

[J Altern Complement Med.](#) 2008 Mar;14(2):139-46.

Restoration of blood total glutathione status and lymphocyte function following alpha-lipoic acid supplementation in patients with HIV infection.

[Jariwalla RJ](#), [Lalezari J](#), [Cenko D](#), [Mansour SE](#), [Kumar A](#), [Gangapurkar B](#), [Nakamura D](#).

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Abstract

OBJECTIVES: To determine whether supplementation with alpha-lipoic acid (ALA), a glutathione-replenishing disulfide, modulates whole blood total glutathione (GSH + GSSG) levels and improves lymphocyte function in human immunodeficiency virus (HIV)-infected subjects with history of unresponsiveness to highly active antiretroviral treatment (HAART). **DESIGN AND SETTING:** Randomized, double-blinded, placebo-controlled trial conducted at two study sites: an eye clinic at a county hospital in San Jose and a research clinic in San Francisco, California. **SUBJECTS:** A total of 33 HIV-infected men and women with viral load >10,000 copies/cm(3), despite HAART, aged 44-47 years, approximately 36% nonwhite, were enrolled. **INTERVENTION:** Patients were randomly assigned to receive either ALA (300 mg three times a day) or matching placebo for 6 months. **MAIN OUTCOME MEASURES:** The change over 6 months in blood total glutathione status, lymphocyte proliferation response to T-cell mitogens, CD4 cell count, and viral load in patients receiving ALA compared to placebo. **RESULTS:** The mean blood total glutathione level in ALA-supplemented subjects was significantly elevated after 6 months (1.34+/-0.79 vs. 0.81+/-0.18 mmol/L) compared to insignificant change (0.76+/-0.34 vs. 0.76+/-0.22 mmol/L) in the placebo group (ALA vs. placebo: p=0.04). The lymphocyte proliferation response was significantly enhanced or stabilized after 6 months of ALA supplementation compared to progressive decline in the placebo group (ALA vs. placebo: p<0.001 with phytohemagglutinin; p=0.02 with anti-CD3 monoclonal antibody). A positive correlation was seen between blood total glutathione level and lymphocyte response to anti-CD3 stimulation (R(2)=0.889). There was no significant change in either HIV RNA level or CD4 count over 6 months in the ALA-supplemented compared to the control group. **CONCLUSION:** Supplementation with alpha-lipoic acid may positively impact patients with HIV and acquired immune deficiency syndrome by restoring blood total glutathione level and improving functional reactivity of lymphocytes to T-cell mitogens.

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Supplemental Content

Mary Ann Liebert,

[J Nutr.](#) 2006 Jun;136(6 Suppl):1660S-1665S.

The effects of sulfur amino acid intake on immune function in humans.

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Abstract

No direct data exist on the influence of supranormal intakes of sulfur amino acids on immune function in humans. However 3 major products of sulfur amino acids, glutathione (GSH), homocysteine (Hcy), and taurine (Tau), influence, mainly, inflammatory aspects of the immune response in vitro and in vivo. Methionine intakes above approximately 1 g/d transiently raise plasma Tau, Hcy, and GSH. Tau and GSH ameliorate inflammation. Hcy has the opposite effect. A biphasic relation, between cellular GSH and CD4+ and CD8+ numbers occurs in healthy men. How changes in sulfur amino acid intake influence this phenomenon is unknown. In animals, high Tau intakes are antiinflammatory. How immune function in humans is affected is unknown. A positive relation between plasma neopterin (a marker of a Th-1-type immune response) and Hcy indicates that Hcy may play a part in inflammatory aspects of Parkinson's disease and aging. In vitro, Hcy, at concentrations seen following consumption of approximately 6 g L-methionine/d in adults, increases the interactions among T lymphocytes, monocytes, and endothelium. Whether a similar phenomenon occurs in vivo is unknown. Polymorphisms in the methylenetetrahydrofolate reductase gene are associated with raised plasma Hcy in young but not old subjects. The relation of this observation to immune function is unknown. The relationships among Hcy, inflammatory aspects of disease, and in vitro alterations in immune cell behavior create a cautionary note about supplementation of diets with l-methionine to raise intake above approximately 1 g/d. Studies directly linking methionine intake, genetics, plasma Hcy, Tau, and GSH and immune function are needed.

