

## L-Cysteine Overview

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 acids 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 very important precursor for synthesis of proteins, glutathione, taurine, coenzyme A, and inorganic sulfate. Glutathione 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. See N-acetylcysteine Overview.

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## Research Overview

Research on L-cysteine shows the following effects:

1. Prevents liver fibrosis
2. Has cytoprotective properties against toxicity
3. May modulate KYNA development in the brain
4. Prevents cataract formation
5. May help prevent ischemia-reperfusion injury in the lung
6. Cysteine deficiency leads to cellular dysfunction in HIV
7. Lowers blood, brain and liver alcohol levels caused by alcohol intoxication
8. Combats severe hypoglycemic attacks
9. May be a factor in cardiovascular control
10. May play a role in heavy metal detoxification

L-Cysteine Abstracts (31)

1. *Neurosci Lett.* 2003 Jul 31;346(1-2):97-100. L-cysteine sulphinate, endogenous sulphur-containing amino acid, inhibits rat brain kynurenic acid production via selective interference with kynurenine aminotransferase II. Kocki T, Luchowski P, Luchowska E, Wielosz M, Turski WA, Urbanska EM. Department of Pharmacology and Toxicology, Medical University, Jaczewskiego 8, 20-090 Lublin, Poland.

In the present study the effect of endogenous sulphur-containing amino acids, L-cysteine sulphinate, L-cysteate, L-homocysteine sulphinate and L-homocysteate, on the production of glutamate receptor antagonist, kynurenic acid (KYNA), was evaluated. The experiments comprised the measurements of (a). KYNA synthesis in rat cortical slices and (b). the activity of KYNA biosynthetic enzymes, kynurenine aminotransferases (KATs). All studied compounds reduced KYNA production and inhibited the activity of KAT I and/or KAT II, thus acting most probably intracellularly. L-cysteine sulphinate in very low, micromolar concentrations selectively affected the activity of KAT II, the enzyme catalyzing approximately 75% of KYNA synthesis in the brain. L-cysteine sulphinate potency was higher than other studied sulphur-containing amino acids, than L-aspartate, L-glutamate, or any other known KAT II inhibitor. Thus, L-cysteine sulphinate might act as a modulator of KYNA formation in the brain.

2. *Biochem Biophys Res Commun.* 2003 May 23;305(1):94-100. L-cysteine administration prevents liver fibrosis by suppressing hepatic stellate cell proliferation and activation. Horie T, Sakaida I, Yokoya F, Nakajo M, Sonaka I, Okita K. Pharmaceuticals Research Laboratories, Ajinomoto Co, Inc, 1-1, Suzuki-cho, Kawasaki-ku, Kawasaki 210-8681, Japan.

Recent studies showed that the function of some amino acids is not only nutritional but also pharmacological. However, the effects of amino acids on liver fibrosis and hepatic stellate cell (HSC) remain unclear. In this research, as a result of screening of amino acids using liver fibrosis induced by DMN administration, L-cysteine was selected as a suppressor of liver fibrosis. Furthermore, the number of activated HSCs, which increased in the fibrotic liver after DMN administration, was decreased in L-cysteine-fed rats. Treatment of freshly isolated HSCs with L-cysteine resulted in inhibition of the increase in smooth muscle alpha-actin (alphaSMA) expression by HSCs and BrdU incorporation into the activated HSCs. These findings suggest that L-cysteine is effective against liver fibrosis. The mechanism of inhibition of fibrosis in the liver is surmised to be direct inhibition of activated HSC proliferation and HSC transformation by L-cysteine.

3. *Russ J Immunol.* 2002 Apr;7(1):48-56. Up-regulation of interferon-gamma production by reduced glutathione, anthocyanine and L-cysteine treatment in children with allergic asthma and recurrent respiratory diseases. Chernyshov VP, Omelchenko LI, Treusch G, Vodyanik MA, Pochinok TV, Gumenyuk ME, Zelinsky GM.

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Negative correlation between serum IgE levels and production of IFN-gamma by lymphocytes and positive correlation between serum IgE levels and production of IL-4 by lymphocytes was detected in 12 children with allergic asthma and recurrent respiratory diseases. Deficiency of reduced glutathione in whole blood and some disorders in phagocytic and oxidative burst activity of monocytes were observed in these children. Use of reduced glutathione, L-cysteine and anthocyanine (Recancostat, Clear Vision, Switzerland) resulted in elevation of IFN-gamma production, lymphocyte response to mitogens, NK cell activity, increase in percentage of naive CD4(+) T lymphocytes (refreshment effect) and improvement of clinical status. Positive clinical results were lasted during 6 months.

4. *Proc Nutr Soc.* 2000 Nov;59(4):595-600. Glutathione and immune function. Droge W, Breitkreutz R. Department of Immunochemistry, Deutsches Krebsforschungszentrum, Im Neuenheimer Feld 280, D-69120 Heidelberg, Germany. W.Droege@dkfz-heidelberg.de

The immune system works best if the lymphoid cells have a delicately balanced intermediate level of glutathione. Even moderate changes in the intracellular glutathione level have profound effects on lymphocyte functions. Certain functions, such as the DNA synthetic response, are exquisitely sensitive to reactive oxygen intermediates and, therefore, are favoured by high levels of the antioxidant glutathione. Certain signal pathways, in contrast, are enhanced by oxidative conditions and favoured by low intracellular glutathione levels. The available evidence suggests that the lymphocytes from healthy human subjects have, on average, an optimal glutathione level. There is no indication that immunological functions such as resistance to infection or the response to vaccination may be enhanced in healthy human subjects by administration of glutathione or its precursor amino acid cysteine. However, immunological functions in diseases that are associated with a cysteine and glutathione deficiency may be significantly enhanced and potentially restored by cysteine supplementation. This factor has been studied most extensively in the case of human immunodeficiency virus (HIV)-infected patients who were found to experience, on average, a massive loss of S equivalent to a net loss of approximately 4 g cysteine/d. Two randomized placebo-controlled trials have shown that treatment of HIV-infected patients with N-acetylcysteine caused in both cases a significant increase in all immunological functions under test, including an almost complete restoration of natural killer cell activity. It remains to be tested whether cysteine supplementation may be useful also in other diseases and conditions that are associated with a low mean plasma cystine level and impaired immunological functions.

