Arginine Metabolism: Enzymology, Nutrition, and Clinical Significance

# Potential Ergogenic Effects of Arginine and Creatine Supplementation[1,2]

Douglas Paddon-Jones, Elisabet Børsheim, and Robert R. Wolfe[3]

*Department of Surgery, The University of Texas Medical Branch and Metabolism Unit, Shriners Hospitals for Children, Galveston, TX 77550*

ABSTRACT The rationale for the use of nutritional supplements to enhance exercise capacity is based on the assumption that they will confer an ergogenic effect above and beyond that afforded by regular food ingestion alone. The proposed or advertised ergogenic effect of many supplements is based on a presumptive metabolic pathway and may not necessarily translate to quantifiable changes in a variable as broadly defined as exercise performance. L-arginine is a conditionally essential amino acid that has received considerable attention due to potential effects on growth hormone secretion and nitric oxide production. In some clinical circumstances (e.g., burn injury, sepsis) in which the demand for arginine cannot be fully met by de novo synthesis and normal dietary intake, exogenous arginine has been shown to facilitate the maintenance of lean body mass and functional capacity. However, the evidence that supplemental arginine may also confer an ergogenic effect in normal healthy individuals is less compelling. In contrast to arginine, numerous studies have reported that supplementation with the arginine metabolite creatine facilitates an increase in anaerobic work capacity and muscle mass when accompanied by resistance training programs in both normal and patient populations. Whereas improvement in the rate of phosphocreatine resynthesis is largely responsible for improvements in acute work capacity, the direct effect of creatine supplementation on skeletal muscle protein synthesis is less clear. The purpose of this review is to summarize the role of arginine and its metabolite creatine in the context of a nutrition supplement for use in conjunction with an exercise stimulus in both healthy and patient populations. J. Nutr. 134: 2888S–2894S, 2004.

KEY WORDS: • *diet* • *anabolism* • *muscle*

L-arginine is a conditionally essential amino acid. A typical Western diet contains ~3–6 g of arginine per day, most of which is derived from plant proteins such as soy (1). The bioavailability of exogenous arginine is ~60% (2). In healthy adults, arginine can be synthesized in sufficient quantities to meet most normal physiological demands with the rate of de novo synthesis remaining unaffected by several days of an arginine free diet (3,4). However, during periods of rapid growth, or in response to a traumatic or pathologic insult (5–7), the demand for arginine may not be fully met by de novo synthesis and normal dietary intake alone. In such instances, exogenous arginine provided parenterally or as a dietary supplement has been shown to facilitate the maintenance of lean body mass and improve functional capacity, benefits consistent with arginine's well documented vasodilatory properties and effect on growth hormone secretion. Nevertheless, despite evidence of ergogenic properties in clinical populations, it remains uncertain if supplemental arginine may also confer an ergogenic effect in normal healthy individuals exposed only to the stress of physical exercise.

The metabolic pathways of arginine have been well described. Endogenous arginine is synthesized primarily in the kidney from L-ornithine and L-citrulline precursors (8). The fate of arginine can be broadly accounted for by a combination of several processes. Following ingestion, a relatively small amount of arginine is metabolized by the enterocytes and the liver, whereas the remainder reaches the systemic circulation. Arginine may be converted to ornithine via the action of the enzyme arginase. It has been reported that as much as 50% of orally ingested arginine undergoes this fate (9). However, perhaps the most widely explored metabolic fate of arginine is its conversion to nitric oxide via nitric oxide synthase. The ergogenic potential of this pathway has received considerable attention and has wide clinical applicability. In addition to its acute vasodilatory properties, chronic exposure to nitric oxide also acts to slow a number of the processes associated with the onset of atherosclerosis. These include a reduction in monocyte and platelet adhesion and a reduction in smooth muscle cell proliferation (10–15).

## *Potential ergogenic effects of arginine*

A nutritional supplement that enhances exercise capacity is said to have an *ergogenic* effect. Potential ergogenic effects of

[1] Prepared for the conference "Symposium on Arginine" held April 5–6, 2004 in Bermuda. The conference was sponsored in part by an educational grant from Ajinomoto USA, Inc. Conference proceedings are published as a supplement to *The Journal of Nutrition.* Guest Editors for the supplement were Sidney M. Morris, Jr., Joseph Loscalzo, Dennis Bier, and Wiley W. Souba.

[2] This project was supported by NSBRI grant NPFR00205, NASA grant NAG9–1155, NIH 5 RO1 GM 57295 and Shriners Hospital grant 8490.

[3] To whom correspondence should be addressed. E-mail: rwolfe@utmb.edu.

L-arginine fall into 2 general categories: acute effects which result in enhanced exercise capacity after ingestion of arginine, and a chronic effect resulting from the stimulation of muscle protein synthesis and thus anabolism of muscle protein. Whereas it is clear that exogenous amino acids stimulate muscle protein synthesis at rest (16), following resistance exercise (17,18) and in association with a variety of clinical conditions including burn injury (19), sarcopenia (20,21), and cancer cachexia (22), evidence regarding the ergogenic effects of supplementation with individual amino acids such as arginine are equivocal.

### *Arginine and muscle protein synthesis*

The potential roles of arginine as a precursor for muscle protein synthesis as well as for nitric oxide (NO)[4] may interact in terms of the net effect of arginine on muscle protein synthesis. Under normal conditions sufficient arginine is produced endogenously to enable the exogenous ingestion of a mixture of essential amino acids (excluding arginine) to effectively stimulate muscle protein synthesis. In a recent study, a balanced mixture of all the amino acids in the same proportions as they appear in muscle protein was given to normal volunteers and muscle protein synthesis was determined by means of tracer methodology and arteriovenous sampling (23). The exact protocol was then repeated in the same subjects, except that only the essential amino acids (EAAs) were given (leucine, isoleucine, valine, methionine, lysine, phenylalanine, threonine, histadine). The amount of amino-N deleted from the mixture as a result of dropping the nonessential amino acids (NEAAs) was not made up by changing the amount of the essential amino acids given. Deletion of all nonessential amino acids, including arginine, did not diminish the anabolic response to the EAAs (23). Thus, under normal conditions arginine ingestion is not necessary for the stimulation of muscle protein synthesis by ingestion of EAAs. Conversely, ingestion of all the NEAAs that were deleted in this experiment, including arginine, had no effect on muscle protein synthesis.