PMID: 16702336 [PubMed - indexed for MEDLINE]Free Article

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[J Infect Dis.](#) 2003 Jul 15;188(2):232-8. Epub 2003 Jun 9.

Disturbed glutathione metabolism and decreased antioxidant levels in human immunodeficiency virus-infected patients

during highly active antiretroviral therapy--potential immunomodulatory effects of antioxidants.

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Abstract

Oxidative stress has been implicated in the pathogenesis of human immunodeficiency virus (HIV) infection. We examined the effect of highly active antiretroviral therapy (HAART) on plasma levels of several antioxidants and intracellular glutathione-redox status in CD4+ T cells, in 20 HIV-infected patients. HAART was accompanied by both an improvement of glutathione-redox status and an increase in levels of antioxidant vitamins, without full normalization. Glutathione supplementation in vitro increases T cell proliferation and suppresses the spontaneous release of tumor necrosis factor-alpha from peripheral blood mononuclear cells, in HIV-infected patients receiving HAART. Our findings suggest that therapeutic intervention aimed at normalization of oxidative disturbances in HIV infection could be of interest, in addition to HAART.

PMID: 12854078 [PubMed - indexed for MEDLINE]

Supplemental Content



[J Mol Med](#). 2001 Nov;79(11):671-8.

Flux of amino acids and energy substrates across the leg in weight-stable HIV-infected patients with acute opportunistic infections: indication of a slow protein wasting process.

[Breitkreutz R](#), [Wagner J](#), [Tokus M](#), [Benner A](#), [Rossol S](#), [Pittack N](#), [Stein J](#), [Dröge W](#), [Holm E](#).

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Abstract

Increased whole-body proteolysis with muscle protein net degradation has been suggested as one of the causes of weight loss in patients infected with human immunodeficiency virus (HIV). We studied the exchange rates of amino acids and energy substrates across the lower extremity in 16 HIV patients and 16 age-matched controls with similar body cell mass. The patients had either opportunistic infections or chronic diarrhea but no signs of clinical malnutrition. The following findings were obtained in the HIV patients: an augmented peripheral net release of arginine and lysine; an increase in both the negative arterial-venous difference and the efflux of the nitrogen contained in nonmetabolized amino acids; diminished export of 3-methylhistidine; lowered plasma and erythrocyte amino acid concentrations; reduced output of glycerol and furthermore; and neither a net release nor a net uptake of free fatty acids. The findings concerning nitrogen metabolism support the hypothesis that, in the presence of a reduction in protein breakdown, peripheral protein synthesis is severely depressed, making a slow protein wasting process likely to occur. The balances of glycerol and free fatty acids are due not only to the leg tissues but perhaps also in part to increased net retention of these substrates by skeletal muscle.

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Supplemental Content



[Proc Nutr Soc.](#) 2000 Nov;59(4):595-600.

Glutathione and immune function.

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Abstract

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 cysteine level and impaired immunological functions.

[AIDS Res Hum Retroviruses](#). 2000 Feb 10;16(3):203-9.

Massive loss of sulfur in HIV infection.

[Breitkreutz R](#), [Holm S](#), [Pittack N](#), [Beichert M](#), [Babylon A](#), [Yodoi J](#), [Dröge W](#).

Division of Immunochemistry, Deutsches Krebsforschungszentrum, Heidelberg, Germany.

Abstract

Skeletal muscle tissue from SIV-infected macaques was previously found to contain abnormally high sulfate and low glutathione levels indicative of an excessive cysteine catabolism. We now confirm the peripheral tissue as a site of massive cysteine catabolism in HIV infection and have determined the urinary loss of sulfur per time unit. The comparison of the sulfate concentrations of the arterial and venous blood from the lower extremities of 16 symptomatic HIV+ patients and 18 HIV- control subjects (study 1) revealed (1) that the peripheral tissue of HIV+ patients with or without highly active antiretroviral therapy (HAART) releases large amounts of sulfate and (2) that plasma sulfate, thioredoxin, and interleukin-6 levels are elevated in these patients. A complementary investigation of 64 asymptomatic HIV+ patients and 65 HIV- subjects (study 2) revealed increased plasma sulfate levels in the asymptomatic patients. The analysis of the daily urinary excretion of sulfate and urea of another group of 19 HIV+ patients and 22 healthy HIV- subjects (study 3) confirmed (1) that HIV+ patients experience a massive loss of sulfur and (2) that this loss is not ameliorated by HAART. The sulfur loss of asymptomatic patients was equivalent to a mean loss of about 10 g of cysteine per day. If extrapolated, this would correspond to an alarming negative balance of approximately 2 kg of cysteine per year under the assumption that the normal sulfate excretion equivalent to approximately 3 g of cysteine per day is balanced by a standard Western diet. The abnormally high sulfate/urea ratio suggests that this process drains largely the glutathione pool.

