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Report on the conference
Creatine in Health, Medicine and Sport 2010
held in Cambridge, UK,
7 - 10 July 2010

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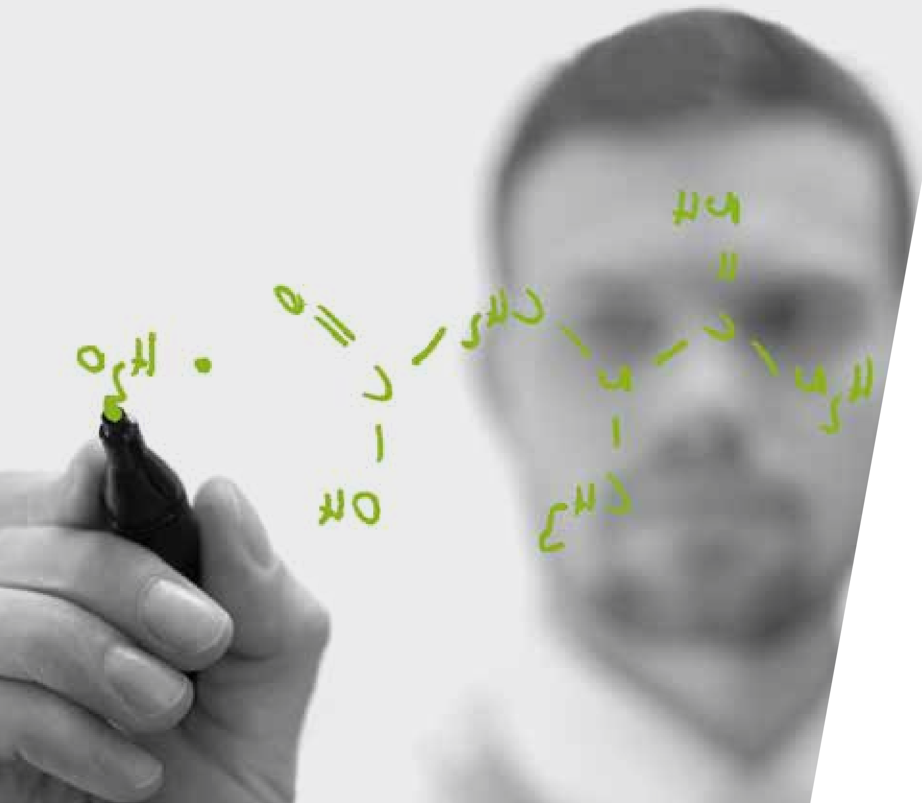
Creatine in health, medicine and sport



Creatine is a substance found naturally in the human body and all other vertebrate animals. It is essential to life.

Creatine is vital to the transport of energy within cells, and the conventional view of creatine is as a reserve fuel for intensive anaerobic exercise. Bodybuilders and athletes commonly and legally take creatine supplements to raise the creatine content of their muscles and improve their performance, a role in which it is proven to be effective and safe.

However, research over the last two decades has shown that creatine is important to the working of many other types of tissue in the body, including the brain. As a result, there is good reason to believe that creatine as a dietary supplement may be useful in treating conditions such as Parkinson's disease and muscular dystrophy, and helping older people to remain active, as well as improving athletic performance.

There is even preliminary evidence that creatine may help in treating depression and traumatic brain injury, in slowing the ageing process, and in protecting against illness through its antioxidant properties.

Most people synthesise roughly half their daily creatine requirement in their own bodies. The rest of our creatine has to come directly from food. Since meat and fish are practically the only dietary sources of creatine, vegetarians generally have lower creatine levels than those of meat-eaters. Anyone who does not eat a balanced diet – and this includes many elderly people – may also have low levels of creatine.

Various metabolic diseases, thankfully rare, stop the body from making or using its own creatine. The resulting creatine deficiency has serious medical consequences. Below-normal levels of creatine in the body rarely cause obvious illness when they result from low dietary intake of creatine, but that does not mean that we cannot improve health or athletic performance by taking additional creatine.

This certainly makes sense if we believe that evolution has fitted the human body to eat much more meat than we do at present. Prehistoric hunters may have eaten an average of 1 kg of meat a day, or even more. This would have provided at least 5 g/d of creatine daily, at the upper end of the 2-5 g/d typically used as a modern food supplement.

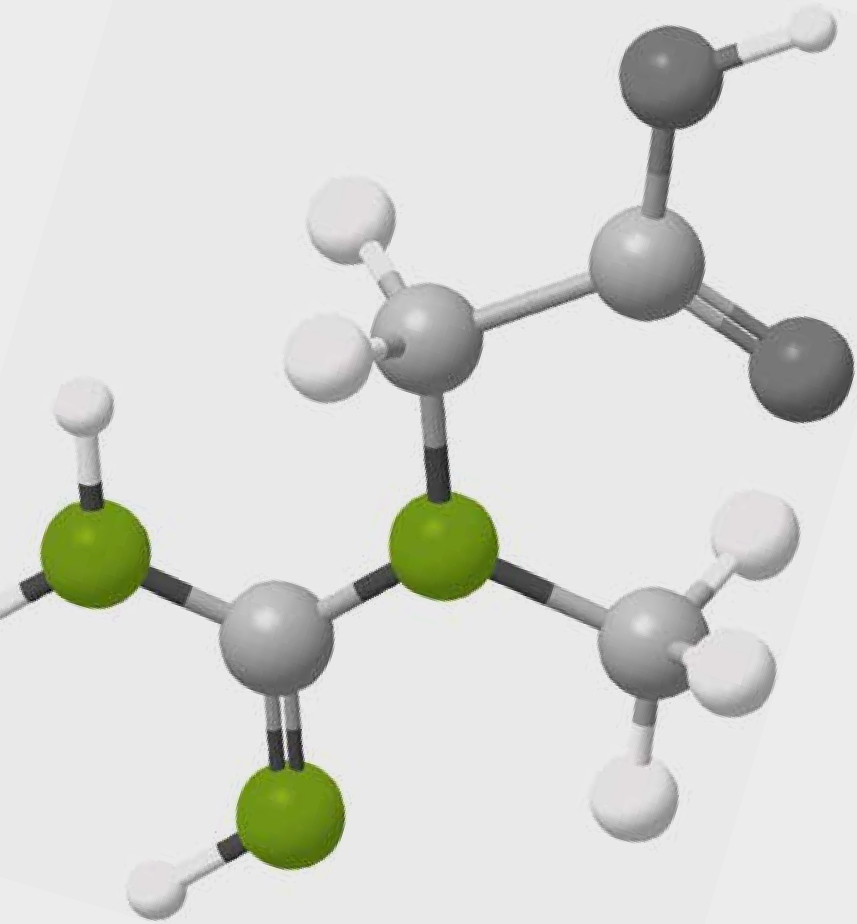
Creatine is affordable, safe, widely available, and approved as a dietary supplement in most countries. Combined with the evidence so far that supplementary creatine can prevent or treat specific illnesses, slow the ageing process and reinforce the benefits of exercise, this suggests that creatine has huge potential to improve public health.

As with all dietary supplements and pharmaceuticals, it is important that creatine is manufactured to strict quality and safety standards. Poorly-manufactured creatine can contain harmful impurities, and creatine is also known to be occasionally adulterated with substances such as steroids that can cause athletes to fail doping tests. Creatine from reputable suppliers, on the other hand, is free from impurities and safe to use. Creatine is manufactured by AlzChem AG in Germany and by a number of companies in China.

This report is based on presentations from the conference Creatine in Health, Medicine and Sport 2010, held in Cambridge, UK, in July 2010. The conference was unprecedented in the number and quality of the speakers and delegates it attracted from across the world. Those present included both the current leaders in the field and most of the famous names from the modern revival of creatine research in the early 1990s.

Many of the scientists at the conference are so convinced of the benefits that they take creatine themselves. The mood was one of wonder that such an apparently simple substance affects so many aspects of health, and that the biological role of creatine, formerly thought to be well-understood, will continue to challenge researchers for many years to come.

Creatine in Health, Medicine and Sport 2010 was organised by Professor Roger Harris, formerly of the University of Chichester, UK, and chaired by Professor Mark Tarnopolsky of McMaster University, Ontario, Canada. The conference was arranged through the Howard Foundation, which controls several patents relating to creatine, and sponsored by AlzChem.



A Cinderella molecule

Creatine occurs naturally in the human body and in all other vertebrate animals. It is essential to life because it plays a fundamental role in the transport of energy within biological cells.