The fact that increased arginine availability neither elicits an anabolic response in muscle nor is even required for the acute anabolic action of EAAs means that any effect of arginine on muscle protein synthesis is likely elicited by means of an indirect action. One possibility is via stimulation of NO synthesis. NO increases muscle blood flow, and this has been proposed to be a mechanism responsible for stimulation of muscle protein synthesis under certain conditions, such as during infusion of insulin-like growth factor 1 (IGF1) (24). However, the relation between muscle blood flow and muscle protein synthesis is complex. It is likely that in the basal state there is more than sufficient ATP available in muscle to supply the energy for required protein synthesis. Thus, when femoral blood flow to the leg was reduced 60% in the anesthetized rabbit by clamping the femoral artery, muscle protein synthesis was not affected (25) Thus, the delivery of substrates and oxygen to the muscle in the basal state is in excess of that required to maintain the basal rate of muscle protein synthesis. It therefore follows that an increase in delivery of oxygen or energy substrates is not required to fuel an increase in muscle protein synthesis. Rather, it is more likely that any relation between muscle blood flow and muscle protein synthesis is related to the delivery of amino acids.

The nature of the relationship between muscle blood flow and muscle protein synthesis is complicated by the fact that in the basal state the concentration of EAAs is higher in the intracellular space of muscle than in plasma [e.g., ref. (26)]. Since an increased perfusion of muscle would be expected to narrow the concentration gradient between plasma and the intracellular fluid, one might therefore expect an increase in the rate of muscle blood flow in the basal state to accelerate the efflux of intracellular EAAs into plasma. In this case the reduction of the intracellular availability of EAAs would be expected to decrease the rate of muscle protein synthesis (unpublished observation, Durham, W. J. & Wolfe, R. R., 2001). Confirmation of this notion comes from an experiment performed in normal volunteers to determine the role of the elevation in the rate of muscle blood flow in the response of muscle protein synthesis to resistance exercise. Subjects were studied during the hour following a bout of lower body resistance exercise. An arterial balloon catheter was inflated in the femoral artery of 1 leg to reduce the postexercise blood flow to the basal (pre-exercise) rate. Blood flow was reduced ~40% by the inflation of the balloon in the decreased-flow leg. As a consequence, the net balance of phenylalanine across the leg, reflecting the net balance between muscle protein synthesis and breakdown, was significantly improved by the reduction of flow due to a significant reduction in the efflux of amino acids from the intracellular space. These results suggest that an increase in muscle blood flow without a concomitant increase in the plasma concentrations of the EAAs would likely decrease, rather than increase, the rate of muscle protein synthesis.

The response to an increase in muscle blood flow would likely be different when amino acids are ingested than in the basal state. Following ingestion of amino acids, an increase in muscle blood flow would channel a higher proportion of absorbed amino acids to the muscle. In circumstances in which plasma EAA concentrations exceed their corresponding concentrations in muscle, one would expect increased delivery of EAAs (via stimulated blood flow) resulting in an increase in muscle uptake and an incorporation into muscle protein. This possibility is supported by the fact that ingestion of EAAs immediately before resistance exercise (so that they are absorbed when muscle blood flow is high during exercise) results in a significantly greater anabolic response of muscle protein than when the same amino acids are given after exercise when muscle blood flow returns towards the basal rate (27). From this observation it could be implied that the response to arginine supplementation would likely depend on whether or not other amino acids or protein are ingested simultaneously. If sufficient arginine is ingested to increase muscle blood flow as a consequence of accelerated NO production, then even though ingestion of arginine alone may not stimulate muscle protein synthesis, if arginine is taken in conjunction with other amino acids, a specific effect of arginine may be expected.

In order to test the potential interaction between arginine supplementation and the ingestion of other amino acids, muscle protein kinetics were determined in 2 groups of rabbits. One group received a commercial mixture of a blend of all 20 naturally-occurring amino acids. In the other group, the dose of the amino acid mixture was halved and the balance of amino acid nitrogen was made up with arginine. The same amount of amino nitrogen was given in both groups. The results are shown in **Table 1**. Whereas arginine alone had no effect, when arginine was added to the balanced amino acid

[4] Abbreviations used: AGAT, amindinotransferase; EAAs, essential amino acids; GAMT, *N*-guanidino-acetate methyltransferase; MPB, muscle protein breakdown; MPS, myofibrillar protein synthesis; mRNA, messenger RNA; NEAAs, nonessential amino acids; NO, nitric oxide; PCr, phosphocreatine.

**TABLE 1**

*Interaction between arginine supplementation and the ingestion of other amino acids in rabbits*

| | Synthesis | Breakdown | Net Balance |
|---|---|---|---|
| | | *μmol Phe/(kg · leg)* | |
| Travasol | 4.29 ± 0.75 | 8.64 ± 0.96 | −4.36 ± 1.18 |
| Travasol + Arginine | 8.11 ± 0.94* | 9.97 ± 1.13 | −1.86 ± 0.75[1] |

[1] Significantly higher. Total N equal in two groups, Infusion rate of 1638 μmol/kg · h in Travasol group and 1024 μmol/kg · h in Travasol + Arginine. Arginine = 25% of total amino acids in Travasol + Arginine group.

mixture, the rate of muscle protein synthesis as well as net protein balance was significantly stimulated compared to the balanced amino acid mixture. Neither insulin nor growth hormone concentrations were affected in the study by the increased proportion of arginine in the amino acid mixture (see below). Thus, whereas arginine supplementation alone is likely not an effective supplement to stimulate muscle protein synthesis, it may be effective if taken in conjunction with other amino acids or possibly with meals. This could be related to enhanced delivery of amino acids to muscle as a result of arginine-induced NO synthesis. Alternatively, it is possible that arginine has a more direct effect on the process of muscle protein synthesis that requires the concurrent elevation of other amino acids to be reflected in an increased amount.

### *Arginine as a secretagogue*

In addition to its role as a precursor for NO production and protein synthesis, in some instances exogenous arginine can act as a secretagogue, promoting growth hormone release via an inhibitition of somatostatin secretion (28–30). In an early study, oral administration of arginine aspartate (250 mg/kg/d) for seven days increased nocturnal growth hormone secretion in healthy male volunteers (20–35 yrs) by ~60% (31).

