impact on nitric oxide metabolism. Br J Clin Pharmacol. 2008;65(1):51-59.

Suzuki A, Yamada R, Yamamoto K. Citrullination by peptidylarginine deiminase in rheumatoid arthritis. *Ann N Y Acad Sci.* 2007;1108:323-339.

Takahara K, Akashi K, Yokota A. Purification and characterization of glutamate N-acetyltransferase involved in citrulline accumulation in wild watermelon. *FEBS J.* 2005;272(20):5353-5364.

Van de Poll MC, Ligthart-Melis GC, Boelens PG, et al. Intestinal and hepatic metabolism of glutamine and citrulline in humans. *J Physiol.* 2007;581(Pt 2):819-827.

Van Gaalen F, Ioan-Facsinay A, Huizinga TW, et al. The devil in the details: the emerging role of anticitrulline autoimmunity in rheumatoid arthritis. *J Immunol*. 2005;175(9):5575-5580.

Wu G, Collins JK, Perkins-Veazie P, et al. Dietary supplementation with watermelon pomace juice enhances arginine availability and ameliorates the metabolic syndrome in Zucker diabetic fatty rats. *J Nutr.* 2007;137(12):2680-2685.

L-Cysteine

DESCRIPTION

L-cysteine is a protein amino acid naturally present in the proteins of life forms. L-cysteine is a sulfur amino acid and contains a sulfhydryl group. Although most cysteine is found in proteins, small amounts of free cysteine are found in body fluids and in plants. The normal diet contributes approximately 1 gram of L-cysteine daily.

L-cysteine is considered a nonessential amino acid, meaning that, under normal physiologic conditions, sufficient amounts of this amino acid are formed from the dietary essential amino acid L-methionine and the nonessential amino acid L-serine via a transsulfuration reaction. L-cysteine is a conditionally essential amino acid under certain circumstances, for example, for preterm infants.

L-cysteine serves as a precursor for synthesis of proteins, glutathione, taurine, coenzyme A and inorganic sulfate. Glutathionine itself has a number of biochemical functions, including maintenance of normal cellular redox state. Certain conditions, e.g. an acetaminophen overdose, can deplete hepatic glutathione, and this can be life-threatening. The antidote to an acetaminophen overdose is L-cysteine, in the delivery form of N-acetylcysteine. The L-cysteine derived from N-acetylcysteine helps to restore hepatic glutathione.

L-cysteine is also known as L-2-amino-3-mercaptopropanoic acid, 2-amino-3-mercaptopropanoic acid, beta-mercaptoalanine, 2-amino-3 mercaptopropionic acid and alpha-amino-beta-thiolpropionic acid. L-cysteine is represented by the following chemical structure:

L-cysteine

Its IUPAC abbreviation is Cys, and its one-letter abbreviation, used when spelling out protein structures, is C. L-cysteine is a white, solid substance that is soluble in water. It is hygroscopic and slowly decomposes and oxidizes. In solution, it undergoes oxidation to L-cystine, which is a dimer of L-cysteine. N-acetylcysteine is a preferred delivery form of L-cysteine because of greater stability and possible higher absorbability. (See N-Acetylcysteine).

ACTIONS AND PHARMACOLOGY

ACTIONS

The most significant action of supplemental L-cysteine is as a redox modulator.

MECHANISM OF ACTION

Certain conditions, e.g. an acetaminophen overdose, deplete hepatic glutathione and subject the tissues to oxidative stress resulting in loss of cellular integrity. L-cysteine serves as a major precursor for synthesis of glutathione.

PHARMACOKINETICS

Following ingestion, some L-cysteine is oxidized to L-cystine, and both L-cysteine and L-cystine are absorbed from the small intestine by active-transport processes. L-cysteine absorption is largely sodium-dependent, while L-cystine is absorbed by a sodium-independent transport system. Following absorption, L-cysteine enters the portal circulation, which distributes it to the liver. There, much of it is metabolized to protein, glutathione, taurine and sulfate. L-cysteine, which does not get metabolized by the liver, enters the systemic circulation which distributes it to various tissues of the body.

INDICATIONS AND USAGE

It has been claimed that L-cysteine has anti-inflammatory properties, that it can protect against various toxins, and that it might be helpful in osteoarthritis and rheumatoid arthritis. More research will have to be done before L-cysteine can be indicated for any of these conditions. Research to date has mostly been in animal models.

RESEARCH SUMMARY

There is some evidence from animal studies that cysteine can help ensure adequate glutathione synthesis during and after inflammatory challenge, thus helping to "ameliorate," in the words of one research group, "adverse effects of oxidative damage induced by disease or drugs."

