efficiency and thereby facilitate muscle relaxation. Furthermore, because sarcoplasmic Ca$^{2+}$-ATPase, compared with myosin ATPase, is much more sensitive to a decrease in free energy of ATP hydrolysis (20, 21), Cr loading may facilitate muscle relaxation without simultaneously affecting force production during contraction (see Fig. 1 and Ref. 30). Furthermore, a higher rate of cross-bridge detachment might also contribute to facilitated muscle relaxation after Cr loading. Thus muscle phosphocreatine depletion, induced by β-guanidinopropionic acid feeding in rats, has been found to decrease the rate of cross-bridge cycling in cardiac muscle fibers (23). However, the excessive disturbance of muscle energy status caused by β-guanidinopropionic acid feeding (22, 24, 25, 30) may not be relevant to the understanding of the normal physiological adaptations of human muscle induced by oral Cr intake (7, 12, 14, 17, 28).

The present findings establish that shortening of muscle relaxation may contribute to the ergogenic action of Cr loading. However, Greenhaff and coworkers (14) also have shown previously that Cr supplementation enhances muscle phosphocreatine resynthesis in individuals with low initial muscle Cr levels. Furthermore, they recently reported improved ATP resynthesis in type II muscle fibers during intermittent exercise (7). Whether type I and/or type II muscle fibers exhibit facilitated muscle relaxation after Cr intake remains to be elucidated. Human biceps is composed of rather equal amounts of slow- and fast-twitch motor units (6), the vast majority of which may be assumed to be recruited during maximal isometric contraction (10). Thus either fiber population may conceivably have contributed to the shortening of muscle RT found after Cr intake in the current study.

In conclusion, short-term high-dose Cr supplementation shortens muscle RT during brief isometric muscle contractions. It is suggested that facilitation of muscle relaxation may contribute to the reported ergogenic action of Cr loading during exercise modes involving fast, repetitive, short muscle contractions and relaxations.

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