### *Effect of arginine on exercise performance*

Arginine has been shown to improve performance-related outcome variables. During a 5 wk progressive strength training program, volunteers were given a placebo or supplement containing 1 g arginine and 1 g ornithine each day. The results suggest that arginine and ornithine taken in conjunction with a high intensity strength training program can significantly increase muscle strength and lean body mass (32). On the other hand, a number of studies have failed to identify any beneficial effect of arginine supplementation. In a study examining a cohort of healthy young and elderly subjects, arginine failed to stimulate growth hormone secretion at rest or in association with a bout of resistance exercise (33). Similarly, ingestion of 15 g arginine daily for 14 d prior to a marathon did not alter insulin, ammonia, plasma creatine kinase activity or respiratory exchange ratio. However, supplementation did lower the plasma concentration of several other amino acids and increase plasma concentrations of glucagon, urea, and somatrophic hormone.

### *Arginine supplementation in healthy and patient populations*

Whereas the results of studies assessing the ergogenic properties of arginine in healthy subjects are equivocal, subject populations whose health and ability to exercise was compromised by underlying pathology have apparently benefited from arginine supplementation. Thus, anti-atherogenic and vasodilatory properties of arginine appear to improve exercise tolerance in patient populations via an improvement in coronary and/or peripheral blood flow (34). In patients with cardiovascular disease, intravenous and oral arginine administration have been shown to support endothelial function by enhancing vasodilation and reducing monocyte adhesion (10–15). In individuals with stable angina pectoris, a key factor contributing to exercise intolerance is an inability to meet myocardial $O_2$ demands due to impaired coronary blood flow. In these patients, ingestion of 6 g of arginine per day for 3 d has been shown to improve exercise workload during a treadmill stress test (6,35). In such instances, the vasodilatory properties of arginine may facilitate an increase in $O_2$ delivery, which helps meet the increased demands caused by physical activity. Arginine supplementation may also play a beneficial role following burn injury. Using an animal model, improved immune function and survival have been noted when arginine ingestion reached 2% of total dietary energy intake (5,36,37). This nutrition strategy has also been extended to the treatment of human burn patients although additional research is warranted (38,39).

### *Creatine*

Creatine (α-methyl guandino-acetic acid) is an amino acid derivative synthesized from arginine, glycine, and methionine (**Fig. 1**) in the kidneys, liver, and pancreas. The synthesis rate is about 1–2 g/d (40). Creatine can also be obtained through the diet, mainly from meat and fish. The average person consumes about 1 g creatine each day from a regular diet. Creatine is degraded into creatinine and excreted in the urine at a rate of about 2 g/d.

About 90–95% of the body's creatine is found in skeletal muscle. Of this, approximately one-third is free creatine, whereas two-thirds exist as phosphocreatine (PCr). The uptake from circulation is an active process facilitated by a $Na^+$-dependent transporter against a concentration gradient (41). PCr serves a major role in energy metabolism. When energy demands increase, PCr donates its phosphate to ADP to produce ATP. The ATP-PCr system can provide energy at high rates, but only for a few (10–15) seconds before the PCr store is emptied. Thus, creatine is involved in temporal energy

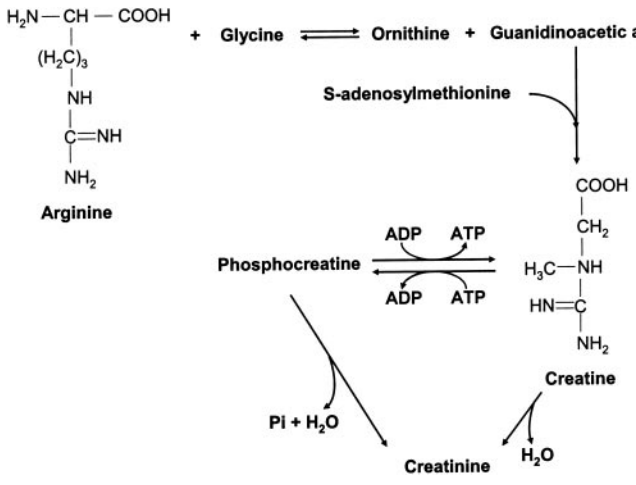


**FIGURE 1** Pathway of creatine synthesis.

buffering, and also in spatial energy buffering, proton buffering, and glycolysis regulation (42). Because PCr is a limiting factor in maintaining ATP resynthesis during maximal short-term exercise, an increased PCr concentration should theoretically increase the energy reserve for such exercise. Therefore, it has been suggested that creatine loading will improve performance during short-term maximal exercise, analogous to the effect of glycogen loading before endurance exercise.

The normal concentration of total creatine in skeletal muscle is about 120 mmol/kg (dry mass) (43,44), whereas the upper limit appears to be about 150–160 mmol/kg. It has repeatedly been shown that the muscle concentration of total creatine can indeed be increased by oral creatine supplementation. The supplementation protocols typically involve a loading phase of ~20 g creatine monohydrate for 4–6 d, followed by a maintenance dose of about 5 g daily for 2–3 wk (43,44). This regimen will theoretically increase the blood concentration of creatine to a level optimal for uptake in the muscle. Ingestion above this amount will likely lead to excess creatine wasted in the urine. Lower dose supplementation of 2–3 g/d will also elevate muscle creatine, but the increase occurs gradually over several weeks, rather than days.

The increase in muscle creatine content with supplementation is usually greatest in subjects with low initial concentration, whereas subjects with higher starting concentration may experience little or no increase (43,44). Hence, it has been shown that vegetarians typically are more responsive to creatine supplementation, since their initial levels are low from a diet that contains little creatine (45). Still the initial creatine content cannot fully explain the large intersubject variability in response to supplementation, suggesting that there are "responders" and "nonresponders" (46).

An increased inward creatine transport has been found when creatine is ingested together with carbohydrates (47,48) or a carbohydrate/protein mixture (49). This seems to be caused by an insulin effect on the uptake (50,51). Ingestion of creatine and 1 g glucose/kg body mass twice per day increased total muscle creatine by 9% vs. creatine intake alone (48).

### *Effects of creatine on exercise performance*

The possible ergogenic effect of creatine has led to a widespread use of supplementation in sport (52–57). It has been estimated that 80% of the athletes competing in the 1996 Olympic Games were probably using, or had been using, creatine and the 1998 sale was estimated at $100 million in the United States alone (58). Many athletes ingest creatine over long periods of time, and not only in connection with special events (57,59). Often it is used during training periods aimed to increase strength and body mass (59).

