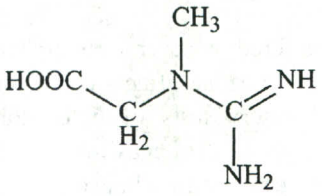
Creatine

DESCRIPTION

Creatine is a non-protein amino acid found in animals and, in much lesser amounts, plants. Creatine is synthesized in the kidney, liver and pancreas from the amino acids L-arginine, glycine and L-methionine. Following its biosynthesis, creatine is transported to the skeletal muscle, heart, brain and other tissues. Most of the creatine is metabolized in these tissues to phosphocreatine (creatine phosphate). Phosphocreatine is a major energy storage form in the body.

Creatine is known chemically as N-(aminoiminomethyl)-N-methyl glycine and its structural formula is:



Creatine

Supplemental creatine is typically a synthetic substance. It is a solid and is water-soluble.

ACTIONS AND PHARMACOLOGY

ACTIONS

Supplemental creatine may have an energy-generating action during anaerobic exercise and may also have neuroprotective and cardioprotective actions.

MECHANISM OF ACTION

Since the action of supplemental creatine has yet to be clarified, the mechanism of action is a matter of speculation. Much is known, however, about the biochemistry of endogenous creatine. Creatine is mainly synthesized in the kidney, liver and pancreas. In its synthesis, the guanidino group of L-arginine is transferred to glycine to form guanidinoacetate and ornithine by a transamidinase reaction, a reaction that takes place in the pancreas, liver and kidney. Guanidinoacetate is methylated by S-adenosylmethione (SAMe) to form creatine. About 1 to 2 grams of creatine are biosynthesized daily and another 1 to 2 grams are obtained from diet.

In muscle and nerve, most of the creatine is phosphorylated to phosphocreatine (PCr) in a reaction that is catalyzed by the enzyme creatine kinase (CK). There are three isoforms (isoenzymes) of CK. CK-MM is the skeletal muscle isoform; CK-BB, the brain isoform, and CK-MB, the isoform found in cardiac muscle. Most of the PCr in the body is in skeletal muscle.

Creatine, creatine kinase and phosphocreatine make up an intricate cellular energy buffering and transport system connecting sites of energy production in the mitochondria with sites of energy consumption. CK is a key enzyme involved in cellular energy homeostasis. It reversibly catalyzes the transfer of the high-energy phosphate bond in PCr to adenosine diphosphate (ADP) to form adenosine triphosphate (ATP), and it catalyzes the transfer of the high-energy phosphate bond in ATP to creatine to form PCr. During periods of intense exercise and skeletal muscle contraction, bioenergetic metabolism switches from one in which oxidative phosphorylation is the major pathway of ATP production to one in which so-called anaerobic glycolysis becomes dominant. Much less ATP would be generated during this period if it were not for phosphocreatine (PCr) being the only fuel available to regenerate ATP during this period. Thus the availability of PCr is the limiting factor of skeletal-muscle performance during high intensity and brief bursts (about 10 seconds) of activity. Supplemental creatine may increase PCr levels in skeletal muscle and hypothetically enhance ATP turnover during maximal exercise.

Creatine supplementation of transgenic amyotrophic lateral sclerosis (ALS) mice carrying the superoxide dismutase (SOD)1 mutation has reportedly produced improvement in motor performance and extension of survival, as well as protection against loss of both motor neurons and substantia nigra neurons. Mitochondrial dysfunction is among the earliest features found in these mice models of familial ALS. Creatine administration to these mice appears to stabilize mitochondrial CK and inhibits opening of the mitochondrial transition pores.

