

Creatine—Not just for muscles anymore; anti-aging and so much more

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Creatine is possibly the most promising anti-aging supplement available in the industry today. A tremendous amount of research has been published between 1998 and now that has helped us to understand this very important nutrient and how it functions in the human body. Creatine supplementation, in a stabilized, alkaline form so it does not raise creatinine, does so much more than simply help athletic performance and muscle building. Creatine supplementation has numerous physiological effects, which have the potential to substantially reduce morbidity and mortality.

What is creatine?

Creatine (methylguanidine-acetic acid) is formed in the liver, kidneys, and pancreas from arginine, glycine and methionine and is transported through the bloodstream to various tissues. Plasma creatine is taken up into the cell by a creatine transporter protein, which is also used to transfer creatine across the blood-brain barrier. Once inside the cell, creatine is readily phosphorylated to produce phosphocreatine, which is the form that acts like a battery recharger for ATP.

Creatine's most important role in human physiology is to contribute to maintenance of ATP levels. When ATP dissociates into ADP and phosphate to produce energy for muscle contraction and other metabolic functions, phosphocreatine donates its phosphate group to ADP to regenerate ATP. This is a reversible reaction, catalyzed by creatine kinase enzymes. At rest, when ATP levels are being replenished via oxidative phosphorylation, ATP will donate a phosphate group to creatine to regenerate phosphocreatine stores.

CREATINE SUPPLEMENTATION MAY HELP SUPPORT:

- Athletes
- Muscle building
- Sarcopenia
- Strength
- Increasing exercise intensity
- Recovery from exercise
- Physical performance recovery after rapid weight loss
- Reduce cell damage and inflammation from ultra-endurance exercise
- Reduce athletes' cramping, heat illness, dehydration, muscle strains and tightness
- Brain health
- Depression
- Neurological problems
- Parkinson's Disease
- Huntington's Disease
- ALS
- Sleep Deprivation
- Memory/Cognitive Function
- Vegetarians
- Atherosclerosis
- High homocysteine
- Post-stroke
- Ischemia
- Traumatic brain injury
- Rehabilitation from bed rest or immobilization
- Recovery from nerve injury
- Bone loss
- Glucose-insulin metabolism
- Posttraumatic stress disorder
- Congestive heart failure
- COPD
- Muscular dystrophies
- Cramping associated with dialysis
- Muscle breakdown from corticosteroids
- Unexplained mental retardation, developmental arrest, neurological deterioration, speech delay, seizures, movement disorders, and autistic-like behavior

About 95% of the body's creatine is found in the skeletal muscles, particularly type 2 fibers. Creatine is also found in other tissues, including the brain, heart, endothelial cells, macrophages, kidneys, liver, smooth muscles and testes. The body has a limited capacity for creatine synthesis and those individuals who consume creatine-rich foods have higher creatine tissue levels. Dietary creatine is most concentrated in herring, pork, beef, salmon and tuna. Consistent with this fact, vegetarians appear to have lower tissue creatine concentrations. Low phosphocreatine levels result in lower levels of ATP. Greater phosphocreatine levels translate into greater cellular energy production. With regard to skeletal muscle, phosphocreatine is involved primarily in the first ten seconds of very high intensity contraction.

The benefits one derives from creatine supplementation depends upon how much his or her tissue creatine levels increase. This depends upon several factors, including the starting level of tissue creatine. Creatine supplementation can increase tissue concentrations to a level that is unobtainable through diet alone. The activity of the creatine transporter plays an important role in the ultimate response to creatine supplementation. It is one thing to raise plasma creatine levels through supplementation but the benefits from creatine come only through transport into the cell, by the creatine transporter. Insulin has clearly been demonstrated to stimulate cellular creatine uptake. Accordingly, concomitant supplementation of large doses of carbohydrate and protein has been found to increase cellular creatine accumulation. There is also evidence that the insulin sensitizing compound alpha lipoic acid can facilitate cellular creatine accretion. High intensity exercise promotes creatine transport into the muscles that are worked. In vitro studies have also shown stimulation of the creatine transporter by IGF-1, triiodothyronine (T3), and norepinephrine.

Aging is associated with lower skeletal muscle creatine and phosphocreatine levels. After age 30, phosphocreatine resynthesis rates after exercise fall 8% per decade. Supplementation of creatine can raise skeletal muscle creatine levels 10-30% and phosphocreatine levels 10-40%. Creatine supplementation has been found to produce gains in strength, energy and muscle mass in people with various conditions and diseases. It also results in quicker restoration of energy after exertion and therefore improves performance in repetitive bouts of very high intensity exercise. Typical responses to creatine supplementation are an additional 10 to 15 % increase in strength and an additional 1 to 3 % increase in muscle mass over one to three months of resistance exercise training.

In a double-blind placebo-controlled study, in which subjects had a leg immobilized for two weeks then underwent an exercise rehabilitation program, creatine supplementation resulted in more rapid restoration of strength and muscle mass. Creatine should therefore benefit older individuals who are recovering from bed-rest or immobilization of a limb due to injury, surgery or illness.

How is creatine good for the heart? Metabolic Syndrome?

Congestive heart failure patients supplemented with creatine have exhibited signs of enhanced skeletal muscle metabolism with reduced lactate and ammonia accumulation. Creatine improved both strength and endurance in this patient population. Creatine has a positive effect on lipids. Creatine supplementation has been found to lower elevated serum cholesterol and triglyceride levels. One study found a 6% reduction in total cholesterol and a 23% reduction in triglycerides and VLDL cholesterol after eight weeks of creatine supplementation. Combining creatine with exercise appears to be synergistic in lowering cholesterol. In one study, creatine even lowered homocysteine when taken (at a dose of two times their creatinine levels) along with a multivitamin, more effectively than multivitamin alone.