Cysteine-supplemented mice and guinea pigs have enjoyed significantly extended life spans, and other animals, challenged with various toxins, have, when pre-supplemented with cysteine, survived considerably longer than non-supplemented controls. In one of these studies, 90% of control rats given large doses of acetaldehyde died. But other rats first given a combination of vitamins C and B, along with cysteine, and then exposed to the same dose of acetaldehyde, all survived. Cysteine's protective mechanisms could relate to its own antioxidant properties, its promotion of glutathione (a major antioxidant) or even, it has been hypothesized, to some ability to participate in DNA repair.

There is inconclusive evidence that cysteine could play a positive role in the treatment of osteoarthritis and rheumatoid arthritis.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS CONTRAINDICATIONS

L-cysteine supplementation is contraindicated in those hypersensitive to any component of the preparation.

PRECAUTIONS

Because of lack of long-term safety studies, L-cysteine supplementation should be avoided by children, pregnant women and nursing mothers.

Although the incidence of cystine renal stones is low, they do occur. Those who form renal stones, particularly cystine stones, should avoid L-cysteine supplements.

L-cysteine, like other sulfhydryl-containing substances, could produce a false-positive result in the nitroprusside test for ketone bodies used in diabetes.

ADVERSE REACTIONS

With typical doses of 1 to 1.5 grams daily, the most commonly reported side effects have been gastrointestinal, such as nausea. There are rare reports of cystine renal stone formation.

INTERACTIONS

NUTRITIONAL SUPPLEMENTS

Zinc: L-cysteine complexes with zinc and may increase the absorption of zinc.

Vitamin C: Ascorbic acid may inhibit the oxidation of L-cysteine to L-cystine.

OVERDOSAGE

There are no reports of overdosage in those taking L-cysteine supplements. However, large doses of L-cysteine are neuroexcitotoxic in several species. Single injections of L-cysteine (0.6-1.5 g/kg) into 4-day-old pups resulted in

massive damage to cortical neurons, permanent retinal dystrophy, atrophy of the brain and hyperactivity.

DOSAGE AND ADMINISTRATION

The usual supplemental dosage of L-cysteine is 500 milligrams to 1.5 grams daily. Those who supplement with L-cysteine should drink at least six to eight glasses of water daily in order to prevent cystine renal stones. Some studies indicate that an intake of 3 to 5 grams daily of vitamin C may prevent cystine stones. However, high-dose vitamin C itself may contribute to renal stones in some (see Vitamin C).

Another delivery form of L-cysteine is N-acetylcysteine (see N-Acetylcysteine).

LITERATURE

Anderson R, Lukey PT, Theron AJ, Dippenaar U. Ascorbate and cysteine-mediated selective neutralization of extracellular oxidants during N-formyl peptide activation of human phagocytes. *Agents Actions*. 1987;20:77-86.

Anderson R, Theron AJ, Ras GJ. Regulation by the antioxidants ascorbate, cysteine, and dapsone of the increased extracellular and intracellular generation of reactive oxidants by activated phagocytes from cigarette smokers. *Am Rev Respir Dis.* 1987; 135:1027-1032

Asper R, Schmucki O. Cystinuric therapy by ascorbic acid. *Urol Int.* 1982;37:91-109.

Campbell NR, Reade PC, Radden BG. Effect of cysteine on the survival of mice with transplanted malignant lymphoma. *Nature*. 1974;251:158-159.

Csako G. False-positive results for ketone with the drug mensa and other free-sulfhydryl compounds. *Clin Chem.* 1987;33(2 pt 1):289-292.

Fettman MJ, Valerius KD, Ogilvie GK. Effects of dietary cysteine on blood sulfur amino acid, glutathione, and malondialdehyde concentrations in cats. *Am J Vet Res.* 1999;60:328-333.

Oeriu S, Vachitu E. The effect of the administration of compounds which contain sulfhydryl groups on the survival rate of mice, rats and guinea pigs. *Journ Geront.* 1965;20;47.

Stipanuk MH. Homocysteine, cysteine and taurine. In: Shils ME, Olson JA, Shike M, Ross AC, eds. *Modern Nutrition in Health and Disease*. Ninth edition. Baltimore, MD: Williams & Wilkins; 1999:543-558.

L-Glutamine

DESCRIPTION

L-glutamine is a protein amino acid found in proteins of all life forms. It is classified as a semi-essential or conditionally essential amino acid. This means that under normal circumstances the body can synthesize sufficient L-glutamine to meet physiological demands. However, there are conditions