The conventional view of creatine is as a reserve fuel for intensive anaerobic exercise. Accordingly, athletes at all levels routinely and legally take creatine as a dietary supplement. Their aim is to build muscle and improve performance, especially in sports which rely on short-term power, strength and speed. These include running, hurdling, swimming, football, basketball, weightlifting, bodybuilding and many others.

However, research over the last two decades has revealed that creatine is also important to the functioning of almost every tissue in the body, including the brain. We now have good reason to believe that creatine may help to treat illnesses such as Parkinson's disease and muscular dystrophy, and to maintain general health especially among older people. There is even some evidence that creatine may help in treating depression, traumatic brain injury and Alzheimer's, that it can slow the ageing process, and that it has antioxidant properties which could protect against illness.

But many of those attending the Cambridge meeting said they felt frustrated by a perception, even among medical professionals, that creatine is only for bodybuilders. As one eminent researcher puts it: "The emphasis on bodybuilding has trivialised the medical applications of creatine". Other concerns were the creatine myths and half-truths circulating in the world of sports supplements, and the lack of practical controls on creatine purity.

Current research suggests that creatine has major potential to improve public health. In some applications this potential is proven. In other cases, however, preliminary research needs to be backed up by large-scale, long-term scientific trials which are likely to require support from government health departments. If creatine fulfils even a small part of its medical promise, this preventive approach would pay for itself many times over by reducing the costs of healthcare for ageing populations.

In short, creatine is a Cinderella molecule. It is often seen as plain and well-understood, useful yet limited. The reality, however, is that creatine may have a huge potential to improve health, according to many eminent scientists.

Sources of creatine

Scientists classify creatine as a nitrogen-containing organic acid. Its molecular formula of $C_4H_9N_3O_2$ makes it a small molecule – a relatively simple substance – in biological terms.

Creatine is found in all vertebrate animals, and the average human adult weighing 70 kg contains 100 - 150 g of creatine. Around 95 percent of this total is in skeletal muscle – the type of muscle we normally think of as such – but creatine also plays important roles in many other types of tissue, including the brain and the heart.

Creatine breaks down in the body to form a substance called creatinine, and each day we lose around 2 g of creatine by this route. To maintain health, this loss needs to be made good.

Roughly half of our daily creatine requirement is made in the body, mainly in the liver and kidneys, from the amino acids arginine, glycine and methionine, which in turn come from our food. Creatine synthesis depends on two enzymes known respectively as AGAT and GAMT, found especially in the liver and pancreas. Genetic deficiencies in this pathway cause rare but serious developmental disorders.

Unless we take creatine supplements, the remainder of our creatine intake has to come from food. Meat and fish are the main sources of creatine in the typical western diet. Lacto-vegetarians receive a little creatine from milk, but vegans have no dietary source of creatine. As a result, vegetarians' creatine levels are generally lower than those of meat eaters. People who do not eat a balanced diet may also have low levels of creatine.

Creatine supplements are known to boost creatine levels in the body, so many people take these in the hope of improving their health or sporting performance. The recommended daily dose is 2-5 g, though some athletes take more than 5 g/d for extended periods.

It is difficult to set a firm figure for the body's daily creatine requirement, and 2 g/d may be simply a lower limit. Some scientists believe that the human body evolved in the context of a diet with a much higher content of creatine than at present. Tribal hunters in cold climates, for instance, may have eaten 1-2 kg of meat a day, which would have provided 5-10 g/d of creatine.

Creatine as a supplement is available in various chemical forms, of which the commonest is creatine monohydrate (CM). This white powder is widely available from sports and health food stores on the high street and over the Internet, with a retail price of around €40 per kilogramme.

According to conference speaker Professor Richard Kreider of Texas A&M University, USA, the US market for sports nutrition supplements is worth an estimated $2.7 billion annually. Supplements containing creatine make up a large part of this market, he said.

In the sections of this report which discuss sporting, medical and safety aspects, "creatine" generally means creatine taken as a dietary supplement in the form of CM. In the context of biochemical research, on the other hand, references to creatine often imply phosphorylcreatine and the various forms of creatine kinase (see below) as well as creatine itself.

Creatine as an energy carrier

Up till now we have referred to creatine as a single substance. However, the ability of creatine (Cr) to transport energy depends on the existence of a closely related compound, phosphorylcreatine (PCr, also called phosphocreatine), and an associated enzyme, creatine kinase (CK), which converts Cr into PCr by adding a phosphate group (P).

The transfer of phosphate groups is key to the energy which animal and plant cells need to survive and grow. The ultimate cellular energy carrier is the substance known as adenosine triphosphate (ATP). Stripping away a phosphate group converts a molecule of ATP to adenosine diphosphate (ADP), and releases energy in the process.

The problem for muscle cells is that they can store only enough ATP for a few seconds of high-intensity anaerobic work. In the long term, ATP is regenerated through oxidative metabolism: complex reaction chains fuelled by (in people and animals) sugars and fats derived from food, plus oxygen. As part of this process the body also makes and stores glycogen, which provides a short-term energy reservoir for anaerobic exercise.

But with ATP in muscle cells depleted after just a couple of seconds' all-out work, even glycogen cannot make up the shortfall quickly enough. This is where creatine comes in: by giving up its P group, a molecule of PCr can quickly regenerate ADP to ATP and thus supply more instant energy. Muscle cells contain enough PCr to keep them working at full power for several seconds. After a bout of exercise, energy from aerobic sources converts Cr back into PCr with the help of CK.

With creatine supplementation shown to increase levels of Cr and PCr in muscle, this classical view of the Cr/PCr system explains why creatine improves the performance of power athletes. It also shows why creatine supplementation was long thought to be unimportant for endurance athletes, whose performance depends on their rate of oxidative metabolism and the amount of glycogen they can store. As many of the conference speakers went on to reveal, however, the classical view is over-simplified.

A short history of creatine research

The French scientist Michel Eugène Chevreul discovered creatine in 1832, identifying it as a component of skeletal muscle. He later named the substance creatine, from *kreas*, the Greek word for flesh. Chevreul, who died in 1889 at the age of 102, was a versatile researcher who was fêted during his lifetime and remains a hero to modern creatine researchers.

The idea of meat as a source of physical strength dates back at least to classical times: in the sixth century BC the wrestler Milo of Croton was said to get his enormous strength from a diet which included 9 kg per day of meat. Ideas like this may have influenced Chevreul and the German scientist Justus von Liebig, who followed up Chevreul's work on creatine. In 1865 Liebig founded a company to produce the beef extract Liebigs Fleischextrakt, later known to English-speakers as Oxo.

Over the following century researchers worked out many details of how creatine acts as an energy transporter in muscle. By the late 1960s the time was right to find out whether creatine as a dietary supplement could raise creatine levels in muscle and ultimately improve athletic performance. Swedish physiologist Eric Hultman, who was guest of honour at the Cambridge conference, and biochemists Roger Harris, Karin Söderlund and Paul Greenhaff investigated this possibility and concluded that it did. Harris, Hultman and Söderlund published the first paper on muscle creatine loading in 1992. That was also the year of the Barcelona Olympics, at which it is widely believed that creatine supplements were taken by a number of British athletes including sprinter Linford Christie and hurdler Sally Gunnell.

Two decades on, creatine supplements are no longer reserved for elite athletes. Instead, creatine is taken widely by adult athletes of all standards, and in the USA this extends down to college level. Meanwhile, as research on its sporting applications continues, creatine has increasingly attracted the interest of medical researchers too.

At a time when the pioneers of modern creatine research are nearing the end of their professional careers, the Cambridge conference was a rare opportunity to bring together many of the biggest names in the field. Creatine in Health, Medicine and Sport 2010 attracted around 25 speakers, 20 poster presenters and 70 delegates in total. The event was arranged through the Howard Foundation, which controls several patents relating to creatine, and sponsored by creatine manufacturer AlzChem AG. The scientific content will be published in the journal Amino Acids.

Basic research on creatine

The evolution of the creatine system

The system comprising creatine, phosphorylcreatine (PCr) and creatine kinase (CK) is one of several which evolved to fill the need for a specialised energy storage and transport mechanism within cells, Professor Ross Ellington of Florida State University, USA, reminded conference delegates.

The release of energy which accompanies the conversion of ATP to ADP is the last step in the energy chain that keeps all plants, bacteria and animals alive. Yet if the concentration of ADP rises too high, this critical reaction heads towards a chemical equilibrium which can seriously reduce the rate of conversion and so starve cells of energy.