There are several lines of evidence to suggest creatine supplementation improves insulin sensitivity. Insulin resistance appears to be a central metabolic aberration contributing to unhealthy aging and reduced lifespan. This was illustrated by a study involving 208 healthy men who were evaluated for their insulin sensitivity and then followed for an average of six years. They were divided into three groups, according to insulin sensitivity. After the study period, one out of every three men in the tertile with the poorest insulin sensitivity had developed hypertension, type 2 diabetes, cancer, heart disease or stroke. All of the men in the group with the best insulin sensitivity remained healthy. The effects of creatine supplementation that point toward improved insulin sensitivity include lowering of elevated plasma triglyceride and VLDL and total cholesterol levels, increasing muscle glycogen stores, and a trend toward lower fasting blood glucose levels. Additionally, levels of Glut 4 protein were found to increase by 40% in response to creatine supplementation compared to placebo. Glut 4 protein is involved in insulin-stimulated muscle glucose uptake. When combined with supplemental protein and resistance training, creatine resulted in improved glucose tolerance test results.

How is creatine anti-aging?

Creatine affects many of the top ten markers of biological aging including loss of muscle mass, drop in resting metabolic rate, aerobic capacity, the body's ability to regulate its internal temperature, glucose tolerance, and bone density. Creatine supplementation has been found to reduce n-telopeptide levels (a biochemical marker for bone loss), and when combined with resistance training, creatine increased bone mineral content.

The number one biomarker of aging is muscle mass. From age 20 to 80, the average person loses 20 to 30 % of their muscle mass. Loss of muscle mass, also known as sarcopenia, produces a multitude of negative metabolic changes, which are incompatible with good health. The number two biomarker is strength. The importance of strength in the elderly is exemplified by simple, yet critical, actions such as being able to arise from a chair or avoid a fall. Inability to carry on activities of daily living due to muscular weakness is a major cause for loss of independence. Creatine monohydrate is, by far, the most effective nutritional supplement for improving these top two biomarkers of aging: muscle mass and strength.

Aging is associated with a reduction in skeletal muscle protein synthesis. Several studies have provided different lines of evidence that creatine supplementation increases muscle protein synthesis. A double-blind, placebo-controlled study of thirty men, average age 70.4 years, who underwent a weight training program, found greater increase in fat-free mass, knee extension strength and endurance, leg press endurance and overall power in the creatine group. Another double-blind placebo-controlled study of 7 days of creatine supplementation in elderly subjects found increases in body weight, fat-free mass, and strength. Importantly, this study also included two assessments of lower-extremity functional capacity, including a timed repetitive sit-stand test, which simulates arising from a chair. On this measure too, creatine-supplemented subjects outperformed those given placebo.

Another anti-aging effect of creatine supplementation is to increase intracellular water content. Aging is associated with loss of intracellular water. Phosphocreatine has also been found to reduce leakage of cytoplasmic contents, such as intracellular enzymes. This may be attributed, in part, to phosphocreatine's ability to stabilize cellular membranes and prevent tissue damage. Creatine uses a sodium transporter. It is important for athletes to maintain normal electrolyte levels. Athletes should consider using Electrolyte Synergy from Designs for Health along with KreAlk-Alert to prevent electrolyte depletion and inability to transport creatine.

How is creatine good for the brain?

In a study of healthy humans, creatine supplementation at 5 grams four times daily for four weeks produced an average 8.7 % increase in brain creatine. Another study, using a double-blind placebo-controlled protocol, examined the effect of supplementing with creatine on mental fatigue. Subjects were asked to perform as many mathematical calculations as possible within a certain time period. Creatine supplementation was found to reduce mental fatigue and improve performance. Additionally, testing by near infrared spectroscopy revealed signs that creatine increased brain oxygen utilization. These effects are of obvious benefit for aging individuals.

Another study found creatine supplementation improves intelligence and working memory. Yet another study examined the effects of creatine supplementation on individuals who were sleep deprived. Creatine supplementation had a beneficial effect on mood, cognitive and psychomotor performance. In animal models of traumatic brain injury, creatine supplementation appeared to protect neurons by maintaining mitochondrial bioenergetics. Intramitochondrial oxidative stress and calcium levels were reduced and ATP levels and mitochondrial membrane potential were increased. Brain damage was reduced by 36 % in mice and 50 % in rats.

In an animal model of Parkinson's disease, animals pre-supplemented with creatine experienced a 10% decrease in brain dopamine levels compared to 70% reduction in non-supplemented animals. In animals, creatine has also been demonstrated to protect against neurotoxicity of malonate, N-methyl-D-aspartate, 3-nitropropionic acid, and glutamate. (3) With regard to animal models of Alzheimer's disease, creatine protects hippocampal neurons from β -amyloid toxicity, and therefore could potentially reduce the formation of plaques. (3)

In an animal model of amyotrophic lateral sclerosis, creatine supplementation was associated with reduced oxidative damage, better motor performance, preservation of substantia nigra neurons, and longer survival. In one human study, creatine provided a temporary benefit to patients with this disease, increasing their strength and resistance to fatigue. However, after six months, these benefits seemed to diminish. Additional studies are underway.

Finally, animal models of Huntington's disease induced by neurotoxins, have also found creatine supplementation to provide significant benefits. Specifically, creatine feeding was associated with signs of less oxidative damage, lower lactate levels, dramatically smaller lesion volume, reduced brain atrophy and striatal aggregates, improved body weight and motor performance, delay in development of diabetes, and reduced mortality.

Oxidative stress is another fundamental mechanism of biological aging. A number of animal studies have found creatine supplementation to protect neurological tissue against ischemic, traumatic, and toxic insults. Protection against ischemic brain damage has obvious implications for defense against stroke. (6)

How do we know creatine is safe?

