

# Effect of creatine supplementation



## **Abstract**

### **Introduction**

The use of creatine supplements as an aid to enhance performance in sports shot to prominence after it was revealed that the British Olympic team had used said nutritional supplements in the build up to the Barcelona games of 1992. The Times (7 August 1992) reported that high profile athletes such as Linford Christie and Sally Gunnell had won gold medals while using creatine during their preparation. Although sometimes viewed as controversial by sections of the sporting community, creatine as a nutritional supplement is perfectly legal and its use is encouraged by certain sporting institutions. An example of this dilemma is within the NCAA (National Collegiate Athletic Association), whereby the distribution of creatine by team coaches is banned but individual athletes are still allowed to procure the supplement themselves, although the Athletic Management journal, among others, postulates that this was done in order to “ level the playing field” rather than as a result of a side effect discovery (‘ NCAA clamps down on supplements’, 2000: 12. 5). Creatine is a naturally occurring substance found mainly in meat and fish {{2 Herda, T. J. 2009; }} that was first isolated in skeletal muscle by Michel-Eugène Chevreul in 1832 and given its name from the derivation of the Greek word for flesh, Kreas. Twelve years later, the German scientist Justus von Liebig theorised that this compound was necessary to produce muscular action in vertebrates after observing foxes in the wild and comparing their creatine levels to those in captivity. He even went as far as to harvest his own supply of creatine from the foxes and marketed it as “ Fleisch Extrakt”, proclaiming that it would allow the body to do more “ work” and for over a century this was the only creatine supplement ever produced.

It has been established by the scientific community that increased ingestion of creatine as a dietary supplement will lead to an increase in the total creatine (TC) and phosphocreatine (PC) concentrations in skeletal muscle {{10 Finn, J. P. 2001; 11 Harris, R. C. 1992; 14 Greenhaff, P. L. 1994; }}. PC is simply the phosphorylated form of creatine that is found mainly in skeletal muscle which is utilized during high-intensity exercise to quickly replace the diminished adenosine triphosphate (ATP) stores {{2 Herda, T. J. 2009; }}. This is achieved through the actions of the enzyme creatine phosphokinase (CPK) which is found in high concentrations in muscles, allowing for swift replenishment of ATP despite the rising levels of intracellular adenosine diphosphate (ADP) that occurs during exercise {{2 Herda, T. J. 2009; }}. Ergo increasing the bodies creatine stores should result in an improved ability to regenerate the skeletal muscle fibre's ATP stores and consequently lead to improved performance and delayed onset of fatigue during bouts of high-intensity exercise (Hargreaves, M. 2006).

The aim of this paper is to review the current literature regarding creatines supposed beneficial effect on muscle performance and determine what is the optimal method of delivering the supplement to the skeletal muscle. Since creatine became fashionable in the mid 1990s, numerous sports supplement companies have been researching how it can best be administered into the body, with regards to dose size, timing and the different forms of creatine now available. Other factors need to be considered such as potential side effects and certain population groups who may be at risk when using creatine. The general consensus is that it does work as an ergogenic aid; defined by Leutholtz and Kreider (2001) as “ a technique or practice that

serves to increase performance capacity, the efficiency to perform work, the ability to recover from exercise, and/or the quality of training thereby promoting greater training adaptations". Another aim of this paper is to examine the mechanisms behind creatines beneficial effects and where these improvements take place i. e. specific muscle fibre types. It is also important to consider what is meant by improvement; does it mean performance in specific exercises or just in muscle development in general? Are there particular sports events where the improvements are marked and easily noticeable?

The two enzymes required for de novo (endogenous) synthesis of creatine in humans, transamidinase and methyltransferase, are found in the kidneys, pancreas and liver {{18 Balsom, P. D. 1994; }}. Therefore creatine needs to be transported via the bloodstream to the muscles where it is needed and it has been found that the normal range of creatine concentration within plasma is between 50 and 100  $\mu\text{mol/L}$  {{18 Balsom, P. D. 1994; }}. To determine the total amount of creatine in the body, the levels of both the free form (FC) and phosphorylated forms need to be combined. The present day analysis is that for a man of 70kg, his TC will amount to approximately 120g, with a turnover (of creatine to creatinine, the break-down product of creatine phosphate in muscle) estimated at about 1. 6% per day {{19 HOBERTMAN, H. D. 1948; }}. This equates to about 2g in an average male, which is replaced by both endogenous and exogenous sources, the latter coming mainly from meat and fish as mentioned earlier, with herring being a particularly good example {{18 Balsom, P. D. 1994; }}. In 1986, Hoogwerf et al calculated that the average creatine intake in a mixed diet was 1g per day

