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REVIEW ARTICLE

Use of creatine in the elderly and evidence for effects on cognitive function in young and old

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Abstract The ingestion of the dietary supplement creatine (about 20 g/day for 5 days or about 2 g/day for 30 days) results in increased skeletal muscle creatine and phosphocreatine. Subsequently, the performance of high-intensity exercise tasks, which rely heavily on the creatine-phosphocreatine energy system, is enhanced. The well documented benefits of creatine supplementation in young adults, including increased lean body mass, increased strength, and enhanced fatigue resistance are particularly important to older adults. With aging and reduced physical activity, there are decreases in muscle creatine, muscle mass, bone density, and strength. However, there is evidence that creatine ingestion may reverse these changes, and subsequently improve activities of daily living. Several groups have demonstrated that in older adults, short-term high-dose creatine supplementation, independent of exercise training, increases body mass, enhances fatigue resistance, increases muscle strength, and improves the performance of activities of daily living. Similarly, in older adults, concurrent creatine supplementation and resistance training increase lean body mass, enhance fatigue resistance, increase muscle strength, and improve performance of activities of daily living to a greater extent than resistance training alone. Additionally, creatine supplementation plus resistance training results in a greater increase in bone mineral density than resistance training alone. Higher brain creatine is associated with improved neuropsychological performance, and recently, creatine supplementation has been shown to increase brain creatine and phosphocreatine. Subsequent studies have demonstrated that cognitive processing, that is either experimentally (following sleep deprivation) or naturally (due to aging) impaired, can be improved with creatine supplementation. Creatine is an inexpensive and safe dietary supplement that has both peripheral and central effects. The benefits afforded to older adults through creatine ingestion are substantial, can improve quality of life, and ultimately may reduce the disease burden associated with sarcopenia and cognitive dysfunction.

Keywords Dietary supplement · Ergogenic aid · Fatigue · Phosphocreatine · Aging

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Introduction

Between 1960 and 2000, the world population doubled, and by 2050 it is predicted to triple; with individuals over 65 years being the fastest growing segment of the population (Department of Health and Human Services 2009; Census Bureau 2010). In 2008, there were about 38.9 million Americans that were over the age of 65, and this is predicted to increase to 55 million by 2020 (Census Bureau 2010). Similar patterns can be seen in the growth of this age group in Europe (Giannakouris 2010). Aging is associated with a decrease in cognitive abilities (Bixby et al. 2007; Bugaiska et al. 2007), loss of muscle mass (sarcopenia), and decreased strength (dynapenia) (Clark and Manini 2010). These aging related phenomena interact and are related to an impaired ability to perform activities of daily living (ADL), increased fall risk (Tinetti et al. 1988, 2006), and subsequently, increased risk of mortality (Alexander et al. 1992). Reportedly, up to one third of

community dwelling adults aged 65 years or older fall each year (Tinetti et al. 1988) resulting in millions of dollars in health care costs (Tinetti et al. 2006). Due to the rapid increase in the number of older adults in the world, there is now a greater need than ever for an intervention that can combat age-related changes that increase morbidity and mortality risk.

Several pharmaceutical drugs and nutrients have been studied in the hope of finding a substance that will off-set age-related declines in muscle and cognitive function. Testosterone therapy may be effective at combating sarcopenia and dynapenia in older adults (Bhasin and Storer 2009), but may also be associated with increased risk of cardiovascular disease and prostate dysfunction (Calof et al. 2005). Nutrients such as antioxidants, polyphenols, omega-3 fatty acids, and herbs such as ginkgo biloba have been investigated as potential treatments to combat age-associated declines in cognitive processing, but the results of these studies have been ambiguous and not as encouraging as had been expected (Montero-Odasso et al. 2009; Brown et al. 2010).

A great deal of research is available to demonstrate that creatine supplementation is effective in improving both muscle and cognitive function. In supplemental form, this nutrient is inexpensive and data are available supporting a track record of excellent safety (Persky and Rawson 2007). The purpose of this review is to describe the fundamentals of creatine metabolism, age-associated changes to the creatine-phosphocreatine energy system, effects of creatine supplementation on muscle function in older adults, and the effects of creatine supplementation on cognitive processing.

History of creatine and early supplementation studies

Before creatine supplementation became a common term in the sport science literature, there were 160 years (from about 1832 to 1992) of investigations into the metabolism of creatine and creatinine and the role of creatine and phosphocreatine in muscle contraction. The discovery of creatine was reported by distinguished scientist Chevreul (1832) in his 1832 article "Sur une nouvelle substance contenue dans la chair de boeuf" (on a new substance in the flesh of beef). Another notable scientist who shaped creatine research was Justus von Liebig, who began selling a concentrated meat extract (*Extractum carnis Liebig*) containing 8% creatine, reportedly, to support his laboratory. Although there were no data to support any health or other promoting properties of Liebig's meat extract, increased body creatine through creatine feeding was documented in humans in the early 1900s (Chanutin and Guy 1926). By measuring urine creatine output during oral creatine feeding, Chanutin and Guy (1926) demonstrated that 7.65 of 10 g ingested in a single day was retained by the body, and, in two adult men, that 58 of 270 g were retained after 20 days of supplementation and 38 of 340 g were retained after 35 days of supplementation. During the first 100 years of creatine research, there was great interest in the study of creatine, culminating in the extensive 1928 review "Creatine and Creatinine Metabolism" by Andrew Hunter which contains more than 800 references (Hunter 1928). Interest in creatine research waned for the next several decades, likely due to the discovery of phosphocreatine (Eggleton and Eggleton 1927; Fiske and Subbarow 1927), the creatine kinase reaction, and adenosine triphosphate (http://nobelprize.org/nobel_prizes/medicine/articles/states/otto-meyerhof.html).