To stop this from happening, living organisms have developed ways to buffer the depletion of ATP and the build-up of ADP. In the case of animals – from single-celled organisms to humans – this involves substances known as phosphagens which take up phosphate and release it on demand in such a way that it can convert ADP back to ATP. Phosphagens are unique to eukaryotic cells (those cells having well-defined nuclei and small functional structures known as organelles).

In addition to the Cr/PCr/CK system, scientists have identified seven other phosphagen systems, including one based on the amino acid arginine (A), phosphoarginine (PA) and arginine kinase (AK). The Cr/PCr/CK and A/PA/AK systems are widely distributed in animals. Since AK is confined to invertebrates, researchers used to think that CK evolved after AK, but both systems are now known to be ancient, Ellington said.

Organisms which depend on creatine have several different types of creatine kinase. The main body of each cell possesses cytoplasmic CK (CytCK); the mitochondria responsible for most of the cell's energy production have their own mitochondrial CK (MtCK); and single-celled organisms which swim with the aid of structures known as flagella or cilia have special flagellar CK (FlgCK) too.

In time, CK diversified further to create varieties specific to individual tissue types, including muscle- and brain-type CytCKs, and MtCKs specially adapted to muscle fibres. This diversification of CK types has allowed the Cr/PCr/CK system to become finely tuned to different functional contexts within the body.

More than a reservoir of high-energy phosphate

The view of PCr as an energy carrier which provides a ready supply of ATP during intense anaerobic exercise turns out to be an oversimplification, explained Professor Kent Sahlin at the Swedish School of Sport and Health Sciences, Stockholm, Sweden.

By 1967, he pointed out, pioneer researcher Eric Hultman had shown that PCr levels fall during exercise, stabilising at a level that is lower the more intense the exercise. Even after exercise, researchers showed that PCr levels remain low if the oxygen supply to the muscle is artificially restricted.

This shows that the energy (in the form of ATP) needed to turn Cr back into PCr does not come from the anaerobic conversion of glucose to lactate (glycolysis). Instead, the source of energy must be oxidative phosphorylation (oxphos), the aerobic mechanism which generates ATP from carbohydrates.

More generally, the aerobic and anaerobic energy systems interact through the creatine system. Oxphos is controlled mainly by changes in ADP concentration, but the sensitivity of this relationship depends on the levels of Cr and PCr.

Although the Cr/PCr/CK system is important as a buffer to maintain ATP levels, its main role may in fact be to stop ADP levels from rising too high and interfering with other reactions, Sahlin said.

Creatine is also important in controlling acidity in muscle. During sustained high-intensity exercise, the release of phosphate (free or bound to sugar molecules) from PCr breakdown contributes to an increase in the muscle's buffering capacity, and so helps to mitigate the effects of lactic acid accumulation. During the early stages of intense exercise PCr breakdown may even result in a small increase in muscle pH.

Looking closely at creatine kinases

Professor Theo Wallimann, formerly at ETH Zürich, Switzerland, discussed the many types of creatine kinase (CK) found in different environments throughout the body.

The Cr/PCr/CK system occurs in all cells which have high energy requirements, he said, transporting energy through the cell or buffering it in time. In muscle cells which may be called on to produce sudden bursts of energy, for instance, PCr acts as a short-term store of extra energy beyond what is immediately available from stored ATP. In cells such as sea urchin spermatozoa, on the other hand, where energy production is limited by the ability of ATP and ADP to diffuse through the cell, the creatine system acts as a spatial energy buffer, transporting energy through the cell.

Cells which benefit from creatine in these ways cover a wide range of functions, Wallimann said. They include not only skeletal and heart muscle, but also the smooth muscle of the gut and other organs, nerve cells in the brain and elsewhere, sperm cells, light-sensitive cells in the eye and even the sensory hair cells of the inner ear.

CK shows subtle variations depending on where in the body it is found – such as muscle, brain and heart cells – and where it is located within a given cell. Different "compartments" within cells have their own ATP supply and their own type of CK; even when a cell is in equilibrium in energy terms, in its individual compartments the reaction that converts Cr to PCr may be running either forwards or backwards.

At the cellular and molecular levels there also seem to be several benefits of creatine which are not directly related to energy transfer, Wallimann said. In fact, the full effects of creatine are probably so complex that they will only be properly understood through the emerging discipline of systems biology.

A systems approach to cellular respiration

The main enzyme controlling respiration in mitochondria, the parts of a cell largely responsible for energy production via ATP, is creatine kinase.

How mitochondrial creatine kinase (MtCK) regulates cellular respiration has been well studied in isolated mitochondria but not previously in whole cells, pointed out pioneer creatine researcher Professor Valdur Saks of Joseph Fourier University, Grenoble, France. Professor Saks has been working with colleagues at the National Institute of Chemical Physics and Biophysics, Tallinn, Estonia.

Following a study involving cultured heart cells, they concluded that in living organisms, as opposed to isolated mitochondria, the mechanisms controlling respiration and energy fluxes are system-level properties.

They propose that muscle cells possess a complex system they call "mitochondrial interactosome", linking:

- the ATP synthesis mechanism (itself a complex system);
- MtCK;
- VDAC, a protein which creates the membrane pores which control diffusion of substances into and out of mitochondria; and
- tubulin, a protein cells use to create the "skeleton" which helps them maintain their physical form and internal structure.

Measuring creatine in the body

Because creatine occurs naturally in the body, it can be difficult to pin down the causes of changes in creatine levels. For instance, taking creatine supplements increases overall creatine levels but appears to reduce the amount of creatine that the body manufactures itself.

Dr. Martin Schönfelder, Dr. Hande Hofmann and colleagues from the Technical University of Munich, Germany, presented a poster showing how they used a mass spectrometer (qTof-MSe) to measure a detailed "chemical fingerprint" of creatine and other substances in the serum of sportsmen who took 6 g/d of creatine for six weeks.

Creatine levels in the volunteers' blood rose as expected, but levels of the breakdown product creatinine remained steady. This suggests that even after six weeks the body was still capable of absorbing more creatine, the researchers said. They also showed an increase in the amino acid sarcosine which they interpret as showing a reduction in the amount of creatine synthesised in the body.

The metabolic burden of creatine synthesis

To synthesise its own creatine the body needs three raw materials: the amino acids arginine, glycine and methionine. Since these amino acids are also required for other purposes, there may be competition for resources, said Professor John Brosnan, who with his wife Professor Margaret Brosnan researches at the Memorial University of Newfoundland, Canada.

A typical 70-kg man in his twenties or thirties synthesises 8 mmol/d of creatine, Brosnan said. This figure declines with age, to around 4 mmol/d for men in their sixties. For women, the figures are 70-80 percent of those for men. Vegetarians need to synthesise up to twice as much because of the lack of creatine in their diets.