Researchers have tested creatine in doses as high as 20 g per day in humans with no ill-effects. Virtually all of the published research has been done with creatine monohydrate powder dissolved in liquid. The weight of scientific evidence to this point is that creatine supplementation is extremely safe. The only documented side effect is weight gain (in the form of desirable fat-free mass). A 21 month study by one of the foremost creatine researchers, Richard Kreider, Ph.D., entitled "Long term creatine supplementation

does not significantly affect clinical markers of health in athletes," presented at the 6th International Meeting on Guanidino Compounds in Biology & Medicine in 2001, was designed to respond to rumors about creatine's adverse effects. It involved ninety college football players, some of who received creatine and some of who did not. Sixty-nine different blood analytes, including measures of liver function, kidney function, red and white blood cells, muscle and liver enzymes, blood lipids and electrolytes were evaluated. The conclusion was that creatine produced no effect on any of these measures in healthy football players. Another fact supporting safety of creatine monohydrate is that patients with gyrate atrophy have been supplementing with creatine for twenty years without ill effect.

This is the conclusion of a study published in the British Journal of Sports Medicine after giving 48 subjects 20 g of creatine for 5 days followed by 3 g creatine for 9 weeks: "Interpretation: These data provide evidence that there are no obvious adverse effects of acute or more chronic creatine supplementation on the haematological indices measured, nor on hepatic, muscle, and renal function. Therefore there is no apparent health risk associated with creatine supplementation to healthy people when it is ingested in quantities that have been scientifically proven to increase muscle creatine stores."

Another factor that makes creatine supplementation likely to be well accepted by patients is the improvement in physique, which most will experience, often within a few days. Weight training enhances the muscle and strength building effects of creatine supplementation. Weight training and creatine supplementation should be a cornerstone of every anti-aging program. The wide-ranging and powerful anti-senescent properties of creatine make it a fundamental nutritional supplement to promote healthy aging.

For information on dosing creatine and why creatine should be buffered, please read the Designs for Health KreAlk-Alert product tech sheet.

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Health implications of creatine: can oral creatine supplementation protect against neurological and atherosclerotic disease?

Neuroscience. 2002;112(2):243-60. WYSS M, SCHULZE A.

Major achievements made over the last several years have highlighted the important roles of creatine and the creatine kinase reaction in health and disease. Inborn errors of metabolism have been identified in the three main steps involved in creatine metabolism: arginine:glycine amidinotransferase (AGAT), S-adenosyl-L-methionine:N-guanidinoacetate methyltransferase (GAMT), and the creatine transporter. All these diseases are characterized by a lack of creatine and phosphorylcreatine in the brain, and by (severe) mental retardation. Similarly, knockout mice lacking the brain cytosolic and mitochondrial isoenzymes of creatine kinase displayed a slightly increased creatine concentration, but no phosphorylcreatine in the brain. These mice revealed decreased weight gain and reduced life expectancy, disturbed fat metabolism, behavioral abnormalities and impaired learning capacity. Oral creatine supplementation improved the clinical symptoms in both AGAT and GAMT deficiency, but not in creatine transporter deficiency. In addition, creatine supplementation displayed neuroprotective effects in several animal models of neurological disease, such as Huntington's disease, Parkinson's disease, or amyotrophic lateral sclerosis. All these findings pinpoint to a close correlation between the functional capacity of the creatine kinase/phosphorylcreatine/creatine system and proper brain function. They also offer a starting-point for novel means of delaying neurodegenerative disease, and/or for strengthening memory function and intellectual capabilities. Finally, creatine biosynthesis has been postulated as a major effector of homocysteine concentration in the plasma, which has been identified as an independent graded risk factor for atherosclerotic disease. By decreasing homocysteine production, oral creatine supplementation may, thus, also lower the risk for developing, e.g., coronary heart disease or cerebrovascular disease. Although compelling, these results require further confirmation in clinical studies in humans, together with a thorough evaluation of the safety of oral creatine supplementation.

Oral creatine supplements lower plasma homocysteine concentrations in humans.

Clin Lab Sci. 2004 Spring;17(2):102-6. KORZUN WJ.

OBJECTIVE: To determine if oral creatine supplements will lower the concentration of total plasma homocysteine (tHcy). **SETTING/PARTICIPANTS:** Apparently healthy volunteers, at least 19 years old, were recruited from the University of South Alabama and surrounding community. **DESIGN/INTERVENTION/MAIN OUTCOME:** Participants took multi-vitamins daily for four weeks, then were randomly divided into two groups. The control group (C) continued to take multi-vitamins daily for an additional four weeks. The experimental group (EX) took multivitamins plus an amount of creatine each day equal to twice their daily creatinine excretion, for the additional four weeks. Total plasma homocysteine concentrations were measured in all participants at the beginning and at the end of the second four week interval. **RESULTS:** There were no statistically significant differences between the two groups in age, initial tHcy, serum folate, erythrocyte folate, serum vitamin B12, or creatinine excretion. After four weeks of creatine supplements, tHcy in EX changed by an average of -0.9 micromol/L (range: -1.8 to 0.0), compared to an average change of +0.2 micromol/L in C (range: -0.6 to 0.9) during the same four weeks. The difference in the changes in tHcy between the two groups was statistically significant ($p < 0.01$). **CONCLUSION:** Creatine supplements may be an effective adjunct to vitamin supplements for lowering tHcy.

Neuroprotective effects of creatine administration against NMDA and malonate toxicity.

Brain Res 2000 Mar 31;860(1-2):195-8

We examined whether creatine administration could exert neuroprotective effects against excitotoxicity mediated by N-methyl-D-aspartate (NMDA), alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainic acid. Oral administration of 1% creatine significantly attenuated striatal excitotoxic lesions produced by NMDA, but had no effect on lesions produced by AMPA or kainic acid. Both creatine and nicotinamide can exert significant protective effects against malonate-induced striatal lesions. We, therefore, examined whether nicotinamide could exert additive neuroprotective effects with creatine against malonate-induced lesions. Nicotinamide with creatine produced significantly better neuroprotection than creatine alone against malonate-induced lesions. Creatine can, therefore, produce significant neuroprotective effects against NMDA mediated excitotoxic lesions in vivo and the combination of nicotinamide with creatine exerts additive neuroprotective effects.