Although there is a report of increased body creatine retention following oral creatine supplementation published in 1926 (Chanutin and Guy 1926), the concept of creatine ingestion to improve muscle function was not explored for several more decades. This delay may have resulted from the absence of a technique to study muscle energetics, but research in this area moved forward quickly with the development and widespread use of the muscle biopsy technique (Bergström 1962). Although there are anecdotal reports of Russian athletes ingesting creatine to enhance performance during the 1970s and 1980s (Kalinski 2003), it is likely that the tipping point of interest in creatine use by athletes was the 1992 article in the London Times revealing that British sprinter and gold medalist Linford Christie had ingested creatine in his preparation for the Barcelona Summer Olympic Games. Reports of creatine use by other champion athletes soon surfaced, and scientists hurried to catch up. To researchers, the publications by Harris et al. (1992) and Greenhaff et al. (1993), which demonstrated increased muscle creatine and improved exercise performance subsequent to oral creatine ingestion, respectively, were the true seminal moments in the modern era of creatine research. Since the publication of these two articles, and in the space of less than 20 years, several hundred investigations on the effects of oral creatine supplementation have been published. Creatine supplementation is widely practiced by athletes, with prevalence of use in some sports as high as 75% (reviewed in Rawson and Clarkson 2004). Today, research on creatine supplementation has shifted from the earlier studies of sports performance enhancement to mechanisms of action and benefits to patient populations.

Biosynthesis, distribution, and degradation of creatine

Creatine is synthesized from arginine, glycine, and methionine (Bloch and Schoenheimer 1941) in the kidneys, liver, and pancreas. Approximately one to two grams are

synthesized per day, and about 95% of this is exported and stored in skeletal muscle. The remaining creatine is stored in the brain, testes, and kidney (Walker 1979). Creatine is also ingested in the diet with meats containing about three to four grams of creatine per kilogram of meat (Balsom et al. 1994). Normal muscle creatine values are about 124.4 mmol/kg dry muscle (dm) for total creatine, 49 mmol/kg dm for free creatine, and 75.5 mmol/kg dm for phosphocreatine (Harris et al. 1974). Creatine and phosphocreatine, along with the enzyme creatine kinase, are used to sustain adenosine triphosphate (ATP) levels during times of high energy demand. The creatine phosphocreatine energy system has been described as both a temporal and spatial energy buffer (via the phosphocreatine shuttle) (Bessman and Geiger 1981; Bessman and Carpenter 1985). Both creatine and phosphocreatine are spontaneously degraded to creatinine, which is excreted in the urine, with a normal 24 h creatine turnover of about two grams per day.

Age-related changes in the creatine-phosphocreatine energy system

Muscle creatine

Age-associated reductions in skeletal muscle creatine/phosphocreatine have been reported in some (Möller et al. 1980; Forsberg et al. 1991; McCully et al. 1991, 1993; Smith et al. 1998; Campbell et al. 1999), but not all studies (Conley et al. 2000; Kent-Braun and Ng 2000; Rawson et al. 2002). Reduced muscle creatine as a consequence of aging (e.g. sarcopenia) and/or subsequent to age-associated changes in behavior (modified physical activity and/or dietary behaviors) is biologically plausible and is supported by empirical evidence. Type II muscle fibers have a greater phosphocreatine content than type I fibers ($\approx$86 vs. $\approx$74 mmol/kg dm) (Tesch et al. 1989), and sarcopenia is characterized by a preferential atrophy of Type II fibers (Lexell and Taylor 1991). Thus, progressive Type II fiber atrophy may partially explain reduced muscle creatine in older adults. Additionally, reduced creatine in older muscle is congruent with research that describes how skeletal muscle becomes more oxidative with aging (e.g. decreased reliance on glycolysis (Lanza et al. 2005); decreased lactate dehydrogenase (Larsson et al. 1979)).

There is evidence to support a connection between physical activity levels and muscle creatine. Physical inactivity reduces muscle phosphocreatine (25%), but this has only been reported following five weeks of experimentally induced immobilization (MacDougall et al. 1977). It is unknown if the level of inactivity achieved in an immobilization study approximates the level of physical activity of inactive older adults. Kent-Braun and Ng (2000) reported similar muscle phosphocreatine in groups of sedentary older (76 year) and younger (34 year) adults when they were matched for habitual physical activity. Further strengthening the tie between physical activity and muscle creatine, MacDougall et al. (1977) showed increased muscle creatine (39%) following 5 months of resistance training in young adults and Möller and Brandt (1982) demonstrated an increased phosphocreatine/creatine ratio following 6 weeks of bicycle ergometer training in older men (61–80 year). So, it is possible that older adults with extremely low levels of physical activity may have inactivity related declines in muscle creatine.

Meat is the primary source of dietary creatine, but is expensive, may present chewing problems for those with dentures, and may be associated with several diseases more common in older adults (e.g. cardiovascular disease, certain cancers). Thus, it is not uncommon for adults to decrease their meat intake as they age, consequently adopting a low creatine diet. It is known that vegetarians have reduced blood (Delanghe et al. 1989; Shomrat et al. 2000; Maccormick et al. 2004; Lukaszuk et al. 2005) and muscle creatine (Lukaszuk et al. 2002; Burke et al. 2003; Watt et al. 2004). In fact, Lukaszuk et al. (2002, 2005) reduced blood and muscle creatine with just 26 days of an experimentally induced lacto-ovo-vegetarian diet in young men. It could be speculated that reduced muscle creatine observed in older adults is, in part, the result of reduced creatine in the diet.

