Nutritional Supplements: Amino Acids and their Derivatives

Cecil K. Joseph1
Arnold & Marie Schwartz College of Pharmacy and Health Sciences, 75 Dekalb Avenue, Long Island University, Brooklyn NY 11201-5497

INTRODUCTION

Vitamins and other nutritional supplements represent a multi-billion-dollar industry (1). Written and oral statements concerning supplements are delivered daily to audiences that span the full spectrum of demographics. Over 13,000 of these products are available to consumers. The ease of availability of these agents coupled with many unsubstantiated claims about their benefits are challenges to health-care providers. The average consumer does not have the knowledge or expertise to evaluate the claims of manufacturers that a specific supplement may be beneficial for a particular ailment or condition. Statements about supplements do not define the parameters on which claims are based. Very little information, if any, is provided about route of delivery, quantity and purity of the supplement and the physiologic status of the recipient. The objective of this course is to provide students with a didactic framework for life-long learning about vitamins and supplements, and also prepare them to counsel those patients who are uncertain about the possible effects of using supplements together with prescribed medications.

Amino acids and their derivatives represent an important class of supplements. This paper describes seven of the major compounds in this category. They include S-adenosylmethionine (SAMe), a possible natural anti-depressant; creatine, also known as "nature's muscle builder", N-acetylcysteine, an antidote for acetaminophen toxicity, and arginine, the precursor of nitric oxide, and the main ingredient in supplements used to alleviate erectile dysfunction and promote general sexual health.

L-ARGININE

Synthesis and Transport

L-arginine is a basic amino acid with a net positive charge at physiological pH. It is a glycogenic amino acid, which means that it can be converted to D-glucose and glycogen if needed by the body. It is essential in young children and therefore is classified as semi-essential or a conditionally essential amino acid. In mammalian cells arginine is synthesized from glutamate (Figure 1). The reactions proceed by a series of intermediates that result in the formation of glutamate-5-semi-aldehyde (2). This molecule is at an important branch point that leads to the formation of the cyclic amino acid, proline, or the non-standard amino acid, ornithine. Proline is a non-essential amino acid that is hydroxylated in a vitamin C-dependent reaction and plays a crucial role in maintaining the structural integrity of collagen. Ornithine is converted to arginine via reactions of the urea cycle. This cycle represents an important role of arginine in the detoxification of ammonia formed during nitrogen catabolism of amino acids that results in the formation of urea.

Under normal circumstances the body can synthesize sufficient L-arginine to meet physiological demands, but in stressful situations the need for L-arginine increases. In fact, L-arginine is an immunonutrient in enteral and parenteral nutrition to help improve the immune status in those suffering from trauma, sepsis, and burn victims (1). In healthy human volunteers, administering 30 grams of L-arginine daily for three days resulted in enhanced natural killer (NK) and lymphocyte-activated-killer cell activity. This finding was interpreted as potentially useful in many immunosuppressed states like HIV infection and burn victims, in which depressed NK cell activity is an important component of the disease process (1). In this context, L-arginine's possible activity in wound repair may be due to its precursor role in the formation of L-ornithine and ultimately, L-proline as described above. L-proline is a key element in the biosynthesis of collagen, a molecule that is present in all tissues and organs, and provides the framework for their form and structural strength.

1Assistant Professor of Biochemistry.

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Following ingestion, supplemental L-arginine is absorbed from the lumen of the small intestine into the enterocytes. Some arginine is metabolized in enterocytes while some is transported to the liver where further metabolism takes place. The remainder is distributed to various tissues of the body. L-arginine shows peak levels in the plasma approximately one to two hours after oral administration (3).

