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Review article

Mechanisms of muscular adaptations to creatine supplementation

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Abstract

Creatine supplementation is a widely used and heavily studied ergogenic aid. Athletes use creatine to increase muscle mass, strength, and muscle endurance. While the performance and muscle-building effects of creatine supplementation have been well documented, the mechanisms responsible for these muscular adaptations have been less studied. **Objective:** The purpose of this review is to examine studies of the mechanisms underlying muscular adaptations to creatine supplementation. **Data sources:** PubMed and SPORTDiscus databases were searched from 1992 to 2007 using the terms creatine, creatine supplementation, creatine monohydrate, and phosphocreatine. **Study selection:** Studies of creatine supplementation in healthy adults were included. **Data extraction:** Due to the small number of studies identified, a meta-analysis was not performed. **Data synthesis:** Several potential mechanisms underlying muscular adaptations to creatine supplementation were identified, including: metabolic adaptations, changes in protein turnover, hormonal alterations, stabilization of lipid membranes, molecular modifications, or as a general training aid. The mechanisms with the greatest amount of support (metabolic adaptations, molecular modifications, and general training aid) may work in concert rather than independently. **Conclusions:** Creatine supplementation may alter skeletal muscle directly, by increased muscle glycogen and phosphocreatine, faster phosphocreatine resynthesis, increased expression of endocrine and growth factor mRNA, or indirectly, through increased training volume. **Keywords:** dietary supplement, creatine monohydrate, phosphocreatine, muscle, sport nutrition

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Introduction

Creatine monohydrate is popular dietary supplement that is used by athletes to increase muscle mass and strength, and improve sports performance. The effects of creatine on exercise performance, strength, and body composition have been described in hundreds of studies, with the majority reporting an ergogenic effect. In the most comprehensive meta-analysis to date, Branch¹ reported that creatine supplementation results in increased lean body mass ($\approx 2\%$), muscle strength ($\approx 11\%$), and high-intensity exercise performance ($\approx 8\%$). Several potential mechanisms of how creatine supplementation exerts an ergogenic effect have been identified. However, these mechanisms have not been described collectively and critically reviewed. The purpose of this review is to examine studies of the mechanisms underlying muscular adaptations to creatine supplementation.

Methods

PubMed and SPORTDiscus databases were searched from 1992 to 2007 using the terms creatine, creatine supplementation, creatine monohydrate, and phosphocreatine. Related studies were located by reviewing the reference lists of the articles identified through the computer database search. There are many studies of the effects of creatine supplementation in patient populations (e.g. Sarcopenic elderly², Amyotrophic Lateral Sclerosis³, Parkinson's disease⁴, Muscular Dystrophy⁵, etc) and in models of muscle atrophy/disuse^{6,7}. Due to the number of confounding variables that might influence the response of these individuals to creatine, the present authors have chosen to examine creatine supplementation research that focused on healthy young subjects under resting or post-exercise conditions.

Additionally, as there appear to be species differences in the response to creatine supplementation⁸⁻¹¹, this review focuses on data from human trials. Only a small number of studies were identified, so a meta-analysis was not performed.

Functions of creatine and phosphocreatine

Creatine and phosphocreatine are often referred to together as an energy system, which serves as a temporal energy buffer under conditions of high energy demand¹². Since 1981, when the term "phosphocreatine shuttle" was introduced, creatine and phosphocreatine have also been studied as a spatial energy buffer, which acts as an energy transport system^{12,13}. During physical activity, declines in adenosine triphosphate (ATP) are prevented when phosphocreatine phosphorylates adenosine diphosphate (ADP) to form ATP. For instance, Hirvonen et al.¹⁴ measured muscle phosphocreatine during sprinting, and found that 88-100% of muscle phosphocreatine was depleted in about 5.5 seconds¹⁴. Phosphocreatine resynthesis is an aerobic process that takes approximately 3 to 6 minutes to complete, depending on exercise intensity, duration, and the number of bouts¹⁵⁻¹⁸. Because the creatine kinase-phosphocreatine energy system is so critical to maintain ATP levels during exercise, increasing or decreasing basal levels of muscle creatine must alter energy metabolism.