The question then remains whether creatine has any ergogenic effects. A large number of studies have been performed to test the effect of creatine on exercise performance. These have been summarized in several previous reviews on this topic (46,60–66). A short summary is given below.

From controlled laboratory tests, it can be concluded that creatine supplementation appears to improve performance on repeated sprints (<30 s), whereas the effect on single sprints and on muscle strength is less conclusive (61,66). Thus, the major advantage of creatine may derive from improved training capacity. Also, the effect on performance during longer exercise (>90 s) is unclear. This is not surprising, since the contribution of the PCr-ATP system decreases as the exercise duration increases. No effect has been found in longer-duration aerobic type exercise (65,67–69). Even though creatine supplementation did not increase the performance during the endurance part of prolonged cycling, it did, however, increase sprint performance within and after this phase (70,71).

The results from more recent field studies are variable, probably caused by factors such as intake of meat in the placebo group, sample size, and type and duration of exercise (62). In meta-analyses of the effect of creatine on exercise performance, the conclusions are also somewhat variable (72). Nevertheless, taken together, it is suggested that creatine supplementation is of benefit to exercise lasting 30 s or less.

### *Effects of creatine on muscle mass*

As mentioned, many athletes use creatine in connection with resistance training as an aid to increase the training effect on muscle mass and strength. Meta-analyses have shown an effect of creatine supplementation on body composition and muscular strength in resistance training program (72,73). Twelve weeks of resistance training combined with creatine supplementation increased muscle fiber diameter by 35% in both Type 1 and 2 muscle fibers in men vs. 6–15% in placebo-supplemented resistance trained subjects (74).

The effect on body mass may result from supplemented subjects training on higher workloads than the placebo control subjects, since higher creatine and PCr stores in the muscle would theoretically improve work capacity during this kind of exercise. Thus, athletes should be able to perform more repetitions and recover faster between sets compared to nonsupplemented controls (75). In accordance with this notion, no difference in strength and weight lifting performance was found between creatine and placebo groups during an 8-wk resistance training program, when the training volume was constant between groups (76). Thus, the beneficial effects of creatine on muscular strength and body composition probably occur by the following sequence: increased muscle creatine, increased training intensity, greater training stimulus, and enhanced physiological adaptations to training.

Creatine supplementation is also associated with an immediate increase in body mass. Typically this amounts to about 1–2 kg in 4–7 d (75,77,78). The mechanism responsible for this appears to be an increase in total body water (43,44). Hultman et al. (44) reported that creatine markedly reduced urinary volume during the initial days of supplementation, suggesting that the increased body weight primarily was water retention. It must be pointed out that this increase in body weight makes a blinding of studies difficult.

Another possibility is that part of the increased body weight is caused by increased protein synthesis, conceivably stimulated by the cell swelling (79,80). Cell swelling has been shown to act as an anabolic signal stimulating protein synthesis and net protein deposition (81). In agreement with this, a stimulating effect of creatine on protein synthesis in animal cardiac and skeletal muscle in vitro has been found (73,82,83), although there are also studies that do not confirm this (84,85).

Recently, the effect of creatine on protein synthesis in human skeletal muscle has been studied more directly. Parise et al. (86) determined the effect of creatine intake (20 g/d for 5 d followed by 5 g/d for 3–4 d) on indices of protein metabolism. [1-$^{13}$C]leucine was infused before and after the supplementation period. Creatine had no effect on mixed muscle protein fractional synthetic rate (m. vastus lateralis). In men, but not in women, reduced leucine oxidation and rate of appearance of plasma leucine (estimate of whole body protein breakdown) were observed. Total body mass or fat free mass was not affected. The author concluded that short-term supplementation may have some anticatabolic action in some

protein in men, but does not increase whole-body or mixed-muscle protein synthesis.

Louis et al. (87) tested the effect of creatine supplementation on myofibrillar protein synthesis (MPS; measured as incorporation of [1-$^{13}$C]leucine in the quadriceps muscle) and muscle protein breakdown (MPB; measured as dilution of [1-$^{13}$C]leucine or [$^{2}H_5$]phenylalanine across the forearm). In this study, 6 men were tested twice, before and after creatine ingestion (21 g/d for 5 d). In each study the subjects were tested both before (fasted) and after intake of maltodextrin and protein (postabsorptive). Feeding led to a doubling of MPS, and a ~40% depression of MPB, but no effect of creatine was found on these parameters either in the fed or fasted states.

The same authors (88) also examined the possible stimulatory effect of creatine in conjunction with acute resistance exercise. Seven healthy men performed 20 × 10 repetitions of leg extension-flexion at 75% of 1-repetition maximum in 1 leg, before and after creatine intake (same dose as in previous study). The subjects were studied both in fasted and fed state, and again no effect of creatine was found on the synthetic rates of myofibrillar and sarcoplasmic proteins or MPB in any state, whereas exercise increased the synthetic rates of proteins by 2–3 fold. In fact, the rate of MPS in the exercised leg in the creatine supplemented subjects was about 60% lower than in the placebo group, but this failed to reach significance ($P < 0.08$). The authors suggested that this may be an indication that creatine feeding acutely inhibits the postexercise increase in MPS, possibly by blunting any stimulus of MPS that depends on lowering of energy status during the exercise bout.

Hence, any effect of creatine on translation of pre-existing messenger RNA (mRNA) seems unlikely. However, it cannot be ruled out that creatine (in combination with resistance exercise) can change transcription or activate satellite cells. Clearly, both exercise in itself and food are much stronger stimuli for protein synthesis than creatine intake in healthy individuals (89).

### *Creatine supplementation in patient groups*

Most studies of the response to creatine supplementation have assessed exercise performance in healthy subjects. However, there are some indications that supplementation may be useful in the treatment of certain diseases, such as muscle fatigue secondary to impaired energy production and diseases resulting in muscle atrophy (90). The mechanisms underlying the effect of creatine in these circumstances are largely unknown, but may be due to the increased energy in the form of PCr, increased muscle accretion, and stabilization of membranes, as discussed by Persky and Brazeau (90).