5. Toxicol Appl Pharmacol. 2000 Oct 1;168(1):72-8. gamma-Glutamyl transpeptidase and L-cysteine regulate methylmercury uptake by HepG2 cells, a human hepatoma cell line. Wang W, Clarkson TW, Ballatori N. Department of Environmental Medicine, University of Rochester School of Medicine, Rochester, New York 14642, USA.

Mechanisms of methylmercury (MeHg) and inorganic mercury (Hg) uptake were examined in HepG2 cells, a human hepatoma-derived cell line. MeHg uptake was faster when it was present as the L-cysteine complex, as compared to the glutathione (GSH), CysGly, gamma-GluCys, d-cysteine, N-acetylcysteine, l-penicillamine, or albumin complexes. Uptake of MeHg-L-cysteine was independent of Na(+), stereoselective, and was inhibited by the amino acid transport system I substrates l-leucine, l-valine, and l-phenylalanine (5 mM). Moreover, [(3)H]l-leucine uptake was inhibited by MeHg-L-cysteine, suggesting that MeHg-L-cysteine is transported into HepG2 cells by an l-type amino acid carrier. Uptake of MeHg as the GSH complex (MeHg-SG) was dependent on the extracellular GSH concentration, and was diminished when cellular gamma-glutamyl transpeptidase activity was inhibited. Inorganic mercury uptake was slower than that of MeHg, but was also sensitive to the type of thiol ligand present. These findings demonstrate that mercury uptake by HepG2 cells is dependent on the chemical structure of the mercury compound, the thiol ligand, and the activity of gamma-glutamyl transpeptidase. gamma-Glutamyl transpeptidase appears to play a key role in the disposition of MeHg-SG by facilitating the formation of MeHg-L-cysteine, which is readily transported into the cells on an amino acid-type carrier. Copyright 2000 Academic Press.

6. Amino Acids. 2000;18(4):319-27. Polyamines and thiols in the cytoprotective effect of L-cysteine and L-methionine on carbon tetrachloride-induced hepatotoxicity. Chen W, Kennedy DO, Kojima A, Matsui-Yuasa I. Department of Food and Nutrition, Faculty of Human Life Science, Osaka City University, Osaka, Japan.

The relationship between cellular glutathione (GSH), protein-SH levels, and lactate dehydrogenase (LDH), with respect to the effect of polyamines on the cytoprotective ability of L-cysteine and L-methionine, the most important components in the sulfur amino acid metabolic pathway, in carbon tetrachloride (CCl4)-induced toxicity in isolated rat hepatocytes was studied. CCl4 induced a LDH release and decreased cellular thiols and polyamines levels but treatment with L-cysteine and L-methionine reversed these decreases. Treating with methylglyoxal bis-(guanylhydrazone), MGBG, an irreversible inhibitor of S-adenosylmethionine decarboxylase, which is a key enzyme in spermidine and spermine biosynthesis, and therefore used to deplete cellular polyamines, prevented the protective effect of L-cysteine and L-methionine, but the addition of exogenous polyamines inhibited the influence of MGBG. These results suggest that the cytoprotective effect of L-cysteine and L-methionine in CCl4-induced toxicity were via maintenance of cellular polyamines, GSH and protein-SH concentrations and prevention of LDH leakage.

7. Z Naturforsch [C]. 2000 Mar-Apr;55(3-4):271-7. Protective effect of L-cysteine and glutathione on rat brain Na+,K+-ATPase inhibition induced by free radicals. Tsakiris S, Angelogianni P, Schulpis KH, Behrakis P. Department of Experimental Physiology, University of Athens, Medical School, Greece. stsakir@cc.uoa.gr

The aim of this study was to investigate whether the preincubation of brain homogenates with L-phenylalanine (Phe), L-cysteine (Cys) or reduced glutathione (GSH) could reverse the free radical effects on Na+,K+-ATPase activity. Two well established systems were used for the production of free radicals: 1) FeSO4 (84 microM) plus ascorbic acid (400 microM) and 2) FeSO4, ascorbic acid and H2O2 (1 mM) for 10 min at 37 degrees C in homogenates of adult rat whole brain. Changes in brain Na+,K+-ATPase activity and total antioxidant status (TAS) were studied in the presence of each system separately, with or without Phe, Cys or GSH. TAS value reflects the amount of free radicals and the capacity of the antioxidant enzymes to limit the free radicals in the homogenate. Na+,K+-ATPase was inhibited by 35-50% and TAS value was decreased by 50-60% by both systems of free radical production. The enzymatic inhibition was completely reversed and TAS value increased by 150-180% when brain homogenates were preincubated with 0.83 mM Cys or GSH. However, this Na+,K+-ATPase inhibition was not affected by 1.80 mM Phe, which produced a 45-50% increase in TAS value. It is suggested that the antioxidant action of Cys and GSH may be due to the binding of free radicals to sulfhydryl groups of the molecule, so that free radicals cannot induce Na+,K+-ATPase inhibition. Moreover, Cys and GSH could regulate towards normal values the neural excitability and metabolic energy production, which may be disturbed by free radical action on Na+,K+-ATPase.

8. Comp Biochem Physiol B Biochem Mol Biol. 1997 Feb;116(2):223-6. L-cysteine metabolism in guinea pig and rat tissues. Wrobel M, Ubuka T, Yao WB, Abe T. Department of Biochemistry, Okayama University Medical School, Japan.