Although decreased muscle creatine has been observed in older adults, it is unknown if this is an unavoidable consequence of aging (i.e. denervation, Type II fiber atrophy), related to physical activity (reduced physical activity or reduced intense physical activities that recruit type II fibers), decreased dietary creatine intake, or if there are synergistic effects between these three factors. It has been shown that creatine transporter (CreaT) mRNA and protein content do not decrease in older adults in response to creatine supplementation (Tarnopolsky et al. 2003), but data on the effects of aging per se on the CreaT are unavailable. Muscle creatine, Type II fiber size, habitual physical activity, muscle power, and dietary creatine intake have not been assessed in a longitudinal study, nor has muscle creatine been compared between older and younger adults matched for these other variables in a cross-sectional investigation. Nonetheless, there is strong evidence to suggest that muscle creatine is not constant throughout the lifespan.

Brain creatine

Relative to the well documented reduction in brain creatine attributed to disease, few data are available on the effects of

healthy aging on brain creatine. For instance, brain creatine is reduced in major depression (Kato et al. 1992), schizophrenia (Öngur et al. 2009), and panic disorder (Massana et al. 2002). Also, cerebral creatine deficiency syndromes caused by inborn errors of metabolism involving creatine biosynthesis (e.g. arginine glycine amidinotransferase (AGAT) deficiency, guanidinoacetate methyltransferase (GAMT) deficiency) have been well described (reviewed in Stockler et al. 2007). Pathologies associated with the AGAT and GAMT deficiencies, which can include mental retardation, learning delays, autism, and seizures (Stockler et al. 2007), and depression (Roitman et al. 2007) may be improved by oral creatine supplementation.

Laakso et al. (2003) reported that in older adults (77 year) with the Apolipoprotein E4 genotype brain creatine was significantly correlated with age ($r = -0.82$) and score on the Mini Mental State Exam ($r = 0.75$), suggesting that brain creatine decreases with age, but that higher levels of brain creatine in older adults are associated with better cognitive function. However, others have reported age-related increases in brain creatine (Angelie et al. 2001). It is known that brain creatine can be increased with memory training (Valenzuela et al. 2003) and that brain creatine correlates with recognition memory (Ferrier et al. 2000). Unfortunately, little more than chronological age and scores on a test of cognitive processing are regularly reported in studies with measures of brain creatine. Any conclusions made regarding the interactions between aging, brain creatine, cognitive processing, mental activity, physical activity, diet, years of education, etc. are speculative, as these data appear unavailable at the present time. It seems plausible that low mental and/or physical activity, combined with aging could hasten decreases in brain creatine and any accompanying functional changes. This may explain why memory training (Valenzuela et al. 2003) and exercise (Angevaren et al. 2008) improve cognitive functioning.

Much like muscle creatine, brain creatine should not be viewed as a constant across the lifespan, and care must be taken when interpreting reports that express brain metabolites as a ratio (e.g. N-acetyl-aspartate (NAA)/creatine) as opposed to providing absolute values. Ferguson et al. (2002) have highlighted this concern noting that a reported reduction in NAA/creatine assumed to reflect reductions in absolute values of NAA, may instead reflect changes in creatine. The assumption that brain creatine levels are constant (i.e. little change with disease, age, lifestyle) and should be used as the denominator is almost certainly erroneous and may add to the discrepant findings reported on the effects of aging on brain creatine. Although age-associated changes in brain creatine have been reported, better phenotyping is necessary to explore changes in brain metabolites. Beyond chronological age, researchers should consider assessments of dietary and physical activity behaviors, physical fitness, multiple aspects of cognitive processing and mood, muscle function, education, and socioeconomic status.

Effects of creatine supplementation on muscle and brain creatine in older adults

Muscle

The seminal works that first demonstrated increased muscle creatine subsequent to oral creatine supplementation were published by Harris et al. (1992) and Hultman et al. (1996). Collectively, these researchers and others have shown that both short-term high-dose oral creatine ingestion (20–25 g/day for 5–7 days) and low-dose longer-term oral creatine ingestion (2–5 g/day for 4–6 week) result in about a 20% increase in skeletal muscle creatine in young adults. Only a small number of studies have been published that included pre- and post-supplementation measures of muscle creatine in older adults (Smith et al. 1998; Rawson et al. 2002; Brose et al. 2003; Eijnde et al. 2003), thus, as is the case with data on resting muscle creatine, much less is known about the effects of oral creatine supplementation on muscle creatine in older than younger adults. Smith et al. (1998) first reported increased muscle phosphocreatine (30%) in middle-aged adults (58 years) following short-term high-dose creatine supplementation (0.3 g/kg/day for 5 days). In a similar study, Rawson et al. (2002) described a smaller increase in muscle phosphocreatine (7 vs. 35%) in older (70 years) compared to younger (24 years) adults in response to creatine ingestion (20 g/day for 5 days). However, baseline muscle phosphocreatine was higher in the young relative to the middle-aged subjects described by Smith et al. (1998), while the older subjects described by Rawson et al. (2002) had higher initial muscle phosphocreatine relative to the young subjects. It is known that baseline muscle creatine is one of the primary determinants of the increase in muscle creatine following creatine supplementation in young adults (Harris et al. 1992; Hultman et al. 1996; Rawson et al. 2002). Thus, one interpretation of these data could be that although the magnitude of the increase in muscle phosphocreatine was dissimilar in these two investigations, because both older and young adults achieved similar post-supplementation muscle phosphocreatine values, older adults do respond to short-term high-dose creatine supplementation.