**Mechanism and Therapeutic Usage**

Most effects of supplemental L-arginine may be due to its role as a precursor of nitric oxide (NO). This molecule is found in all tissues of the body and plays very important roles in the cardiovascular, immune and nervous systems. The conversion to NO is catalyzed by the enzyme nitric oxide synthase (NOS), a heme-containing enzyme with isoforms in vascular endothelium (eNOS), brain, spinal cord, nervous system (nNOS), and immune system (iNOS). NO inhibits mononuclear cell adhesion, platelet aggregation, proliferation of vascular smooth muscle, production of reactive oxygen species, such as super-oxide anions, and promotes endothelium-dependent vasodilation (4). These effects may play pivotal roles in the possible anti-atherogenic activities of L-arginine. In addition, L-arginine itself has been found to inhibit the oxidation of low-density lipoproteins (LDL), to oxidized LDL (oxLDL), an early step in atherogenesis (5). In vivo studies show that supplemental L-arginine could enhance endothelial-dependent vasodilation, NO production, and decrease plasma endothelin concentrations(5). Arginine is also used for patients with angina and congestive heart failure. Blood cells in people with angina are known to make insufficient nitric oxide, possibly due to abnormalities of arginine metabolism. Taking two grams of arginine three times per day for as little as three days has improved the ability of angina sufferers to exercise(6).

Claims that L-arginine enhances exercise performance and promotes development of lean body mass while burning fat in healthy individuals are poorly supported. High dose oral L-arginine has, however, been shown to induce the release of growth hormone, prolactin, and pancreatic release of glucagon and insulin, but no studies have been conducted to determine any meaningful ergogenic or anabolic effect (4).

Foods high in arginine are peanuts, cashews and chocolate. Other good sources are dairy, meat, fish, and poultry. Soy protein and other plant proteins are richer in L-arginine than animal proteins. It is believed that the possible hypocholesterolemic effect of soy protein is due, in part, to the higher L-arginine content in this protein. Arginine appears to counteract the hypercholesterolemic effect of the essential amino acids lysine and methionine. The mechanism for this effect has not been established fully. One possible explanation is that changes in the endocrine status may lead to increased cholesterol metabolism and lower levels of LDL cholesterol(7,8).

Studies have shown that L-arginine improves sperm count and motility and help some men with erectile dysfunction. Ingestion of four grams of L-arginine daily for two months resulted in marked increase in sperm number and motility and pregnancies in 28 out of 178 patients (9). This may be related to the role of arginine as a biochemical precursor in the synthesis of putrescine, spermidine, and spermine, which are believed to be essential to sperm motility. The effect of L-arginine for erectile dysfunction is short-lived, so in order to improve sexual performance, you need to take it about 45 minutes before having sexual intercourse (10).

**Pharmacological Correlations and Side Effects**

L-arginine, if taken concomitantly, may increase the absorption of ibuprofen. Preliminary studies show that this combination is helpful in reducing migraine pain intensity (10). L-arginine may also counteract the antinatriuretic effect of cyclosporine, potentiate the effects of sildenafil citrate, and enhance the effect of yohimbe. These latter effects may be due to the production and actions of NO. Intra-arterial, intravenous, and oral supplementation with L-arginine at doses up to 15 grams daily are generally well tolerated. Some side effects include hypotension from NO production, allergic reactions, acidosis and hyperkalemia (3). The most common adverse reactions of higher doses are abdominal cramps and diarrhea.

**CREATINE**

**Synthesis and Transport**

Creatine is synthesized in the kidney, liver, and pancreas from the amino acids L-arginine and L-glycine (Figure 2). S-adenosylmethionine (SAMe), a derivative of L-methionine, is required to complete the synthesis of creatine (12). Once synthesized, creatine is then transported to the skeletal muscle, heart, brain, and other tissues. In muscle and nerve, most of the creatine is metabolized to phosphocreatine (PCr), a reaction...
that is catalyzed by the enzyme creatine kinase (CK). CK reversibly catalyzes the transfer of the high-energy phosphate bond in PCr to adenosine diphosphate (ADP) to form adenosine triphosphate (ATP), and it catalyzes the transfer of the high-energy phosphate bond in ATP to creatine to form PCr. During periods of intense exercise and skeletal muscle contraction, the availability of PCr is a limiting factor in skeletal muscle performance. Supplemental creatine may increase PCr levels in skeletal muscle and hypothetically enhance ATP turnover during maximal exercise. It has been shown that catecholamines, insulin-like growth factor (IGF) - 1, insulin, and exercise can influence the net uptake of creatine into skeletal muscle(13).