Inborn errors of energy metabolism have been identified in 3 of the main steps in creatine metabolism: arginine:glycine amindinotransferase (AGAT), S-adenosyl-L-methionine:*N*-guanidino-acetate methyltransferase (GAMT) and the creatine transporter. Oral creatine has been shown to improve the clinical symptoms in both AGAT and GAMT deficiency, but not in the creatine transporter deficiency (91). Supplementation has also been shown to have neuroprotective effects in several animal models of neurological diseases, e.g., Huntington's disease, Parkinson's disease, and amyotropic lateral sclerosis (91). However, this has to be confirmed in clinical studies in humans.

### *Side effects of creatine*

Potential side effects of long-term use of creatine are unknown. Since the majority of the creatine ingested is removed from the plasma by the kidneys and excreted in the urine, concerns have particularly been related to a possible effect on renal function, and especially in subjects with impaired renal capacity. However, Poortmans and Francaux (92) did not find any effect of creatine supplementation on kidney function in healthy athletes.

Further concerns are the possibility for muscle dysfunction and the association between supplementation and heat illness, because creatine may increase intracellular water and dilute electrolytes. However, increased prevalence of muscle injury and cramping (93,94) or heat illness (95) has not been reported in creatine users vs. nonusers, but long-terms studies are lacking.

Because creatine affects fluid balance, users should be advised to pay attention to fluid need in hot climates. Further, because commercially marketed creatine products do not meet the same quality control standards as pharmaceuticals, there is always a concern of impurities or doses higher or lower than those on the labeling. Intake of large doses of creatine can reduce endogenous synthesis, probably via feedback regulation, but the enzymes involved in creatine synthesis seem to be reactivated when supplementation is discontinued. Finally, despite the fact that creatine is normally found in cardiac muscle, brain, and testes, these areas remain essentially unstudied with respect to oral creatine supplementation. The effect on these organ systems also needs to be included in long-term, randomized, controlled studies.

### *Summary*

The primary mechanism explaining the acute ergogenic effect of creatine is enlargement of the phosphagen pool available for rapid resynthesis of ATP during periods of maximal ATP turnover. Thus, the depletion of PCr and associated reduction in the ability to produce force is delayed, especially in fast muscle fibers. An enhanced rate of PCr resynthesis during recovery periods allows for a higher PCr level at the start of a subsequent bout, when intermittent work is performed. No direct effect of creatine supplementation on muscle protein synthesis has been found.

## LITERATURE CITED

1. Visek, W. J. (1986) Arginine needs, physiological state and usual diets. A reevaluation. J. Nutr. 116: 36–46.
2. Reyes, A. A., Karl, I. E. & Klahr, S. (1994) Role of arginine in health and in renal disease. Am. J. Physiol. 267: F331–F346.
3. Castillo, L., deRojas, T. C., Chapman, T. E., Vogt, J., Burke, J. F., Tannenbaum, S. R. & Young, V. R. (1993) Splanchnic metabolism of dietary arginine in relation to nitric oxide synthesis in normal adult man. Proc. Natl. Acad. Sci. U.S.A. 90: 193–197.
4. Castillo, L., Ajami, A., Branch, S., Chapman, T. E., Yu, Y. M., Burke, J. F. & Young, V. R. (1994) Plasma arginine kinetics in adult man: response to an arginine-free diet. Metabolism 43: 114–122.
5. Saito, H., Trocki, O., Wang, S. L., Gonce, S. J., Joffe, S. N. & Alexander, J. W. (1987) Metabolic and immune effects of dietary arginine supplementation after burn. Arch. Surg. 122: 784–789.
6. Ceremuzynski, L., Chamiec, T. & Herbaczynska-Cedro, K. (1997) Effect of supplemental oral L-arginine on exercise capacity in patients with stable angina pectoris. Am. J. Cardiol. 80: 331–333.
7. Witte, M. B. & Barbul, A. (2003) Arginine physiology and its implication for wound healing. Wound Repair Regen. 11: 419–423.
8. Dhanakoti, S. N., Brosnan, J. T., Herzberg, G. R. & Brosnan, M. E. (1990) Renal arginine synthesis: studies in vitro and in vivo. Am. J. Physiol. 259: E437–E442.
9. Castillo, L., Sanchez, M., Vogt, J., Chapman, T. E., DeRojas-Walker, T. C., Tannenbaum, S. R., Ajami, A. M. & Young, V. R. (1995) Plasma arginine, citrulline, and ornithine kinetics in adults, with observations on nitric oxide synthesis. Am. J. Physiol. 268: E360–E367.
10. Tangphao, O., Chalon, S., Moreno, H., Jr., Hoffman, B. B. & Blaschke, T. F. (1999) Pharmacokinetics of L-arginine during chronic administration to patients with hypercholesterolaemia. Clin. Sci. (Lond.) 96: 199–207.
11. Tsao, P. S., Theilmeier, G., Singer, A. H., Leung, L. L. & Cooke, J. P.