Rhodanese, gamma-cystathionase and 3-mercaptopyruvate sulfurtransferase activities were examined in guinea pig and rat liver, kidney and brain. In the liver of both species rhodanese showed the same high range of activity but in guinea pig kidney and brain a slightly lower level was determined than that in corresponding rat tissues. The 3-mercaptopyruvate sulfurtransferase and gamma-cystathionase activities in all the investigated tissues of guinea pig were significantly lower than those in rat. The sulfane sulfur pool, a source of sulfur transferred by rhodanese, can be augmented in vitro in guinea pig liver, but not in rat liver when 3-mercaptolactate-cysteine disulfide is used as a substrate of gamma-cystathionase.

9. Elevated hepatic gamma-glutamylcysteine synthetase activity and abnormal sulfate levels in liver and muscle tissue may explain abnormal cysteine and glutathione levels in SIV-infected rhesus macaques. Gross A, Hack V, Stahl-Hennig C, Droge W. AIDS Res Hum Retroviruses. 1996 Nov 20;12(17):1639-41.

To establish whether the low cysteine and glutathione levels in HIV-infected patients and SIV-infected rhesus macaques may be consequences of an abnormal cysteine catabolism, we analyzed sulfate and glutathione levels in macaques. Muscle tissue (m. vastus lateralis and m. gastrocnemius) of SIV- infected macaques (n = 25) had higher sulfate and lower glutathione and glutamate levels than that of uninfected controls (n = 9). Hepatic tissue, in contrast, showed decreased sulfate and glutathione disulfide (GSSG) levels, and increased gamma-glutamylcysteine synthetase (gamma-GCS) activity. These findings suggest drainage of the cysteine pool by increased cysteine catabolism in skeletal muscle tissue, and by increased hepatic glutathione biosynthesis. Cachectic macaques also showed increased urea levels and decreased glutamine/urea ratios in the liver, which are obviously related to the abnormal urea excretion and negative nitrogen balance commonly observed in cachexia. As urea production and net glutamine synthesis in the liver are strongly influenced by proton-generating processes, the abnormal hepatic urea production may be the direct consequence of the cysteine deficiency and the decreased catabolic conversion of cysteine into sulfate and protons in the liver.

10. *Biochem Pharmacol.* 1996 May 3;51(9):1111-6. Maintenance of hepatic glutathione homeostasis and prevention of acetaminophen-induced cataract in mice by L-cysteine prodrugs. Rathbun WB, Killen CE, Holleschau AM, Nagasawa HT. Department of Ophthalmology, University of Minnesota, Minneapolis, USA.

Administration of acetaminophen (ACP, 3.0 mmol/kg, i.p.) to beta-naphthoflavone-induced C57 BL/6 mice led to the formation of bilateral cataracts within 8 hr with a 71% incidence. The hepatic glutathione (GSH) levels were reduced 99% and lenticular GSH levels reduced 42% in cataractous mice. Cataract formation was completely prevented by the co-administration of the L-cysteine prodrugs 2(R, S)-methylthiazolidine-4(R)-carboxylic acid (MTCA) and 2(R, S)-n-propylthiazolidine-4(R)-carboxylic acid (PTCA) in two divided i.p. doses totaling 4.5 mmol/kg. 2-Oxo-L-thiazolidine-4-carboxylic acid (OTCA) was nearly equipotent, yielding only one cataract in 16 mice, but D-ribose-L-cysteine (RibCys, 5/16) and N-acetyl-L-cysteine (NAC, 9/14) were much less effective. Hepatic and lenticular GSH were maintained at near normal levels by MTCA, PTCA and OTCA. These results suggest that maintenance of adequate cellular GSH levels in the presence of ACP protects against cataract induction.

11. *Jpn J Physiol.* 1995;45(5):771-83. The central effect of L-cysteine on cardiovascular system of the conscious rat. Takemoto Y. Department of Physiology, Hiroshima University School of Medicine, Minami-ku, Japan.

The hemodynamic effects of intracisternal injection of the nonessential amino acid L-cysteine were studied in conscious chronically instrumented rats. Injections of L-cysteine (0.05-0.2 M in artificial cerebrospinal fluid, 10 microliters) into the cisterna magna dose-relatedly elicited an increase in arterial pressure but a decrease in superior mesenteric blood flow as measured by an electromagnetic flow probe. Injections of the excitatory amino acid transmitter L-glutamate at comparable doses caused much the same pressor and vasoconstrictor effects as did L-cysteine. Prior I.V. injection of vasopressin V1-receptor antagonist, (d(CH<sub>2</sub>)<sub>5</sub>(1), O-Me-Tyr<sub>2</sub>, Arg<sub>8</sub>)-vasopressin (10 micrograms/kg), markedly attenuated the effects of L-glutamate but not of L-cysteine. Ganglionic blockade with chlorisondamine (5.0 mg/kg) failed to attenuate the effects of either amino acid, whereas an additional intravenous injection of vasopressin antagonist, completely abolished the effects. These results indicate that the circulatory effects of L-cysteine are probably due to autonomic nervous activation combined with vasopressin release, unlike those of L-glutamate which acts mainly through vasopressin release. L-cysteine may contribute to central cardiovascular control, since it induces the marked circulatory effects comparable to or greater than those of L-glutamate.

12. *Eur Surg Res.* 1995;27(6):363-70. Effect of the combination of human thioredoxin and L-cysteine on ischemia-reperfusion injury in isolated rat lungs. Wada H, Hirata T, Decampos KN, Hitomi S, Slutsky AS. Department of Thoracic Surgery, Kyoto University, Japan.