Supplemental creatine is absorbed from the small intestine and enters the portal circulation and the liver. Both ingested and endogenous creatine is distributed to various tissues of the body by crossing the cell membrane via a specific creatine -transporter system against a 200:1 gradient. It has been shown that chronic creatine supplements in rats down-regulates creatine transporter protein expression(14). Thus, it is likely that chronic supplementation in humans would lead to lower amounts being synthesized and entering cells at any given time. However, studies indicate that although endogenous production decreases, normal rates return upon termination of supplementation(15).

Mechanisms and Therapeutic Usage

A review of creatine data has shown that supplemental creatine achieves an ergogenic effect, at least in the laboratory, in repeated stationary cycling sprints but no convincing evidence of any effect in single sprints. Investigators in this study discerned a possible ergogenic effect in weightlifting, but none in running or swimming sprints of any kind(16). It is possible that the weight gain that typically accompanies creatine supplementation offsets any ergogenic effect that might otherwise benefit runners and swimmers. The dosing for those who use creatine to attempt to improve in brief, high-intensity activities, is a loading dose of no more than two grams daily or 0.03 grams per kilogram in divided doses four times a day for two to five days, followed by a maintenance dose of no more than two grams daily or 0.03 grams per kilogram. Weight gain may occur from water retention. During a five-day loading period, weight gains of 1.1 to 3.5 pounds have been reported (17). It is postulated that creatine-induced hydration may act as an anabolic signal to stimulate protein synthesis or it may prevent the degradation of proteins (18).

Many reports also assert a positive role for supplemental creatine in the treatment of a variety of diseases. Creatine has been shown to be beneficial in diseases in which there is mitochondrial dysfunction and disruption of energy production. Preliminary results show positive effects on Parkinson's and Huntington's diseases (14). In patients with muscular dystrophy, ten grams of creatine daily for five days, followed by five grams daily for an additional five to seven days against placebo, produced increases in handgrip, and ankle and knee strength (19). People with congestive heart failure have also been found with improved heart function when given creatine. Oral supplementation has led to increased exercise performance in regard to both strength and endurance (20).

Pharmacological Correlations and Side Effects

No known drug, nutritional supplement or herb interactions have been reported. Caffeine appears to interfere with any beneficial effects of creatine supplementation. One study showed that oral caffeine (5 mg/kg/day as capsules) completely eliminated creatine's effect on muscle contraction (21). Some side effects from creatine supplementation have been reported both anecdotally and in the scientific literature. Creatine supplementation has been documented as being associated with weight gain, gastrointestinal distress, and renal dysfunction. Typically weight gain is 1-2 kg and is initially brought on by water retention, but may be maintained by changes in amount of lean body mass. Anecdotal reports of adverse events to the FDA have included rash, dyspnea, vomiting, diarrhea, nervousness, anxiety, migraine, fatigue, muscle cramping, polymyositis, myopia, seizures and atrial fibrillation. Generally, it appears that short-term supplementation may be safe, but the effect of long-term supplementation is still unknown. One major concern is the quality of products on the market. Contaminants such as dicyandiamide and arsenic are by-products of the commercial production of creatine. These represent potential health hazards.

CARNITINE AND ACETYL-L-CARNITINE

Synthesis and Transport

Carnitine (4-trimethylamino-3-hydroxybutyrate) is an amino acid derivative that is found in nearly all cells of the body and occurs naturally in animal products. Only very small amounts are found in plants like avocado and some fermented

soy products like tempeh. It is synthesized chiefly in the liver and kidneys from the essential amino acid L-lysine. It is synthesized not from free lysine but rather from lysine residues in certain proteins. The first step is the trimethylation of the ε-amino group of the lysine side chain, with s-adenosylmethionine (SAMe) as the methyl donor. Free trimethyllysine is obtained from hydrolysis of the protein. It is then hydroxylated and cleaved to form glycine and g-butyrobetaine aldehyde. The latter is oxidized to g-butyrobetaine using NAD+ as a cofactor, and then hydroxylated to carnitine (Figure 3). Both hydroxylated steps require vitamin C as a cofactor. Skeletal muscle can also form g-butyrobetaine but must release it for its final conversion to carnitine by liver or kidney. Thus, chronic kidney disease and some forms of liver disease may be indications for L-carnitine supplementation. Preliminary work suggests that L-carnitine can reduce fat deposits in some fatty livers (22), and there is evidence that dialysis patients can benefit from supplementation since dialysis removes low-molecular-weight L-carnitine.