(1994) L-arginine attenuates platelet reactivity in hypercholesterolemic rabbits. Arterioscler. Thromb. 14: 1529–1533.
12. Cooke, J. P. & Tsao, P. S. (1994) Is NO an endogenous antiatherogenic molecule? Arterioscler. Thromb. 14: 653–655.
13. Drexler, H., Fischell, T. A., Pinto, F. J., Chenzbraun, A., Botas, J., Cooke, J. P. & Alderman, E. L. (1994) Effect of L-arginine on coronary endothelial function in cardiac transplant recipients. Relation to vessel wall morphology. Circulation 89: 1615–1623.
14. Wang, B. Y., Singer, A. H., Tsao, P. S., Drexler, H., Kosek, J. & Cooke, J. P. (1994) Dietary arginine prevents atherogenesis in the coronary artery of the hypercholesterolemic rabbit. J. Am. Coll. Cardiol. 23: 452–458.
15. Tsao, P. S., McEvoy, L. M., Drexler, H., Butcher, E. C. & Cooke, J. P. (1994) Enhanced endothelial adhesiveness in hypercholesterolemia is attenuated by L-arginine. Circulation 89: 2176–2182.
16. Paddon-Jones, D., Sheffield-Moore, M., Creson, D. L., Sanford, A. P., Wolf, S. E., Wolfe, R. R. & Ferrando, A. A. (2003) Hypercortisolemia alters muscle protein anabolism following ingestion of essential amino acids. Am. J. Physiol. Endocrinol. Metab. 284: E946–E953.
17. Tipton, K. D., Ferrando, A. A., Phillips, S. M., Doyle, D. & Wolfe, R. R. (1999) Post-exercise net protein synthesis in human muscle from orally administered amino acids. Am. J. Physiol. Endocrinol. Metab. 276: E628–E634.
18. Børsheim, E., Tipton, K. D., Wolf, S. E. & Wolfe, R. R. (2002) Essential amino acids and muscle protein recovery from resistance exercise. Am. J. Physiol. Endocrinol. Metab. 283: E648–E657.
19. Wolfe, R. R., Goodenough, R. D., Burke, J. F. & Wolfe, M. H. (1983) Responses of protein and urea kinetics in burn patients to different levels of protein intake. Ann. Surg. 197: 163–171.
20. Volpi, E., Ferrando, A. A., Yeckel, C. W., Tipton, K. D. & Wolfe, R. R. (1998) Exogenous amino acids stimulate net muscle protein synthesis in the elderly. J. Clin. Invest. 101: 2000–2007.
21. Volpi, E. & Rasmussen, B. B. (2000) Nutrition and muscle protein metabolism in the elderly. Diabetes Nutr. Metab. 13: 99–107.
22. Mantovani, G., Maccio, A., Madeddu, C. & Massa, E. (2003) Cancer-related cachexia and oxidative stress: beyond current therapeutic options. Expert Rev. Anticancer Ther. 3: 381–392.
23. Volpi, E., Kobayashi, H., Sheffield-Moore, M., Mittendorfer, B. & Wolfe, R.R. (2003) Essential amino acids stimulate muscle protein anabolism in healthy older adults regardless of the presence of non-essential amino acids. Am. J. Clin. Nutr. 78: 250–258.
24. Fryburg, D. A. (1996) $N^G$-monomethyl-L-arginine inhibits the blood flow but not the insulin-like response of forearm muscle to IGF-1: possible role of nitric oxide in muscle protein synthesis. J. Clin. Invest. 97: 1319–1328.
25. Zhang, X. J., Irtun, O., Chinkes, D. L. & Wolfe, R. R. (2004) Responses of muscle blood flow and protein metabolism to femoral artery clamp. Am. J. Physiol. (In press).
26. Bohe, J., Low, A., Wolfe, R. R. & Rennie, M. J. (2003) Human muscle protein synthesis is modulated by extracellular but not intracellular amino acid availability: A dose response study. J. Physiol. 552: 315–324.
27. Tipton, K. D., Rasmussen, B. B., Miller, S. L., Wolf, S. E., Owens-Stovall, Petrini, B. E. & Wolfe, R. R. (2001) Timing of amino acid-carbohydrate ingestion alters anabolic response of muscle to resistance exercise. Am. J. Physiol. 281: E197–E206.
28. Merimee, T. J., Rabinowitz, D., Riggs, L., Burgess, J. A., Rimoin, D. L. & McKusick, V. A. (1967) Plasma growth hormone after arginine infusion. Clinical experiences. N. Engl. J. Med. 276: 434–439.
29. Fisker, S., Nielsen, S., Ebdrup, L., Bech, J. N., Christiansen, J. S., Pedersen, E. B. & Jorgensen, J. O. (1999) The role of nitric oxide in L-arginine-stimulated growth hormone release. J. Endocrinol. Invest. 22: 89–93.
30. Fisker, S., Nielsen, S., Ebdrup, L., Bech, J. N., Christiansen, J. S., Pedersen, E. B. & Jorgensen, J. O. (1999) L-arginine-induced growth hormone secretion is not influenced by co-infusion of the nitric oxide synthase inhibitor N-monomethyl-L-arginine in healthy men. Growth Horm. IGF Res. 9: 69–73.
31. Besset, A., Bonardet, A., Rondouin, G., Descomps, B. & Passouant, P. (1982) Increase in sleep related GH and Prl secretion after chronic arginine aspartate administration in man. Acta Endocrinol. (Copenh.) 99: 18–23.
32. Elam, R. P., Hardin, D. H., Sutton, R. A. & Hagen, L. (1989) Effects of arginine and ornithine on strength, lean body mass and urinary hydroxyproline in adult males. J. Sports Med. Phys. Fitness 29: 52–56.
33. Marcell, T. J., Taaffe, D. R., Hawkins, S. A., Tarpenning, K. M., Pyka, G., Kohlmeier, L., Wiswell, R. A. & Marcus, R. (1999) Oral arginine does not stimulate basal or augment exercise-induced GH secretion in either young or old adults. J. Gerontol. A Biol. Sci. Med. Sci. 54: M395–M399.
34. Rector, T. S., Bank, A. J., Tschumperlin, L. K., Mullen, K. A., Lin, K. A. & Kubo, S. H. (1996) Abnormal desmopressin-induced forearm vasodilatation in patients with heart failure: dependence on nitric oxide synthase activity. Clin. Pharmacol. Ther. 60: 667–674.
35. Bednarz, B., Wolk, R., Chamiec, T., Herbaczynska-Cedro, K., Winek, D. & Ceremuzynski, L. (2000) Effects of oral L-arginine supplementation on exercise-induced QT dispersion and exercise tolerance in stable angina pectoris. Int. J. Cardiol. 75: 205–210.
36. Madden, H. P., Breslin, R. J., Wasserkrug, H. L., Efron, G. & Barbul, A. (1988) Stimulation of T cell immunity by arginine enhances survival in peritonitis. J. Surg. Res. 44: 658–663.