We studied the role of human thioredoxin and L-cysteine in ischemia-reperfusion lung injury. Thirty adult Wistar rats were allocated to five groups, according to the drug added to the pulmonary artery flush solution before ischemia (groups 1 and 2: none; group 3: human thioredoxin; group 4: L-cysteine, and group 5: human thioredoxin and L-cysteine) and according to the ex vivo ischemic interval at 37 degrees C (group 1: no ischemia; groups 2-5: 90 min). After ischemia, the lungs were reperfused for 60 min with Krebs-Henseleit solution containing 4% bovine serum albumin. In nonischemic lungs, the pulmonary arterial pressure, airway pressure, wet to dry lung weight ratio and the albumin concentration in bronchoalveolar fluid were within normal ranges. In contrast, all parameters of ischemic untreated lungs were generally poor. Compared to the ischemic untreated lungs, treatment with the combination of human thioredoxin and L-cysteine significantly reduced the wet to dry lung weight ratio (group 2: 9.18 +/- 0.25, group 5: 7.88 +/- 0.27), and the albumin concentration in the bronchoalveolar lavage fluid (group 2: 78.3 +/- 17.1 micrograms/ml, group 5: 24.0 +/- 3.8 micrograms/ml). No significant improvement was found in pulmonary arterial pressure and airway pressure. These results suggested that treatment with human thioredoxin (adult T cell leukemia-derived factor) and L-cysteine attenuates ischemia-reperfusion injury in isolated rat lungs.

13. *FASEB J.* 1994 Nov;8(14):1131-8. Functions of glutathione and glutathione disulfide in immunology and immunopathology. Droge W, Schulze-Osthoff K, Mihm S, Galter D, Schenk H, Eck HP, Roth S, Gmunder H. Department of Immunochemistry, Deutsches Krebsforschungszentrum, Heidelberg, Germany.

Even a moderate increase in the cellular cysteine supply elevates the intracellular glutathione (GSH) and glutathione disulfide (GSSG) levels and potentiates immunological functions of lymphocytes in vitro. At low GSSG levels, T cells cannot optimally activate the immunologically important transcription factor NF kappa B, whereas high GSSG levels inhibit the DNA binding activity of NF kappa B. The effects of GSSG are antagonized by reduced thioredoxin (TRX). As the protein tyrosine kinase activities p56lck and p59fyn are activated in intact cells by hydrogen peroxide, they are likely targets for GSSG action. These redox-regulated enzymes trigger signal cascades for NF kappa B activation and transduce signals from the T cell antigen receptor, from CD4 and CD8 molecules, and from the IL-2 receptor beta-chain. The effector phase of cytotoxic T cell responses and IL-2-dependent functions are inhibited even by a partial depletion of the intracellular GSH pool. As signal transduction is facilitated by prooxidant conditions, we propose that the well-known immunological consequences of GSH depletion ultimately may be results of the accompanying GSSG deficiency. As HIV-infected patients and SIV-infected rhesus macaques have, on the average, significantly decreased plasma cyst(e)ine and intracellular GSH levels, we also hypothesize that AIDS may be the consequence of a GSSG deficiency as well.

14. Pharmacology. 1993;46(2):61-5. Cysteine and glutathione deficiency in AIDS patients: a rationale for the treatment with N-acetyL-cysteine. Droge W. Division of Immunochemistry, Deutsches Krebsforschungszentrum, Heidelberg, BRD.

A series of clinical studies and laboratory investigations suggests that the acquired immunodeficiency syndrome (AIDS) may be the consequence of a virus-induced cysteine deficiency. HIV-infected persons at all stages of the disease were found to have decreased plasma cystine and cysteine concentrations and decreased intracellular glutathione levels. In rhesus macaques, cysteine levels decrease already within 1-2 weeks after infection with the closely related virus SIVmac. HIV-infected persons and SIV-infected rhesus macaques have also, on the average, substantially increased plasma glutamate levels. Increased glutamate levels aggravate the cysteine deficiency by inhibiting the membrane transport of cystine. Even moderately elevated extracellular glutamate levels as they occur in HIV-infected persons cause a substantial decrease of intracellular cysteine levels. Clinical studies revealed that individual cystine and glutamate levels are correlated with the individual lymphocyte reactivity and T4+ cell counts but not T8+ cell counts. This phenomenon was demonstrated not only in HIV-infected persons but also in healthy human individuals. The cellular cysteine supply affects amongst others the intracellular glutathione level and IL-2-dependent proliferation of T cells and (inversely) also the activation of the transcription factor NF-kappa B. The cysteine deficiency of HIV-infected persons is, therefore, possibly responsible not only for the cellular dysfunction but also for the overexpression of tumor necrosis factor-alpha (TNF-alpha), interleukin-2 receptor alpha-chain, and and beta 2-microglobulin. All the corresponding genes are associated with kappa-like enhancer sequences.(ABSTRACT TRUNCATED AT 250 WORDS)

15. Cysteine and glutathione deficiency in HIV-infected patients. The basis for treatment with N-acetyL-cysteine Droge W. AIDS-FORSCHUNG (Germany), 1992, 7/4 (197-199)

Clinical studies and complementary laboratory investigations suggest that the deterioration of the immune system in HIV-infected patients may be the consequence of a virus-induced cysteine deficiency. HIV-infected persons at all stages of the disease have, on the average, decreased plasma cystine and cysteine and decreased intracellular glutathione levels. Cysteine levels also decrease in rhesus macaques within 1 to 2 weeks after infection with SIV(mac). HIV-infected persons and SIV-infected macaques also have, on the average, markedly increased plasma glutamate levels, which aggravate the cysteine deficiency by inhibiting the membrane transport of cystine. Even moderately increased extracellular glutamate levels as they are found in HIV-infected persons cause a profound decrease of intracellular cyst(e)ine levels. A correlation between individual T4+ cell counts (but not T8+ cell counts) and individual cystine and glutamate levels has been found not only in HIV-infected persons but also in healthy individuals, indicating that the linkage between cysteine supply and immune system is demonstrable even in the absence of the virus. There is suggestive evidence that the HIV-induced cysteine deficiency is not only responsible for the 'cellular dysfunction' but also for the abnormal activation which is exemplified by the lymphadenopathy syndrome and abnormal antibody production. HIV-infected persons were found to have abnormally high TNFalpha, IL-2 receptor alpha-chain and beta2-microglobulin levels. All the corresponding genes are associated with kappaB-like enhancer sequences. And the activation of the transcription factor NFkappaB is negatively regulated by cysteine or cysteine derivatives. We have, therefore, suggested that N-acetyL-cysteine (NAC) may be considered for the replenishment of cysteine and glutathione levels in HIV-infected persons, since NAC is a well-established and safe drug with well-documented pharmacokinetics.