About 60 to 75 percent of L-carnitine from food is absorbed. The percentage absorbed from supplements appears to be lower (approximately 20 percent). Following absorption from the intestine, about 25 percent may be acylated in the intestinal mucosa. Uptake into cells is believed to occur by facilitated diffusion and in some instances, by active transport. L-carnitine and its acylated derivative are distributed to most tissues of the body. However, most of the body’s stores are found in cardiac and skeletal muscle.

**Mechanisms and Therapeutic Usage**

Carnitine transports long-chain fatty acids across the inner mitochondrial membranes in the mitochondria for beta-oxidation to produce ATP. The series of reactions begin in the cytosol where fatty acids are acylated by combining with coenzyme A (CoA), a derivative of the vitamin B₃, also known as pantothenic acid. The acyl-CoA penetrates the outer membrane of the mitochondria and reacts with carnitine to yield an acyl-carnitine derivative. Acyl-carnitine is transported across the inner membrane by a specific carrier protein to the mitochondrial matrix where it is converted back to the acyl-CoA derivative. The carnitine is released and recycled to perform another round of reactions.

L-carnitine is available in many forms. Oral L-carnitine is available as a nutritional supplement and as a prescribed orphan drug treatment for primary and secondary L-carnitine deficiencies. Intravenous L-carnitine (levocarnitine) is available as a prescription orphan drug for the treatment of primary and secondary L-carnitine deficiencies, and Propionyl-L-carnitine is available in Europe but not in the United States. Acetyl-L-carnitine, the acetyl ester of L-carnitine, is another delivery form of L-carnitine and is available as a nutritional supplement. It occurs naturally in animal products and also functions as a source of acetyl groups. The acetyl component is utilized in the formation of the neurotransmitter acetylcholine. This may be beneficial in the treatment of cholinergic deficits, such as those found in Down’s syndrome and Alzheimer’s disease. In one double-blind placebo-controlled study of 130 Alzheimer’s patients receiving acetyl-L-carnitine, a slower rate of deterioration was observed in 13 out of 14 outcome measures (23).

Acetyl-L-carnitine may enhance sperm motility. In one human trial, 4 grams daily of this substance given to 20 oligoasthenospermic men, produced increased progressive sperm motility, which was associated with a greater number of pregnancies (24). It has been shown that carnitine contributes directly to sperm motility and may be involved in the successful maturation of sperm. Since low levels of carnitine reduce fatty acid concentrations in the mitochondria, this may lead to decreased energy production and potential alterations in sperm motility (9).

L-carnitine may have cardioprotective effects and may beneficially affect cardiac function. The strongest evidence for the use of supplemental L-carnitine may be the management of cardiac ischemia and peripheral arterial disease. It may have general cardioprotective activity, lowering triglyceride levels and increasing HDL-cholesterol in some subjects. Both L-carnitine (two grams bid) and propionyl-L-carnitine, (one gram per day increasing to 2 grams per day after two months and three grams per day after an additional two months, if needed) increased walking distance in people with intermittent claudication (25). It was suggested that L-carnitine enhances pyruvate utilization and oxidative phosphorylation efficiency in the skeletal muscle of the ischemic leg.

Although abnormal carnitine metabolism is associated with diabetes, there is no evidence that it will prevent diabetes. However, administration of L-carnitine holds potential to improve insulin sensitivity. One study showed that a two-hour infusion of L-carnitine administered to patients with type-2 diabetes created a short-term improvement in insulin sensitivity by enhancing whole-body glucose uptake and increasing glucose storage (26).