Brose et al. (2003) reported increased muscle total creatine (30% men; 17% women) in older adults (70 year) undergoing 14 weeks of resistance training plus creatine ingestion (5 g/day), which approximates increases reported in younger adults (Vandenberghe et al. 1997; Volek et al.

1999). Eijnde et al. (2003) also reported increased muscle total creatine (5%) and free creatine (21%) following a 6-month muscular endurance exercise training program plus creatine ingestion (5 g/day). The effect of high-dose, short-term, and low-dose, longer-term creatine supplementation on muscle creatine in older adults is described in Table 1. From this small number of observations, it appears that muscle creatine in older adults can be increased with oral creatine supplementation, but that the magnitude of the response may be tempered by initial muscle creatine. Wyss et al. (1998) have theorized that increased extracellular creatine may decrease muscle creatine uptake by decreasing CreaT activity. Although Rawson et al. (2002) have reported higher blood creatine in older adults (old 68.5 μmol/l; young 34.9 μmol/l), Tarnopolsky et al. (2003) has shown no decrease in CreaT activity following creatine ingestion in older men and women.

Brain

There are currently no reports of changes in brain creatine in older adults undergoing oral creatine supplementation. Several groups have demonstrated increased brain creatine in young adults ingesting creatine (Dechent et al. 1999; Lyoo et al. 2003; Pan and Takahashi 2007), but this has not

Table 1 Effect of creatine supplementation on muscle creatine in older adults

Mean age	*n*	Study design	Creatine dose	Resting muscle creatine	Δ Muscle creatine	Reference
O: 58 Y: 31	O: 4 (3 M; 1 W) Y: 5 (4 M; 1 W)	Acute Single-blind	0.3 g/kg/day for 5 days	O: 35.0 ± 5.2 Y: 39.5 ± 5.1 (PCr mmol/kg ww)	O: ↑ 30% Y: ↑ 15%	Smith et al. (1998)
O: 70 Y: 24	O: 7 M Y: 8 M	Acute	20 g/day for 5 days	O: 23.9 ± 0.7 Y: 20.5 ± 0.7 (PCr mmol/kg ww)	O: ↑ 7% Y: ↑ 35%	Rawson et al. (2002)
OCM: 69 OCW: 71	OC: 13 (7 M; 6 W)	Double-blind placebo-controlled Fourteen week resistance training intervention	5 g/day for 14 weeks	OCM: TCr 116.8 ± 14.5 Cr 49.4 ± 16.0 PCr 67.4 ± 19.7 OCW: TCr 129.7 ± 25.4 Cr 46.6 ± 13.8 PCr 83.1 ± 15.2	OCM: TCr ↑ 36.4% Cr ∅ PCr ↑ 30.6% OCW: TCr ↑ 17.0 Cr ∅ PCr ∅	Brose et al. (2003)
OPM: 68 OPW: 70	OP: 13 (7 M; 6 W)			OPM: TCr 140.8 ± 20.6 Cr 51.6 ± 22.9 PCr 89.2 ± 25.6 OPW: TCr 138.5 ± 14.0 Cr 63.6 ± 15.9 PCr 74.8 ± 13.8 (mmol/kg dw)	OPM: TCr ∅ Cr ∅ PCr ∅ OPW: TCr ∅ Cr ∅ PCr ∅ (mmol/kg dw)	
OC: 64	OC: 13 M	Double-blind placebo-controlled	5 g/day for 6 month	OC: TCr 145.8 ± 6.1 Cr 42.2 ± 1.9 PCr 103.6 ± 5.7	OC: TCr ↑ 5% Cr ↑ 21% PCr ∅	Eijnde et al. (2003)
OP: 62	OP: 12 M	Six month resistance training intervention		OP: TCr 143.4 ± 3.1 Cr 45.2 ± 2.4 PCr 98.1 ± 2.8 (mmol/kg dw)	OP: TCr ∅ Cr ∅ PCr ∅	

O old group, *Y* young group, *OC* old creatine group, *OP* old placebo group, *M* men, *W* women, *TCr* total creatine, *Cr* creatine, *PCr* phosphocreatine, ∅ no difference from baseline

been shown in every case (Wilkinson et al. 2006). The dosing protocols used in these studies varied from 28 days of a loading dose (20 g/day) (Dechent et al. 1999), to a 7 day loading dose (0.3 g/kg/day) followed by a 7 day maintenance dose (0.03 g/kg/day) (Lyoo et al. 2003), to a traditional 7 day loading dose (20 g/day) (Pan and Takahashi 2007). Dechent et al. (1999) reported a trend for increased brain total creatine 8 h following a single 20 g dose (3.1% in gray matter, 3.1% in white matter, 7.7% in thalamus), and a statistical increase after 28 days (8.7% in total brain, 4.7% in gray matter, 11.5% in white matter, 5.4% in cerebellum, and 14.6% in thalamus). Smaller, but statistically significant increases, were reported by Pan and Takahashi (2007) (5.2% increase) and Lyoo et al. (2003) (3.9% increase in phosphocreatine). There is no clear indication why Wilkinson and colleagues (Wilkinson et al. 2006) were unable to detect an increase in brain creatine following a loading dose (20 g/day for 5 days). It is curious, that the population studied in this investigation were described as sportsmen, leading to speculation that chronic exposure to physical activity can increase baseline brain creatine. As there is an upper limit of both brain and muscle creatine, higher initial levels will reduce the magnitude of the response to supplementation. The effects of oral creatine supplementation on brain creatine in young adults are detailed in Table 2.