16. Biochem Pharmacol. 1992 Jul 7;44(1):129-35. Acetaminophen-induced depletion of glutathione and cysteine in the aging mouse kidney. Richie JP Jr, Lang CA, Chen TS. American Health Foundation, Valhalla, NY 10595.

Glutathione (GSH) plays an essential role in the detoxification of acetaminophen (APAP) and the prevention of APAP-induced toxicity in the kidney. Our previous results demonstrated that a GSH deficiency is a general property of aging tissues, including the kidney, suggesting a hypothesis that senescent organisms are at greater risk to APAP-induced renal damage. To test this, C57BL/6NIA mice of different ages through the life span were injected with various doses of APAP, and the extent of GSH and cysteine (Cys) depletion and recovery were determined. At time intervals up to 24 hr, kidney cortex samples were obtained, processed and analyzed for glutathione status, namely GSH, glutathione disulfide (GSSG), Cys and cystine, using an HPLC method with dual electrochemical detection. In the uninjected controls, GSH and Cys concentrations decreased about 30% in the aging mouse, but the GSSG and cystine levels were unchanged during the life span. APAP administration depleted the kidney GSH and Cys contents in a dose

17. *Biochem Pharmacol.* 1992 Feb 4;43(3):483-8. Cysteine isopropylester protects against paracetamol-induced toxicity. Butterworth M, Upshall DG, Smith LL, Cohen GM. Toxicology Unit, School of Pharmacy, University of London, U.K.

Cysteine isopropylester (CIPE), a novel ester of cysteine, has been synthesized in order to evaluate its potential as a chemoprotectant. The increased lipophilicity of the ester relative to cysteine should facilitate its entry into cells where, following hydrolysis, it should act as an intracellular source of cysteine or be utilized for the synthesis of glutathione so protecting the cell against various types of chemical insult. In this study, we evaluate the ability of CIPE to protect against paracetamol-induced hepatotoxicity in mice. When administered to mice, CIPE produced a rapid but transient elevation of levels of non-protein sulphhydryls (NPSH) in liver, lung, kidney and spleen. The greatest increase in NPSH was seen in the lung, but after 60 min all NPSH values had returned to control levels, demonstrating the capacity of the mouse to rapidly metabolize both CIPE and cysteine. In mice pretreated with benzo(a)pyrene, CIPE protected against paracetamol-induced toxicity as measured by the prevention of

18. *Blood.* 1992 Sep 1;80(5):1247-53. Antithrombotic properties of L-cysteine, N-(mercaptoacetyl)-D-Tyr-Arg-Gly-Asp-sulfoxide (G4120) in a hamster platelet-rich femoral vein thrombosis model. Imura Y, Stassen JM, Bunting S, Stockmans F, Collen D. Center for Thrombosis and Vascular Research, University of Leuven, Belgium.

Platelet aggregation plays an important role in the pathogenesis in arterial thrombotic disorders. The binding of fibrinogen via the Arg-Gly-Asp (RGD) recognition sequence to the platelet glycoprotein IIb/IIIa (GPIIb/IIIa) receptor is an essential step of platelet aggregation induced by various physiologic agonists, and RGD-containing peptides that bind to the GPIIb/IIIa receptor inhibit thrombus formation *in vivo*. L-cysteine, N-(mercaptoacetyl)-D-tyrosyl-L-arginylglycyl-L alpha-aspartyl-cyclic (1----5)-sulfide, 5-oxide (G4120), a cyclic RGD-containing synthetic pentapeptide, inhibits adenosine diphosphate (ADP)-induced platelet aggregation with 50% inhibition (IC<sub>50</sub>) at a concentration of 0.05 microgram/mL in human plasma, 0.12 microgram/mL in hamster plasma, and 11 micrograms/mL in rat plasma. Corresponding values for the linear tetrapeptide Arg-Gly-Asp-Phe (RGDF) were 7 and 100 micrograms/mL in human and hamster plasma. The antithrombotic effects of G4120 and RGDF were evaluated in a hamster model consisting of a mural platelet-rich femoral vein thrombus induced by standardized endothelial cell damage. Bolus intravenous injection of G4120 was followed by a biphasic disappearance of G4120 from plasma with t<sub>1/2</sub> alpha of 3.7 minutes and t<sub>1/2</sub> beta of 63 minutes, corresponding to a plasma clearance of 5.2 +/- 0.68 mL/min. Bolus intravenous injection of G4120 inhibited *ex vivo* platelet aggregation with 0.5 mumol/L ADP and *in vivo* thrombus formation in a dose-dependent manner, with ID<sub>50</sub> of 11 and 11 micrograms/kg, respectively. Bolus injection of RGDF inhibited *in vivo* thrombus formation; 43% inhibition was obtained at a dose of 30 mg/kg. Thus, this hamster platelet-rich femoral vein thrombosis model may be useful for the investigation of the antithrombotic properties of platelet GPIIb/IIIa antagonistic peptides. The cyclic synthetic peptide G4120 appears to have a very potent antithrombotic activity *in vivo*.