There is little evidence that supplemental L-carnitine boosts energy, increases athletic performance or inhibits obesity. Clinical studies suggest that carnitine supplementation does not improve maximal oxygen uptake or metabolic status during exercise in healthy humans. These studies also indicated that carnitine administration in humans increases plasma carnitine concentrations but did not increase carnitine muscle content (27). In this context, one study showed that in chronic fatigue syndrome, serum carnitine levels appear to be a biochemical marker for both symptom severity and ability to function (28). Although it was common practice to add carnitine to...
the diet of newborns, current studies indicate that among infants supplemented with carnitine, there was no evidence of effect on weight gain, lipid utilization or ketogenesis(29).

**Pharmacological Correlations and Side Effects**

Supplemental L-carnitine is generally well tolerated. However, some people with seizure disorders taking acetyl-L-carnitine, experience an increase in seizure frequency and/or severity. Valproic acid (an antiepileptic drug), and the nucleoside analogues didanosine (ddI), zalcitabine (ddC) and stavudine (d4T) may produce secondary L-carnitine deficiencies. Vitamin C deficiency may also lead to secondary L-carnitine deficiency. Finally, there is no support for the claim that healthy vegetarians require L-carnitine supplementation. Plasma carnitine concentrations in strict vegetarians are only an insignificant 10 percent lower than omnivores(30).

**L-CYSTEINE, N-ACETYL CYSTEINE (NAC) AND GLUTATHIONE**

**Synthesis and Transport**

Under normal physiologic conditions, a sufficient amount of L-cysteine is formed from the dietary essential amino acid L-methionine. As long as the supply of methionine is adequate, cysteine is considered as nonessential. The initial reaction in the synthesis of cysteine involves the combination of methionine with the adenosine moiety of ATP to form S-adenosylme-thionine (SAMe), catalyzed by the enzyme methionine adenosyltransferase. Loss of the methyl group from SAMe results in the formation of S-adenosylhomocysteine, which is then cleaved to homocysteine and serine. The final step is a transsulfuration reaction that results in the formation of L-cysteine (Figure 4).

Although it is a nonessential amino acid, the normal diet contributes approximately 1 gram of L-cysteine daily. Following ingestion, some cysteine is oxidized to L-cystine, and both are absorbed from the small intestine by active-transport processes. L-cysteine enters the portal circulation, which distributes it to the liver.

N-acetylcysteine (NAC) is the N-acetyl derivative of L-cysteine and functions as the delivery form of this amino acid. It is more soluble than L-cysteine and may be better absorbed. In fact it is rapidly absorbed from the gastrointestinal tract and transported to the liver where it undergoes extensive first-pass metabolism. Metabolites derived from NAC include N,N-diacylcysteine and L-cysteine, which is also a precursor of glutathione.

**Mechanism and Therapeutic Usage**

Research on L-cysteine to date has been mostly in animals. Animals challenged with various toxins have, when presupplemented with L-cysteine, survived longer than non-supplemented controls. In one study, 90 percent of control rats given large doses of acetaldehyde died, but other rats first given a combination of vitamins C and B, along with L-cysteine, and then exposed to the same dose of acetaldehyde, all survived(31).

NAC is available as a nutritional supplement, but it is also prescribed in the U.S. and given orally or by slow intravenous infusion in the treatment of acetaminophen overdose. Overdose of acetaminophen leads to the formation of N-acetyl-benzoquinoneimine. This metabolite depletes hepatic glutathione stores, placing an enormous oxidative stress on the liver, which can lead to hepatic failure. Thus, the antidote to an acetaminophen overdose is L-cysteine in the delivery form of N-acetylcysteine, which helps to restore hepatic glutathione.

NAC appears to be beneficial in HIV-infected individuals as a result of its ability to restore normal glutathione levels in lymphocytes and thereby reduce free radical production. Two randomized placebo-controlled trials have shown that treatment of HIV-infected patients with N-acetyl cysteine caused in
both cases a significant increase in all immunological functions under test, including an almost complete restoration of natural killer cell activity (32).

NAC is also used in the treatment of respiratory disorders, such as acute and chronic bronchitis associated with the production of excessive mucus. Its mucolytic activity may be linked to its incorporation into glutathione and subsequently its ability to reduce disulfide bonds in mucoproteins found in mucus, liquefying this viscous substance. For such disorders it is delivered as an inhalant (33).