Muscle creatine and phosphocreatine can be reduced with a vegetarian diet^{19,20}, or increased approximately 25% following high-dose short-term ($\approx 20\text{g d}^{-1}$ for 5 d) or low-dose long-term ($\approx 3\text{g d}^{-1}$ for 28d) creatine supplementation^{2,19,21-27}. The effects of creatine supplementation on muscle function (i.e. strength, endurance, power) have been studied in hundreds of investigations



(reviewed in ¹), ²⁸⁻³¹. Generally, if an individual is able to significantly increase muscle creatine and phosphocreatine levels with supplementation there is the potential for an ergogenic effect. About 70% of creatine supplementation studies report enhanced performance subsequent to creatine supplementation (reviewed in ²⁸). Creatine appears to be most effective when exercise time is brief (<30sec), intensity is maximal, and contractions occur over repeated bouts ¹. Additionally, creatine supplementation may enhance sprint performance when intense exercise follows or is interspersed during an endurance exercise task (i.e. cycling) ^{32,33}.

Potential mechanisms for the ergogenic effect of creatine

It is unknown through what mechanism of action creatine supplementation produces an ergogenic effect. Potential mechanisms include: metabolic adaptations, changes in protein turnover, hormonal alterations, stabilisation of lipid membranes, molecular modifications, or as a general training aid (Figure 1 – see at end of text). These mechanisms of action are not mutually exclusive and most likely the mechanism of action is multifaceted.

Metabolic adaptations

There are several metabolic changes resulting from creatine supplementation that may influence exercise performance, including: increased muscle creatine and phosphocreatine, increased muscle glycogen, and faster phosphocreatine resynthesis. Creatine supplementation is considered by some to be analogous to carbohydrate loading. That is, by ingesting large quantities of creatine during the days before exercise performance, muscle phosphocreatine is increased, and subsequently performance will be improved. Thus creatine supplementation may simply provide more fuel and enhance the buffering capacity of skeletal muscle by increasing basal levels of muscle phosphocreatine. One would assume that a caveat of this paradigm would be that the exercise must rely heavily on the creatine kinase-phosphocreatine energy system (i.e. <30sec of maximal intensity exercise).

However, performance-enhancing effects of creatine supplementation have been noted in studies with significantly longer exercise tasks (30-150sec) (reviewed in ¹). In a meta-

analysis, Branch ¹ reported that creatine supplementation increased performance ($\approx 5\%$) during exercise tasks that rely on anaerobic glycolysis including bicycle ergometry, isometric force production, and isotonic strength. Increased muscle phosphocreatine is an unlikely explanation for improved exercise performance in tests >30 seconds in duration, which rely on the glycolytic pathway for ATP production. Creatine supplementation, in fact, significantly increases muscle glycogen (reviewed in ³¹). Five of six studies reviewed by Volek and Rawson ³¹ showed that creatine supplementation alone or in combination with carbohydrate and/or protein, increases muscle glycogen greater than carbohydrate or placebo supplementation. This metabolic alteration may explain the improvement in exercise performance subsequent to creatine ingestion in tasks >30 seconds.

Creatine supplementation may also enhance recovery during repeated bouts of exercise due to enhanced phosphocreatine resynthesis ^{22, 34}, although this has not been shown in every case ³⁵. Greenhaff et al. ²² took biopsies from the vastus lateralis muscle of eight subjects following 0-, 20-, 6, and 120 seconds respectively of recovery from electrically evoked contractions following creatine supplementation (20g/d for 5d). In responders (mean 24% increase in basal muscle creatine), phosphocreatine resynthesis was increased (35%) during the second minute of recovery. Yquel et al. ³⁴ used ³¹P nuclear magnetic resonance spectroscopy to demonstrate increased phosphocreatine resynthesis during recovery from 7 bouts of plantar flexion exercise. Thus there are sufficient data to indicate that metabolic adaptations (i.e. increased muscle glycogen and phosphocreatine, faster phosphocreatine resynthesis) are one of the mechanisms through which creatine exerts an ergogenic effect. The mechanism for the increased glycogen storage is not fully understood, but may be mediated through increased GLUT-4 protein content, as has been described in creatine-supplemented subjects following immobilisation and rehabilitation exercise training ^{6,7}.

Protein turnover

Prior to creatine becoming a popular dietary supplement, a series of in vitro and in vivo investigations by Ingwall and colleagues ³⁶⁻³⁹



showed that myosin heavy-chain, actin and creatine kinase synthesis increased in cardiac and skeletal muscle subsequent to creatine exposure. Additionally, Häussinger et al.⁴⁰ demonstrated that hyperhydrating a cell, which may happen during creatine supplementation, is an anabolic signal which positively impacts protein turnover. Although the theory for a role of creatine in protein synthesis is based on sound logic and data, there appears to be little effect of creatine supplementation on protein synthesis in humans