Although brain creatine can be increased with oral creatine supplementation, it appears that the response is smaller than for skeletal muscle (muscle about 20%; brain about 9%). Two factors likely contribute to the discrepancy between muscle and brain creatine uptake in response to supplementation. First, skeletal muscle relies on peripheral creatine uptake, while nervous tissue relies on endogenous synthesis (Braissant et al. 2007). This likely reduces the

Table 2 Effect of creatine supplementation on brain creatine

Mean age	*n*	Creatine dose	Δ Brain creatine	Pre/post cognitive tests	Reference
26	Creatine: 6 (2 M; 4 W)	Single 20 g dose	TCr: Gray matter ↑ 3.1% White matter ↑ 3.1% Thalamus ↑ 7.7%	No	Dechent et al. (1999)
26	Creatine: 6 (2 M; 4 W)	20 g/day for 28 days	TCr: Total brain ↑ 8.7% Gray matter ↑ 4.7% White matter ↑ 11.5% Cerebellum ↑ 5.4% Thalamus: ↑ 14.6%	No	Dechent et al. (1999)
23	Creatine: 10 M	0.3 g/kg/day for 7 days; 0.03 g/kg/day for 7 days;	PCr : ↑ 3.9% Cr/NAA: ↑ 8.1% Cr/choline: ↑ 9.3%	No	Lyoo et al. (2003)
23	Placebo: 5 M		No change in placebo group		
23	Creatine: 12 M Placebo: 6 M	20 g/day for 5 days	Cr: ∅ No change in placebo group	No	Wilkinson et al. (2006)
32	Creatine: 12 (7 M; 5 W)	20 g/day for 7 days	Occipital lobe: PCr/ATP ↑ 1.2% PCr ↓ 3.1% Medial Temporal: PCr/ATP ↑ 6.3% PCr ∅ Stratium: PCr/ATP ↑7.2% PCr ∅ Hippocampus: Cr ↑5.2%	No	Pan and Takahashi (2007)

TCr total creatine, *Cr* creatine, *PCr* phosphocreatine, *Cr/NAA* creatine:N-acetyl aspartate ratio, *Cr/choline* creatine:choline ratio, ∅ no effect of the creatine supplement

ability of brain tissue to take up orally ingested creatine. Second, the capacity of the brain to increase creatine levels may be smaller than skeletal muscle. At this time, simultaneous measures of muscle and brain creatine uptake in response to supplementation in humans have not been reported. Muscle and brain creatine uptake comparisons in other species may not be appropriate to generalize to humans as others have reported unique species differences (Ipsiroglu et al. 2001). For instance, Ipsiroglu et al. (2001) reported very large increases in brain total creatine of 54, 32, and 30% in guinea pig, mouse, and rat, respectively, in response to creatine feeding. Nearly 100 years ago, Chanutin (1927) reported increased liver creatine in rats, with no concomitant increase in brain creatine in response to creatine feeding. The ideal dose of creatine to maximize brain uptake is not known. Clinical trials on patients with Huntington's disease are using 40 g per day (www.clinicaltrials.gov, Clinical Trials Identifier: NCT00712426), while doses in healthy adults have been about 20 g per day. Interestingly, studies that support a beneficial effect of creatine on cognitive processing have used a variety of different dosing protocols (see Table 5).

Effects of creatine supplementation on muscle function in older adults

Acute studies

Creatine supplementation improves muscle function in young adults through metabolic means (e.g. increased pre-exercise phosphocreatine and/or faster post-exercise phosphocreatine resynthesis (Greenhaff et al. 1994; Yquel et al. 2002), increased pre-exercise glycogen (Nelson et al. 2001)), increased fat free mass (many studies e.g. Volek et al. 1999; Mihic et al. 2000), reduced muscle damage (Bassit et al. 2010), spontaneously increased training volume (Volek et al. 1999), increased mRNA and protein expression of myogenic regulatory factors (e.g. IGF-1, Myo-D, myogenin, MFR-4, Myf5 (Willoughby and Rosene 2003; Deldicque et al. 2005)), increased satellite cell number (Olsen et al. 2006), or upregulation of the mRNA content and protein content of various genes and protein kinases (e.g. osmosensing, signal transduction, cytoskeleton remodeling, protein/glycogen synthesis regulation, satellite cell proliferation/differentiation, DNA replication/

Table 3 Functional effects of creatine supplementation without exercise training in older adults

Mean age	*n*	Creatine dose	Strength/ power	Fatigue resistance	ADL	Reference
O: 58	O: 4 (3 M; 1 W)	0.3 g/kg/day for 5 days	–	↑	–	Smith et al. (1998)
Y: 31 (single-blind crossover study)	Y: 5 (4 M; 1 W)					
OC: 67	OC: 10 M	20 g/day for 10 days; 4 g/day for 20 days	∅	↑	–	Rawson et al. (1999)
OP: 67	OP: 10 M					
OC: 65	OC: 9 M	20 g/day for 5 days	∅	↑	–	Rawson and Clarkson (2000)
OP: 66	OP: 8 M					
O sedentary: 70	OC sedentary: 7 M	15 g/day for 5 days	↑	↑	–	Wiroth et al. (2001)
	OP sedentary: 7 M					
O trained: 66	OC trained: 7 M		∅	∅	–	
	OP trained: 7 M					
OC: 72	OC: 7 M	20 g/day for 5 days	∅	∅	–	Jakobi et al. (2001)
OP: 73	OP: 5 M					
OC: 65	OC: 10 M	0.3 g/kg/day for 7 days	↑	↑	↑	Gotshalk et al. (2002)
OP: 66	OP: 8 M					
OC: 67	OC: 10 W	0.3 g/kg/day for 7 days	–	∅	↑	Canete et al. (2006)
OP: 68	OP: 6 W					
OC/P: 75 (crossover study)	OC/P: 23 (15 M; 8 W)	20 g/day for 7 days; 10 g/day for 7 days	↑	↑	∅	Stout et al. (2007)
OC: 63	OC: 15 W	0.3 g/kg/day for 7 days	↑	↑	↑	Gotshalk et al. (2008)
OP: 63	OP: 12 W					