Pharmacological Correlations and Side Effects

No known interactions of NAC with nutritional supplements, food or herbs are known. Common adverse reactions with oral and intravenous NAC include nausea, vomiting, diarrhea and headache. It has also been reported that use of NAC with nitrates may cause headache (34). NAC may also lower serum levels of the anti-convulsant drug carbamazepine (35).

GLUTATHIONE

Synthesis and Transport

Glutathione is the tripeptide g-glutamylcysteinylglycine. Synthesis of glutathione occurs in the liver and is largely regulated by the availability of L-cysteine. It is synthesized in two ATP-dependent steps: first, the dipeptide γ-glutamylcysteine is synthesized from L-glutamate and cysteine via the enzyme glutathione synthetase - the rate-limiting step; and second, glycine is added to the C-terminal of the dipeptide via the enzyme glutathione synthetase. Monomeric glutathione is also known as reduced glutathione and its dimer is known as oxidized gluthalione or glutathione disulfide. In healthy tissue, more than 90 percent of the total glutathione pool is in the reduced form (36).

Following oral administration, it appears that glutathione is hydrolyzed in the intestine via the enzyme gamma-glutamyl transferase. A small amount may reach the liver but this is also rapidly metabolized by hepatic gamma-glutamyltransferase. There is also some evidence that glutathione may be absorbed into enterocytes following ingestion. Thus, most human studies have not detected circulating glutathione levels following oral administration.

Mechanism and Therapeutic Usage

Glutathione has several important functions. It is the principal intracellular non-protein thiol and plays a major role in the maintenance of the intracellular redox state. Its reducing ability is a function of the electron-donating capacity of the sulfhydryl group, which helps to maintain molecules in their reduced state. As a reductant, it is very important in maintaining the stability of erythrocyte membranes and the structure of hemoglobin. Its sulfhydryl group can also be used to reduce peroxides formed during oxygen transport and normal metabolism. The resulting oxidized form denoted as GSSG is reduced to GSH at the expense of NADPH formed during the pentose phosphate pathway. Glutathione is also involved in the transport of amino acids across cell membranes, a process that is especially important in renal epithelial cells. The enzyme γ-glutamyl transpeptidase, which is located in the cell membrane, shuttles GSH to the cell surface to interact with the amino acid. γ-Glutamyl amino acid is transported into the cell, and the complex is hydrolyzed to liberate the amino acid.

Glutathione is a cofactor for Glutathione S-transferases (GSTs). GSTs catalyze reactions that are involved in the detoxification of xenobiotic compounds and in the protection against such degenerative diseases as cancer. Essentially, glutathione conjugates with xenobiotic compounds are more soluble than the original substrates and thus more easily exported from the cell. Glutathione is also a cofactor for glutathione peroxidases. These enzymes, which also require selenium for full activity, detoxify hydrogen peroxide and fatty acid-derived hydroperoxides. Selenium and glutathione are essential to the formation of phospholipid hydroperoxide glutathione peroxidase, an enzyme present in spermatids that becomes a structural protein comprising over 50 percent of the mitochondrial capsule in the mid-piece of mature spermatozoa. Thus, deficiencies of either substance can lead to defective sperm motility.

Glutathione may have other effects some of which may be related to its antioxidant activity. It has been helpful to depress cell-derived oxidants in patients with cystic fibrosis and to augment glutathione deficiency in HIV patients. In fact Glutathione is an orphan drug for the treatment of AIDS-associated cachexia (37). In addition to being investigated as an antitumor agent, glutathione may also function to diminish the toxicities of some cancer drugs (38).

No adverse reactions to glutathione have been reported. In fact, one study indicates that it may ameliorate the toxicity of cisplatin in cancer patients (39).

L-METHIONINE AND S-ADENOSYL-L-METHIONINE (SAME)

Synthesis and Transport

SAME is used as a drug in Europe for the treatment of depression, liver disorders, osteoarthritis and fibromyalgia. It is used in the United States as a dietary supplement for the support of bone and joint health, elevating mood, and increasing emotional well-being. Supplemental SAME can be a synthetic replication of a compound that the body makes naturally from methionine, an essential amino acid found in protein-rich foods. Synthesis occurs primarily in the liver from ATP and methionine by the action of the enzyme L-methionine adenosyl transferase. The synthesis of SAME is directly linked to folate and vitamin B12 metabolism, and deficiencies in these vitamins are associated with reduced levels of SAME in the central nervous system and with neuropsychiatric disorders (40).