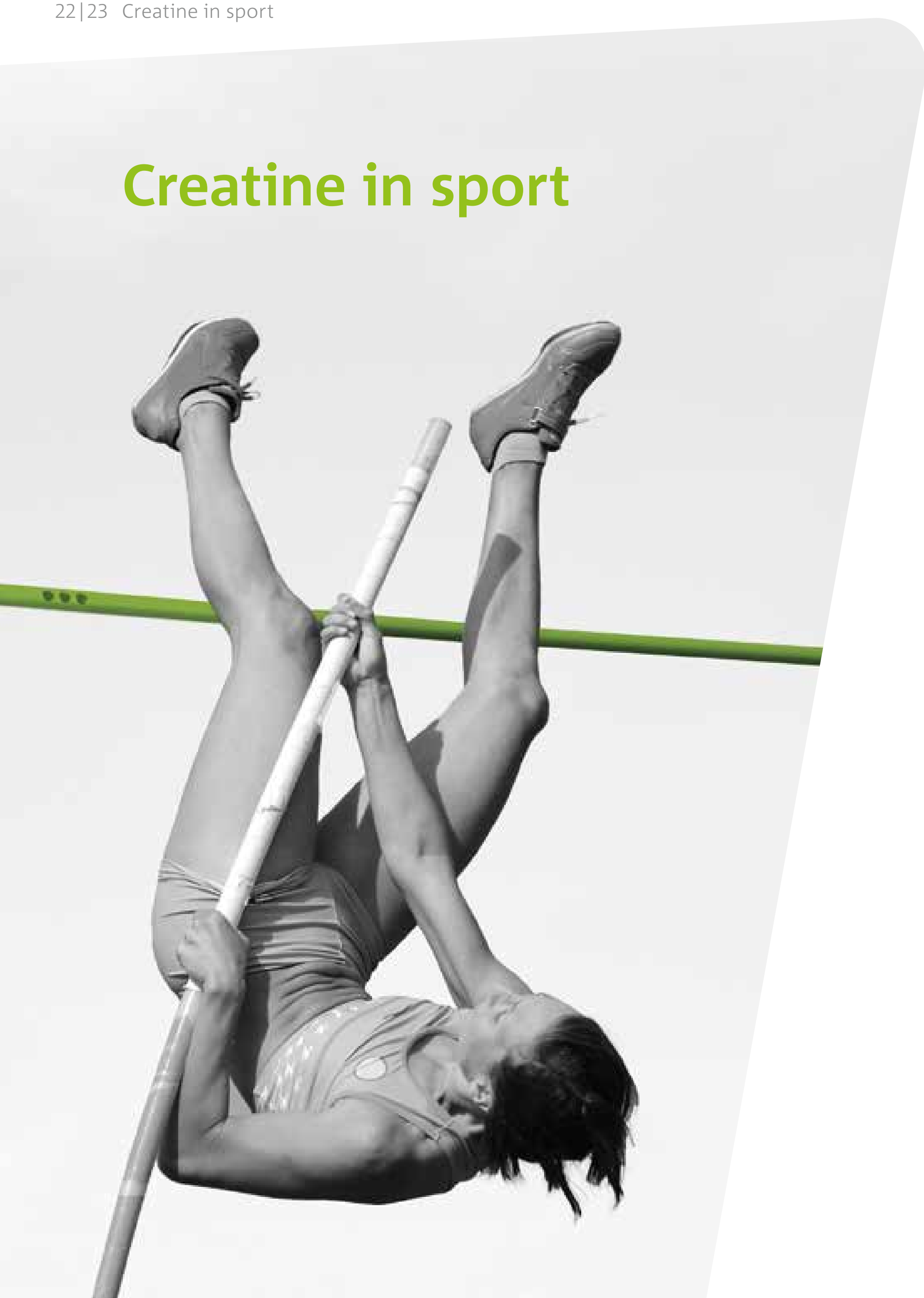
Creatine synthesis is unlikely to cause a shortage of glycine. A typical US adult takes in 48 mmol/d of dietary glycine, and can easily synthesise more when necessary, so dedicating 8 mmol/d to creatine production should not cause problems.

Arginine is in shorter supply: typical figures are 27 mmol/d from diet and 15 mmol/d synthesised by the body, so synthesising 8 mmol/d of creatine would require nearly one-fifth of all the available arginine. People whose diet is low in protein, or who have illnesses which impair their ability to synthesise arginine (such as urea cycle disorders and diseases of the small intestine) might end up deficient in creatine.

The potential for shortage of raw materials is highest in the case of methionine, even though creatine synthesis requires not the whole methionine molecule but simply a methyl (CH_3) group donated by the methionine derivative S-adenosylmethionine (SAM). An average diet provides just 13 mmol/d of methionine, to which we can add 8 mmol/d of SAM regenerated by adding back the methyl group lost during creatine synthesis.

With a total SAM availability of around 21 mmol/d, synthesising 8 mmol/d of creatine therefore requires nearly 40 percent of the body's methionine intake. A diet that is low in protein or the vitamins folate and B_{12}, which are needed to remethylate SAM, will make this situation worse, Brosnan said.

Creatine in sport



For several decades athletes have been taking creatine as a dietary supplement to build muscle and improve performance in sports which rely on short-term power, strength and speed, such as track and field events, cycling, racquet sports, football, basketball, weightlifting, bodybuilding and many others.

Creatine supplementation first became widely known after British athletes used it in training for the Barcelona Olympics in 1992, though there are stories that Russian and East German athletes took creatine in the 1960s or even before.

As a dietary supplement approved in most countries of the world, and not banned by any sports authorities, creatine is now used widely and openly at all levels of sport, from schools to the Olympics.

Athletes typically take up to 5 g/d of creatine monohydrate (CM), a dose that provides two or three times the amount of creatine contained in a very-high-protein diet. A few athletes are also known to take much higher doses of creatine for extended periods.

Creatine for building muscle

Professor Matthew Vukovich of South Dakota State University, USA, gave an overview of past research on the effectiveness of creatine in sports. Creatine monohydrate (CM) is widely taken by athletes, he said, and studies over the last 18 years have reported that CM supplementation improves performance and recovery during repeated bouts of intense exercise.

Comparing trials can be difficult, he said, because many are not large enough to yield statistically reliable results, and the sizes and timing of the creatine doses often differ from one study to the next. There is also the problem that researchers measure athletic performance in many different ways. Activities include cycling, running, jumping, swimming, rowing and weightlifting, with variations in time, distance and number of repetitions, and performance measures including peak power, total work, time taken, and degree of exhaustion.

However, Vukovich said, studies on trained athletes show clearly that CM increases isotonic strength, peak power and total work for a given degree of fatigue, regardless of age or gender. Intense activities lasting less than a minute show greater improvement than those which last longer. For people classed as "active" or "untrained" the data is less clear-cut. Most studies have used large doses of creatine – 20g/d – for six days or less, Vukovich said, but longer-term trials have tended to produce better results.

According to Professor Jacques Poortmans of the Free University of Brussels, Belgium, studies on cell cultures and animals suggest that creatine supplementation directly increases the formation of muscle protein – but experiments have failed to confirm this in humans. It therefore seems that most of the muscle gain comes from creatine's ability to allow athletes to train harder. By increasing the maximum force they can produce and the number of repetitions they can manage before exhaustion, creatine encourages athletes to get more from their training sessions.

A recognised side-effect of creatine is weight gain. Poortmans said that creatine supplementation increases body mass by 1.0-2.3 percent, with figures at the high end of this range generally found when creatine is taken for more than 10 days. The effect is most pronounced in muscle, which gains in weight by 6 percent on average. About two-thirds of the increase in muscle weight comes from extra water retained in the spaces between cells; bodybuilders value this "volumising" effect because it increases muscle size as well as strength. Weight gain is one reason why creatine has not traditionally found favour with endurance athletes.

Aiding recovery

Some athletes believe that creatine not only makes them stronger but also speeds their recovery from intense exercise. Dr. Reinaldo Abunasser Bassit of the University of São Paulo, Brazil, explained how he and his colleagues tested this theory by giving contestants in 30 km running races and "ironman" competitions 20 g/d of creatine for five days beforehand. Based on levels of inflammatory cytokines and other indicators of muscle damage found in their blood, the researchers concluded that creatine did indeed reduce muscle damage and inflammation following extreme endurance competitions.

Professor Bruno Gualano, also from the University of São Paulo, explained how he and his colleagues had confirmed that in rats creatine supplementation led to higher levels of glycogen and lower levels of lactic acid after strenuous exercise. As expected, rats given creatine were able to exercise for longer before becoming exhausted.

Creatine and carbohydrates

Professor Paul Greenhaff of the University of Nottingham, UK, explained how carbohydrates and creatine can have mutually beneficial effects.

Taking carbohydrate together with creatine boosts insulin levels, and this in turn raises the creatine content of muscle – at least in the short term – above the levels shown with creatine alone, Greenhaff said. An important point is that this works even for those few people whose muscle creatine levels remain unaffected when they take creatine on its own.

The large amount (95 g) of carbohydrate used in the original studies is not very palatable, so the experimenters tried mixing smaller quantities of carbohydrate with protein and amino acids instead, and showed similar results. Greenhaff said that there is plenty of room for new research on how to increase muscle creatine levels in the longer term, both with and without carbohydrates and other substances capable of raising insulin levels.

In an interesting corollary of carbohydrate's ability to boost creatine levels, Greenhaff said that creatine may also help with carbohydrate loading.

Endurance athletes, for whom glycogen availability is a key factor in performance, use carbohydrate loading to build up extra reserves of glycogen just before a competition. As the name suggests, carbohydrate loading involves eating extra carbohydrate for a few days before the event, sometimes after first having deliberately exhausted the body's glycogen reserves. The idea that creatine supplementation might reinforce carbohydrate loading is an important step away from the traditional idea that creatine supplementation is only of value to power athletes.

Creatine supplementation reinforces carbohydrate loading to an extent that would be expected to significantly improve athletic performance, Greenhaff said, increasing the amount of stored glycogen by around 150 mmol/kg of dry muscle. The mechanism by which this happens is not yet clear, and nor is the timescale; all that we know at the moment, Greenhaff said, is that the effect occurs between 6 and 120 hours after taking creatine. For comparison, conventional carbohydrate loading takes 48 - 72 hours to double the body's glycogen reserves in muscle and liver.

