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Review

The nutritional biochemistry of creatine

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Creatine is a naturally occurring compound that is synthesized endogenously and is present in a meat eaters diet. It is stored in abundance in skeletal muscle, where it exists in free and phosphorylated forms and plays a pivotal role in maintaining a high adenosine triphosphate:adenosine diphosphate ratio during intense contraction. Fatigue development during short-term maximal exercise has been associated with the inability of skeletal muscle to maintain this ratio, at least partly because of phosphocreatine depletion. Ingestion of creatine monohydrate in solution at a rate of 20 g/day for 5 to 6 days has been shown to increase muscle total creatine concentration by approximately 25 mmol/kg dry mass in man, but the variation between subjects is large. After this initial loading phase, muscle stores can be maintained by ingesting 2 g/day. A positive relationship has since been demonstrated between muscle creatine uptake and improvements in performance during repeated bouts of maximal exercise and rates of phosphocreatine resynthesis during recovery from maximal exercise. The mechanism by which improvements in maximal exercise performance are achieved following creatine ingestion possibly relates to an increase in phosphocreatine concentration, specifically in Type II muscle fibres, maintaining adenosine triphosphate resynthesis during exercise. Recently, muscle creatine accumulation has been shown to be substantially increased by combining creatine supplementation with carbohydrate ingestion, elevating muscle creatine concentration in all subjects close to the upper limit of 160 mmol/kg dm. Creatine supplementation should be viewed as a significant development in sports-related nutrition. (J. Nutr. Biochem. 8:610–618, 1997) © *Elsevier Science Inc. 1997*

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Creatine distribution and biosynthesis

Creatine, or methyl guanidine-acetic acid, is a naturally occurring compound found in abundance in skeletal muscle. It is also found in small quantities in brain, liver, kidney, and testes. In a 70-kg man, the total body creatine pool amounts to approximately 120 g, of which 95% is situated in muscle.[1,2]

In the early part of this century there was already literature pointing to an important function for creatine in muscle contraction, the knowledge of its fairly specific distribution and its absence from normal urine led to the realization that it is not merely a waste product of metabolism. This realisation was confirmed when Chanutin[3] observed that creatine administration resulted in a major portion of the compound being retained by the body.

Creatine synthesis has been shown to proceed via two successive reactions involving two enzymes (*Figure 1*). The first reaction is catalyzed by glycine transamidinase, and results in an amidine group being reversibly transferred from arginine to glycine, forming guanidinoacetic acid. The second reaction involves irreversible transfer of a methyl group from *S*-adenosylmethionine (SAM) catalyzed by guanidinoacetate methyltransferase, resulting in the methylation of guanidinoacetate and the formation of creatine.[4,5] The distribution of the two enzymes differs between tissues across mammalian species. In the case of man, however, it is generally accepted that the majority of de novo creatine

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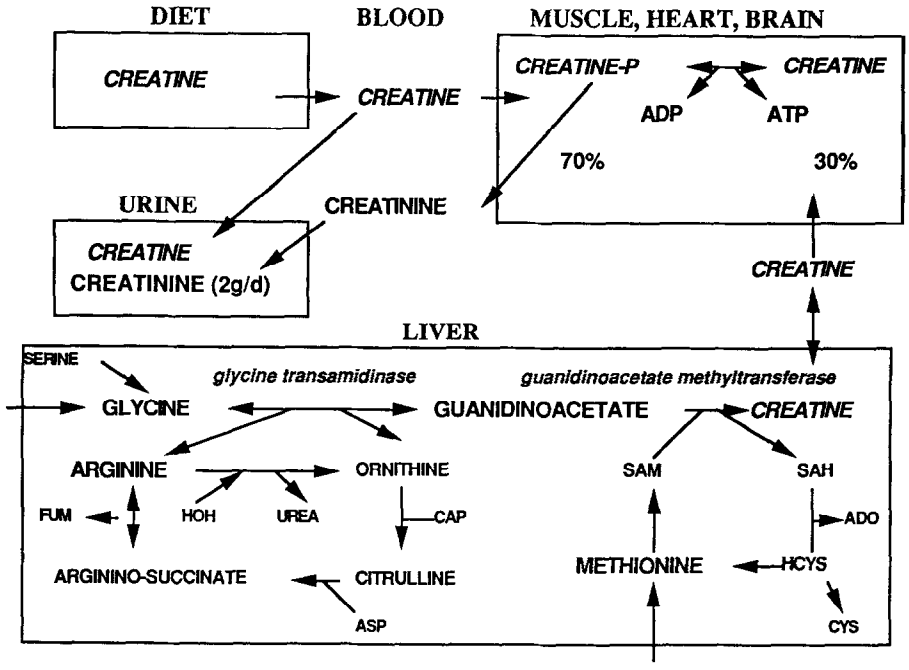

Figure 1 The biosynthesis of creatine (from reference 5).

synthesis occurs in the liver. As little creatine is found in the major sites of synthesis, it is logical to assume that transport of creatine from sites of synthesis to storage must occur, thus allowing a separation of biosynthesis from utilization.

