Creatine: a simple molecule with enormous potential to improve health

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

Creatine is a substance found naturally in the bodies of humans 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 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 almost every type of tissue in the body, including the brain. As a result, there is good reason to believe that creatine as a dietary supplement can help to treat or prevent illnesses such as Parkinson's disease and muscular dystrophy, helps older people to stay active, and improves performance in aerobic sports.

There is even preliminary evidence that creatine may help in treating depression and traumatic brain injury, slow the ageing process, and possess antioxidant properties which could protect against illness. 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 extra 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, 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 which 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 Trostberg GmbH 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 attracted around 25 speakers, 20 poster presenters and around 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 Trostberg GmbH. The scientific content will be published in the journal Amino Acids.

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.

A Cinderella molecule

Creatine occurs naturally in the bodies of humans and 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 can also help to treat or prevent 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.

This report is based on presentations from the conference Creatine in Health, Medicine and Sport 2010. The conference was unprecedented in the number and quality of the speakers and delegates it attracted from Europe, the USA, Canada and elsewhere. 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 meeting believe firmly in the health benefits of creatine and take it themselves. The general mood was one of wonder and optimism at the amount of work still to be done to understand how creatine works throughout the body. But many of those attending also said they felt frustrated by a perception – even among medical professionals – that creatine is only for bodybuilders. According to conference organiser Professor Roger Harris, recently retired from the University of Chichester, UK, "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 suggest that creatine has enormous 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. Often seen as plain and well-understood, useful yet limited, creatine has instead 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 adult human body (70 kg) contains 100–150 g of creatine. Around 95 percent of this total is in skeletal muscle – the muscle we normally think of as such – but creatine also plays an important role in most 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 get 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 much higher in 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 €20–30 per kilogram.

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 phosphocreatine 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, phosphocreatine (PCr, also called phosphorylcreatine), 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 the Greek word for flesh, kreas. 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/d 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, and by the late 1960s the time was right to find out whether creatine as a dietary supplement could improve athletic performance. Two young scientists, British biochemist Roger Harris and Swedish physiologist Eric Hultman – now Professor Eric Hultman, who was a guest of honour at the Cambridge conference – experimented on themselves and concluded that it did. Harris, Hultman and others published the first modern creatine papers in 1992. That was also the year of the Barcelona Olympics, at which it is widely believed that creatine helped the performance of British athletes including sprinter Linford Christie and hurdler Sally Gunnell. Two decades on, creatine supplements are

Professor Eric Hultman

no longer reserved for elite athletes. Instead, creatine is taken widely by adult athletes of all standards; in the USA, this extends down to college level. Meanwhile, though research on its sporting applications continues, creatine has become increasingly interesting to medical researchers.

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 business. "There has never been a meeting with so many creatine experts," said Roger Harris. "You could say that it represents the state of the art in creatine research."

The evolution of the creatine system

The system comprising creatine, phosphocreatine (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 which 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 were the last to evolve of the various cellular energy transport mechanisms, and are unique in not deriving from bacteria. Scientists have identified eight different phosphagens, of which the commonest are creatine and arginine. Each phosphagen has its own kinase, so the Cr/PCr/CK system has its counterpart in arginine (A), phosphoarginine (PA) and arginine kinase (AK). 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.

More than a reservoir of high-energy phosphate

The view of phosphocreatine as an energy carrier which provides a ready supply of ATP during intense anaerobic exercise turns out to be an over-simplification, explained Professor Kent Sahlin of the Karolinska Institutet, 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 found that PCr levels remain low if they restrict the oxygen supply to the muscle. This shows that the energy needed to turn Cr back into PCr does not come from the anaerobic conversion of glucose to ATP (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 so interfering with other reactions, Sahlin said. Creatine is also important in controlling acidity in muscle. At the start of exercise, PCr breakdown creates an alkaline environment which helps to activate the glycolysis needed once PCr reserves are exhausted. This alkalinity also mitigates the painful effects of lactic acid, a waste product of glycolysis.

Looking closely at creatine kinases

Professor Theo Wallimann, formerly at ETH Zürich, Switzerland, examined 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 in space 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 shortterm 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. 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 which 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.

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.

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, 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.

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 ($CH3$) 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 Vitamin B12, 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, 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.

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 very 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 bloodstream was still capable of absorbing more creatine, the researchers said. They also found an increase in the amino acid sarcosine which they interpret as showing a reduction in the amount of creatine synthesised in the body.

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 sex. 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 have used large doses of creatine – 20 g/d – for six days or less, Vukovich said, but longer-term trials have 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, however.

Professor Roger Harris (l.), Professor Jacques Poortmans

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 from the University of São Paulo, Brazil, 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 found 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 amount of carbohydrate used in the original studies – 95 g – is not very palatable, so the experimenters tried mixing smaller quantities of carbohydrate with protein and amino acids instead, and found 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.

In fact, 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 reported a study of 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 possibly helps in building muscle. By staving off 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 and found that, while creatine supplementation increased strength in knee-bending exercises by up to 10 percent, this gain was cancelled out by adding caffeine (5 mg/d 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 have affected the results. For a person weighing 70 kg, a caffeine dose of 5 mg/kg·d equates to 350 mg/d. For comparison, a cup of coffee typically contains 50–150 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.

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 with 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 found that skilled climbers taking creatine recorded faster times on a repetitive exercise 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 thepreviously 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 metabolic diseases, thankfully rare, 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 oily fish; as well as vegetarians, this probably includes 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 likely 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 also excellent evidence that creatine supplements help to cure or 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 can synthesis 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.

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 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 fatfree 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.

Professor Mark Tarnopolsky

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 CoQ10, 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 2 kg 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 amyotrophic lateral sclerosis (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.