OC old creatine group, *OP* old placebo group, *M* men, *W* women, ∅ no effect of the creatine supplement, ↑ beneficial effect of the creatine supplement, – not assessed

repair, RNA transcription control, cell survival (Safdar et al. 2008)) (reviewed in Rawson and Persky 2007). If these mechanisms are active in older adults, then increased muscle creatine subsequent to creatine ingestion should improve exercise performance in older adults as well. Beginning in the late 1990s, several groups reported the effects of creatine supplementation without exercise training on muscle function (Smith et al. 1998; Rawson et al. 1999; Rawson and Clarkson 2000; Jakobi et al. 2001; Wiroth et al. 2001; Gotshalk et al. 2002; Canete et al. 2006; Stout et al. 2007; Gotshalk et al. 2008) in older adults. The most typical finding is enhanced fatigue resistance, which has been demonstrated in many different studies using a variety of exercise tests (Smith et al. 1998; Rawson et al. 1999; Rawson and Clarkson 2000; Wiroth et al. 2001; Gotshalk et al. 2002; Stout et al. 2007). Some investigators have reported increased strength (Gotshalk et al. 2002, 2008; Stout et al. 2007), but this is not always found (Rawson et al. 1999; Rawson and Clarkson 2000). Importantly, in later publications, investigators began to test for performance of activities of daily living (ADL), and demonstrated that creatine ingestion could improve the performance of daily tasks (Gotshalk et al. 2002, 2008; Canete et al. 2006). Improved performance of ADLs is an important finding, due to the link between performance of ADLs, fall risk, and mortality. Although only one study has reported changes in muscle creatine and muscle function in the same study (Smith et al. 1998) (in middle-aged and young adults), it does appear that creatine supplementation improves muscle function in older adults independent of exercise training. The functional effects of creatine supplementation without exercise training in older adults are described in Table 3.

Exercise training studies

The effects of creatine supplementation combined with exercise training on changes in fatigue resistance, strength, and performance of ADLs in older adults have also been reported (Bermon et al. 1998; Chrusch et al. 2001; Brose et al. 2003; Eijnde et al. 2003; Tarnopolsky et al. 2007; Candow et al. 2008; Bemben et al. 2010). When comparing the benefits of creatine supplementation plus exercise training to the benefits of exercise training alone, it has been reported that creatine can augment exercise training resulting in greater improvements in fatigue resistance (Chrusch et al. 2001; Tarnopolsky et al. 2007), strength (Chrusch et al. 2001; Tarnopolsky et al. 2007; Candow et al. 2008), and performance of ADLs (Chrusch et al. 2001). Not all groups have reported an additional effect of creatine when combined with exercise training (Bermon et al. 1998; Eijnde et al. 2003; Bemben et al. 2010). Discrepancies between these studies are difficult to explain, but small group sample size (Bermon et al. 1998), disconnect between training program and outcome measures (Eijnde et al. 2003), heterogeneity of subject age (Bemben et al. 2010), or difficulty detecting the effects of creatine when combined with the variable response to resistance training (Hubal et al. 2005), may have played a role. Recently Candow et al. (2004) reported on cessation of creatine supplementation and reduced training volume following 12 weeks of creatine supplementation plus resistance training in older adults. Discontinuing the creatine supplements did not influence the rate of strength, endurance, or lean mass loss, indicating that gains made during creatine supplementation plus exercise training programs do not rapidly disappear when the supplement is discontinued. The functional effects of creatine supplementation and concurrent resistance training in older adults are reported in Table 4.

Of the studies that assessed muscle mass, the majority showed a greater increase in lean tissue accretion following creatine ingestion plus resistance training than resistance training alone (Chrusch et al. 2001; Brose et al. 2003; Tarnopolsky et al. 2007; Candow et al. 2008). A final benefit of combining creatine supplementation with resistance exercise is increased bone mineral content. Chilibeck et al. (2005) showed a greater increase (3.2 vs. 1%) in bone mineral content in older men (71 year) following 12 weeks of creatine supplementation (0.3 g/kg for 5 days, 0.07 g/kg for 11 weeks) plus resistance training versus resistance training alone. Dalbo et al. (2009) have stated that creatine supplementation is an effective intervention for combating sarcopenia.

Effects of creatine supplementation on cognitive processing in older adults

As with skeletal muscle, during brain activity, phosphocreatine donates its phosphate to adenosine diphosphate (ADP) to prevent a rapid decrease in adenosine triphosphate (Sappey-Marinier et al. 1992; Rango et al. 1997). Because cognitive tasks rely on creatine and phosphocreatine to maintain brain ATP levels, increasing brain creatine through creatine supplementation may improve cognitive processing. Additionally, creatine supplementation may reduce homocysteine (Korzun 2004), which has been implicated in age-related cognitive decline (Tucker et al. 2005).

Four groups have assessed the effects of creatine supplementation on cognitive processing in young, unstressed adults, using low-dose creatine (Watanabe et al. 2002; Rae et al. 2003; Rawson et al. 2008) or low-dose creatine ethyl-ester supplementation protocols (Ling et al. 2009). While Rae et al. (2003) and Watanabe et al.