Caffeine and creatine

A poster by Dr. Craig Sale of Nottingham Trent University, UK, and Roger Harris investigated whether caffeine interferes with creatine taken to improve sporting performance. This is an important question because some athletes take caffeine as an aid to training and competition. There are reports of athletes who avoid creatine supplements simply because they drink coffee and believe that this will make creatine ineffective.

The theory behind caffeine for training is that it saves glycogen by promoting the metabolism of fat, and by delaying fatigue. Caffeine may also allow athletes to train harder.

Sale and Harris noted that two previous studies, in 1996 and 2002 respectively, seemed to show that caffeine counteracted the effects of creatine, but involved subjects who may have suffered caffeine withdrawal symptoms which would have made the results unreliable.

They accordingly set up a new trial using the same high level of caffeine and showed that, while creatine supplementation alone increased strength in knee-extension exercises by up to 10 percent, this gain was cancelled out by adding caffeine (5 mg per kg of body weight).

However, several of the subjects suffered stomach upsets caused by the high doses of caffeine, and the researchers cautioned that this may again have influenced the results. For a person weighing 70 kg, a dose of 5 mg/kg·d equates to 350 mg of caffeine. For comparison, a cup of coffee typically contains 50-100 mg of caffeine.

The subjects took their caffeine at the same time as one of their four daily doses of creatine. It is possible that taking caffeine and creatine at different times of day would cause less interference. What remains less well known is whether or not habitual caffeine intake has any effect on the ergogenic potential of creatine.

Pros and cons in aerobic sports

Recent studies have shown that besides its traditional use by power athletes, creatine can improve performance in intense, short-duration aerobic exercise. Several studies presented at the conference explored the compromise between creatine's ability to increase strength and its less-desirable effects: weight gain and a possible loss of flexibility.

Dr. Scott Graham and Marianne Baird of the University of the West of Scotland (formerly Paisley University), UK, presented details of their work on hill running, rock climbing and alpine skiing. In the hill running experiment, subjects ran for 30 minutes on an inclined treadmill carrying a 10 kg load. Creatine did not increase performance; any increase in muscle power due to creatine was offset by a significant gain in weight. Perhaps surprisingly in view of this result, however, the researchers showed that skilled climbers taking creatine recorded faster times on a repetitive exercise test despite an increase in weight.

In contrast to hill running and climbing, competitive alpine skiing is a sport in which heavier athletes find an advantage, especially in speed disciplines such as super giant slalom. Testing volunteers on a slalom machine, the researchers concluded that the combination of extra weight and increased strength produced by creatine supplementation improved skiers' performance.

Dr. Nick Sculthorpe of the University of Bedfordshire, UK, and colleagues presented a poster suggesting that people taking creatine might lose flexibility in their joints. The researchers wondered if their measured decrease in the angles through which subjects could move their shoulders might be due to asymmetrical development of muscles during training. However, loss of flexibility is not commonly associated with creatine use.

A poster from Joanna Richards of the University of Bedfordshire, UK, looked at the previously unexplored effect of creatine on the stretch reflex. This phenomenon, which causes a muscle to maintain its tension when it is passively stretched, protects muscles from damage and is important in balance and posture. Richards found that the calf muscle had a faster stretch reflex in subjects taking creatine.

Creatine for health

Important as creatine is to athletes, it is in healthcare that creatine research over the last decade or two has really begun to cause a stir. We now know that creatine supplementation is an effective treatment for certain serious neurodegenerative disorders, and that it seems to promote general health and well-being, especially in elderly people.

Various rare metabolic diseases stop the body from making or using its own creatine. The resulting severe creatine deficiency has serious medical consequences.

Less clear is the effect of low creatine levels resulting from a diet that is low in meat and fish. As well as vegetarians, this probably applies to anyone who does not eat a balanced diet, including many elderly people. If we take the view that evolution has fitted us to eat a great deal more meat than most people do today, it is even possible that we are all deficient in creatine to some degree.

What does seem possible is that extra creatine in the diet can improve general health and prolong healthy life, for instance by reducing osteoporosis and the muscle wasting (sarcopenia) which affects elderly people. However, this remains to be proven on a large scale.

There is increasing evidence that creatine supplements may help to protect against neurodegenerative diseases including Parkinson's and muscular dystrophy. Quite how this happens is uncertain, since some scientists have come to believe that creatine travels from the bloodstream to the brain only with difficulty, and the brain also has its own capability to synthesise creatine. However, clinical studies so far strongly suggest that creatine supplements can indeed help people with muscular dystrophy and Parkinson's, and it is possible that this effect will extend to Alzheimer's.

Creatine deficiency syndromes

An obvious pointer to the importance of creatine beyond its role in skeletal muscle is the terrible effects seen in children whose bodies are unable to synthesise or transport creatine, said Dr. Olivier Braissant of the Centre Hospitalier Universitaire de Lausanne, Switzerland.

Genetic creatine deficiency happens because of a lack of AGAT or GAMT, the two enzymes the body needs to make its own creatine, or the protein known as CrT which transports creatine. The resulting lack of creatine in the brain causes mental retardation, autism, epilepsy and other serious problems.

Creatine supplementation greatly improves the condition of children with AGAT or GAMT deficiency, supporting the traditional view that the brain gets most or all of its creatine from elsewhere in the body.

However, creatine supplements do not work for CrT-deficient patients, Braissant said. Recent research shows that a healthy brain can make its own CrT, and that CrT seems to be absent from the blood-brain barrier; the implication is that creatine travels from the bloodstream to the brain only with difficulty.

There is also evidence that a healthy brain also synthesises AGAT and GAMT. This fits with the fact that high doses of creatine for patients with AGAT and GAMT deficiencies take effect only slowly, and generally cannot restore brain creatine to normal levels. The emerging picture, therefore, is that the healthy brain makes a significant proportion of its own creatine.

Brain injury

Since creatine is so important to the proper functioning of the brain, can it also help to heal physical brain injuries? Dr. Athanasios Evangeliou of the Papageorgiou Hospital, Aristotle University, Thessaloniki, Greece, revealed encouraging results from a preliminary trial.

Brain damage is the main cause of death in around a quarter of all trauma cases involving children, Evangeliou said. Typical causes are falls, car accidents and child abuse. Any therapy that can increase survival rates, help patients get better more quickly or ensure a more complete recovery is valuable.

Building on promising results from previous animal studies, Evangeliou's team gave creatine to 20 children and adolescents, aged from 1 to 18, with traumatic brain injury. The patients took creatine for six months at 0.4 g/d per kg of body weight.

Compared to a control group, the doctors found significant improvements in many measures of well-being for the patients taking creatine: less post-traumatic amnesia, a shorter stay in the intensive care unit, faster recovery, less remaining disability, and fewer changes in mood, behaviour or ability to learn. There were no negative effects, Evangeliou reported.

Neurodegenerative disease

We have good reason to think that creatine may protect against degenerative brain diseases in adults, said Professor Flint Beal of Weill Cornell Medical College, New York, USA. Though most of the evidence to date comes from laboratory tissue cultures and animal studies, several human clinical trials are now under way. Therapy may be most effective if it starts before symptoms appear and creatine is taken in conjunction with other substances, Beal said.

There is substantial evidence that creatine protects brain cells from “excitotoxic” agents such as glutamate. Glutamate, an amino acid salt, has a vital role in transmitting signals between nerve cells, but in high concentrations glutamate and similar substances cause damage associated with Huntington’s disease, Parkinson’s disease and amyotrophic lateral sclerosis (ALS), a form of motor neuron disease. In cell cultures, creatine also protects against beta amyloid, the fragmented protein associated with Alzheimer’s disease.

In tissue cultures, Beal’s research group found that creatine mitigates the effects of several common excitotoxic substances: N-methyl-D-aspartate, malonate, 3-nitropropionic acid (3-NP), and the chemical known as MPTP, which produces symptoms of Parkinson’s. Transgenic mice bred to develop ALS or Huntington’s disease lived longer and had better muscle control and less brain damage when given creatine, though unfortunately the mouse results for ALS do not translate to humans, Beal said.

The researchers also looked at a combination of creatine with coenzyme Q_{10} (CoQ_{10}), a vitaminlike substance which plays an important part in cellular energy conversion and is widely taken as a dietary supplement. For several test-tube and mouse models of neuron damage, the combination of CoQ_{10} and creatine was more effective than either substance on its own.

A short-term phase II clinical trial in 2006 of creatine for Huntington’s disease was followed by the ongoing CREST phase III trial, which involves large doses (30 g/d) of creatine.