Two mechanisms have been proposed to explain the very high creatine concentration within skeletal muscle. The first involves the transport of creatine into muscle by a specific Na^+-dependent saturable entry process, and the second entails the trapping of creatine within muscle.[4,6,7] Early studies demonstrated that creatine entry into muscle occurs actively against a concentration gradient, possibly involving creatine interacting with a specific membrane site that recognizes the amidine group.[4,6,7] Recently, the specific Na^+-dependent creatine transporter has been identified in rat skeletal muscle, heart, and brain.[8] It has been suggested that some skeletal muscles do not demonstrate a saturable uptake process, thereby supporting the idea of intracellular entrapment of creatine.[4] About 60 to 70% of muscle total creatine exists in the form of phosphocreatine which is, therefore, unable to pass through membranes because of its polarity, thus trapping creatine. This entrapment will result in the generation of a concentration gradient, but phosphorylation alone cannot be the sole mechanism of cellular retention of creatine. Other mechanisms that have been proposed include binding to intracellular components and the existence of restrictive cellular membranes.[4]

Creatinine has been established as the sole end product of creatine degradation being formed nonenzymatically in an irreversible reaction.[7,9] As skeletal muscle is the major store of the body creatine pool, this is the major site of creatinine production. The daily renal creatinine excretion is relatively constant in an individual, but can vary between individuals,[4] being dependent on the total muscle mass in healthy individuals.[10] Once generated, creatinine enters circulation by simple diffusion and is filtered in a nonenergy-dependant process by the glomerulus and excreted in urine.

The effect of dietary creatine supplementation on muscle creatine concentration in man

In normal healthy individuals, muscle creatine is replenished at a rate of approximately 2 g/day by endogenous creatine synthesis and/or dietary creatine intake.[5] Oral ingestion of creatine has also been demonstrated to suppress biosynthesis, an effect that has been shown to be removed on cessation of supplementation.[5] Conversely, the absence of creatine from the diet has been shown to result in low rates of urinary creatine and creatinine appearance,[11] and augmented creatine retention during subsequent dietary creatine supplementation, suggesting that endogenous synthesis may not match creatine requirements in these individuals. In this respect, creatine could be viewed as an essential constituent of a 'normal' diet.

Early studies demonstrated that creatine ingestion resulted in a small increase in urinary creatinine excretion. In general, urinary creatinine excretion rose slowly during prolonged creatine administration and, on cessation, around 5 weeks elapsed before a significant fall in creatinine excretion was observed.[3,12] From these early studies, creatine retention in the body pool was thought to be much greater during the initial stages of administration. These early studies also demonstrated that there was no increase in creatinine excretion until a significant amount of the administered creatine had been retained.[3,12]

These early studies invariably involved chronic periods of creatine ingestion. With the application of the muscle biopsy technique, however, it has now become clear that the ingestion of 20 g of creatine each day for 5 days by healthy volunteers can lead to, on average, more than a 20% increase in muscle total creatine concentration, of which approximately 20% is in the form of phosphocreatine (PCr; *Figure 2*).[13] It is important to note that the most studies to date have involved 5 g of creatine being ingested in a warm solution on four equally spaced occasions per day, princi-