37. Barbul, A., Wasserkrug, H. L., Yoshimura, N., Tao, R. & Efron, G. (1984) High arginine levels in intravenous hyperalimentation abrogate post-traumatic immune suppression. J. Surg. Res. 36: 620–624.
38. Hildreth, M. & Gottschlich, M. (1996) Nutritional support of the burned patient. In: Total Burn Care (Herndon, D. N., ed.), p. 240. W.B Saunders Company Ltd., London, UK.
39. Bower, R. H., Cerra, F. B., Bershadsky, B., Licari, J. J., Hoyt, D. B., Jensen, G. L., Van Buren, C. T., Rothkopf, M. M., Daly, J. M. & Adelsberg, B. R. (1995) Early enteral administration of a formula (Impact) supplemented with arginine, nucleotides, and fish oil in intensive care unit patients: results of a multicenter, prospective, randomized, clinical trial. Crit. Care Med. 23: 436–449.
40. Walker, J. B. (1979) Creatine: biosynthesis, regulation, and function. Adv. Enzymol. Relat. Areas Mol. Biol. 50: 177–242.
41. Guimbal, C. & Kilimann, M. W. (1993) A Na(+)-dependent creatine transporter in rabbit brain, muscle, heart, and kidney. cDNA cloning and functional expression. J. Biol. Chem. 268: 8418–8421.
42. Greenhaff, P. L. (2001) The creatine-phosphocreatine system: there's more than one song in its repertoire. J. Physiol. 537: 657.
43. Harris, R. C., Soderlund, K. & Hultman, E. (1992) Elevation of creatine in resting and exercised muscle of normal subjects by creatine supplementation. Clin. Sci. (Lond.) 83: 367–374.
44. Hultman, E., Soderlund, K., Timmons, J. A., Cederblad, G. & Greenhaff, P. L. (1996) Muscle creatine loading in men. J. Appl. Physiol 81: 232–237.
45. Burke, D. G., Chilibeck, P. D., Parise, G., Candow, D. G., Mahoney, D. & Tarnopolsky, M. (2003) Effect of creatine and weight training on muscle creatine and performance in vegetarians. Med. Sci. Sports Exerc. 35: 1946–1955.
46. Demant, T. W. & Rhodes, E. C. (1999) Effects of creatine supplementation on exercise performance. Sports Med. 28: 49–60.
47. Green, A. L., Hultman, E., Macdonald, I. A., Sewell, D. A. & Greenhaff, P. L. (1996) Carbohydrate ingestion augments skeletal muscle creatine accumulation during creatine supplementation in humans. Am. J. Physiol. 271: E821–E826.
48. Preen, D., Dawson, B., Goodman, C., Beilby, J. & Ching, S. (2003) Creatine supplementation: a comparison of loading and maintenance protocols on creatine uptake by human skeletal muscle. Int. J. Sport Nutr. Exerc. Metab. 13: 97–111.
49. Steenge, G. R., Simpson, E. J. & Greenhaff, P. L. (2000) Protein- and carbohydrate-induced augmentation of whole body creatine retention in humans. J. Appl. Physiol. 89: 1165–1171.
50. Koszalka, T. R., Andrew, C. L. & Brent, R. L. (1972) Effect of insulin on the uptake of creatine-1–14 C by skeletal muscle in normal and x-irradiated rats. Proc. Soc. Exp. Biol. Med. 139: 1265–1271.
51. Haugland, R. B. & Chang, D. T. (1975) Insulin effect on creatine transport in skelatal muscle (38464). Proc. Soc. Exp. Biol. Med. 148: 1–4.
52. Greenwood, M., Farris, J., Kreider, R., Greenwood, L. & Byars, A. (2000) Creatine supplementation patterns and perceived effects in select division I collegiate athletes. Clin. J. Sport Med. 10: 191–194.
53. LaBotz, M. & Smith, B. W. (1999) Creatine supplement use in an NCAA Division I athletic program. Clin. J. Sport Med. 9: 167–169.
54. McGuine, T. A., Sullivan, J. C. & Bernhardt, D. T. (2001) Creatine supplementation in high school football players. Clin. J. Sport Med. 11: 247–253.
55. McGuine, T. A., Sullivan, J. C. & Bernhardt, D. A. (2002) Creatine supplementation in Wisconsin high school athletes. Wisconsin Medical Journal 101: 25–30.
56. Rønsen, O., Sundgot-Borgen, J. & Mæhlum, S. (1999) Supplement use and nutritional habits in Norwegian elite athletes. Scand. J. Med. Sci. Sports 9: 28–35.
57. Sheppard, H. L., Raichada, S. M., Kouri, K. M., Stenson-Bar-Maor, L. & Branch, J. D. (2000) Use of creatine and other supplements by members of civilian and military health clubs: a cross-sectional survey. Int. J. Sport Nutr. Exerc. Metab. 10: 245–259.
58. Williams, M. H., Kreider, R. B. & Branch, J. D. (1999) Creatine: The Power Supplement., pp. 1–264. Human Kinetics, Champaign, IL.
59. Juhn, M. S., O'Kane, J. W. & Vinci, D. M. (1999) Oral creatine supplementation in male collegiate athletes: a survey of dosing habits and side effects. J. Am. Diet. Assoc. 99: 593–595.
60. Mesa, J. L., Ruiz, J. R., Gonzalez-Gross, M. M., Gutierrez, S. A. & Castillo Garzon, M. J. (2002) Oral creatine supplementation and skeletal muscle metabolism in physical exercise. Sports Med. 32: 903–944.
61. Kreider, R. B. (2003) Effects of creatine supplementation on performance and training adaptations. Mol. Cell Biochem. 244: 89–94.
62. Lemon, P. W. (2002) Dietary creatine supplementation and exercise performance: why inconsistent results? Can. J. Appl. Physiol. 27: 663–681.
63. Maughan, R. J. (1995) Creatine supplementation and exercise performance. Int. J. Sport Nutr. 5: 94–101.
64. Rawson, E. S. & Volek, J. S. (2003) Effects of creatine supplementation and resistance training on muscle strength and weightlifting performance. J. Strength Cond. Res. 17: 822–831.
65. Terjung, R. L., Clarkson, P., Eichner, E. R., Greenhaff, P. L., Hespel, P. J., Israel, R. G., Kraemer, W. J., Meyer, R. A., Spriet, L. L., Tarnopolsky, M. A., Wagenmakers, A. J. & Williams, M. H. (2000) American College of Sports Medicine roundtable. The physiological and health effects of oral creatine supplementation. Med. Sci. Sports Exerc. 32: 706–717.
66. Williams, M. H. & Branch, J. D. (1998) Creatine supplementation and exercise performance: an update. J. Am. Coll. Nutr. 17: 216–234.
67. Balsom, P. D., Harridge, S. D., Soderlund, K., Sjodin, B. & Ekblom, B. (1993) Creatine supplementation per se does not enhance endurance exercise performance. Acta. Physiol. Scand. 149: 521–523.