For Parkinson's, a preliminary phase II trial showed that after one year, patients taking creatine scored around 50 percent higher on the standard rating scale than those who did not. Creatine is now the subject of a phase III trial under the auspices of the US National Institutes of Health. The NET-PD trial, launched in 2007, is sponsored by the US National Institute of Neurological Disorders and Stroke (NINDS). It covers 1,720 people, making it one of the largest clinical trials for Parkinson's to date, and will run for five years. The creatine dose rate is 5 g/d.

In the discussion following Flint Beal's presentation, conference chair Professor Mark Tarnopolsky of McMaster University, Ontario, Canada, said that therapies such as creatine and CoQ_{10} could mark a paradigm shift in the treatment of genetic disorders. These treatments seem to work best if they are started before symptoms appear, yet many young people at risk of incurable genetic disorders currently prefer not to undergo screening, Tarnopolsky pointed out.

Depression

Professor Douglas Kondo, a psychiatrist at the University of Utah, USA, spoke about creatine in the treatment of serious depression in young women.

In the USA, according to Kondo, major depressive disorder (MDD) affects up to 20 percent of children and adolescents at some point, and 14 percent of children have thought about suicide in the last year. By their mid-teens, girls are twice as likely as boys to suffer from depression, and this gender imbalance persists until the menopause.

A review of 13 controlled trials involving 2,750 young people with depression showed that 60 percent of them improved when they took antidepressant drugs such as fluoxetine. However, 48 percent of the patients also improved when they took a placebo.

Several lines of evidence suggest that depression is associated with changes in the brain's energy supply. When adults become depressed, levels of ATP in their brains fall, and levels of phosphorylcreatine rise, Kondo said. This suggests that the brain of a depressed person has energy reserves that it is unable to use, and that creatine supplements may help.

Kondo's trial has so far enrolled five girls with major depression who have failed to respond to fluoxetine. During the eight-week treatment they take both fluoxetine and creatine.

Though Kondo stressed that this is only a preliminary study, he said the results had been encouraging. “These kids are very ill. They have been depressed for a long time and many of them have attempted suicide,” he explained. By the end of the treatment period, he said, none of the patients were reporting suicidal feelings.

Muscle disease

As well as helping to build muscle in healthy people, creatine is also a useful therapy for muscle disease, said Professor Mark Tarnopolsky of McMaster University, Ontario, Canada.

Around one person in a thousand suffers from a muscle disease (myopathy) which causes muscle weakness and atrophy. Many myopathy sufferers have lower-than-normal levels of creatine in their muscles, and the idea that low creatine levels are associated with muscular dystrophy (MD), one form of myopathy, goes back to the 1940s.

Various kinds of myopathy respond to creatine supplementation in different ways. For instance, creatine produced an increase in strength during a small trial on the mitochondrial myopathy known as MELAS syndrome, but no effect with CPEO, another type of mitochondrial myopathy, or in patients with the two types of myotonic myopathy.

Patients with inflammatory myopathies (dermato- and poly-myositis) do show benefits from creatine, Tarnopolsky said. Creatine also helps mice with an inherited myopathy designed to mimic Duchenne MD in people, and increases strength or fat-free mass by around 4 percent in boys and young men with Duchenne and Becker’s MDs.

Inflammatory myopathies and MD are normally treated with corticosteroids such as prednisone, which improves strength by the same amount as creatine – around 4 percent. Unlike creatine, however, prednisone has severe side effects. Taking this into account, Tarnopolsky said, it is frustrating that creatine is not more widely accepted as a treatment for MD.

Taken together, creatine and prednisone increase strength by around 8 percent. Though this may not sound much, he said, it is enough to delay by two years the point at which a young person with MD becomes confined to a wheelchair.

Healthy ageing

The ability both to build muscle and to protect the function of nerve cells suggests that creatine may be especially useful as a supplement to help elderly people stay healthy for longer.

As well as building muscle in both athletes and people with muscle disease, creatine can help to reduce the loss of muscle associated with ageing (sarcopenia). 10-20 percent of all old people have sarcopenia serious enough to cause them problems in daily life, Mark Tarnopolsky said.

Healthy older people can benefit from creatine supplementation as long as they also follow a programme of weight training, Tarnopolsky said. Studies by his own group and others showed higher levels of creatine in muscles after long-term creatine use accompanied by resistance training. Neither creatine nor training on their own were as effective in increasing strength or fat-free mass.

For people at risk of sarcopenia – and myopathy patients too – it makes sense to take creatine along with other promising treatments such as CoQ_{10}, vitamin E, alpha lipoic acid (ALA) and linoleic acid, Tarnopolsky suggested. His group combined creatine with conjugated linoleic acid in a study of older people who also used weight training. As well as the expected increases in strength and fat-free mass they found that participants lost an average of 2kg of fat, an effect they attributed to the linoleic acid.

Professor Eric Rawson of Bloomsburg University, Pennsylvania, USA confirmed Mark Tarnopolsky's picture of the benefits of creatine supplementation for older people who also follow a programme of resistance training. They have higher lean body weight, fatigue resistance and muscle strength, he said, and can better perform activities associated with daily living. Creatine supplementation also increases the effectiveness of resistance training, which is already used to lessen the effects of osteoporosis.

However, he said, several groups have also shown that in older adults, short-term high-dose creatine supplementation has similar benefits even without exercise training. Given that creatine supplementation may also improve older people's mental performance, Rawson said, it has great potential to improve all-round quality of life.

The normal consequences of ageing in the brain have much in common with neurodegenerative diseases, pointed out Professor Thomas Klopstock, a neurologist at the University of Munich, Germany, who has been investigating the effects of creatine on ageing in otherwise healthy mice.

Creatine supplementation has a marked effect in rodent models of neurodegenerative diseases including Parkinson's, Huntington's and ALS, Klopstock said. This, he explained, arises from the ability of creatine to provide energy, to reduce programmed cell death (apoptosis), to combat excitotoxicity and to act as an antioxidant.

Significantly, the same mechanisms appear to lie behind many of the effects of ageing. The "mitochondrial theory of ageing", first put forward in the 1950s, describes a vicious circle: mutations in mitochondrial DNA damage cells' ability to generate energy through respiration, and this leads to the formation of more oxygen radicals which damage the mitochondrial DNA still further, as well as possibly increasing apoptosis. Because it helps to supply energy and combats both oxidative damage and apoptosis, Klopstock said, creatine therefore has great promise as a way to protect against ageing.

For the Munich mice the picture is certainly encouraging. Giving mice creatine increased their healthy lifespan by 9 percent on average. The creatine-fed mice spent more time playing, and they performed significantly better in other tests of behaviour, memory and other brain functions, Klopstock said. Their bodies showed lower levels of damaging oxygen radicals and lipofuscin, a substance associated with ageing. Genes associated with the growth and protection of neurons, and with learning, were more active.

Chronic lung disease

A poster by Dr. Alicja Olejniczak-Mania from the Wielkopolskie Centre for Pulmonology and Thoracic Surgery, Poznan, Poland, suggested that creatine can help patients with chronic lung disease.

Chronic obstructive pulmonary disease (COPD) in Poland affects more than 2 million people and ranks fourth among causes of death.

In COPD, difficulty in breathing goes on to cause weakness and atrophy of limb muscles.

Three weeks of breathing exercises and strength training improved the condition of patients with stage II and III COPD. Patients who took creatine as well did significantly better.

Creatine in heart surgery

How phosphorylcreatine (PCr) solution can reduce damage to the heart muscle following a heart attack was the subject of a presentation by Professor Valdur Saks of Joseph Fourier University, Grenoble, France, working with colleagues at the National Institute of Chemical Physics and Biophysics, Tallinn, Estonia.

Research over the last five decades has shown that the concentration of creatine and the Cr/PCr ratio are important in regulating respiration in muscle cells, as well as their traditional role in anaerobic energy transport. This "systems" approach has revealed complex interactions between different compartments within individual cells, and has overturned the classic theory which says that PCr and ATP levels do not change as the heart works faster.

One practical application of this is that PCr solution is sold under the trade name Neoton for use in cardiac medicine. In this form PCr is added to the solutions which cardiac surgeons infuse into the heart to stop it and protect it from damage during surgery. When injected, it also aids recovery in patients who have just had a heart attack.