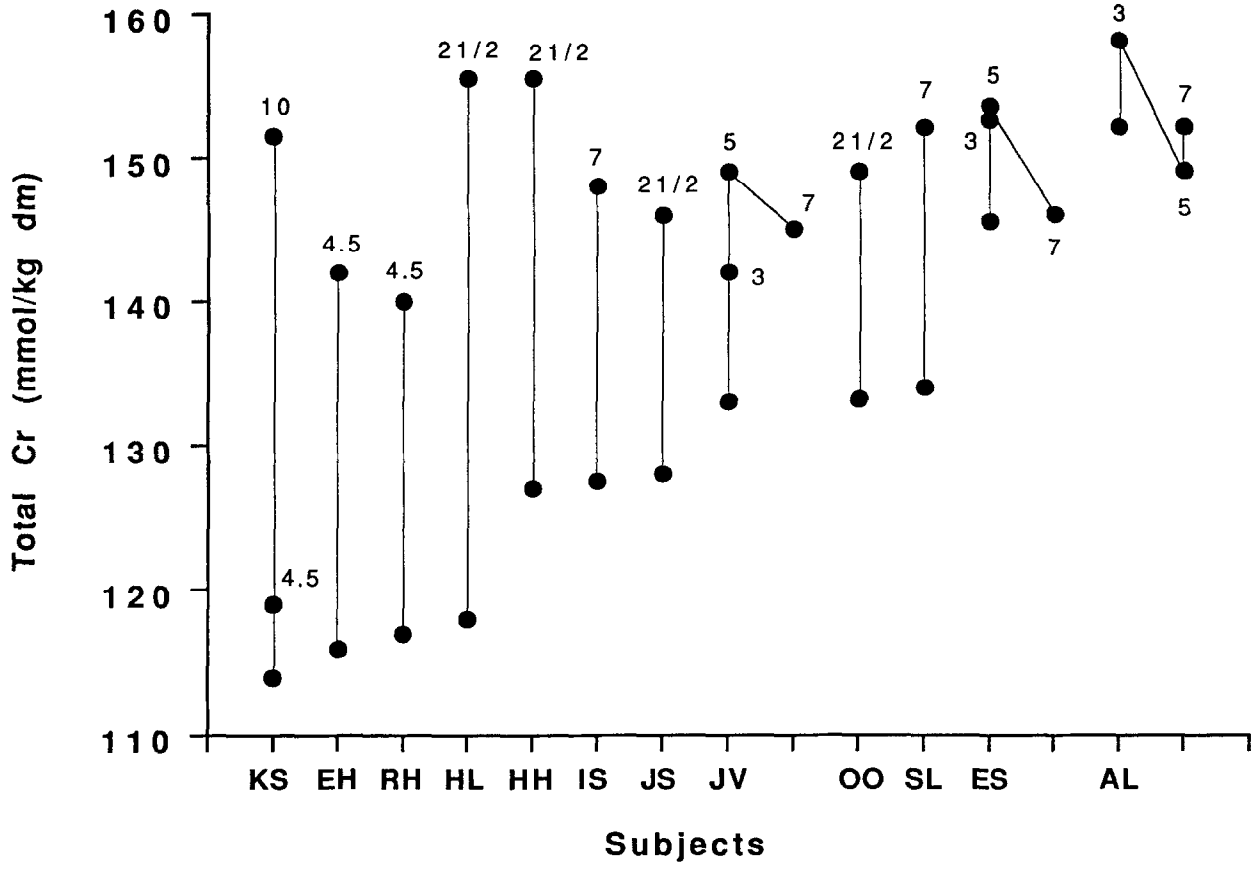

Figure 2 Muscle total creatine (Cr) concentration before and after different duration's (3 days–21 days) of Cr ingestion at rates of 20 g/day (subjects KS, EH, RH, IS, SL, and ES) and 30 g/day (subjects HL, HH, JS, JV, OO, and AL). 21/2 indicates creatine was ingested every other day for a duration of 21 days (from 13).

pally because this results in a rapid (within 20 min), marked (~1000 μmol/L increase), and sustained (~3 h) rise in the plasma creatine concentration.[13] A warm liquid is used because this has been shown to facilitate the dissolving of creatine. Unpublished work by this author has shown that creatine ingested in solution is more effective at raising the plasma creatine concentration when compared with the ingestion of creatine in tablet form, presumably because intestinal creatine absorption is more rapid when creatine is ingested in solution. In agreement with earlier work, it has also been demonstrated that the majority of tissue creatine uptake occurs during the initial days of supplementation, with close to 30% of the administered dose being retained during the initial 2 days of supplementation, compared with 15% from days 2 to 4.[13] It was also shown by Harris et al.[13] that the initial presupplementation muscle total creatine concentration is an important determinant of creatine accumulation during supplementation in healthy volunteers (*Figure 2*). Furthermore, when submaximal exercise is performed by healthy subjects during the period of supplementation, muscle uptake can be increased by a further 10%.[13] With the exception of vegetarians and some disease states, it is not yet clear what determines whether a person has a high or low muscle creatine store. Interestingly, normal healthy females, for reasons as yet unknown, seem to have a slightly higher muscle creatine concentration than males.[14] This may be a consequence of their muscle mass, and therefore their creatine distribution space, being smaller.

Based on recently published experimental findings,[15] it seems that, as might be expected, lower dose creatine supplementation (3 g/day) is slower at raising tissue creatine levels during a 2- to 3-week period of ingestion compared with a 6-day regimen of 20 g/day. However, after 4 weeks of supplementation, no difference in muscle creatine stores is evident when comparing the two dosage regimens. The same study clearly demonstrated that muscle creatine stores can be maintained at an elevated concentration when the 6-day supplementation dose of 20 g/day is immediately followed by a lower dose of 2 g/day (*Figure 3*). This lower dose was aimed at sustaining dietary creatine intake at a slightly higher level than degradation of muscle creatine to creatinine. The natural timecourse of muscle creatine decline after supplementation was also investigated by Hultman et al.,[15] where it was found to take at least 3 weeks for muscle creatine "wash-out" to occur after 6 days of creatine ingestion at the rate of 20 g/day. This fits with earlier studies that investigated the timecourse of creatinine excretion after creatine ingestion,[3,12] and with the suggestion of Fitch[4] that creatine is "trapped" within skeletal muscle once absorbed. Thus, it would seem that a rapid way to "load" and then