Parise et al.⁴¹ supplemented 27 men and women with creatine (20g/d for 5d followed by 5g/d for 3-4d) or placebo respectively, and found no effect on plasma rate of leucine appearance, leucine oxidation, non-oxidative rate of leucine disposal, mixed muscle protein synthesis, nitrogen balance, and fat free mass. However, creatine reduced plasma leucine rate of appearance (-7.5%) and leucine oxidation rate (-19.6%) in men. Because there was no muscle-specific measure of protein turnover, and no change in fat free mass (muscle composes ≈30% of whole body protein turnover), the authors speculated that these changes may have occurred in liver or splanchnic proteins. Subsequently, Louis et al.^{42, 43} investigated the effects of creatine on muscle protein turnover at rest, and in post-absorptive and post-exercise states using [¹³C] leucine and [²H₅] phenylalanine. In the first study, six males ingested creatine (21g/d for 5d) and myofibrillar protein synthesis and muscle protein breakdown were assessed in post-absorptive and fed states⁴³. Creatine had no effect on myofibrillar protein synthesis or muscle protein breakdown⁴³. In a second study, seven males ingested creatine (21g/d for 5d) and myofibrillar protein synthesis and muscle protein breakdown were assessed following 20 sets of 10 repetitions of knee extension/flexion exercise (75% 1RM)⁴². Again, there was no effect of creatine on muscle protein turnover⁴². Based on these data, it seems unlikely that the increase in fat-free mass associated with creatine supplementation is mediated through increased protein synthesis or decreased protein breakdown.

Stabilisation of lipid membranes

There is some indication that creatine supplementation reduces muscle damage and enhances recovery from stressful exercise. Greenwood and colleagues reported fewer⁴⁴ instances of muscle dysfunction (cramping,

muscle tightness, strains, injuries, etc) between creatine and non-creatine users, and survey data^{44, 45} and anecdotal reports⁴⁶ indicate that exogenous creatine and phosphocreatine decrease muscle soreness and increase recovery between workouts. It is possible that increased muscle phosphocreatine levels resulting from creatine supplementation could reduce muscle dysfunction, reducing muscle soreness or enhancing recovery. Exogenous phosphocreatine reduces muscle damage in cardiac tissue by stabilising the membrane phospholipid bilayer, decreasing membrane fluidity, and turning the membrane into a more ordered state^{47, 48}. In cardiac tissue, this decreases the loss of cardiac muscle proteins, which indicates less muscle tissue damage⁴⁷.

The results of clinical trials of the effects of oral creatine supplementation on skeletal muscle damage and recovery from stressful exercise are discrepant; some data indicate no effect of creatine on post-exercise muscle function^{49, 50}, while other data demonstrate decreased muscle damage (i.e. reduced muscle serum proteins)⁵¹. Santos et al.⁵¹ reported a blunted increase in plasma creatine kinase (19%), prostaglandin E₂ (61%), tumour necrosis factor- α (34%), and plasma lactate dehydrogenase (100%) in creatine supplemented athletes following a 30km run. Rawson et al.^{49, 50} found no attenuation of creatine kinase, lactate dehydrogenase, range of motion, soreness, or strength following 50 maximal eccentric contractions of the elbow flexors⁴⁹ or a high-repetition squat test (15 to 20 reps at 50% 1RM)⁵⁰. Currently, there are insufficient data to claim that oral creatine supplementation reduces muscle damage or enhances recovery from stressful exercise, but these studies do indicate that creatine supplementation does not worsen muscle damage as has been promulgated in the popular media.

Hormonal alterations

Based on the fact that creatine supplementation results in a rapid increase in body mass and fat-free mass, it has been hypothesised that creatine induces hypertrophy through endocrine mechanisms. Volek et al.⁵² assessed testosterone and cortisol immediately post-exercise (5 sets of bench presses and jump squats) in creatine (25g/d for 7d) and placebo-supplemented subjects, and found no effect of creatine on endocrine status. Op't Eijnde and Hespel⁵³



examined the combined effects of resistance exercise and an acute creatine bolus (10g) in creatine-loaded subjects (20g/d for 5d), and found that the growth hormone response to exercise was unaltered by creatine. Schedel et al.⁵⁴, however, found increased growth hormone levels (83%) in response to a 20g oral creatine bolus. It is difficult to resolve a practical application for these data, as the increase in growth hormone was similar to what is seen following exercise, and athletes do not typically ingest 20g of creatine per serving. These available data indicate that creatine supplementation (20-25g/d for 5-7d), as it is ordinarily practiced by athletes, does not alter exercise responses to testosterone, cortisol, and growth hormone. Thus it seems unlikely that increases in body mass and fat-free mass secondary to creatine supplementation are hormonally mediated. The fact that a large unaccustomed dose of creatine (20g/serving) can increase growth hormone requires further investigation.