Creatine, as well as a creatine analogue called cyclocreatine, inhibit growth of a broad range of solid tumors in rat models of cancer; these tumors express high levels of CK. Although the mechanism of tumor inhibition is unknown, there is speculation about what it may be. Creatine feedback inhibits the transamidination step in its biosynthesis. This results in sparing L-arginine, the limiting precursor in creatine synthesis. More available L-arginine can lead to increased levels of nitric oxide (NO), which is a factor in macrophage activation. Another possibility is that glycolysis is inhibited in these tumors. Phosphocreatine inhibits enzymes in the glycolitic pathway, including glyceraldehyde-3-phosphate dehydrogenase, phosphofructokinase and pyruvate kinase.

PHARMACOKINETICS

Creatine is absorbed from the small intestine and enters the portal circulation and is transported to the liver. The ingested creatine, along with creatine made in the liver, is then transported into the systemic circulation and distributed to various tissues of the body, including muscle and nerves, by crossing the cell membrane via a specific creatine-transporter

system against a 200:1 gradient. Chronic creatine supplementation in rats down-regulates creatine transporter protein expression. If this is also the case in humans, then chronic creatine supplementation would lead to lower amounts entering cells at any given time.

Within muscle and nerve cells, about 60 to 67% of the creatine entering the cells gets converted to phosphocreatine via the enzyme creatine kinase. About 2% of creatine is converted to creatinine, and both creatine and creatinine are excreted by the kidneys.

INDICATIONS AND USAGE

There is some evidence that supplemental creatine may enhance performance in a limited number of high-intensity, short-term physical activities, but the data are mixed, and no ergogenic effect has been convincingly demonstrated outside of laboratory settings. Adequate safety data are still lacking. There is some very preliminary data that creatine may be helpful in treating muscular dystrophy and amyotrophic lateral scleroses and may improve skeletal muscle function in some with congestive heart failure and gyrate atrophy of the retina. Creatine has inhibited the growth of some solid tumors in rats, but no human cancer data exist.

RESEARCH SUMMARY

Limited muscle function benefit has been noted in some early studies of creatine. All of these studies have been of short duration (mostly lasting one or two weeks and, in no case, more than eight weeks). Many other studies have found no benefit.

A recent review article summarized the results of 71 trials published between 1993 and 1997. Of those that studied effects of supplemental creatine (usually 20 grams daily for 4 to 21 days) on short term, high-intensity performance, 23 reported positive effects and 20 reported no effect. Studies examining the effects of creatine on oxidative energy systems, muscle isokinetic torque and isometric force produced similarly mixed results. Among the few field tests that have been conducted (all related to swim sprints) none detected any effect on athletic performance. Only among studies of cycle ergometer performance was there any superiority of creatine over placebo (11 trials reported improvement, while six others reported no improvement).

Since this review was published there have been a few more positive than negative reports, but, again, the positive effects are almost entirely seen in laboratory settings and are confined to short-term, high-intensity performance.

One author recently reviewed the creatine data and has concluded that supplemental creatine achieves an ergogenic effect, at least in the laboratory, in repeated stationary cycling sprints. But he found no convincing evidence that it does so in single sprints. He also discerned a possible ergogenic effect in weightlifting, but none in running or swimming sprints of any kind. He and others have speculated that the weight gain that typically accompanies creatine supplementation offsets any ergogenic effect that might otherwise benefit runners and swimmers.

Some have claimed that this weight gain, typically 0.5 to 1.6 kilograms occurring in the first few days to first two weeks of creatine supplementation, is evidence of increased muscle mass. Most researchers, however, believe that this weight gain is accounted for by creatine-induced water retention. The longer-term studies needed to confirm or refute claims that chronic creatine supplementation can result in greater muscle mass have not been conducted.

Another caveat offered by several researchers is that almost all of the positive creatine effects so far noted have been achieved in laboratory tests of elite athletes and were observed only in the sort of maximal intermittent exercise that non-athletes can rarely achieve. No benefit for any aerobic activity has been demonstrated.

In addition, safety data are lacking and are urgently needed, especially for long-term use of creatine and for use among the pediatric population (including adolescents) and among those in poor health. There are some reports that long-term use of creatine may be nephrotoxic. This needs further investigation before long-term creatine supplementation can be recommended under any circumstance.