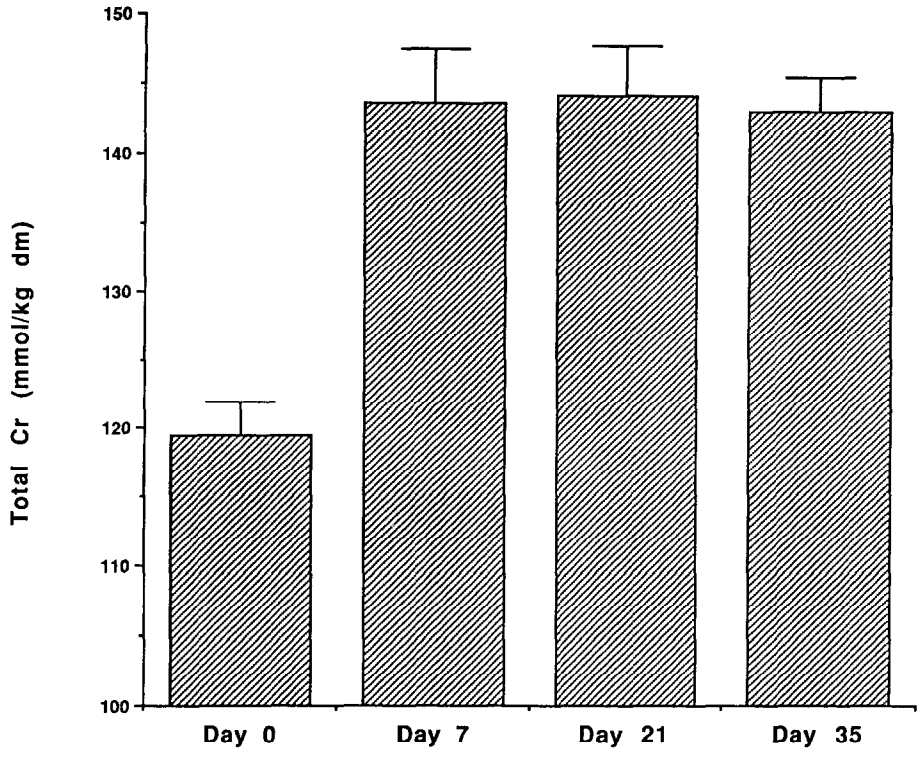

Figure 3 Muscle total creatine (Cr) concentration before and after 34 days of Cr ingestion. Creatine was ingested at a rate of 20 g/day for the initial 6 days and at a rate of 2 g/day thereafter. Values represent mean ± SEM.

maintain muscle creatine stores is to ingest 20 g/day for 5 to 6 days followed by 2 g/day thereafter.

It is also clear from the literature that there is considerable variation between subjects in the extent of muscle creatine accumulation during supplementation.[13,16] A concentration of 160 mmol/kg dry muscle (dm) seems to be the maximal total creatine concentration achievable as a result of creatine supplementation, and occurs in about 20% of subjects. Conversely, about 20 to 30% of subjects do not respond to creatine ingestion i.e., they demonstrate <10 mmol/kg dm increase in muscle total creatine as a result of supplementation. Of particular importance, recent work has revealed that muscle total creatine accumulation can be increased by a further 60% when creatine is ingested in solution (5 days of creatine at 20 g/day) in combination with simple carbohydrates (370 g of carbohydrate/day),[17,18] elevating muscle creatine concentration in *all* subjects close to the upper limit of 160 mmol/kg dm. As might be expected, urinary creatine excretion and plasma creatine concentration are reduced in parallel with the increase in muscle total creatine.[17,18]

The mean and individual increases in muscle total creatine concentration from the study of Green et al.[18] are shown in *Figure 4*. This figure highlights the major difference between ingesting creatine in combination with carbohydrate compared with ingesting creatine alone. As can be seen, 50% of the subjects who ingested creatine alone (4 × 5 g/day for 5 days) experienced an increase in muscle total creatine concentration of less than 20 mmol/kg dm (*Figure 4a*). This contrasts with the subjects who ingested creatine in combination with carbohydrate, all of whom experienced more than a 20 mmol/kg dm increase (*Figure 4b*). In agreement with the work of Harris et al.[13] there was a significant inverse relationship between the initial muscle total creatine concentration and the magnitude of accumulation seen following creatine supplementation alone ($r = -0.579$, $n = 12$; $P < 0.05$). However, this was not the case for those subjects who ingested creatine in combination with carbohydrate ($r = 0.058$, $n = 9$; $P > 0.05$), i.e., the initial muscle creatine concentration was found to have no significant effect on the extent of muscle creatine accumulation when creatine was ingested in combination with carbohydrate. Evidence was also presented in the studies of Green et al.[17,18] to indicate that the augmentation of muscle creatine accumulation following carbohydrate ingestion occurred as a result of a stimulatory effect of insulin on muscle creatine transport, and that this effect outweighed the positive effect that exercise has on muscle creatine accumulation. This work extended earlier animal experiments demonstrating that supraphysiological insulin concentrations could increase muscle creatine concentration, albeit less markedly (see Ref. 5). The exact mechanism by which muscle contraction stimulates muscle creatine transport is currently unknown. However, it is likely that insulin achieves its effect by stimulating Na^+/K^+ ATPase pump activity, thereby stimulating Na^+-dependent muscle creatine transport.