Table 4 Functional effects of creatine supplementation and concurrent resistance training in older adults

Mean age	*n*	Creatine dose	Strength/ power	Fatigue resistance	ADL	Reference
OC trained: 71	OC trained: 8 (4 M; 4 W)	20 g/day for 5 days; 3 g/day for 47 days	∅	∅	–	Bermon et al. (1998)
OP trained: 69	OP trained: 8 (4 M; 4 W)					
OC no training: 72	OC no training: 8 (4 M; 4 W)					
OP no training: 69	OP no training: 8 (4 M; 4 W)					
OC: 70	OC: 16 M	0.3 g/kg/day for 5 days; 0.07 g/kg/day for 12 weeks	↑	↑	↑	Chrusch et al. (2001)
OP: 71	OP: 14 M					
OCM: 69	OC: 13 (7 M; 6 W)	5 g/day for 14 weeks	↑	∅	∅	Brose et al. (2003)
OCW: 71						
OPM: 68	OP: 13 (7 M; 6 W)					
OPW: 70						
OC: 64	OC: 23 M	5 g/day for 6 month	∅	∅	–	Eijnde et al. (2003)
OP: 62	OP: 23 M					
OCM: 72	OC: 21 (11 M; 10 W)	5 g/day (plus 6 g/day of CLA) for 24 weeks	↑	↑	∅	Tarnopolsky et al. (2007)
OCW: 70						
OPM: 75	OP: 18 (8 M; 10 W)					
OPW: 68						
OC: 66	OC: 13 M	Old creatine: 0.1 g/kg/day on training days for 10 weeks	↑	–	–	Candow et al. (2008)
OC + protein: 67	OC + protein: 10 M	Old creatine/protein: 0.1 g/kg/day (plus 0.3 g/kg/day of protein) on training days for 10 weeks				
OP: 64	OP: 12 M					
OC: 56	OC: 10 M	7 g/day 3 × week for 2 weeks;	∅	–	–	Bemben et al. (2010)
OC + protein: 57	OC + protein: 11 M	5 g/day for 14 weeks;				
		5 g/day (plus 35 g pro/day) for 14 weeks				
O protein: 58	O protein: 11 M	35 g pro/day for 14 weeks				
OP: 56	OP: 10 M					

OC old creatine group, *OP* old placebo group, *M* men, *W* women, *CLA* conjugated linoleic acid, ∅ no effect of the creatine supplement in addition to the resistance training intervention, ↑ beneficial effect of the creatine supplement in addition to the resistance training intervention, – not assessed

(2002) showed improved aspects of cognition following creatine ingestion using a limited number of tests, Rawson et al. (2008) showed no benefit of creatine supplementation when assessed with a battery of cognitive tests. It is difficult to explain these discrepancies, but different dietary practices (e.g. vegetarian vs. non-vegetarian), race (e.g. Japanese vs. Caucasian), or dose of creatine (8 g/day for 5 days (Watanabe et al. 2002); 5 g/day for 6 weeks (Rae et al. 2003); 2.2 g/day for 6 weeks (Rawson et al. 2008)) may have been an influence. Ling et al. (2009) reported improvements on several cognitive outcomes following creatine ethyl-ester supplementation (5 g/day for 15 days). This was surprising given that creatine ethyl-ester appears to be a "pro-nutrient" for creatinine rather than creatine, and has been shown to be ineffective at improving muscle function (Giese and Lecher 2009a, b; Katseres et al. 2009; Spillane et al. 2009).

The greatest effect of creatine on cognitive processing may be in individuals who are stressed (through sleep deprivation) (McMorris et al. 2006; McMorris et al. 2007a) or cognitively impaired (by aging or disease) (Bender et al. 2005, 2006; McMorris et al. 2007b). McMorris et al. (2006; 2007a) reported benefits of creatine ingestion (20 g/day for 7 days) in young adults following 24 or 36 h of sleep deprivation on several cognitive outcomes. This same group improved cognitive processing in older adults (76 year) following creatine supplementation (20 g/day for 14 days). It is interesting that the improved cognition reported by McMorris and colleagues in these three studies was not found on the same tests, and potentially, not in the same aspects of cognition. The effects of creatine supplementation on cognitive processing are detailed in Table 5.

There are only a small number of studies on the effects of creatine supplementation on cognitive processing, which

Table 5 Effects of creatine supplementation on cognitive processing

Age	*n*	Study design	Creatine dose	Cognitive processing benefits	Reference
All: 24	C: 12 M & W P: 12 M & W	Double-blind placebo-controlled; Volunteers unstressed	32 g/day for 5 days	Decreased mental fatigue	Watanabe et al. (2002)
C/P M: 28 C/P W: 29 (crossover study)	12 M; 33 W 18 vegan; 27 vegetarian	Double-blind placebo-controlled crossover (6 week washout); Volunteers unstressed	5 g/day for 6 weeks	Improved memory Increased intelligence	Rae et al. (2003)
All: 21	C: 10 (9 M; 1 W) P: 9 (7 M; 2 W)	Double-blind placebo-controlled; Volunteers sleep deprived for 24 h	20 g/day for 7 days	Smaller decline in RMG, CRT, balance, and mood than placebo group	McMorris et al. (2006)
All: 21	C: 10 M P: 10 M	Double-blind placebo-controlled; Volunteers sleep deprived for 36 h	20 g/day for 7 days	Improved RNG at 36 h compared to placebo group	McMorris et al. (2007a)
All: 76	C: 15 (8 M; 7 W) P: 17 (8 M; 9 W)	Double-blind placebo-controlled; Volunteers unstressed	20 g/day for 14 days	Improved forward number recall, spatial recall, long term memory	McMorris et al. (2007b)
C: 21 P: 21	C: 11(6 M; 5 W) P: 11 (7 M; 4 W)	Double-blind placebo-controlled; Volunteers unstressed	0.03 g/day (2.2 g/day) for 6 weeks	∅ SRT, CS, CSD, LRS, MP, RM, MR	Rawson et al. (2008)
All: 21	C: 17 P: 17 Total: 22 M; 12 W	Double-blind placebo-controlled; Volunteers unstressed	5 g/day for 15 days of creatine ethyl ester	Improved memory scanning, number-pair matching, sustained attention, arrow flankers, IQ	Ling et al. (2009)