19. Effects of amino acids on acute alcohol intoxication in mice--concentrations of ethanol, acetaldehyde, acetate and acetone in blood and tissues. Tsukamoto S, Kanegae T, Nagoya T, Shimamura M, Mieda Y, Nomura M, Hojo K, Okubo H. *Arukuru Kenkyuto Yakubutsu Ison.* 1990 Oct;25(5):429-40.

Condensation reactions between some SH-amino acids (L- and D-cysteine 1%) and acetaldehyde (50 microM) were studied *in vitro* experiment. In the aqueous solution, free acetaldehyde was reduced to 41.3% by L-cysteine and to 36.4% by D-cysteine. In the reaction with human blood medium, after the medium was deproteinized with perchloric acid reagent, acetaldehyde was reduced to 47.0% by L-cysteine and to 43.8% by D-cysteine. D-Cysteine appears to have great stability of reacting acetaldehyde. *In vitro* experiment reactivity for D-cysteine exhibited 3-8% higher than that for L-cysteine. Next, effects of some amino acids on alcohol metabolism were studied in male ICR mice. The animals were given ethanol through a gastric catheter at a dose of 2 g/kg and they were intraperitoneally injected L-cysteine (300 mg/kg), D-cysteine (300 mg/kg), L-alanine (300 mg/kg) and control (saline), respectively in the period of one hour before the injection of ethanol. Blood and tissues samples were analyzed for ethanol, acetaldehyde, acetate and acetone during alcohol intoxication in mice by head space gas chromatography. In the groups administered D-cysteine and L-cysteine, the mice showed a definitely faster oxidation and disappearance of ethanol. Especially in the D-cysteine group, ethanol levels in blood, liver and brain remained lower than that in the other groups (p less than 0.01). Acetaldehyde levels in blood, liver and brain remained low by L-cysteine. Ethanol metabolites during alcohol oxidation by chemical reactivities of L- and D-cysteine showed different distribution in the mice, respectively. In the mice received L-alanine, acetate and acetone levels in blood, liver and brain were distinctly reduced (p less than 0.01). L-Alanine is reported to supply an abundance of pyruvic acid that performs the NAD-generating system. NAD produced is introduced to alcohol metabolism and the TCA cycle. It was thus presumed that the L- or/and D- cysteine, and L-alanine was effective in acute alcohol intoxication by heavy drinking.

20. *Jpn J Cancer Res.* 1989 Feb;80(2):182-7. Enhanced antitumor effect of 5'-deoxy-5-fluorouridine by oral administration with L-cysteine. Iigo M, Nakajima Y, Araki E, Hoshi A. Chemotherapy Division, National Cancer Center Research Institute, Tokyo.

When given orally in combination with L-cysteine, 5'-deoxy-5-fluorouridine (DFUR) brought about a significant reduction in the growth of adenocarcinoma 755 and a significant prolongation of life-span in mice bearing Lewis lung carcinoma without increased toxicity to the host as compared with DFUR alone, though L-cysteine alone did not show an appreciable antitumor activity.

Moreover, the combination of DFUR and L-cysteine resulted in a marked retardation of growth of human colon tumor LS174T transplanted into nude mice. Thus, the potency of DFUR was increased by L-cysteine. Pharmacokinetic studies revealed that after DFUR administration, plasma DFUR and 5-fluorouracil (5-FU) levels rapidly declined, but that, in the combination with L-cysteine, the plasma clearances of DFUR and 5-FU were slowed down considerably. In the tumor, DFUR and 5-FU levels were similar to those in the plasma. Such a prolongation of DFUR and 5-FU levels in plasma and tumor may produce the enhancement of antitumor effect seen with the combination of DFUR and L-cysteine.

21. *Am Rev Respir Dis.* 1985 Nov;132(5):1049-54. Investigation of the protective effects of the antioxidants ascorbate, cysteine, and dapsone on the phagocyte-mediated oxidative inactivation of human alpha-1-protease inhibitor in vitro. Theron A, Anderson R.

Oxidants derived from the atmosphere or from activated pulmonary phagocytes mediate functional inactivation of alpha-1-protease inhibitor (alpha-1-PI). Chronic exposure to these oxidants may cause emphysema. In this study we have investigated the effects of the antioxidants ascorbate, cysteine ( $10^{-4}$  M to  $10^{-1}$  M), and dapsone ( $10^{-6}$  M to  $10^{-3}$  M) on the oxidative inactivation of human alpha-1-PI by leukoattractant-activated polymorphonuclear leukocytes (PMNL) in vitro. During exposure of alpha-1-PI to stimulated PMNL in the presence of ascorbate and cysteine at concentrations of greater than  $10^{-4}$  M and dapsone at greater than  $10^{-6}$  M, the elastase inhibitory activity of alpha-1-PI was preserved. However, exposure of the alpha-1-PI to the antioxidants subsequent to PMNL-mediated oxidative inactivation was not associated with reactivation of elastase inhibitory capacity. Ascorbate, cysteine, and dapsone at concentrations that caused 50% protection of alpha-1-PI did not affect degranulation or the binding of radiolabeled leukoattractant to PMNL. It is suggested that the protective effects of the antioxidants are related to their ability to scavenge superoxide and oxidants generated by the PMNL-myeloperoxidase/H<sub>2</sub>O<sub>2</sub>/halide system. Because the effects of ascorbate and especially those of dapsone were observed at concentrations of these agents that are attainable in vivo, our results may have clinical significance

22. *J Biol Chem.* 1984 May 10;259(9):5606-11. Free radical metabolites of L-cysteine oxidation. Harman LS, Mottley C, Mason RP.