68. Juhn, M. S. & Tarnopolsky, M. (1998) Oral creatine supplementation and athletic performance: a critical review. Clin. J. Sport Med. 8: 286–297.

69. van Loon, L. J., Oosterlaar, A. M., Hartgens, F., Hesselink, M. K., Snow, R. J. & Wagenmakers, A. J. (2003) Effects of creatine loading and prolonged creatine supplementation on body composition, fuel selection, sprint and endurance performance in humans. Clin. Sci. (Lond.) 104: 153–162.

70. Engelhardt, M., Neumann, G., Berbalk, A. & Reuter, I. (1998) Creatine supplementation in endurance sports. Med. Sci. Sports Exerc. 30: 1123–1129.

71. Vandebuerie, F., Vanden Eynde, B., Vandenberghe, K. & Hespel, P. (1998) Effect of creatine loading on endurance capacity and sprint power in cyclists. Int. J. Sports Med. 19: 490–495.

72. Branch, J. D. (2003) Effect of creatine supplementation on body composition and performance: a meta-analysis. Int. J. Sport Nutr. Exerc. Metab. 13: 198–226.

73. Nissen, S. L. & Sharp, R. L. (2003) Effect of dietary supplements on lean mass and strength gains with resistance exercise: a meta-analysis. J. Appl. Physiol. 94: 651–659.

74. Volek, J. S., Duncan, N. D., Mazzetti, S. A., Staron, R. S., Putukian, M., Gomez, A. L., Pearson, D. R., Fink, W. J. & Kraemer, W. J. (1999) Performance and muscle fiber adaptations to creatine supplementation and heavy resistance training. Med. Sci. Sports Exerc. 31: 1147–1156.

75. Greenhaff, P. L., Bodin, K., Soderlund, K. & Hultman, E. (1994) Effect of oral creatine supplementation on skeletal muscle phosphocreatine resynthesis. Am. J. Physiol. 266: E725–E730.

76. Syrotuik, D. G., Game, A. B., Gillies, E. M. & Bell, G. J. (2001) Effects of creatine monohydrate supplementation during combined strength and high intensity rowing training on performance. Can. J. Appl. Physiol. 26: 527–542.

77. Earnest, C. P., Snell, P. G., Rodriguez, R., Almada, A. L. & Mitchell, T. L. (1995) The effect of creatine monohydrate ingestion on anaerobic power indices, muscular strength and body composition. Acta. Physiol. Scand. 153: 207–209.

78. Mihic, S., MacDonald, J. R., McKenzie, S. & Tarnopolsky, M. A. (2000) Acute creatine loading increases fat-free mass, but does not affect blood pressure, plasma creatinine, or CK activity in men and women. Med. Sci. Sports Exerc. 32: 291–296.

79. Clarkson, P. M. & Rawson, E. S. (1999) Nutritional supplements to increase muscle mass. Crit. Rev. Food Sci. Nutr. 39: 317–328.

80. Berneis, K., Ninnis, R., Haussinger, D. & Keller, U. (1999) Effects of hyper- and hypoosmolality on whole body protein and glucose kinetics in humans. Am. J. Physiol. (Endocrinol. Metab.) 276: E188–E195.

81. Lang, F., Busch, G. L., Ritter, M., Volkl, H., Waldegger, S., Gulbins, E. & Haussinger, D. (1998) Functional significance of cell volume regulatory mechanisms. Physiol. Rev. 78: 247–306.

82. Ingwall, J. S., Weiner, C. D., Morales, M. F., Davis, E. & Stockdale, F. E. (1974) Specificity of creatine in the control of muscle protein synthesis. J. Cell Biol. 62: 145–151.

83. Ingwall, J. S. (1976) Creatine and the control of muscle-specific protein synthesis in cardiac and skeletal muscle. Circ. Res. 38: I115–I123.

84. Fry, D. M. & Morales, M. F. (1980) A reexamination of the effects of creatine on muscle protein synthesis in tissue culture. J. Cell Biol. 84: 294–297.

85. Young, R. B. & Denome, R. M. (1984) Effect of creatine on contents of myosin heavy chain and myosin-heavy-chain mRNA in steady-state chicken muscle-cell cultures. Biochem. J. 218: 871–876.

86. Parise, G., Mihic, S., MacLennan, D., Yarasheski, K. E. & Tarnopolsky, M. A. (2001) Effects of acute creatine monohydrate supplementation on leucine kinetics and mixed-muscle protein synthesis. J. Appl. Physiol. 91: 1041–1047.

87. Louis, M., Poortmans, J. R., Francaux, M., Hultman, E., Berre, J., Boisseau, N., Young, V. R., Smith, K., Meier-Augenstein, W., Babraj, J. A., Waddell, T. & Rennie, M. J. (2003) Creatine supplementation has no effect on human muscle protein turnover at rest in the postabsorptive or fed states. Am. J. Physiol. (Endocrinol. Metab.) 284: E764–E770.

88. Louis, M., Poortmans, J. R., Francaux, M., Berre, J., Boisseau, N., Brassine, E., Cuthbertson, D. J., Smith, K., Babraj, J. A., Waddell, T. & Rennie, M. J. (2003) No effect of creatine supplementation on human myofibrillar and sarcoplasmic protein synthesis after resistance exercise. Am. J. Physiol. Endocrinol. Metab. 285: E1089–E1094.

89. Rennie, M. J. & Tipton, K. D. (2000) Protein and amino acid metabolism during and after exercise and the effects of nutrition. Annu. Rev. Nutr. 20: 457–483.

90. Persky, A. M. & Brazeau, G. A. (2001) Clinical pharmacology of the dietary supplement creatine monohydrate. Pharmacol. Rev. 53: 161–176.

91. Wyss, M. & Schulze, A. (2002) Health implications of creatine: can oral creatine supplementation protect against neurological and atherosclerotic disease? Neuroscience 112: 243–260.

92. Poortmans, J. R. & Francaux, M. (1999) Long-term oral creatine supplementation does not impair renal function in healthy athletes. Med. Sci. Sports Exerc. 31: 1108–1110.

93. Greenwood, M., Kreider, R. B., Melton, C., Rasmussen, C., Lancaster, S., Cantler, E., Milnor, P. & Almada, A. (2003) Creatine supplementation during college football training does not increase the incidence of cramping or injury. Mol. Cell Biochem. 244: 83–88.

94. Rawson, E. S., Gunn, B. & Clarkson, P. M. (2001) The effects of creatine supplementation on exercise-induced muscle damage. J. Strength Cond. Res. 15: 178–184.

95. Williams, M. H. (1999) Facts and fallacies of purported ergogenic amino acid supplements. Clin. Sports Med. 18: 633–649.