Creatine and cyclocreatine attenuate MPTP neurotoxicity.

Exp Neurol 1999 May;157(1):142-9

Systemic administration of 1-methyl-4-phenyl-1,2,3, 6-tetrahydropyridine (MPTP) produces parkinsonism in experimental animals by a mechanism involving impaired energy production. MPTP is converted by monoamine oxidase B to 1-methyl-4-phenylpyridinium (MPP⁺), which blocks complex I of the electron transport chain. Oral supplementation with creatine or cyclocreatine, which are substrates for creatine kinase, may increase phosphocreatine (PCr) or cyclophosphocreatine (PCCr) and buffer against ATP depletion and thereby exert neuroprotective effects. In the present study we found that oral supplementation with either creatine or cyclocreatine produced significant protection against MPTP-induced dopamine depletions in mice. Creatine protected against MPTP-induced loss of Nissl (granular endoplasmic reticulum and ribosomes) and tyrosine hydroxylase immunostained neurons in the substantia nigra. Creatine and cyclocreatine had no effects on the conversion of MPTP to MPP⁺ in vivo. These results further implicate metabolic dysfunction in MPTP neurotoxicity and suggest a novel therapeutic approach, which may have applicability for Parkinson's disease.

Role of creatine and phosphocreatine in neuronal protection from anoxic and ischemic damage.

Amino Acids 2002;23(1-3):221-9

Phosphocreatine can to some extent compensate for the lack of ATP (Adenosine Triphosphate) synthesis that is caused in the brain by deprivation of oxygen or glucose. Treatment of in vitro rat hippocampal slices with creatine increases the neuronal store of phosphocreatine. In this way it increases the resistance of the tissue to anoxic or ischemic damage. In vitro brain slices pretreatment with creatine delays anoxic depolarization (AD) and prevents the irreversible loss of evoked potentials that is caused by transient anoxia, although it seems so far not to be active against milder, not AD-mediated, damage. Although creatine crosses the blood-brain barrier poorly, its administration in vivo at high doses through the intracerebroventricular or the intraperitoneal way causes an increase of cerebral phosphocreatine that has been shown to be of therapeutic value in vitro. Accordingly, preliminary data show that creatine pretreatment decreases ischemic damage in vivo.

Neuroprotective effects of creatine and cyclocreatine in animal models of Huntington's disease.

J Neurosci 1998 Jan 1;18(1):156-63

The gene defect in Huntington's disease (HD) may result in an impairment of energy metabolism. Malonate and 3-nitropropionic acid (3-NP) are inhibitors of succinate dehydrogenase that produce energy depletion and lesions that closely resemble those of HD. Oral supplementation with creatine or cyclocreatine, which are substrates for the enzyme creatine kinase, may increase phosphocreatine (PCr) or phosphocyclocreatine (PCCr) levels and ATP generation and thereby may exert neuroprotective effects. We found that oral supplementation with either creatine or cyclocreatine produced significant protection against malonate lesions, and that creatine but not cyclocreatine supplementation significantly protected against 3-NP neurotoxicity. Creatine and cyclocreatine increased brain concentrations of PCr and PCCr, respectively, and creatine protected against depletions of PCr and ATP produced by 3-NP. Creatine supplementation protected against 3-NP induced increases in striatal lactate concentrations in vivo as assessed by ¹H magnetic resonance spectroscopy. Creatine and cyclocreatine protected against malonate-induced increases in the conversion of salicylate to 2,3- and 2,5-dihydroxybenzoic acid, biochemical markers of hydroxyl radical generation. Creatine administration protected against 3-NP-induced increases in 3-nitrotyrosine concentrations, a marker of peroxynitrite-mediated oxidative injury. Oral supplementation with creatine or cyclocreatine results in neuroprotective effects in vivo, which may represent a novel therapeutic strategy for HD and other neurodegenerative diseases.

Neuroprotective effects of creatine in a transgenic mouse model of Huntington's disease.

J Neurosci 2000 Jun 15;20(12):4389-97

Huntington's disease (HD) is a progressive neurodegenerative illness for which there is no effective therapy. We examined whether creatine, which may exert neuroprotective effects by increasing phosphocreatine levels or by stabilizing the mitochondrial permeability transition, has beneficial effects in a transgenic mouse model of HD (line 6/2). Dietary creatine supplementation significantly improved survival, slowed the development of brain atrophy, and delayed atrophy of striatal neurons and the formation of huntingtin-positive aggregates in R6/2 mice. Body weight and motor performance on the rotarod test were significantly improved in creatine-supplemented R6/2 mice, whereas the onset of diabetes was markedly delayed. Nuclear magnetic resonance spectroscopy showed that creatine supplementation significantly increased brain creatine concentrations and delayed decreases in N-acetylaspartate concentrations. These results support a role of metabolic dysfunction in a transgenic mouse model of HD and suggest a novel therapeutic strategy to slow the pathological process.

Neuroprotective effects of creatine in a transgenic animal model of amyotrophic lateral sclerosis.

Nat Med 1999 Mar;5(3):347-50

Mitochondria are particularly vulnerable to oxidative stress, and mitochondrial swelling and vacuolization are among the earliest pathologic features found in two strains of transgenic amyotrophic lateral sclerosis (ALS) mice with SOD1 mutations. Mice with the G93A human SOD1 mutation have altered electron transport enzymes, and expression of the mutant enzyme in vitro results in a loss of mitochondrial membrane potential and elevated cytosolic calcium concentration. Mitochondrial dysfunction may lead to ATP depletion, which may contribute to cell death. If this is true, then buffering intracellular energy levels could exert neuroprotective effects. Creatine kinase and its substrates creatine and phosphocreatine constitute an intricate cellular energy buffering and transport system connecting sites of energy production (mitochondria) with sites of energy consumption, and creatine administration stabilizes the mitochondrial creatine kinase and inhibits opening of the mitochondrial transition pore. We found that oral administration of creatine produced a dose-dependent improvement in motor performance and extended survival in G93A transgenic mice, and it protected mice from loss of both motor neurons and substantia nigra neurons at 120 days of age. Creatine administration protected G93A transgenic mice from increases in biochemical indices of oxidative damage. Therefore, creatine administration may be a new therapeutic strategy for ALS.