Health risks associated with dietary creatine supplementation

There have been recent anecdotal and press reports of creatine supplementation being linked with kidney damage and muscle cramping. However, at the time of writing this author is unaware of any published data to support these

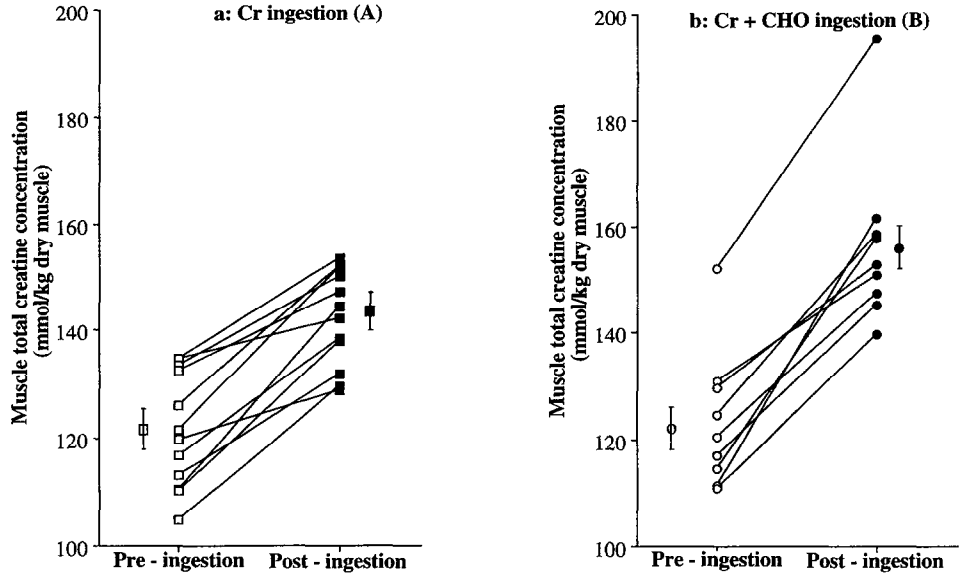

Figure 4 Mean (+SEM) and individual values for muscle total creatine concentration before (open symbols) and after (closed symbols) 5 days of Cr (20 g/day, A) ingestion and after 5 days of Cr (20 g/day) and carbohydrate (370 g/day, B) ingestion.

conclusions. Creatine supplementation does cause an increase in urinary creatinine excretion, which is often used as an indicator of kidney function, but this increase correlates well with the increase in muscle creatine observed during supplementation and reflects the increased rate of muscle creatine degradation to creatinine rather than any abnormality of renal function.[15] Furthermore, preliminary reports have shown that chronic high dose creatine supplementation (20 g/day for 5 days followed by 10 g/day for 51 days) has no effect on serum markers of hepatorenal function and routine clinical chemistry.[19,20] It should be stressed, nevertheless, that the long-term health risks of chronic creatine ingestion are presently unknown. Indeed, there are no data available concerning the health risks of long-term creatine supplementation in athletes involved in intensive training programs. Equally, however, the regimen of ingesting 20 g/day for 5 to 6 days has been reported to have no known side effects, providing the creatine is dissolved prior to ingestion (undissolved creatine may cause slight gastrointestinal discomfort). Furthermore, the 2 g/day "maintenance dose" of creatine ingestion currently advocated to maintain muscle creatine concentration during chronic periods of creatine supplementation[15] is perhaps no greater a quantity of creatine than that found in a meat eaters diet.

The effect of dietary creatine supplementation on exercise performance

In human skeletal muscle, creatine is present at a concentration of about 125 mmol/kg dm, of which approximately 60% is in the form of PCr at rest. A reversible equilibrium exists between creatine and PCr:

$$(PCr + ADP + H^+ \leftrightarrow ATP + \text{creatine}), \qquad (1)$$

and together they function to maintain intracellular adenosine triphosphate (ATP) availability, modulate metabolism and buffer hydrogen ion accumulation during contraction. The availability of PCr is generally accepted to be one of the most likely limitations to muscle performance during intense fatiguing short lasting contractions; its depletion resulting in an increase in cellular adenosine diphosphate (ADP) concentration and, thereby, the development of fatigue via an inhibition of muscle cross-bridge formation. This conclusion has been drawn from studies involving short bouts of maximal electrically evoked contraction[21] and voluntary exercise[22] and from animal studies in which the muscle creatine store has been depleted, before maximal electrical stimulation, using the creatine analogue β-guanidinopropionate.[23,24] Recent studies from this laboratory[25] and from others[26] have demonstrated that the extent of PCr resynthesis during recovery after a single bout of maximal exercise is positively correlated with exercise performance during a subsequent bout of exercise. For example, in the study of Casey et al.[25] eight subjects performed two bouts of maximal exercise each lasting 30 seconds, which were separated by 4 min of recovery. Rapid PCr resynthesis occurred during this recovery period, but was incomplete, reaching on average 88% of the pre-exercise concentration. However, the extent of PCr resynthesis during recovery was positively correlated with performance during the second bout of exercise ($r = 0.80$, $P < 0.05$). More detailed analysis also revealed that whilst the magnitude of PCr degradation in the second bout of exercise was less than that in the first, this fall in PCr utilization was restricted solely to the fast twitch muscle fibres (*Figure 5*), and was probably attributable to incomplete PCr resynthesis in this fibre type during recovery following the initial bout of exercise.[25] Creatine in its free and phosphorylated forms seems, therefore, to occupy a pivotal role in the regulation and homeostasis of skeletal muscle energy metabolism and fatigue. This being the case, it is pertinent to suggest that any mechanism capable of increasing muscle creatine availability might be expected to delay PCr depletion and the rate of ADP accumulation during maximal exercise and/or stimulate PCr resynthesis during recovery.