The oxidation of L-cysteine by horseradish peroxidase in the presence of oxygen forms a thiyl free radical as demonstrated with the spin-trapping ESR technique. Reactions of this thiyl free radical result in oxygen consumption, which is inhibited by the spin trap 5,5'-dimethyl-1-pyrroline-N-oxide. Cysteine sulfinic acid, a cysteine metabolite, is a poorer substrate for horseradish peroxidase than cysteine and is oxidized to form both sulfur-centered and carbon-centered free radicals.

23. Preventing Hypoglycemia *Anti-Aging News*, January 1982 Vo.2, No. 1 pg 6-7

Cysteine is a strong reducing agent (it can prevent oxidation of some other substances). In fact, it has been found that too much cysteine in a cell culture medium can inactivate the hormone insulin contained in the medium. The insulin molecule contains three disulfide bonds, at least one of which can be reduced by cysteine. When this happens, the insulin molecule can no longer maintain the proper shape to function normally in stimulating the metabolism of sugar. In hypoglycemia attacks, there is too much insulin and too little sugar in the blood stream. Cysteine can inactivate insulin, thereby allowing the sugar level to begin to rise again. We and others have used the combination of vitamins B1, C, and cysteine to successfully abort severe attacks of hypoglycemia. A reasonable dose for a healthy adult is 5 grams of C, 1 gram of B1, and 1 gram cysteine. Although cysteine is a nutrient, its use on a long-term basis should be considered experimental. Start with a low dose (250 milligrams per day) and work your way up. Always use at least three times as much vitamin C as cysteine. Be sure to consult with your physician and have regular clinical tests of basic body functions, especially liver and kidney. Diabetics should not use cysteine supplements due to its anti-insulin effects.

24. *Hum Genet.* 1979;50(1):51-7. Chromosomal breakage in Crohn's disease: anticlastogenic effect of D-penicillamine and L-cysteine. Emerit I, Emerit J, Levy A, Keck M.

The incidence of chromosome breakage was found to be elevated in 42 patients with Crohn's disease. This phenomenon was much more striking in cultures set up with TCM 199 than in cultures set up with RPMI 1629 rich in L-cysteine. The drug D-penicillamine, a close analog of L-cysteine, gave an apparent therapeutic response in several patients and reduced the chromosome breakage frequency in the lymphocytes of these patients in vitro and in vivo.

25. *Annu Rev Plant Biol.* 2002;53:159-82. Phytochelatin and metallothioneins: roles in heavy metal detoxification and homeostasis. Cobbett C, Goldsbrough P. Department of Genetics, University of Melbourne, Parkville, Australia 3052. ccobbett@unimelb.edu.au

Among the heavy metal-binding ligands in plant cells the phytochelatin (PCs) and metallothioneins (MTs) are the best characterized. PCs and MTs are different classes of cysteine-rich, heavy metal-binding protein molecules. PCs are enzymatically synthesized peptides, whereas MTs are gene-encoded polypeptides. Recently, genes encoding the enzyme PC synthase have been identified in plants and other species while the completion of the Arabidopsis genome sequence has allowed the identification of the entire suite of MT genes in a higher plant. Recent advances in understanding the regulation of PC biosynthesis and MT gene

expression and the possible roles of PCs and MTs in heavy metal detoxification and homeostasis are reviewed.

26. *J Biol Chem.* 2001 Jun 15;276(24):20817-20. Epub 2001 Apr 19. A new pathway for heavy metal detoxification in animals. Phytochelatin synthase is required for cadmium tolerance in *Caenorhabditis elegans*. Vatamaniuk OK, Bucher EA, Ward JT, Rea PA. Department of Biology, Plant Science Institute, University of Pennsylvania, Philadelphia, Pennsylvania 19104-6018, USA.

Increasing emissions of heavy metals such as cadmium, mercury, and arsenic into the environment pose an acute problem for all organisms. Considerations of the biochemical basis of heavy metal detoxification in animals have focused exclusively on two classes of peptides, the thiol tripeptide, glutathione (GSH, gamma-Glu-Cys-Gly), and a diverse family of cysteine-rich low molecular weight proteins, the metallothioneins. Plants and some fungi, however, not only deploy GSH and metallothioneins for metal detoxification but also synthesize another class of heavy metal binding peptides termed phytochelatins (PCs) from GSH. Here we show that PC-mediated heavy metal detoxification is not restricted to plants and some fungi but extends to animals by demonstrating that the *ce-pcs-1* gene of the nematode worm *Caenorhabditis elegans* encodes a functional PC synthase whose activity is critical for heavy metal tolerance in the intact organism.

27. *Biol Trace Elem Res.* 2000 Jul;76(1):19-30. Study of the effect of the administration of Cd(II), cysteine, methionine, and Cd(II) together with cysteine or methionine on the conversion of xanthine dehydrogenase into xanthine oxidase. Esteves AC, Felcman J. Department of Chemistry, Pontificia Universidade Catolica do Rio de Janeiro, Rio de Janeiro, Brazil.

Cadmium is known as to be a potent pulmonary carcinogen to human beings and to induce prostate tumor. The sequestration of cadmium, an extremely toxic element to living cells, which is performed by biological ligands such as amino acids, peptides, proteins or enzymes is important to minimize its participation in such deleterious processes. The synthesis of metallothionein is induced by a wide range of metals, in which cadmium is a particularly potent inducer. This protein is usually associated with cadmium exposure in man. Because metallothioneins may act as a detoxification agent for cadmium and chelation involves sulfur donor atoms, we administered only cadmium, cysteine, or methionine to rats and also each of these S-amino acids together with cadmium and measured the production of superoxide radicals derived from the conversion of xanthine dehydrogenase to xanthine oxidase. It could be seen in this work that the presence of cadmium enhances this conversion. However, its inoculation with cysteine or methionine almost completely diminishes this effect and this can be the result of the fact that these amino acids complex Cd(II). Thus, these compounds can be a model of the action of metallothionein, removing cadmium from circulation and preventing its deleterious effect.