Creatine-enhanced diet alters levels of lactate and free fatty acids after experimental brain injury.

Neurochem Res. 2004 Feb;29(2):469-79. SCHEFF SW, DHILLON HS.

Free fatty acids (FFA) and lactic acid are markers of secondary cellular injury following traumatic brain injury (TBI). We previously showed that animals fed a creatine (Cr)-enriched diet are afforded neuroprotection following TBI. To further characterize the neuroprotective Cr diet, we studied neurochemical changes in cortex and hippocampus following a moderate injury. Adult rats were fed either a control or Cr-supplemented diet (0.5%, 1%) for 2 weeks before TBI. At 30 min or 6 h after injury, tissue was processed for quantitative analysis of neurochemical changes. Both lactate and FFA were significantly increased in all tissues ipsilateral to the injury. Cr-fed animals had significantly lower levels, although the levels were elevated compared to sham controls. Animals fed a 1% Cr-diet were afforded greater neuroprotection than animals fed a 0.5% Cr diet. These results support the idea that a Cr-enriched diet can provide substantial neuroprotection in part by suppressing secondary brain injury.

Brain creatine functions to attenuate acute stress responses through GABAergic system in chicks.

Neuroscience. 2005;132(1):65-71. KOGA Y, TAKAHASHI H, OIKAWA D, TACHIBANA T, DENBOW DM, FURUSE M.

The involvement of brain creatine in the adaptation to acute stress responses was investigated in chicks. In experiment 1, brain creatine content of chicks exposed to social separation stress was significantly increased compared with control chicks. The effects of i.c.v. injection of creatine (2 mug) on vocalizations, spontaneous activity and plasma corticosterone concentration in chicks under social separation stress were investigated in experiment 2. All measurements were attenuated by the i.c.v. injection of creatine compared with the controls under separation stress. Creatine also significantly decreased the active posture, but increased the motionless eye-opened posture, compared with the control. To clarify the relationship between creatine function and GABA receptors, the i.c.v. co-injection of creatine with picrotoxin, a GABA-A receptor antagonist, or CGP54626, a GABA-B receptor antagonist, was investigated in experiments 3 and 4. The effects of creatine on vocalizations and spontaneous activity were attenuated by co-injection of picrotoxin. In this case, active postures decreased by creatine were recovered by co-injection with picrotoxin. However, these effects were not obtained with CGP54626. The results suggest that central creatine functions within the CNS to attenuate the acute stress response by acting through GABA-A receptors in chicks.

Is the use of oral creatine supplementation safe?

J Sports Med Phys Fitness. 2004 Dec;44(4):411-6. BIZZARINI E, DE ANGELIS L.

School of Sports Medicine, University of Trieste, Trieste, Italy.

This review focuses on the potential side effects caused by oral creatine supplementation on gastrointestinal, cardiovascular, musculoskeletal, renal and liver functions. No strong evidence linking creatine supplementation to deterioration of these functions has been found. In fact, most reports on side effects, such as muscle cramping,

gastrointestinal symptoms, changes in renal and hepatic laboratory values, remain anecdotal because the case studies do not represent well-controlled trials, so no causal relationship between creatine supplementation and these side-effects has yet been established. The only documented side effect is an increase in body mass. Furthermore, a possibly unexpected outcome related to creatine monohydrate ingestion is the amount of contaminants present that may be generated during the industrial production. Recently, controlled studies made to integrate the existing knowledge based on anecdotal reports on the side effects of creatine have indicated that, in healthy subjects, oral supplementation with creatine, even with long-term dosage, may be considered an effective and safe ergogenic aid. However, athletes should be educated as to proper dosing or to take creatine under medical supervision.

Dietary creatine supplementation does not affect some haematological indices, or indices of muscle damage and hepatic and renal function.

Br J Sports Med. 2000 Aug;34(4):284-8. ROBINSON TM, SEWELL DA, CASEY A, STEENGE G, GREENHAFF PL.

BACKGROUND: The use of creatine (Cr) as a nutritional supplement to aid athletic performance has gained widespread popularity among athletes. However, concerns have recently been expressed over potentially harmful effects of short and long term Cr supplementation on health. **METHODS:** Forty eight young healthy subjects were randomly allocated to three experimental protocols aimed at elucidating any potential health risks associated with five days (20 g/day) to nine weeks (3 g/day) of Cr supplementation. Venous blood samples were collected before and after periods of Cr supplementation and were analysed for some haematological indices, and for indices of hepatic, muscular, and renal dysfunction. **FINDINGS:** All measured indices were well within their respective normal range at all times. Serum creatinine concentration tended to be increased the day after Cr supplementation. However, values had returned to baseline six weeks after the cessation of supplementation. These increases were probably attributable to increased creatinine production rather than renal dysfunction. No indication of impairment to the haematological indices measured, hepatic function, or muscle damage was apparent after Cr supplementation.

INTERPRETATION: These data provide evidence that there are no obvious adverse effects of acute or more chronic Cr supplementation on the haematological indices measured, nor on hepatic, muscle, and renal function. Therefore there is no apparent health risk associated with Cr supplementation to healthy people when it is ingested in quantities that have been scientifically proven to increase muscle Cr stores.

Acute and moderate-term creatine monohydrate supplementation does not affect creatine transporter mRNA or protein content in either young or elderly humans.

Mol Cell Biochem. 2003 Feb;244(1-2):159-66. TARNOPOLSKY M, PARISE G, FU MH, BROSE A, PARSHAD A, SPEER O, WALLIMANN T.