so the remaining gram has to be made up by endogenous synthesis, while those individuals whose diet lacks creatine completely due to insufficient animal produce intake, such as vegetarians or vegans, will have to make up their daily intake entirely through endogenous means {{21 Delanghe, J. 1989; }}. In terms of distribution, skeletal muscle is home to 95% of the TC found in the body, two-thirds of which is in the phosphorylated form {{18 Balsom, P. D. 1994; }}. The remaining 5% is found mostly in the brain, heart and testes.

Ageing appears to have no effect on the total amount of TC found within skeletal muscles, but levels of PC were found to be lower in untrained elderly individuals compared to their younger counterparts, while FC was found in higher concentrations in the elderly cohort {{22 Moller, P. 1982; }}. A subsequent training study by Moller and co-workers revealed that once the elderly individuals had undertaken some basic exercise, their FC and PC levels more closely resembled those of the younger group. This points to a conclusion that inactivity will result in the dephosphorylation of creatine, a process that can easily be reversed by a return to training.

A 1989 study by Tesch et al showed that type II muscle fibres have higher concentrations of PC than their type I counterparts, during resting state. These findings are to be expected since the anaerobic type II fibres use PC as their major storage fuel so that ATP can be generated quickly, as opposed to the type I slow twitch fibres that primarily use triglycerides as their main source of fuel.

Before exploring creatines proposed effects on muscle performance and development, it is important to consider how it's ingestion actually influences the bodies stores. In 1992 Harris et al showed that ingesting 5g of creatine monohydrate resulted in the elevation of the level of creatine in plasma, one hour later, from 50-100  $\mu\text{mol/L}$  to over 500  $\mu\text{mol/L}$ .

Unfortunately the only research conducted that has uncovered the mechanism behind creatines transport from bloodstream into muscle was done in rats {{27 Fitch, C. D. 1966; }}. It was found that the intracellular trapping of creatine and a saturable process allowed for transport of the compound from the bloodstream across to the muscle and explained the high creatine content of the skeletal muscle. Perhaps surprisingly, this is still the most we know about this particular mechanism after over 40 years and is definitely an area that is prime for future research.

### **Creatine monohydrate versus creatine ethyl ester**

While creatine monohydrates (CM) use is widespread, creatine ethyl ester (CEE) is less well known in the public domain. Manufacturers of the latter claim it is more readily absorbed into the body due to being more lipophilic and therefore having a longer half-life once ingested. It is converted back into creatine once digested as it is an ethyl ester derivative of creatine, specifically developed by the University of Nebraska Medical Centre's technology transfer entity, UNeMed. The claims of the various manufacturers of this specific type of creatine were disputed by a study by Child and Tallon that was presented at the International Society of Sports Nutrition 4th annual meeting. They had found that CEE was quickly broken down into creatinine due in part to the decreased acid stability caused by the addition of the ethyl

group (Child & Tallon 2007). The proposed beneficial benefits of the two varieties will be discussed in length later on.

### **Effect on body mass**

In 1975, Ingwall et al hypothesized that creatine could stimulate both cardiac and skeletal muscle into a state of hypertrophy by myofibrillar protein synthesis. In vitro and in vivo skeletal muscle had increased synthesis of the contractile proteins actin and myosin as well as the muscle specific iso-enzyme creatine phosphokinase, all of which were due to creatines selectivity. With the increased accumulation of these myofibrillar proteins, skeletal muscle went into a state of hypertrophy. This study is considered as the initial groundbreaking research into the methods behind creatines effect and a lot of the subsequent papers mentioned in this piece reference it extensively.

Ingwall followed this initial study up a year later {{16 Ingwall, J. S. 1976; }} with a paper on creatines effect as a potential chemical signal that links increased muscular activity with increased contractile mass. An important factor to note is that this paper is not referring to creatine as a dietary supplement, as its effects as an ergogenic aid were not fully understood until the early 1990s, but rather as an end product of the contraction mechanism. Its aim was to establish the biochemical and physiological mechanisms by which muscular hypertrophy occurs after increased muscular activity and measure the effects of increased intracellular creatine levels in differentiating skeletal muscle cells in culture. The conclusion was that although creatine probably does play a role in selectively controlling the rate

of synthesis of muscle-specific proteins, it is hard to determine whether these results would apply in vivo.