In 1934, Boothby (see Ref. 27) reported that the devel-

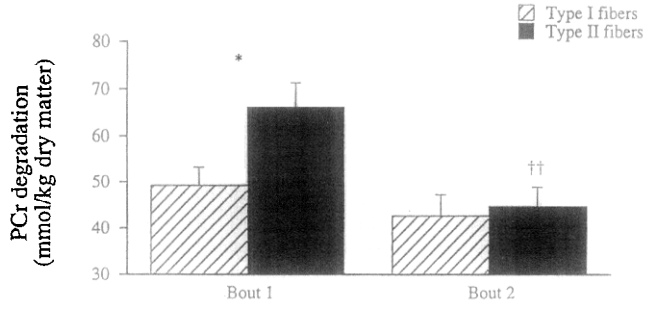

Figure 5 Changes (pre-post) in phosphocreatine (PCr) in slow (Type I) and fast (Type II) muscle fibres during two bouts of 30 second maximal intensity, isokinetic cycling exercise in man. Each bout of exercise was performed at 80 pedal revolutions/min and separated by 4 min of passive recovery. Values represent mean +SEM. * indicates significant differences between fibre types ($P < 0.05$) and †† indicates significantly different from exercise bout 1 ($P < 0.01$).

opment of fatigue in man could be delayed by the addition of large amounts of the creatine precursor glycine to the diet, which he attributed to an effect on muscle creatine concentration. Later, in 1939 Ray et al.[28] concluded that the ingestion of 60 g of gelatin/day for several weeks could also postpone the development of fatigue in man. The authors reasoned that because glycine constitutes 25% of gelatin by weight, the increased ingestion of gelatin would result in an increased muscle creatine concentration and thereby an increase in muscle function. Maison,[29] however, could not reproduce these findings and concluded that gelatin, and therefore glycine, had no effect on work capacity during repeated bouts of fatiguing muscle contractions. Shortly after this however, Chiakelis[27] reported that the ingestion of 6 g of glycine/day in tablet form for 10 weeks markedly improved performance (approximately 20%) in a number of different muscle groups and reduced creatinine excretion by 30%. In the discussion of results, the author implicated a change in the muscle creatine pool as being responsible for the observations made.

Other than these initial reports, which do not relate to creatine ingestion per se, little has been published concerning creatine ingestion and exercise performance until very recently. In 1981, Sipila et al.[30] reported that in a group of patients receiving 1 g of creatine/day as a treatment for gyrate atrophy (a condition in which creatine biosynthesis is impaired), there was a comment from some of a sensation of strength gain after a 1-year period of supplementation. Indeed, creatine ingestion was shown to reverse the Type II muscle fibre atrophy associated with this disease and one athlete in the group of patients improved his personal best record for the 100 m by 2 seconds. Muscle creatine availability has been implicated in the control of muscle protein synthesis,[31] and the pathology of muscle wasting diseases[4,9] and in born errors of metabolism[32] have been related to abnormalities of creatine metabolism.

Based on published results from placebo controlled laboratory experiments, it would seem that the ingestion of 4×5 g of creatine/day for 5 days can significantly increase the amount of work that can be performed by healthy normal volunteers during repeated bouts of maximal knee extensor exercise,[33] maximal dynamic exercise,[34] and maximal isokinetic cycling exercise.[35] In addition, it has been demonstrated that creatine supplementation can facilitate muscle PCr resynthesis during recovery from maximal intensity exercise in individuals who demonstrate a 20 mmol/kg dm or more increase in muscle creatine accumulation as a consequence of supplementation.[16] The author is aware of published work demonstrating that creatine ingestion has no effect on maximal exercise performance,[36–38] but may[37] or may not[38] reduce the accumulation plasma markers of muscle energy crisis. However, the most prevalent finding from published performance studies is that creatine ingestion can significantly increase exercise performance by sustaining force or work output during maximal exercise, particularly during repeated bouts of exercise. For example, in the study of Greenhaff et al.[32] two groups of subjects ($n = 6$) performed five bouts of 30 maximal voluntary unilateral knee extensions at a constant angular velocity of 180°/second before and after placebo or creatine ingestion (4×5 g of creatine/day for 5 days). No difference was seen when comparing muscle torque production during exercise before and after placebo ingestion. However, after creatine ingestion torque production was increased by 5 to 7% in all subjects during the final 10 contractions of exercise bout 1 and throughout the whole of exercise bouts 2, 3, and 4. In the study of Birch et al.[35] two groups of seven healthy male subjects performed three bouts of maximal isokinetic cycling exercise at 80 rev/min before and after creatine or placebo ingestion (4×5 g of creatine/day for 5 days). Each exercise bout lasted for 30 seconds and was interspersed by a 4 min rest. The total amount of work performed during bouts 1 to 3 were similar when comparing values obtained before and after placebo ingestion (<2% change). After creatine ingestion, work output was increased in all 7 subjects during exercise bouts 1 ($P < 0.05$) and 2 ($P < 0.05$), but no difference was observed during exercise bout 3. It should be noted, however, that recent results[39,40] suggest that creatine ingestion has no effect on performance or metabolism during submaximal exercise, which is perhaps not surprising given that PCr availability is not thought to limit energy production during this type of exercise.