Animal studies have shown that supra-physiological creatine monohydrate (Cr-mH) supplementation for 3 months reduced skeletal muscle creatine transporter (CRT) content. The doses of Cr-mH (1-2 g/kg/day) used in these studies were between 5 and 10 times those usually used in human studies, and it is unclear whether a down-regulation of CRT would occur in humans at the recommended doses of 0.1-0.2 g/kg/day. We measured CRT, and citrate synthase (CS) protein content using Western blotting before and after 2 months of Cr-mH supplementation and weight training in young men (N = 11 Cr-mH (0.125 g/kg/day); N = 8 placebo). CRT and CS were also measured before and after 4 months of Cr-mH supplementation and weight training in elderly (> 65 years) men and women (N = 14 Cr-mH (0.075 g/kg/day); N = 14 placebo). Finally, CRT mRNA was measured using competitive RT-PCR before and after 8-9 days of Cr-mH loading in young men and women (N = 14, Cr-mH (mean = 0.18 g/kg/day); N = 13, PL). Total creatine content was significantly elevated after the Cr-mH supplementation period as compared to placebo in each of the studies. Neither Cr-mH supplementation, nor exercise training resulted in measurable alterations in CRT protein content and acute Cr-mH loading did not alter CRT mRNA. There were no gender differences in CRT mRNA or total creatine content in the young subjects and no gender differences in total creatine content or CRT protein content in the elderly subjects. Weight training in young men did not increase CS protein content, however, in the elderly there was a significant increase in CS protein content after exercise training (p < 0.05). These results demonstrated that Cr-mH supplementation during weight training resulted in increases in skeletal muscle total creatine without reductions in CRT protein and acute Cr-mH loading did not decrease CRT mRNA content.

Kinetics of creatine ingested as a food ingredient.

Eur J Appl Physiol. 2007 Sep 13. DELDICQUE L, DÉCOMBAZ J, ZBINDEN FONCEA H, VUICHOUD J, POORTMANS JR, FRANCAUX M.

The aim of the present study was to test if the consumption of creatine incorporated in food bars modifies creatine plasma kinetics, erythrocyte retention and loss in urine and in feces when compared with its consumption in the form of an aqueous solution (AS). Seventeen healthy young men ingested 2 g creatine either in the form of AS, or incorporated in a protein (PP)- or in a beta-glucan (BG)-rich food bar. Kinetics of plasma creatine was measured for 8-h duration and urinary excretion for 24 h. Then, the subjects received the same treatment thrice a day for 1 week at the end of which creatine contents were determined in erythrocytes and in feces ($n = 4$ for feces). The three crossover treatments were interspaced by a 40 ± 1.2 -day wash-out. Absorption of creatine was slowed down by 8-fold in the presence of BG ($P < 0.001$) and by 4-fold with PP ($P < 0.001$) whereas the velocity rate constant of elimination and the area under the curve were not modified. Urinary loss of creatine in the first 24 h following ingestion was $15 \pm 1.9\%$ in AS and $14 \pm 2.2\%$ in PP conditions (NS), whereas it was only $8 \pm 1.2\%$ with BG ($P = 0.004$). Increase in creatine concentration in erythrocyte was similar in whatever form the creatine was ingested. Creatine seems to be totally absorbed since no creatine or creatinine was detectable in feces. No side effects were reported. In conclusion, ingestion of creatine combined with BG facilitates its retention by slowing down its absorption rate and reducing its urinary excretion.

Few adverse effects of long-term creatine supplementation in a placebo-controlled trial.

Int J Sports Med. 2005 May;26(4):307-13. GROENEVELD GJ, BEIJER C, VELDINK JH, KALMIJN S, WOKKE JH, VAN DEN BERG LH.

Although oral creatine supplementation is very popular among athletes, no prospective placebo-controlled studies on the adverse effects of long-term supplementation have yet been conducted. We performed a double-blind, placebo-controlled trial of creatine monohydrate in patients with the neurodegenerative disease amyotrophic lateral sclerosis, because of the neuroprotective effects it was shown to have in animal experiments. The purpose of this paper is to compare the adverse effects, and to describe the effects on indirect markers of renal function of long-term creatine supplementation. 175 subjects (age = 57.7 ± 11.1 y) were randomly assigned to receive creatine monohydrate 10 g daily or placebo during an average period of 310 days. After one month, two months and from then on every fourth month, adverse effects were scored using dichotomous questionnaires, plasma urea concentrations were measured, and urinary creatine and albumin concentrations were determined. No significant differences in the occurrence at any time of adverse effects due to creatine supplementation were found (23 % nausea in the creatine group, vs. 24 % in the placebo group, 19 % gastro-intestinal discomfort in the creatine group, vs. 18 % in the placebo group, 35 % diarrhoea in the creatine group, vs. 24 % in the placebo group). After two months of treatment, oedematous limbs were seen more often in subjects using creatine, probably due to water retention. Severe diarrhoea ($n = 2$) and severe nausea ($n = 1$) caused 3 subjects in the creatine group to stop intake of creatine, after which these adverse effects subsided. Long-term supplementation of creatine did not lead to an increase of plasma urea levels (5.69 ± 1.47 before treatment vs. 5.26 ± 1.44 at the end of treatment) or to a higher prevalence of micro-albuminuria (5.4 % before treatment vs. 1.8 % at the end of treatment).

Multinuclear magnetic resonance spectroscopy of high-energy phosphate metabolites in human brain following oral supplementation of creatine-mono-hydrate.

Psychiatry Res. 2003 Jun 30;123(2):87-100. LYOO IK, KONG SW, SUNG SM, HIRASHIMA F, PAROW A, HENNEN J, COHEN BM, RENSHAW PF.