There are two schools of thought when it comes to assessing the change in body composition that comes with creatine supplementation; an increase in fat-free mass, first proposed by Earnest et al in 1996, and/or an increase in the relative water content of skeletal muscles. Francaux and Poortmans found that after nine weeks of training and creatine supplementation, there was an increase in the absolute value of both total body water (TBW) content and intracellular water (ICW) levels but not the relative value, indicating that the gain of 1-2kg of total body mass they observed was due to dry matter growth {{17 Francaux, M. 1999; }}. These results were similar to those obtained by Kreider et al in 1996 in that there was an increase in total body mass without a change in the TBW percentage {{28 Kreider, R. B. 1996; }}. When specifically studying the effects of creatine ethyl ester (CEE) supplementation, Spillane et al found no significant changes in TBW between the CEE, creatine monohydrate and placebo groups after heavy resistance training lasting 48 days {{26 Spillane, M. 2009; }}. This study paid particular interest to the supposed water retention qualities of CEE as many of the manufacturers of the supplement claim that the esterification process it undergoes increases cells permeability to creatine and minimizes the amount of extracellular water (ECW) retained during supplementation {{26 Spillane, M. 2009; }}. As suggested by Mesa and colleagues {{80 Mesa, J. L. 2002; }}, one of the potential benefits of creatine supplementation is the accompanied increase in TBW and ICW that help facilitate skeletal muscle hypertrophy. Furthermore in 1998 Kreider et al conducted a study that used



bioelectrical impedance to evaluate the changes in body composition after short term (28d) creatine supplementation during training. They concluded that the increases in body mass that they found “ could not be explained by disproportionate increases in total body water content” and the majority of the increase could be attributed to lean tissue accretion {{29 Kreider, R. B. 1998; }}. Powers et al study in 2003 is perhaps the definitive work done on the subject of water retention within muscle during creatine supplementation. They concentrated solely on the fluid distribution, in a similar way to Francaux and Poortmans; by measuring total body water as well as the intra- and extracellular levels and found that although water was retained, fluid distribution remained the same {{31 Powers, M. E. 2003; }}. The theory that water retention is the main stimulus for skeletal muscle hypertrophy due to preferential retention by the intracellular component is without any evidence in the literature researched for this paper. The increase in TBW is relative to the increase in total body mass, the majority of which is formed of fat-free mass.

### **Effect on maximal performance**

Maximal performance can be defined in many ways depending on the discipline; within the gym environment it is known as the 1 repetition maximum (1RM), the most weight an individual can lift in a single repetition for a given exercise. Out on the athletics track, maximal anaerobic performance can be measured with a short sprint, between 60-120m for example. Most of the studies that will be subsequently mentioned in this section have sought to discover the effects of combining creatine supplementation with various forms and intensities of resistance training.

The duration of the training period also varies from one study to the next. Beck et al combined ten weeks of resistance training with supplementation of a drink that contained creatine, amino acids and protein {{6 Beck, T. W. 2007; }}. The control group drank a placebo mixture that contained just carbohydrates, and both groups were tested for their anaerobic power production before and after training. Both groups experienced improved performances in their leg extension and bench press 1RM scores as well as their muscular endurance (number of repetitions performed at 80% of their 1RM). Also of note were increases in fat-free mass and percentage fat reduction for both groups. Most significantly however, were the changes elicited by the test drink when it came to peak power (PP) and mean power (MP) production; quantitative values that were determined using two 30 second Wingate Anaerobic Tests (WAnT). A good summary of this test is provided by -zkan et al (2010): it requires 30 seconds of pedalling at maximal speed on a cycle ergometer, against a resistance that is determined by the users body weight. As mentioned, it tests the individuals muscle power, endurance and fatigability and these were all improved in the test group but not in the placebo group.

Their reasons for using a combined supplement drink was to assess whether the creatine, protein and amino acids combined effect would be greater than the benefits that would be expected from ingesting just one of the ingredients alone. It was hoped that examining the changes expected in body composition after resistance training would help to differentiate between the mechanisms that assist in supplement-induced performance enhancement. In that respect the study revealed no new information. The

combination drink did improve the test subjects anaerobic capabilities compared to the carbohydrate placebo but provided no additional benefit for improving muscular strength or endurance when combined with medium term resistance training. A possible improvement to the study would have been to add in placebo groups that were to consume just protein and amino acid isolate drinks and perhaps it would have then been easier to differentiate between the respective beneficial effects of each supplement. It does confirm that when exercising at near maximal level, increased PC levels within the muscle can be advantageous at replenishing the ATP-PC pathway in anaerobic conditions.