More recently, data have been published to indicate that creatine supplementation mediates its performance enhancing effect during maximal-intensity exercise by increasing PCr availability principally in fast twitch muscle fibres.[41] This finding is in agreement with previous suggestions of a specific depletion of PCr in fast muscle fibres limiting exercise performance under these conditions,[21,25] and with the hypothesis that PCr acts as a temporal buffer of cytosolic ADP accumulation in this fibre type during exercise.[42]

As mentioned previously, it is important to note that the extent of muscle creatine retention during supplementation is highly variable between subjects. This finding is of special interest because it has recently been shown that this will have important implications to individuals wishing to gain exercise performance benefits from creatine supplementation. For example, work has revealed that the extent of improvement in exercise performance[41] and the magnitude of post-exercise PCr resynthesis following creatine supplementation[16] are closely related to the extent of muscle

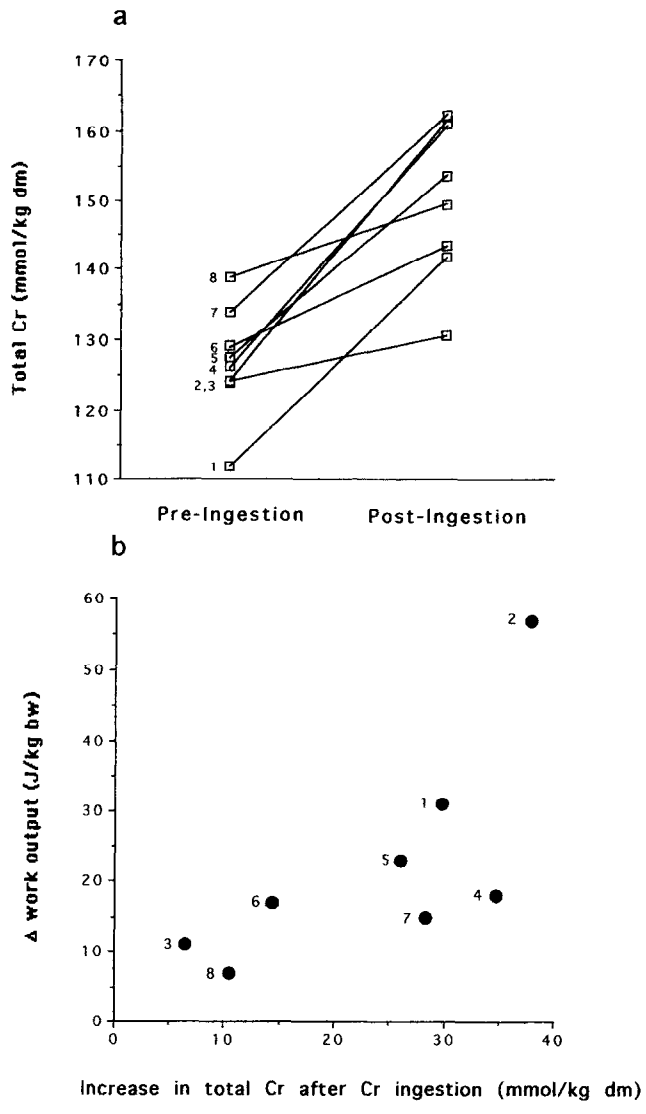

Figure 6 The upper *Figure* (*a*) shows individual values for muscle total creatine (Cr) concentration before and after 5 day of Cr ingestion (20 g/day). Subjects have been numbered 1–8 based on initial muscle total Cr concentration. The lower *Figure* (*b*) shows individual increases in muscle total Cr for the same group of subjects, plotted against the cumulative change in work production during 2 × 30 second bouts of maximal isokinetic cycling after Cr ingestion. Values on the *y*-axis were calculated by subtracting total work output during exercise before Cr ingestion from the corresponding value after Cr ingestion.