Molecular modifications

Creatine researchers have benefited from advances in laboratory techniques and the recent surge of interest in genomics. It has been hypothesised that, if creatine supplementation itself causes skeletal muscle adaptations; perhaps, these changes occur at the molecular level. Willoughby and Rosene⁵⁵ demonstrated that creatine supplementation (6g/d for 12wk) plus resistance training results in a significantly greater increase in fat-free mass (4%), muscle volume (21.9%), strength (65%), myofibrillar protein (58%), Type I (33%), IIa (31%), and IIx (36%) myosin heavy chain mRNA expression and Type I (17%) and Type IIx (16%) myosin heavy chain protein expression than resistance training alone. In a subsequent study⁵⁷, these researchers demonstrated that creatine supplementation (6g/d for 12wk) plus resistance training increased creatine kinase, myogenin, and MRF-4 mRNA expression, and myogenin and MRF-4 protein expression compared with resistance training and placebo ingestion. More recently, Deldicque and colleagues⁵⁶ reported that creatine supplementation (21g/d for 5d) increased IGF-I (30%) and IGF-II (40%) mRNA in resting muscle. Whereas the work of Willoughby and Rosene^{55,57} provides evidence of a molecular effect of creatine plus resistance training on skeletal muscle, the work of Deldicque et al.⁵⁶ offers evidence of an independent effect of creatine. In support of cell culture⁵⁸ and animal research⁵⁹, Olsen

et al.⁶⁰ demonstrated that 16 weeks of creatine supplementation, combined with resistance training, augments increases in satellite cell number and myonuclei concentration in healthy males. Collectively, these studies indicate that creatine alone, or in combination with resistance training, causes molecular and cellular adaptations leading to skeletal muscle hypertrophy.

Training aid

Rawson and Volek³⁰ reported that creatine supplementation and concurrent resistance training result in an 8% greater increase in strength and a 12% increase in muscular endurance than does resistance training alone. It could be hypothesised that chronic creatine supplementation does not have a direct effect on skeletal muscle (e.g. protein synthesis), but simply enhances the ability of athletes to train hard in the weights room (e.g. complete more repetitions of each exercise, faster recovery between sets, etc), via increased basal muscle phosphocreatine and glycogen, and faster phosphocreatine resynthesis. In this manner, creatine supplementation acts as a training aid, by allowing athletes to train at higher volumes/intensities over time. Evidence to support this includes spontaneously higher training volumes in creatine- vs. placebo-supplemented subjects during a 12-week resistance training intervention²⁷. Additionally, others have found that when training volume is controlled for through voluntary- (i.e. creatine-supplemented subjects cannot exceed the prescribed training programme)⁶¹ or electrically-stimulated contractions⁶², there is no apparent effect of the creatine. Thus there is evidence to support the contention that muscular adaptations to creatine supplementation are dependent on increased training loads. However, Arciero et al.⁶³ showed that chronic creatine ingestion (20g/d for 5d followed by 10g/d for 23d), with or without resistance training, result in significant increases in bench press (creatine no training 8%; creatine plus resistance training 18%) and leg press (creatine no training 16%; creatine plus resistance training 42%) strength. More work needs to be done in this area as certain variables, such as creatine supplementation duration, training load, and training status of the subjects, may all confound interpretation of the results.



Discussion

Supplementation with creatine gained popularity in the early 1990s and to date remains one of the most popular performance-enhancing strategies used by athletes. Creatine has target effects in tissues with high metabolic demands, such as skeletal muscle, brain tissue, and the eye, but the effects of creatine on skeletal muscle is of primary interest to athletes. In general, the entry of creatine into target tissues is capacity-limited,

with movement governed by creatine transport proteins. Once in the cell, however, the exact cascade of events that governs performance enhancement is unresolved, though several theories have been proposed. Table 1 is a summary of clinical studies of the mechanisms through which creatine supplementation causes muscular adaptations. The strength of evidence from available clinical trials is ranked from weak to strong.

Table 1: Summary table of mechanisms supporting muscular adaptations to creatine supplementation from clinical studies. ✓ = weak evidence; ✓✓✓✓ = strong evidence

Mechanism	Examples	Strength of support	References
Metabolic adaptation	↑ muscle glycogen and phosphocreatine; ↑ phosphocreatine resynthesis rate	✓✓✓✓	6, 7, 22, 34, 64-66
Protein turnover	↑ protein synthesis and/or ↓ protein degradation	✓	41-43
Lipid membrane stabilisation	↓ muscle damage and/or ↑ recovery from stressful exercise	✓✓	49-51
Hormonal alterations	↑ growth hormone	✓	53, 54
Molecular modifications	↑ myosin heavy chain mRNA expression; ↑ growth factor (i.e. myogenin and MRF-4) mRNA expression; ↑ IGF-I and IGF-II mRNA expression; ↑ satellite cell number and myonuclei concentration	✓✓✓✓	55-57, 60
Training aid	↑ training volume	✓✓✓✓	27