C creatine group, *P* placebo group, *M* men, *W* women, *RMG* random movement generation, *CRT* choice reaction time, *RNG* random number generation, *SRT* simple reaction time, *CS* code substitution, *CSD* code substitution delayed, *LRS* logical reasoning symbolic, *MP* mathematical processing, *RM* running memory, *MR* memory recall, ∅ no effect of the creatine supplement

leaves some unanswered questions. Currently, there is only one study on the effects of creatine supplementation on cognitive processing in older adults, and comparisons to sleep deprived young adults may not be appropriate. Also, as previously described, there are no reports of brain creatine uptake and changes in cognition in the same study. At this point, it would be difficult to make recommendations on the optimal dose of creatine to enhance cognitive processing, and even though a great deal of information is available on muscle creatine uptake, it is unclear if these data can be applied to nervous tissue. For instance, while low-dose longer-term creatine supplementation (0.03 g/kg/day for 6 weeks) was ineffective at improving cognitive processing in young adults (Rawson et al. 2008), this same dosing protocol resulted in enhanced fatigue resistance (Rawson et al. 2011). Certainly, there are differences in creatine uptake between skeletal muscle and nervous tissue, which may necessitate different supplementation protocols. The specifics at this time are unclear. Potentially, a larger dose of creatine is needed to penetrate the blood brain barrier (as opposed to skeletal muscle), increase brain creatine, and subsequently improve cognition, but this has not been clearly demonstrated. It is possible that over time, it will be revealed that the greatest benefit of creatine across the broadest range of cognitive outcomes will be in individuals when cognitive function is already impaired.

Conclusions

A number of studies support beneficial effects of creatine supplementation, both with and without concomitant exercise training, on fatigue resistance, strength, performance of ADLs, and muscle mass in older adults. Additionally, new data, point to a potential benefit of creatine supplementation in cognitive processing. When battling age-related declines in muscle strength (dynapenia), muscle mass (sarcopenia), and cognitive processing, it appears that creatine supplementation and physical activity are the two most successful interventions. Other interventions have not yielded as consistent results, and have not demonstrated benefits in both muscle and cognitive function. Additionally, creatine supplementation has an excellent safety profile in young, old, and patient populations (reviewed in Persky and Rawson 2007).

The current body of literature, however, is not without limitations. When compared to studies of young adults, there are few studies that have assessed both muscle function and muscle creatine uptake in response to supplementation in older adults. Additionally, it is not known if muscle creatine declines with aging per se, or if this is a consequence of reduced physical activity and dietary creatine intake. We have observed daily dietary creatine intakes of about 0.28 g/day (range 0.07–1.0 g/day) in older adults (unpublished observations by the authors), which is considerably lower than what is typically quoted as normal dietary creatine intake. No study has been published that includes cognitive processing outcomes and brain creatine uptake in response to creatine ingestion. Although there is one study published (McMorris et al. 2007b), and another in progress (National Institutes of Health, National Center for Complementary and Alternative Medicine R15 AT003938-01-Central Adaptations to Creatine Supplementation in Older Men and Women, PI: E. S. Rawson), regarding changes in cognitive processing in response to creatine supplementation, there are no studies with cognitive processing outcomes that include a measure of brain creatine uptake in response to creatine supplementation in older adults. Thus, the proper dosing scheme to increase brain creatine and benefit cognition is unknown. Also, there are no reports of the simultaneous response of muscle and nervous tissue to creatine supplementation in humans, a study which is necessary to answer questions about potential differences in dosing protocols needed to improve muscle versus cognitive function. Finally, the mechanistic studies that demonstrate how creatine influences satellite cells (Olsen et al. 2006), growth factors (Willoughby and Rosene 2003; Deldicque et al. 2005), and modifies gene expression (Safdar et al. 2008) have not been conducted in older adults.

Future studies on the effects of creatine supplementation in older adults need to improve phenotyping of research volunteers by including measures of dietary and physical activity behaviors, physical fitness, multiple aspects of cognitive processing and mood, muscle function, education, and socioeconomic status. These assessments, combined with measures of brain and muscle creatine uptake in response to supplementation, will help to clarify lingering questions about the benefits of creatine ingestion in older adults. To date, research volunteers appear to be predominantly free living, independent adults. Without better phenotyping, it will be difficult to ascertain if the population studied was a group of elderly or a group of "well-derly" (well elderly adults). It is possible that by studying frail elders, or at least by including an old group (60–80 year) and an oldest old group (>80 year), more will be revealed. In practice, it appears that there are real benefits to be obtained by older adults from the use of creatine. However, as there are potential declines in the function of some systems with aging (e.g. decreased renal function), consultation with a knowledgeable health care professional would be advised before taking any dietary supplement.

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