Protecting the heart

High levels of the amino acid homocysteine in the bloodstream are associated with increased risk of heart disease, noted Rafael Deminice of the University of São Paulo, Brazil. Homocysteine is a by-product of creatine synthesis within the body, and previous research has shown that creatine supplementation decreases homocysteine levels because it reduces the need for creatine synthesis. However, no work had been done on how creatine supplementation affects the elevated homocysteine levels found after intense exercise, Deminice said.

The Brazilian group experimented with rats. They found that in rats who did not receive creatine, intense anaerobic exercise caused plasma homocysteine levels to peak at around 55 percent higher than normal. Giving the rats creatine for a month beforehand reduced homocysteine levels before exercise to just 17 percent of those in the control group on average, and restricted the peak rise after exercise to 7 percent compared with the pre-exercise level for the control group.

Creatine as an antioxidant

There is growing evidence that creatine protects cells against stress, said Professor Piero Sestili of the University of Urbino, Italy. Often this has to do with creatine's function as an energy transporter, but there is also reason to believe that creatine works as an anti-oxidant, helping to protect the body from damage by the highly-reactive chemicals known as free radicals.

Sestili and his colleagues have shown that creatine works against two kinds of radical – peroxides and peroxynitrite – in many types of cultured animal cells. In particular, they found that creatine protects mitochondrial DNA, which is especially vulnerable to oxidative damage, though it does not help the repair of DNA that has already been damaged.

The antioxidant effect depends on the presence of higher than normal levels of free creatine within the cell, so it occurs only when creatine is taken as a supplement, Sestili said.

Compared to more conventional antioxidants, creatine displays rather modest activity. However, it also has several unusual antioxidant properties which apply to specific cell types, plus other protective effects stemming from its ability to control osmotic pressure and to transport energy.

Creatine is also inexpensive, safe, and when taken as a dietary supplement is easily stored at relatively high levels in tissues, Sestili said. Taken together, these factors mean that creatine's antioxidant powers may well be important and should be further studied.

Possibilities in cancer

Can creatine supplementation help to prevent or even cure cancer? This was the assertion of speaker Professor Manju Ray of the Indian Association for the Cultivation of Science, Kolkata.

Ray's research group induced cancer in mice by injecting them with the toxic chemical 3-methylcholanthrene or with live cancer cells. As the cancer progressed, levels of creatine, phosphorylcreatine and creatine kinase in nearby tissue fell by around 90 percent. The group confirmed a similar effect in human cancers.

They also found that levels of AGAT and GAMT, the enzymes the body needs to synthesise its own creatine, increased, while the level of the creatine transporter CrT remained constant. Ray said that perhaps the tumour hijacks the creatine synthesis mechanism, turning it instead to produce other substances which help the tumour to grow.

In mice, the researchers also found that creatine reinforces the anti-cancer activity of methylglyoxal, a toxic substance found naturally within the body. Methylglyoxal by itself worked well, and together with ascorbic acid it worked better. The mice who received methylglyoxal, ascorbic acid and creatine, however, fared best of all.

Protecting the liver

Consuming too much fat or alcohol can produce the condition known as fatty liver, in which droplets of fat accumulate in the cells of the liver. Dr. Rafael Deminice of the University of São Paulo, Brazil, and colleagues including John and Margaret Brosnan of the Memorial University of Newfoundland, Canada, presented a poster showing that creatine can prevent fatty liver in rats.

Non-alcoholic fatty liver disease (NAFLD) is associated with impaired metabolism of the amino acid methionine in the liver. Since the liver is an important site for the body's own creatine synthesis, and methionine is one of the raw materials needed, the researchers reasoned that NAFLD may reduce creatine levels.

They fed rats a high-fat diet and compared the effects of creatine with that of betaine (trimethylglycene), an amino acid derivative known to protect the liver from fat accumulation. Both betaine and creatine were effective in preventing the build-up of fat in the liver and other related undesirable effects, the researchers found.

Improving control of type 2 diabetes

The relation between creatine and carbohydrates (see, for instance, Paul Greenhaff's presentation in the section *Creatine in sport*, above) suggests that creatine might help in the management of diabetes.

Some previous research has shown that creatine supplementation may reduce the insulin resistance that characterises type 2 (adultonset) diabetes, said Professor Bruno Gualano from the University of São Paulo, Brazil.

Gualano and his colleagues carried out a 12-week placebo-controlled trial in which all the patients exercised and half also took 5 g/d of creatine. Compared to the control group the patients taking creatine had higher PCr levels in their muscles, though they were no stronger.

A thorough analysis showed that creatine did not produce any significant changes in kidney or liver function, or anything else that the researchers considered could indicate that people with type 2 diabetes should not take creatine.

The patients taking creatine had lower blood glucose levels both when fasting and after meals, Gualano said, making creatine supplementation a useful aid to managing type 2 diabetes.

Creatine safety and purity

Creatine safety

As a dietary supplement approved in most countries, creatine already has to meet safety standards comparable to those which apply to pharmaceutical drugs. Regulatory authorities reason that while some side effects may be acceptable in drugs used to treat sick people, supplements taken by healthy people should be absolutely safe.

In 2004 the European Food Safety Authority (EFSA) confirmed that pure creatine monohydrate is safe at dose rates of up to 3 g/d, pointed out Dr. Barbara Nieß of creatine manufacturer AlzChem AG. Similar approvals apply in most other parts of the world.

Nevertheless, warnings about the safety of creatine continue to appear in the scientific literature, in the general press and on Internet forums, Jacques Poortmans reminded conference delegates. Clearly it is important to establish the truth about creatine safety – not least, as another speaker noted, because many athletes are known to greatly exceed the recommended doses of dietary supplements, on the principle that more is always better.

This section concentrates on the evidence presented at the conference that taking pure creatine monohydrate is not harmful, especially to the liver and kidneys.

Cramps and gastrointestinal effects

Some athletes allege that creatine can cause muscle cramps and upset stomachs. Gastrointestinal upset is a reported side-effect in people who take creatine without combining it with food or drinking enough liquid. Poortmans was not convinced: reports of cramps and gastrointestinal complaints can rarely be attributed directly to creatine use, he said. The effects also depend on the dose: gastrointestinal problems are rare or unknown in people taking the standard 3-5 g/d of creatine.

Liver and kidneys

Some medical researchers continue to claim that creatine supplementation can cause liver or kidney damage. The reasoning is that as creatine breaks down in the body it generates trace quantities of toxic substances including methylamine and formaldehyde.

In 2005, Poortmans showed that people taking large doses (20 g/d) of creatine did indeed have raised levels of methylamine and formaldehyde in their urine, though not beyond the normal upper limits for healthy people.

Working with Craig Sale and Roger Harris, Poortmans recently followed up this work by testing nine men who took 20 g/d of creatine at two different dose regimes. The researchers showed that frequent small doses of creatine were taken up more efficiently than fewer, larger doses, leading to lower creatine levels in the urine, and much lower levels of methylamine.

All the research to date shows that the functions of both liver and kidneys are unaffected when healthy people take creatine for extended periods, Poortmans said. He added that people who already have kidney disease or risk developing it (such as patients with diabetes, hypertension, or reduced glomerular filtration rate) should ask a doctor before taking creatine.

Cancer allegation unfounded

One particularly serious allegation – that creatine supplementation can cause gene mutations and cancer by producing toxic heterocyclic amines – is completely unfounded, Poortmans said. In 2001 the French food safety agency AFSSA caused a big stir by claiming that creatine supplementation could produce heterocyclic amines, and news media quickly spread the story.

The agency later admitted that it had misinterpreted the science. Creatine in meat can indeed give rise to heterocyclic amines, but only when the meat is grilled or barbecued. Nevertheless, said Poortmans, echoes of this allegation continue to be heard, so it would be a good idea to carry out a definitive study which would finally lay the story to rest.

Creatine and creatinine

Some of the worry about creatine and kidney disease may stem from confusion with creatinine, a breakdown product of creatine.

Like creatine, creatinine is found naturally in the body. People with kidney disease have higher than normal levels of creatinine in their blood, and as a result creatinine has a rather negative public image. However, it is important to realise that creatinine is an indicator, not a cause, of kidney problems, and is not harmful in itself.

People who take more creatine than they need may show raised levels of creatinine, so a doctor who does not know that a patient is taking extra creatine might diagnose a kidney problem where none exists. But in people with healthy kidneys, raised levels of creatinine are no cause for concern, and in any case are unlikely to be seen at moderate creatine doses.

Creatine purity

Just because pure creatine appears to be safe does not mean that commercial creatine supplements are necessarily free from problems. There are two basic concerns: impurities introduced through lack of care in manufacturing or storage, and deliberate adulteration with steroids or other performance-enhancing substances. On top of any safety concerns, professional athletes also face the risk that contaminants, whether accidental or deliberate, could cause them to fail drugs tests.