28. *Altern Med Rev.* 1998 Aug;3(4):262-70. Cysteine metabolism and metal toxicity. Quig D. Doctor's Data, Inc., West Chicago, IL, USA. [dquig@doctorsdata.com](mailto:dquig@doctorsdata.com)

Chronic, low level exposure to toxic metals is an increasing global problem. The symptoms associated with the slow accumulation of toxic metals are multiple and rather nondescript, and overt expression of toxic effects may not appear until later in life. The sulfhydryl-reactive metals (mercury, cadmium, lead, arsenic) are particularly insidious and can affect a vast array of biochemical and nutritional processes. The primary mechanisms by which the sulfhydryl-reactive metals elicit their toxic effects are summarized. The pro-oxidative effects of the metals are compounded by the fact that the metals also inhibit antioxidative enzymes and deplete intracellular glutathione. The metals also have the potential to disrupt the metabolism and biological activities of many proteins due to their high affinity for free sulfhydryl groups. Cysteine has a pivotal role in inducible, endogenous detoxication mechanisms in the body, and metal exposure taxes cysteine status. The protective effects of glutathione and the metallothioneins are discussed in detail. Basic research pertaining to the transport of toxic metals into the brain is summarized, and a case is made for the use of hydrolyzed whey protein to support metal detoxification and neurological function. Metal exposure also affects essential element status, which can further decrease antioxidation and detoxification processes. Early detection and treatment of metal burden is important for successful detoxification, and optimization of nutritional status is paramount to the prevention and treatment of metal toxicity.

29. *J Nutr.* 1987 Jun;117(6):1003-10. Pharmacologic role of cysteine in ameliorating or exacerbating mineral toxicities. Baker DH, Czarnecki-Maulden GL.

Cysteine, via chelation reactions, ameliorates biochemical lesions caused by excessive ingestion of several trace elements. Because oral cysteine per se is considerably more protective than the in vivo metabolic cysteine precursors, methionine or cystine, chelation of cysteine with trace elements likely occurs primarily in the gut, thereby decreasing absorption of both cysteine and the trace element in question. Hence, using copper as an example, orally administered cysteine markedly improves growth and reduces liver copper deposition in chicks or rats fed a high level of inorganic copper. Likewise, excessive copper ingestion impairs sulfur amino acid (SAA) utilization and increases the dietary requirement for SAA. Cobalt and selenium toxicities are also ameliorated by oral cysteine ingestion, with the responses being even more striking than those occurring with copper toxicity. While inorganic arsenic poisonings are generally ameliorated by administering cysteine or a cysteine derivative (e.g., dimercaptopropanol), organic pentavalent arsenic toxicity is exacerbated by cysteine administration. Cysteine in this instance acts as a reducing agent, facilitating conversion of organic pentavalent arsenicals such as roxarsone and arsanilic acid to the more toxic trivalent state.

30. J Infect Dis. 2000 Sep;182 Suppl 1:S81-4. Regulation of cysteine-rich intestinal protein, a zinc finger protein, by mediators of the immune response. Cousins RJ, Lanningham-Foster L. Food Science and Human Nutrition Department, Center for Nutritional Sciences, University of Florida, Gainesville, FL 32611-0370, USA.

Cysteine-rich intestinal protein (CRIP), a member of the LIM protein family, has a unique double zinc finger motif as the defining feature. CRIP is highly expressed in intestine and immune cells. CRIP transgenic (Tg) mice and nontransgenic controls were challenged with lipopolysaccharide (LPS). Serum concentrations of interferon-gamma and tumor necrosis factor-alpha were less while those of interleukin-6 and -10 were greater in the Tg mice following LPS administration. CRIP-overexpressing splenocytes produce the same cytokine profile. These responses are consistent with a regulatory role for this protein in cell differentiation, which produces an imbalance in Th1 and Th2 cytokines. Stimulation of CRIP protein levels by LPS is eliminated in metallothionein knockout mice, suggesting metallothionein is the source of zinc for this zinc finger protein and, further, that this could reflect a relationship to the zinc nutritional status and to the aberrant Th1/Th2 cytokine balance observed in zinc deficiency.

31. Am J Med. 1991 Sep 30;91(3C):140S-144S. Modulation of lymphocyte functions and immune responses by cysteine and cysteine derivatives. Droge W, Eck HP, Gmunder H, Mihm S. Division of Immunochemistry, Deutsches Krebsforschungszentrum, Heidelberg, F.R.G.

Mitogenically stimulated human peripheral blood lymphocytes and T cell clones were found to have weak membrane transport activity for the disulfide cystine but strong membrane transport activity for the thiol amino acid cysteine. Cysteine, however, is represented at the lowest concentration among all protein-forming amino acids in the blood plasma. Complementary laboratory experiments have shown that the cysteine supply is indeed limiting for important lymphocyte functions. Proliferative responses of mitogenically stimulated lymphocytes and T-cell clones and the activation of cytotoxic T cells in allogeneic mixed lymphocyte cultures are strongly influenced by small variations in the extracellular cysteine concentration even in the presence of relatively high and approximately physiologic concentrations of cystine. Cysteine can be substituted by N-acetylcysteine but not by cystine. The more detailed analysis revealed that the extracellular supply of cysteine influences strongly the intracellular level of glutathione (GSH) and also the activity of the transcription factor NF kappa B that regulates the expression of several immunologically relevant genes. In vitro experiments including double-chamber experiments with macrophages and lymphocytes revealed, moreover, that cysteine plays an important role as a regulatory mediator between these cell types. The cysteine supply is impaired directly or indirectly in several pathologic conditions that are associated with immunodeficiencies, including the acquired immune deficiency syndrome (AIDS). Cysteine or cysteine derivatives may therefore be considered for the treatment of patients with HIV-1 infection.

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