Limited trials in healthy volunteers show low limited bioavailability following oral intake of SAME indicating significant first-pass metabolism (41). SAME is mainly metabolized in the liver. It is metabolized to homocysteine, which is eventually converted to cysteine or methionine. The cofactor in the metabolism of homocysteine to cysteine is vitamin B6. Cofactors for the metabolism of homocysteine to methionine are folic acid, vitamin B12 and trimethylglycine (betaine). It is advisable to take SAME with supplemental B6, B12, folic acid and trimethylglycine. These nutrients help metabolize homocysteine which, at elevated levels, increases the risk of cardiovascular diseases, cancer, depression, arthritis, birth defects and other disorders (42).

Mechanism and Therapeutic Use

Orally administered SAME follows the same metabolic pathways as the natural compound found in cells. SAME crosses the blood-brain-barrier with slow accumulation in the cerebrovascular fluid. It can also get into joint synovial fluid. SAME was first given to patients for use in treating depression, but when some of those same patients began to report relief
from osteoarthritis joint pain, researchers began to study this second benefit of the product. Over 22,000 arthritis sufferers reported, after only four weeks of treatment, that SAMe gave comparable results to nonsteroidal anti-inflammatory drug (NSAID) pain relievers like ibuprofen and naproxen. The vital distinction is that instead of causing stomach upset like NSAIDs often do, SAMe may actually protect the stomach lining (43). Furthermore, animal studies show that SAMe could help restore damaged cartilage in addition to relieving pain (44).

The mechanism of action of supplemental SAMe is unclear. Extensive studies, however, have established the mechanism of action of endogenous SAMe. S-Adenosylmethionine is a potent methylating agent by virtue of its destabilizing sulfonium ion (Figure 4). The methyl group is subject to attack by nucleophiles and is about 1000 times more reactive than the methyl group of another common methylating agent N5-methyltetrahydrofolate (5-MTHF).

SAMe is the methyl donor for the synthesis of creatine, melatonin, glutathione, and polyamines spermine and spermidine. Methylation is also required for the production of DNA, RNA and proteins, and various components of the cell membrane like phosphatidylserine (PS) and phosphatidylcholine (PC). Its methylating properties promote the fluidity of liver lipid membranes. Methylation also plays an important role in the synthesis of neurotransmitters like serotonin, dopamine, norepinephrine, and epinephrine. A decrease in these neurotransmitters is linked to depression.

It has been reported that the efficacy of SAMe in treating depression is superior when compared with placebo and comparable to that of standard tricyclic antidepressants (45). SAMe, unlike traditional antidepressants, has few side effects and a rapid onset of action (usually within one or two weeks compared with three to four weeks or longer for standard antidepressants).

SAMe has been shown to improve functions measured by standard liver and liver-function tests. It increases hepatic glutathione levels in patients with both alcohol and non-alcoholic cirrhosis, restores normal hepatic function in various forms of cholestasis and prevents or reverse hepatotoxicity induced by drugs, alcohol and various chemicals (46).

No adverse reactions with SAMe and other drugs, dietary supplements or foods have been reported. Toxicological studies in animals indicate that SAMe is nontoxic at relatively high doses. However, more data is needed to accurately define its place in therapy. Recommendations for its use must be tempered by the fact that there is lack of consensus with regard to dosing, monitoring, and standardization of SAMe products.

CONCLUSION

Although there exists significant potential for therapeutic application of many nutritional supplements, at this point in time an incomplete knowledge base exists for most of these agents. Most of these compounds have not been tested for their effectiveness or safety over prolonged periods of time and many statements concerning supplements do not define the specific parameters of the studies on which the statements are based. Thus, many consumers accept claims about the actions of supplements without assessing the validity of these claims. Pharmacists and other health-care providers must educate their patients that additional clinical trials integrating physiologic, biochemical, and pharmacologic assessments are needed to definitively clarify any effects of most of these supplements.

References