creatine accumulation during supplementation. *Figure 6a* demonstrates the muscle total creatine concentration of eight subjects before and after 5 days of dietary creatine supplementation (4 × 5 g/day) from the study of Casey et al.[41] Each subject has been assigned a number based on their initial muscle total creatine concentration (1 being the lowest and 8 being the highest). *Figure 6b* shows the change in cumulative work production achieved during 2 bouts of maximal exercise (each lasting 30 seconds) after creatine ingestion plotted against the increase in muscle total creatine as a result of supplementation in the same eight subjects. The positive relationship found ($r = 0.71$, $P < 0.05$) led to conclusion that it may be necessary to increase muscle total creatine concentration by close to or more than 20 mmol/kg dm to obtain substantial improvements in exercise performance as a result of creatine supplementation. These findings may provide some insight to those individuals who have "unexplainably" gained no benefit from creatine supplementation.[36–38] In this context, the combination of results from several recent studies undertaken in the author's laboratory has revealed that ~20 to 30% of individuals "do not respond" to creatine supplementation i.e. they demonstrate less than a 10 mmol/kg dm (8%) increase in muscle total creatine following 5 days of 20 g/day oral creatine supplementation (4 × 5 g doses dissolved in ~250 mL). Thus, as suggested previously, to gain 'optimal' functional and metabolic benefits from creatine supplementation recent data indicate that it is essential to consume creatine in combination with a carbohydrate solution.[17,18]

The mechanism of action of dietary creatine supplementation on exercise performance

As previously stated, the literature indicates that if the muscle creatine concentration can be increased by close to or more than 20 mmol/kg dm as a result of acute creatine ingestion then it is likely performance during single and repeated bouts of maximal short-duration exercise will be significantly improved. However, the exact mechanism by which this improvement in exercise performance is achieved is not yet clear. The available data indicate that it may be related to the stimulatory effect that creatine ingestion has on pre-exercise PCr availability, especially in fast-twitch muscle fibres.[41] Given that PCr availability is generally accepted to limit exercise capacity during maximal exercise,[21,25] this effect, together with the acceleration of post-exercise PCr resynthesis that has been reported to occur as a result of creatine supplementation,[16] would be expected to increase muscle contractile capability by maintaining ATP turnover during exercise. This suggestion is supported by reports showing that the accumulation of plasma ammonia and hypoxanthine are reduced during maximal exercise following creatine ingestion (both metabolites are accepted plasma markers of the disruption of muscle ATP resynthesis), despite a higher work output being achieved.[33,34] Furthermore, more direct supportive evidence comes from a recent study showing that creatine supplementation reduced the decline in muscle ATP by ~30% during maximal isokinetic cycling exercise, while, at the same time, increasing work output.[41]

Of further interest, it has recently been demonstrated that caffeine (5 mg/kg body mass/day, single dose) ingested in combination with creatine (0.5 g/kg body mass/day, 8 equal doses/day) can counteract the positive effect of creatine supplementation on performance during repeated bouts of high-intensity exercise.[43] The authors hypothesised that caffeine ingestion would augment muscle creatine accumulation via a direct and indirect (catacholamine mediated) stimulation of Na^+-dependent muscle creatine transport and thereby may enhance exercise performance further. However, caffeine appeared to have no stimulatory effect on muscle creatine accumulation as the authors demonstrated a 4 to 6% increase in resting muscle PCr concentration,

irrespective of whether caffeine was ingested or not (muscle total creatine was not assessed directly but PCr was determined using phosphorous magnetic resonance spectroscopy). Surprisingly, therefore, the ergolytic effect of caffeine ingestion was not attributable to caffeine inhibiting muscle creatine accumulation during supplementation. The authors offered no clear alternative explanation for their performance findings, but did point out that it was unlikely to be attributable to an effect of caffeine on "muscle energetics" as the final caffeine dose preceded the postsupplementation exercise test by at least 20 h, which is easily sufficient time for caffeine elimination to have occurred. They did conclude, however, that caffeine containing beverages are an inappropriate vehicle for ingestion of creatine supplements. This conclusion seems rather harsh given the very high single dose of caffeine administered in this study. Indeed, the first reports of creatine supplementation increasing muscle creatine accumulation,[13] maximal exercise performance,[33] and PCr postexercise resynthesis[16] involved subjects dissolving creatine in everyday caffeine containing beverages immediately before consumption.

In conclusion, information relating to the effects of dietary creatine ingestion on muscle function and metabolism during exercise in healthy normal individuals and in disease states is relatively limited. Based on recent findings, it would seem that it is important to optimize tissue creatine uptake to maximize performance benefits, and, therefore, further work is required to elucidate the principle factors regulating tissue creatine uptake in man. More information is needed about the exact mechanisms by which creatine achieves its ergogenic effect and on the long-term effects of creatine supplementation. With respect to this last point, it should be made clear that the health risks associated with prolonged periods of high dose creatine supplementation are unknown, equally, however, research to date clearly shows it is not necessary to consume large amounts of creatine to load skeletal muscle. Creatine supplementation may be viewed as a method for producing immediate improvements to athletes involved in explosive sports. In the long run, creatine may also allow athletes to benefit from being able to train without fatigue at an intensity higher than that to which they are normally accustomed. For these reasons alone, creatine supplementation could be viewed as a significant development in sports-related nutrition.

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