The metabolic changes resulting from creatine supplementation appear to be the most logical mechanism of action and are supported by observed changes in intramuscular phosphocreatine and glycogen. Individuals who consume creatine have increases in muscle strength and lean body mass, thus changes in protein turnover have been proposed. Although potential mechanisms of

muscle gain have been hypothesised (e.g., increased cellular hydration), studies to date have not confirmed a net change in protein synthesis/degradation. Though changes in muscle protein turnover have not been found, changes in satellite cells may, in part, explain enhanced muscle function. While most mechanisms proposed focus on muscle as a target, systemic changes via hormonal



alterations have not been ruled out; evidence suggests a role for human growth hormone. Creatine has been shown to increase training volume, which may or may not be a function of the mechanisms proposed in this review.

Conclusions

Creatine supplementation causes adaptations to skeletal muscle through both direct and indirect mechanisms. These adaptations partially explain the increases in fat-free mass and strength and improvements in exercise performance following oral creatine ingestion. While several potential mechanisms identified that support muscular adaptations to creatine supplementation have strong support (i.e. metabolic adaptations, molecular modifications, and training aid), others (i.e. protein turnover, lipid membrane stabilisation, and hormonal alterations) have less support.

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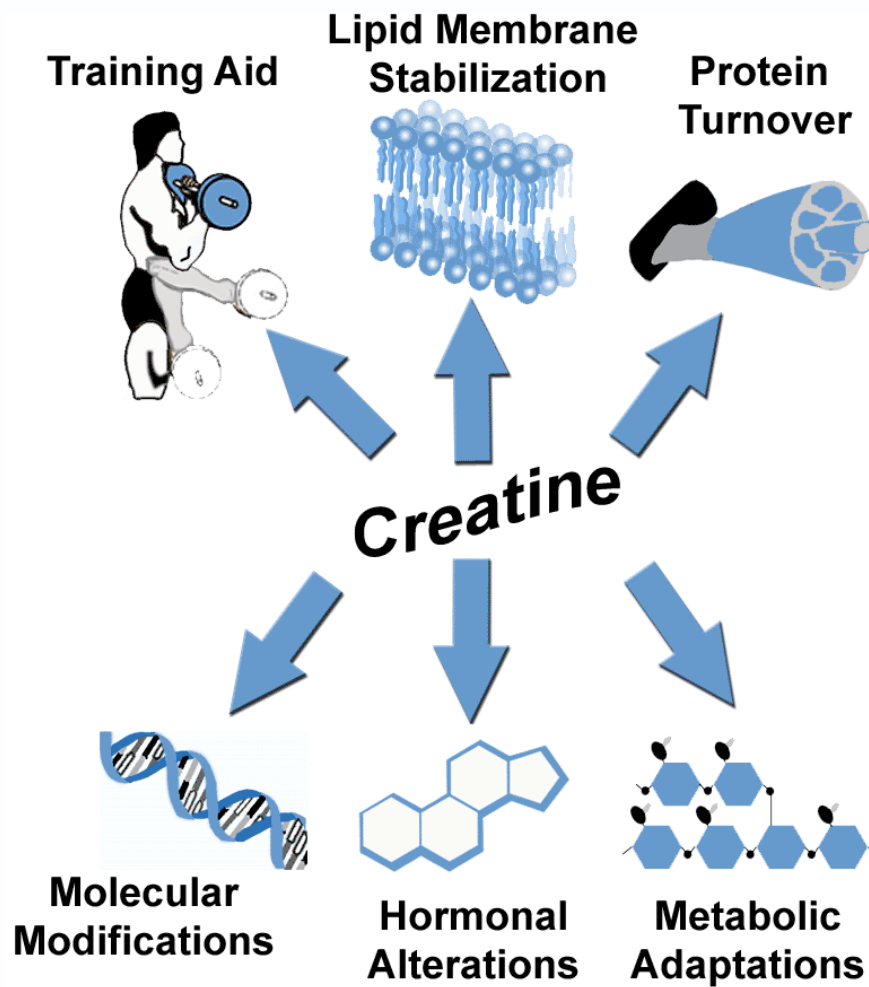


Figure 1: Potential mechanisms of action for muscular adaptations to creatine supplementation include: metabolic adaptations, protein turnover, hormonal alterations, stabilisation of lipid membranes, molecular modifications, or as a general training aid.