A near identical study by Chromiak et al in 2004 had differing results when it came to comparing the final PP and MP values of the two groups {{48 Chromiak, J. A. 2004; }}. They found that those who had taken the carbohydrate-only drink had identical results, in respect to improved PP and MP values, to those who had received the combination one. Differing levels of training intensity and volume could account for these differences, as well as the fact that the test conducted by Beck et al was evaluated using two WAnTs, as opposed to the Chromiak study , who only used one.

When the results are compared to other studies that have tested similar protein, carbohydrate and creatine mixes, creatine does appear to produce the most consistent improvements in performance related activities so one can assume that the isolated increases in PP and MP are due to creatine, rather than the protein or amino acids. Open to discussion however, is the possibility that protein and amino acids could have contributed to the post-

exercise recovery and tissue repair, therefore becoming a factor in the PP and MP training-induced increases.

When creatine ingestion is isolated during short-term supplementation, the results of several studies appear to show encouraging results. Tarnopolsky and colleagues showed that short-term, high-dose creatine supplementation (20g a day for 4 days) markedly improved high intensity exercise performance, specifically in anaerobic cycling power and dorsi-flexor maximal voluntary contraction torque. They also found that males and females responded to the supplementation in a similar manner, with no gender effects apparent {{49 Tarnopolsky, M. A. 2000; }}. Volek et al found comparable results when they looked at maximal effort muscle contractions in individuals during repetitive sets of bench press and jump squats, after receiving 25g doses of creatine every day for a week {{50 Volek, J. S. 1997; }}.

### **CM vs. PEG**

A subsequent study by Beck with Herda et al {{2 Herda, T. J. 2009; }} compared the effects of CM with that of differing doses of polyethylene glycosylated creatine (PEG), another form of CEE. Using the standard recommended safe dose of 5g a day of CM, the results after training were compared to those obtained taking 1. 25g and 2. 5g of PEG. Similar tests to the ones previously mentioned in other studies were used to measure muscle strength, endurance and power output in a group of young, healthy men. The difference with this study was that there was no extra training (aerobic or resistance) undertaken by any of the subjects from the level of exercise that they performed regularly before entering into this study.

Instead it was just the simple administration of their respective supplement or placebo for a period of 30 days. CM had the effect of increasing body mass and muscle strength in the 1RM tests using the bench press and leg press. Those individuals taking the PEG doses found similar improvements in muscle strength but no change in their body mass. Neither group had improved PP performance or muscle endurance when compared to the placebo group, respectively measured using the countermovement vertical jump and WAnT, and repetitions to failure at 80% of 1RM using bench press and leg press.

It had been suggested by Fry et al that PEG could help facilitate creatines movement across the sarcolemma during gastrointestinal (GI) absorption, therefore a smaller dose of this form of creatine would be needed to obtain potentially the same results as CM (Fry, CF. 2007). This study showed that while a smaller dose of PEG did show comparable results to those obtained using CM, further studies are required to determine its effects when combined with resistance training. One notable practical application is that both CM and PEG groups experienced improved 1RM performance without undertaking a “ loading period”. Many manufacturers of CM encourage a week of loading of the creatine supplement i. e. a larger dose of 20-25g followed by a maintenance period taking a normal 5g dose. Going on from this, with further research required, it might be possible to achieve the same improved performance in 1RM exercises usually seen after 5g. d-1 of CM, by taking a smaller daily dose of PEG. Again, it is possible results may vary when combined with a set period of resistance training and further research is required in this area.