Alterations in brain high-energy phosphate metabolism, determined by in vivo magnetic resonance spectroscopy (MRS), have been reported in subjects with a number of brain disorders including major depression, schizophrenia, and substance abuse. It is not clear to what extent these changes can be modified by pharmacological or nutritional means. To address this possibility, we evaluated changes in brain chemistry that were associated with oral creatine (Cr) administration. We hypothesized that oral Cr supplementation, by increasing brain creatine and high-energy phosphate stored in phosphocreatine, would result in an increase in the creatine resonance, as measured using proton 1H-MRS, and a decrease in the beta-nucleoside triphosphate (NTP) peak and an increase in the phosphocreatine (PCr) peak, as measured by phosphorus 31P-MRS, in brain of healthy human subjects. Fifteen healthy male subjects (age= 22.9 ± 2.2 ; body mass index= 22.9 ± 1.7), who were without any axis I

disorders or physical or neurological illness, were recruited. Ten subjects took creatine-monohydrate, 0.3 g/kg/day for the first 7 days and 0.03 g/kg/day for the next 7 days (creatine group). Five comparison subjects took equivalent amounts of sucrose as placebo (placebo group). Both ¹H- and ³¹P-MRS scans were acquired at baseline, as well as at day 7 and day 14 of oral supplementation. ¹H-MRS: Water suppressed localized spectra were acquired using a single-voxel (1.5 cm x 2 cm x 2 cm) proton MRS PRESS sequence in the left frontal lobe. ³¹P-MRS: Phosphorus spectral data were recorded from a 5-cm-thick axial brain slice using a short-TE slice selective spin-echo pulse sequence. The creatine group had significantly increased brain creatine levels (8.1% and 9.3%, in creatine/N-acetyl aspartate and creatine/choline ratios, respectively) compared to the placebo group over the 2-week period. The creatine group had significantly decreased beta-NTP levels (7.8%) and marginally increased PCr (3.4%) over the same period. In addition, the brain inorganic phosphate level increased over the same period in the creatine group (9.8%). The current study is the first multinuclear (¹H and ³¹P) MRS study to evaluate changes in brain high-energy phosphate metabolism following oral creatine supplementation in healthy human subjects. These findings suggest the possibility of using oral creatine supplementation to modify brain high-energy phosphate metabolism in subjects with various brain disorders, including major depression, schizophrenia, cocaine and opiate abuse, where alterations in brain high-energy phosphate metabolism have been reported.

Metabolic changes in rat brain after prolonged ethanol consumption measured by ¹H and ³¹P MRS experiments.

Cell Mol Neurobiol. 2000 Dec;20(6):703-15. BRAUNOVÁ Z, KASPAROVÁ S, MLYNÁRIK V, MIERISOVÁ S, LIPTAJ T, TKÁČ I, GVOZDJÁKOVÁ A.

In vivo ¹H and ³¹P magnetic resonance spectroscopy techniques were applied to reveal biochemical changes in the rat brain caused by prolonged ethanol consumption. 2. Three models of ethanol intoxication were used. 3. ¹H MRS showed a significant decrease in the concentration of myo-inositol in the brain of rats fed with 20% ethanol for 8 weeks. This change is consistent with perturbances in astrocytes. On the other hand, N-acetyl aspartate and choline content did not differ from controls. 4. ³¹P MRS did not reveal any significant changes in the high-energy phosphates or intracellular free Mg²⁺ content in the brain of rats after 14 weeks of 20% ethanol drinking. The intracellular pH was diminished. 5. By means of a ³¹P saturation transfer technique, a significant decrease was observed for the pseudo first-order rate constant k(for) of the creatine kinase reaction in the brain of rats administered 30% ethanol for 3 weeks using a gastric tube. 6. The ¹H MRS results may indicate that myo-inositol loss, reflecting a disorder in astrocytes, might be one of the first changes associated with alcoholism, which could be detected in the brain by means of in vivo ¹H MRS. 7. The results from ³¹p MRS experiments suggest that alcoholism is associated with decreased brain energy metabolism. 8. ³¹P saturation transfer, which provides insight into the turnover of high-energy phosphates, could be a more suitable technique for studying the brain energetics in chronic pathological states than conventional ³¹P MRS.

Effects of creatine supplementation and three days of resistance training on muscle strength, power output, and neuromuscular function.

J Strength Cond Res. 2007 Aug;21(3):668-77. CRAMER JT, STOUT JR, CULBERTSON JY, EGAN AD.

Previous studies have demonstrated increases in peak torque (PT) and decreases in acceleration time (ACC) after only 2 days of resistance training, and other studies have reported improvements in isokinetic performance after 5 days of creatine supplementation. Consequently, there may be a combined benefit of creatine supplementation and short-term resistance training for eliciting rapid increases in muscle strength, which may be important for short-term rehabilitation and return-to-play for previously injured athletes. The purpose of this study, therefore, was to examine the effects of 3 days of isokinetic resistance training combined with 8 days of creatine monohydrate supplementation on PT, mean power output (MP), ACC, surface electromyography (EMG), and mechanomyography (MMG) of the vastus lateralis muscle during maximal concentric isokinetic leg extension muscle actions. Twenty-five men (mean age +/- SD = 21 +/- 3 years, stature = 177 +/- 6 cm, and body mass = 80 +/- 12 kg) volunteered to participate in this 9-day, double-blind, placebo-controlled study and were randomly assigned to either the creatine (CRE; n = 13) or placebo (PLA; n = 12) group. The CRE group ingested the treatment drink (280 kcal; 68 g carbohydrate; 10.5 g creatine), whereas the PLA group received an isocaloric placebo (70 g carbohydrate). Two servings per day (morning and afternoon) were administered in the laboratory on days 1-6, with only 1 serving on days 7-8. Before (pre; day 1) and after (post; day 9) the resistance train-