Possible additional uses for creatine have been suggested by preliminary work. There is some evidence of creatine synthesis in the retina, and supplementation with 1.5 grams of creatine daily for a year has been reported to bring improvement in genetic gyrate atrophy—not in the blindness that results from this condition but in the skeletal muscle abnormalities that also characterize it. Giving 5 grams of creatine four times a day for a period of five days has similarly been reported to improve skeletal muscle function in some with congestive heart failure. The effect was small.

In a mouse model of amyotrophic lateral sclerosis (ALS), supplemental creatine significantly prolonged survival. Improvement was seen on motor-performance tests, and there was histologic evidence of neuron protection associated with creatine supplementation. Because creatine protected neurons in the substantia nigra, there is speculation that the supplement could also have positive effects in Parkinson's disease.

These researchers have suggested that creatine may exert the favorable results seen in the mouse model through an intracellular energy-buffering effect that may help prevent

the sort of mitochondrial dysfunction that they postulate plays a role in neuronal cell death. More research is needed.

Another recent, preliminary report asserts a positive role for supplemental creatine in the treatment of muscular dystrophy and some other neuromuscular disorders. This study tested 10 grams of creatine daily for five days, followed by 5 grams daily for an additional 5 to7 days, against placebo. Increases were noted in handgrip, ankle and knee strength among those taking creatine. Again, more research is needed.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS

Creatine is contraindicated in those with renal failure and renal disorders such as nephrotic syndrome and to those with known hypersensitivity to a creatine-containing product.

PRECAUTIONS

Creatine supplements should be avoided by children, adolescents, pregnant women, nursing mothers and anyone at risk for renal disorders such as diabetics. Those taking creatine should have serum creatinine levels monitored.

ADVERSE REACTIONS

The deaths of three American college wrestlers had been linked to the use of creatine supplements. However, results of post mortem tests led to the conclusion that the deaths were caused by severe dehydration and renal failure, and were not due to creatine. Apparently, the wrestlers were trying to lose enough weight through perspiration to allow them to compete in lower-weight classes. Typical adverse effects are gastrointestinal and include nausea, diarrhea and indigestion. Also common are muscle cramping and strains. Weight gain may occur from water retention. During a five day loading period, weight gains of 1.1 to 3.5 pounds have been reported. There are reports of elevated serum creatinine, a metabolite of creatine and a marker of kidney function, in some who take creatine and have normal renal function. This is reversible upon discontinuation of creatine.

Anecdotal reports of adverse events to FDA have included rash, dyspnea, vomiting, diarrhea, nervousness, anxiety, migraine, fatigue, polymyositis, myopathy, seizures and atrial fibrillation.

INTERACTIONS

There are as yet no known drug, nutritional supplement or herb interactions. Caffeine (in coffee, tea and caffeinated beverages) appears to interfere with any beneficial effects of creatine supplementation.

DOSAGE AND ADMINISTRATION

The typical form of creatine available is a creatine monohydrate powder.

The dosing for those who use creatine to attempt to improve performance in brief, high-intensity activities, is a loading dose of 20 grams or 0.3 grams per kilogram in divided doses four times a day for two to five days, followed by a maintenance dose of no more than 2 grams daily or 0.03 grams per kilogram. Those who use creatine supplements should take them with adequate water, six to eight glasses per day.

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Curcuminoids

DESCRIPTION

Curcuminoids are polyphenolic pigments found in the spice turmeric. The term turmeric is used both for the plant *Curcuma longa* L. and the spice derived from the rhizomes of the plant. The major curcuminoids are curcumin, demethoxycurcumin and bisdemethoxycurcumin. These substances comprise 3 to 6% of *Curcuma longa.* Curcumin makes up 70 to 75% of the curcuminoids, demethoxycurcumin 15 to 20% and bisdemethoxycurcumin about 3%.