**CM vs. CEE, with special reference to the creatine transporter**

A 2009 study by Spillane et al concentrated on looking into the effects of CEE supplementation on muscle performance after a seven week period of heavy resistance training {{26 Spillane, M. 2009; }}. As mentioned briefly earlier, CEEs proposed advantage over CM is that it is more bio-available due to the esterification process it undergoes, thereby making it less hydrophilic. The manufacturers of this particular variety of creatine also claim that due to enhanced sarcolemma permeability in favour of CEE, it is able to be taken up into muscle without the need for the creatine transporter (CT) {{26 Spillane, M. 2009; }}. The CT mediates the uptake of creatine in skeletal muscle against a concentration gradient and is helped by a Na<sup>+</sup>-dependent transporter {{94 Guimbal, C. 1993; }}. A review by Snow and Murphy looked at the literature concerning the CT, primarily how it is regulated and what gene expression is responsible for its activity {{51 Snow, R. J. 2001; }}. They found that the CreaT1 gene was expressed in a variety of tissues, including neural, cardiac and skeletal muscle, and that the activity of the transporter protein itself was regulated by substrate concentration, cellular location and a host of other factors. A subsequent review in 2003 by the same authors demonstrated that the creatine content in muscle was predominantly determined by extracellular supply and the expression and activity of the CTs {{52 Snow, R. J. 2003; }}. They also found that after creatine supplementation, the increases seen in total muscle creatine levels were variable and hypothesized that potential factors responsible for these differences could be carbohydrate intake, average level of exercise and possibly fibre type.

Supplement companies make specific reference to CEEs supposed benefits over CM, indicating that it is “easier to absorb than other versions” and “offers faster results” (MyProtein. co. uk web site, accessed 27-1-2010). However, these claims have been disputed, not only by the International Society of Sports Nutrition, as mentioned earlier, but also by another independent study that showed that CEE was unstable at low pH conditions and as a result, would be taken up less by muscle than an equivalent dose of CM (Mold et al 1955). The results of the comparative study by Spillane et al seemed to concur with these objections. Performance and muscle strength were improved to a similar level of those using CM and those in the placebo group, while body composition was unchanged. They concluded that the improvements seen in the study were most likely due to the training regime, rather than the supplementation and that CEE ingestion markedly increased the serum creatinine levels without any notable change in serum and total muscle creatine levels. This can only lead to the observation that the CEE was being degraded while in GI transit and its uptake by skeletal muscle was insufficient enough to prevent further degradation to creatinine or increase the levels of creatine within the muscles {{26 Spillane, M. 2009; }}. This is a very interesting revelation considering the manufacturers claims of increased absorption and it shouldn't go unnoticed that all supplementation mentioned in the study (placebo, CM and CEE) provided no additional benefit to the training specification undertaken by the volunteers. A loading phase (approx. 20g/day) of five days was followed by a maintenance period lasting 6 weeks (approx. 5g/day) and the training programme was a fairly intense one with participants required to train four times a week. Perhaps the more demanding training schedule was sufficient in providing maximal muscle

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strength increases and supplementation could not possibly have had any beneficial effect. This is open to discussion however, as so far every study that has been reviewed in researching for this paper has shown that creatine increased the effects of training.

### **Effect on repetitive sub-/supra-maximal exercise**

Improved performance in repetitive exercises such as repeated sprints (6x60m) are more relevant than one-off maximal performances when it comes to assessing creatine's effect in a sporting environment. The ability to perform longer and harder during interval training sessions gives way to better results and hopefully better performance in competitions. It is essential to differentiate this form of exercise from endurance training, which involves long concerted efforts with little, if any, rest time. It could be said that improving this aspect of your training will give rise to improved performance in 1RM tests so the effect of creatine supplementation needs to be evaluated in both aspects. High intensity interval training (HIIT) is a specific type of interval training and is utilised by some of the studies subsequently mentioned. It requires maximal effort for a short duration of time, interspersed with active recovery at a lower intensity to the main workout. The thinking behind this form of training is that intramuscular levels of H<sup>+</sup> will be elevated when the next set of exercise begins and this should force the body into improving intramuscular buffering capacity { {54 Costill, D. L. 1984; } }. This should then improve performance in future training/events by delaying fatigue.

A 2003 study by van Loon et al looked at the effects of CM supplementation, without training, on performance during repeated supra-maximal sprints on

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a cycle ergometer as well as an endurance cycling exercise {{24 van Loon, L. J. 2003; }}. Whole-body and muscle oxidative capacity and substrate utilisation as well as body mass were also measured before and after to monitor any potential changes. The main aim of the researchers was to determine any differences in the results of the aforementioned values, between creatine loading and prolonged use of the supplement. Performance in the repeated sprints was improved in both groups, while there was no improvement at all in the endurance exercise. Muscle oxidative capacity was also unaffected. The researchers had based their predictions, on a possible change in the oxidative capacity, on findings by Brannon et al that showed increased muscle citrate synthase activity in rats after prolonged creatine supplementation {{53 Brannon, T. A. 1997; }}. Their results suggested improvements in the values mentioned because citrate synthase is a mitochondrial marker enzyme, although almost every study that has looked into creatines effect on endurance has found no (or even negative) effect. Unfortunately this study also came to the same conclusion.