ing, maximal voluntary concentric isokinetic leg extensions at 30, 150, and 270 degrees \times s(-1) were performed on a calibrated Biodex System 3 dynamometer. Three sets of 10 repetitions at 150 degrees \times s(-1) were performed on days 3, 5, and 7. Peak torque increased ($p = 0.005$; $\eta^2(2) = 0.296$), whereas ACC decreased ($p < 0.001$; $\eta^2(2) = 0.620$), from pretraining to posttraining for both the CRE and PLA groups at each velocity (30, 150, and 270 degrees \times s(-1)). Peak torque increased by 13% and 6%, whereas ACC decreased by 42% and 34% for the CRE and PLA groups, respectively, but these differences were not statistically significant ($p > 0.05$). There were no changes in MP, EMG, or MMG amplitude; however, EMG median frequency (MDF) increased, and MMG MDF increased at 30 degrees \times s(-1), from pretraining to posttraining for both the CRE and PLA groups. These results indicated that 3 days of isokinetic resistance training was sufficient to elicit small, but significant, improvements in peak strength (PT) and ACC for both the CRE and PLA groups. Although the greater relative improvements in PT and ACC for the CRE group were not statistically significant, these findings may be useful for rehabilitation or strength and conditioning professionals who may need to rapidly increase the strength of a patient or athlete within 9 days.

Creatine supplementation combined with resistance training in older men.

Med Sci Sports Exerc. 2001 Dec;33(12):2111-7. CHRUSCH MJ, CHILIBECK PD, CHAD KE, DAVISON KS, BURKE DG.

PURPOSE: To study the effect of creatine (Cr) supplementation combined with resistance training on muscular performance and body composition in older men. **METHODS:** Thirty men were randomized to receive creatine supplementation (CRE, N = 16, age = 70.4 \pm 1.6 yr) or placebo (PLA, N = 14, age = 71.1 \pm 1.8 yr), using a double blind procedure. Cr supplementation consisted of 0.3-g Cr.kg(-1) body weight for the first 5 d (loading phase) and 0.07-g Cr.kg(-1) body weight thereafter. Both groups participated in resistance training (36 sessions, 3 times per week, 3 sets of 10 repetitions, 12 exercises). Muscular strength was assessed by 1-repetition maximum (1-RM) for leg press (LP), knee extension (KE), and bench press (BP). Muscular endurance was assessed by the maximum number of repetitions over 3 sets (separated by 1-min rest intervals) at an intensity corresponding to 70% baseline 1-RM for BP and 80% baseline 1-RM for the KE and LP. Average power (AP) was assessed using a Biodex isokinetic knee extension/flexion exercise (3 sets of 10 repetitions at 60 degrees.s(-1) separated by 1-min rest). Lean tissue (LTM) and fat mass were assessed using dual energy x-ray absorptiometry. **RESULTS:** Compared with PLA, the CRE group had significantly greater increases in LTM (CRE, +3.3 kg; PLA, +1.3 kg), LP 1-RM (CRE, +50.1 kg; PLA +31.3 kg), KE 1-RM (CRE, +14.9 kg; PLA, +10.7 kg), LP endurance (CRE, +47 reps; PLA, +32 reps), KE endurance (CRE, +21 reps; PLA +14 reps), and AP (CRE, +26.7 W; PLA, +18 W). Changes in fat mass, fat percentage, BP 1-RM, and BP endurance were similar between groups. **CONCLUSION:** Creatine supplementation, when combined with resistance training, increases lean tissue mass and improves leg strength, endurance, and average power in men of mean age 70 yr.

Resistance training with creatine monohydrate improves upper-body strength in patients with Parkinson disease: a randomized trial.

Neurorehabil Neural Repair. 2007 Mar-Apr;21(2):107-15. HASS CJ, COLLINS MA, JUNCOS JL.

BACKGROUND: Persons with Parkinson disease (PD) exhibit decreased muscular fitness including decreased muscle mass, muscle strength, bioenergetic capabilities and increased fatigability. **OBJECTIVE:** This purpose of this investigation was to evaluate the therapeutic effects of resistance training with and without creatine supplementation in patients with mild to moderate PD. **METHODS:** Twenty patients with idiopathic PD were randomized to receive creatine monohydrate supplementation plus resistance training (CRE) or placebo (lactose monohydrate) plus resistance training (PLA), using a double-blind procedure. Creatine and placebo supplementation consisted of 20 g/d for the first 5 days and 5 g/d thereafter. Both groups participated in progressive resistance training (24 sessions, 2 times per week, 1 set of 8-12 repetitions, 9 exercises). Participants performed 1-repetition maximum (1-RM) for chest press, leg extension, and biceps curl. Muscular endurance was evaluated for chest press and leg extension as the number of repetitions to failure using 60% of baseline 1-RM. Functional performance was evaluated as the time to perform 3 consecutive chair rises. **RESULTS:** Statistical analyses (ANOVA) revealed significant Group \times Time interactions for chest press strength and biceps curl strength, and post hoc testing revealed that the improvement was significantly greater for CRE. Chair rise performance significantly improved only for CRE (12%, $P = .03$). Both PLA and CRE significantly improved 1-RM for leg extension (PLA: 16%; CRE: 18%). Muscular endurance improved significantly for both groups. **CONCLUSIONS:** These findings demonstrate that creatine supplementation can enhance the benefits of resistance training in patients with PD.

Effect of creatine supplementation during resistance training on muscle accretion in the elderly.

J Nutr Health Aging. 2007 Mar-Apr;11(2):185-8. CANDOW DG, CHILIBECK PD.

Sarcopenia, defined as the age-related loss of muscle mass, is a serious health concern. Contributing factors to sarcopenia include physical inactivity and undernutrition. Resistance training has a positive effect on muscle mass in the elderly. However, muscle loss is still observed in older adults who perform weight bearing exercise; suggesting that nutrition is important. Creatine supplementation has the potential to increase muscle accretion during resistance training, although the mechanism for its ergogenic effect is unclear. Creatine has the potential to increase cellular hydration and myogenic transcription factors and facilitate the up-regulation of muscle specific-genes such as myosin heavy chain possibly leading to muscle hypertrophy.