The true extent of contamination of creatine products is hard to judge, said Professor Ron Maughan of Loughborough University, UK. The Web contains plenty of reported analyses of creatine showing significant levels of contaminants resulting from poor manufacturing techniques (see below), but even if this information is reliable and up-to-date, fear of litigation usually means that it is not possible to identify specific products or manufacturers.

Maughan pointed out that there is currently no legal requirement to analyse commercial dietary supplements, including creatine, and widespread buying of supplements over the Internet allows consumers to bypass such laws as do exist. As a result, the current best protection for consumers is to buy creatine only from reputable manufacturers.

Contaminants in manufacturing

Commercial creatine is manufactured by reacting the amino acid sarcosine with either cyanamide or S-methylthiourea.

Creatine produced from sarcosine and cyanamide can contain dicyandiamide (DCD) and dihydrotriazine (DHT) as contaminants. Creatine properly prepared by this route contains a few tens of parts per million (ppm) of DCD, but should have no detectable DHT.

Creatine manufactured from sarcosine and S-methylthiourea can contain the toxic by-product methanethiol (methyl mercaptan), plus thiourea and dimethyl sulphate, the latter two being the precursors to S-methylthiourea.

Some analyses of impure creatine have reported high levels of DHT, DCD and other contaminants. Ron Maughan pointed out that these might be responsible for some of the side effects anecdotally reported for creatine.

The breakdown of creatine during manufacture or storage can produce creatinine. Creatinine is not dangerous but offers no performance benefit and may indicate sloppy manufacturing techniques when present in large quantities – levels above 1 percent have been measured in some commercial creatine samples.

Manufacturing quality standards

Reputable suppliers ensure that their products are safe by following stringent pharmaceutical and food industry standards and practices, said Maughan. These include Good Manufacturing Practice (GMP), which ensures the quality of the manufacturing process in general; Hazard Analysis and Critical Control Points (HACCP), which is geared towards identifying and eliminating sources of contamination or process upsets, and detecting contamination early in the production chain; and more general principles such as the use of dedicated plants to eliminate risks of cross-contamination with other products. Barbara Nieß explained how AlzChem, the only remaining manufacturer of creatine outside China, takes great care to ensure the purity of its product.

At its plant in Trostberg, southern Germany, AlzChem follows GMP and HACCP procedures to make Creapure® brand creatine monohydrate via a process from sarcosine and cyanamide, which is considered the safer of the two manufacturing routes.

Though straightforward in chemical terms, the synthesis of Creapure® forms part of a complex production flow that includes the handling of raw materials and finished product. At AlzChem, written protocols for every process step are backed up by tight process control and a full analysis of every product batch using high-performance liquid chromatography (HPLC) before it is released for shipping, Nieß said, resulting in a product of consistently high purity.

Deliberate adulteration

As well as the "expected" contaminants arising from faulty manufacturing processes, commercial creatine supplements may also contain other undeclared substances arising from careless packaging or deliberate adulteration.

For instance, the anabolic steroids which have been reported in creatine supplements could cause athletes to fail doping tests, said Ron Maughan, even when they are present at levels too low to affect sporting performance. One white powder looks just like another, Maughan pointed out, and some dietary supplements do not even contain the ingredients listed on the label. Dr. David Hall of the UK anti-doping laboratory HFL Sport Science explained the background to the contamination of nutritional supplements in general. In 2001/2002, he said, Germany's official anti-doping laboratory in Cologne tested 634 supplements bought from retail outlets in 13 countries. Almost 15 percent of these were found to contain undeclared steroids.

HFL Sport Science's own studies have shown broadly similar results. When the company tested 58 US products in 2007, 25 percent contained steroids and 11 percent contained stimulants – including cocaine. In the UK in 2008, out of 152 products tested, 10.5 percent were contaminated with either steroids or stimulants. The laboratories agree that in many cases contamination with banned substances is probably accidental rather than deliberate. As Hall pointed out, however, this is no consolation to athletes whose careers have been ruined by positive drug tests after they have taken trace amounts of banned substances in their supplements. Again, buying from reputable suppliers is the best safeguard.

Other forms of creatine

Creatine monohydrate (CM) is the form of creatine most widely used as a dietary supplement and most studied by researchers. It is stable during storage, effective, safe, and well absorbed by the body.

These advantages have not stopped supplement manufacturers marketing other forms of creatine, however. Consumers buy these in the belief they work better than CM, are more easily taken up by the body or have fewer side effects, said Professor Richard Kreider of Texas A&M University.

But there is no good evidence that any of the novel forms work better than CM, Kreider said, and some of them are known to perform worse or not at all. As Matthew Vukovich pointed out earlier, there is evidence that some creatine derivatives break down to useless creatinine before they can do any good. In addition, while there is a legal framework supporting the safety, efficacy, and regulatory status of CM, the status of other forms of creatine is less clear.

The novel forms of creatine include creatine ethylester, creatinol-O-phosphate (COP, an alcohol), "alkaline creatine", "creatine serum", and a wide variety of simple creatine salts including creatine citrate, creatine pyruvate, creatine malate, creatine decanoate and creatine gluconate. Also occasionally met with are various other compounds such as creatine amino-butyrate, creatine D-ketoglutarate, creatine pyroglutamate, creatine ketoisocaproate and carnitine creatinate.

Creatine salts have the advantage of dissolving more easily in water than CM does, so some people prefer them. Once in solution they are effectively identical to CM, however, and according to Kreider there is no evidence that they work better than CM. Creatine salts contain rather less creatine than does CM: sodium creatine phosphate, for example, has 51 percent creatine by weight compared to the 88 percent found in CM, and creatine gluconate is only 40 percent creatine.

Creatine ethylester (CEE) is less well understood than CM, and being chemically different it may be metabolised in a different way. There is good evidence that CEE cannot be effective, Kreider said, because in the body it is converted to creatinine rather than creatine.

Several speakers singled out "creatine serum", which is administered in very small doses placed under the tongue and contains only tiny amounts of creatine, as a product that is particularly unlikely to provide the advantages claimed by the companies selling it.

Creatine stability

Stored as a dry powder, CM remains stable for years. In solution, however, there is a risk that creatine will break down to form creatinine, which is harmless but useless to the body. To be effective as a supplement, we must be sure that creatine does not degrade significantly when mixed into drinks, or in the stomach.

Under moderately acid conditions, such as in orange juice, CM shows less than 5 percent degradation after eight hours. There is therefore no problem in mixing CM into a drink for consumption the same day. In milk or yoghurt drinks, which are alkaline, CM is stable for a couple of weeks in the refrigerator. No manufacturer has yet discovered a form of creatine that is stable enough to allow it to be used in off-the-shelf sports drinks.

A claim used to market some novel forms of creatine is that CM is quickly destroyed by the acid found in the stomach. But this is not true, Kreider said: under strongly acid conditions creatine actually becomes more stable. Creatinine, the breakdown product of creatine, is a ring-shaped molecule formed when the amide group (NH_2) of creatine bends round and attaches itself to the carbon atom of the acid group (COOH). At a pH below 2.5, however, the amide group takes up a proton (H^+) and becomes electrically positive, so the cyclisation reaction to creatinine does not take place.

For a similar reason, creatine is also stable at a pH that is high enough to remove a proton from the acid group, Kreider pointed out. This fact forms the main marketing claim for the product known as "alkaline" or "buffered" creatine. But although the necessary high pH can be created in the laboratory, it cannot exist under the very acid conditions found in the stomach.

Much of the research presented at the conference confirms that taking CM orally is an effective way to boost levels of creatine in the bloodstream. If CM really were destroyed in the stomach, this would not be the case. In fact, more than 98 percent of CM ingested is either taken up by muscle or excreted in urine, Kreider said.

Monohydrate is best

In contrast to some marketing claims, CM is known to be stable in the stomach for long enough to allow the body to absorb it effectively, Kreider noted. For newer forms of creatine, on the other hand, stability has either not been independently investigated or appears to be worse.

The higher solubility of creatine salts can be useful, but almost all the new forms of creatine contain less creatine than CM does.

Some novel forms of creatine, notable creatine ethylester and creatine serum, probably do not work at all well, Kreider concluded.

Since CM is inexpensive and many other forms of creatine cost considerably more, it is tempting to suppose that the novel forms increase suppliers' profits as well as help to differentiate products in the marketplace. In the case of creatine it appears that the simplest form is the best.

09|2015

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