Kendall et al carried out a similar, subsequent study in 2009, looking into the effects of combining HIIT with creatine supplementation and assessing any changes in critical power or anaerobic working capacity {{3 Kendall, K. L. 2009; }}. Critical power reflects the individuals ability to sustain their highest power output for an extended period time while anaerobic working capacity is their total metabolic work capacity, independent of oxygen use {{3 Kendall, K. L. 2009; }}. Creatine significantly improved critical power compared to the placebo and control groups while anaerobic working capacity was unchanged in all test subjects after treatment. This suggests

that HIITs effects on endurance performance changes may be enhanced by creatine supplementation. A possible explanation for this is that PC is a major component of biological buffering and, as has been shown already, creatine supplementation can increase the bodies total creatine stores therefore allowing for improved pre-exercise PC availability. Although the participants of this particular study did not have their intramuscular levels of PC measured, other studies have repeatedly shown a significant increase after varying levels of supplementation (3-20g/day) {{11 Harris, R. C. 1992; 1 Vandenberghe, K. 1997; 55 Casey, A. 1996; }}. Therefore, not only does creatine supplementation help to replenish PC stores and increase energy production in the ATP-PC energy system, but it also serves to delay the onset of muscle fatigue by prolonging the build up of ADP and inorganic phosphate (Pi), known factors in the activation of anaerobic glycolysis (Cramer 2007).

The studies covered in this paper have mostly used young, healthy males to test the effects of creatine supplementation so to ensure fair coverage of the population the next study to be considered examines the effect of the ergogenic aid in sedentary older women. Gotshalk et al (2008) showed significant increases in upper- and lower-body maximal strength in thirty 58-71 year old women after CM supplementation

### **The effect of creatine supplementation on muscle development**

The aim of this section is to attempt and explain the structural changes that take place after creatine supplementation that facilitate the improvement in muscle performance shown in the aforementioned studies. It has already been shown by numerous studies that exogenous creatine can replenish the PC stores and lead to faster regeneration of ATP and therefore allow a longer

and more intense exertion. This next section will focus on how creatine potentially alters the morphology of skeletal muscle and how it can amplify the effects of training.

### **Muscle fibre type and size**

A study by Volek et al examined the cross-sectional area and proportion of muscle fibre types before and after supplementation and twelve weeks of heavy resistance training {{56 Volek, J. S. 1999; }}. Those subjects in the creatine group had significant increases in the cross-sectional area of all four types (Type I, IIA, IIAB & IIB) while increases in the placebo group were much smaller, with only Type IIA fibres reaching a significant value of change.

Interestingly it was this type of fibre that increased in proportion in both groups after training, but more so in the creatine subjects (9% vs. 7%). They also found a significant decrease in Type IIB fibres in both groups (9% and 6%) indicating that the training was responsible for a slight shift from the fast glycolytic type towards the fast oxidative type of fibres, with creatine accentuating this change. This change is to be expected as resistance training has previously been shown to decrease the percentage of Type IIB fibres and encourage the transformation from Type IIA > Type IIAB > Type IIB in as little as five workouts {{18 Balsom, P. D. 1994; }}.

As the authors state in their discussion section, the greater gains in muscle fibre hypertrophy seen by the creatine group implies enhanced myofibrillar synthesis and/or reduced breakdown.

### **Myosin heavy chain synthesis**

Ingwall and colleagues had shown in 1972 that skeletal muscle, formed both in vitro and in vivo, would synthesise myosin heavy chain faster when

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supplied with creatine in vitro {{57 Ingwall, J. S. 1972; }}. Ingwall had been one of the first to postulate that the hypertrophy of skeletal muscle as a result of increased muscular activity might be due to an end product of the activity promoting contractile protein synthesis {{57 Ingwall, J. S. 1972; }}. The results of his early experiment were consistent with the idea that creatine acts as a “ positive-feedback effector” within the system relating muscular activity and muscle protein synthesis. However it is still unclear whether the same mechanism is applicable in vivo as creatines beneficial effects appear to act indirectly through the enhancement of the intensity of trai