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Supplemental Content

Mary Ann Liebert,

[J Mol Med.](#) 2000;78(1):55-62.

Improvement of immune functions in HIV infection by sulfur supplementation: two randomized trials.

[Breitkreutz R](#), [Pittack N](#), [Nebe CT](#), [Schuster D](#), [Brust J](#), [Beichert M](#), [Hack V](#), [Daniel V](#), [Edler L](#), [Dröge W](#).

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Comment in:

- [J Mol Med.](#) 2000;78(1):1-2.

Abstract

To determine the therapeutic effect of sulfur amino acid supplementation in HIV infection we randomized 40 patients with antiretroviral therapy (ART; study 1) and 29 patients without ART (study 2) to treatment for 7 months with N-acetyl-cysteine or placebo at an individually adjusted dose according to a defined scheme. The main outcome measures were the change in immunological parameters including natural killer (NK) cell and T cell functions and the viral load. Both studies showed consistently that N-acetyl-cysteine causes a marked increase in immunological functions and plasma albumin concentrations. The effect of N-acetyl-cysteine on the viral load, in contrast, was not consistent and may warrant further studies. Our findings suggest that the impairment of immunological functions in HIV+ patients results at least partly from cysteine deficiency. Because immune reconstitution is a widely accepted aim of HIV treatment, N-acetyl-cysteine treatment may be recommended for patients with and without ART. Our previous report on the massive loss of sulfur in HIV-infected subjects and the present demonstration of the immunoreconstituting effect of cysteine supplementation indicate that the HIV-induced cysteine depletion is a novel mechanism by which a virus destroys the immune defense of the host and escapes immune elimination.

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Supplemental Content



[Eur J Clin Invest. 2000 Oct;30\(10\):915-29.](#)

N-acetylcysteine replenishes glutathione in HIV infection.

[De Rosa SC](#), [Zaretsky MD](#), [Dubs JG](#), [Roederer M](#), [Anderson M](#), [Green A](#), [Mitra D](#), [Watanabe N](#), [Nakamura H](#), [Tjioe I](#), [Deresinski SC](#), [Moore WA](#), [Ela SW](#), [Parks D](#), [Herzenberg LA](#), [Herzenberg LA](#).

Department of Genetics, Stanford University, USA.

Comment in:

- [Eur J Clin Invest. 2000 Oct;30\(10\):841-2.](#)

Abstract

BACKGROUND: Glutathione (GSH) deficiency is common in HIV-infected individuals and is associated with impaired T cell function and impaired survival. N-acetylcysteine (NAC) is used to replenish GSH that has been depleted by acetaminophen overdose. Studies here test oral administration of NAC for safe and effective GSH replenishment in HIV infection.

DESIGN: Oral NAC administration in a randomized, 8-week double-blind, placebo-controlled trial followed by optional open-label drug for up to 24 weeks.

SUBJECTS: HIV-infected, low GSH, CD4 T cells < 500 micro L(-1), no active opportunistic infections or other debilitation; n = 81. Study conducted prior to introduction of protease inhibitors.

RESULTS: Whole blood GSH levels in NAC arm subjects significantly increased from 0.88 mM to 0.98 mM, bringing GSH levels in NAC-treated subjects to 89% of uninfected controls (P = 0.03). Baseline GSH levels in the placebo group (0.91) remained essentially the same during the 8 week placebo-controlled trial. T cell GSH, adjusted for CD4 T cell count and beta2-microglobulin levels, also increased in the NAC-treated subjects (P = 0.04). Adverse effects were minimal and not significantly associated with NAC ingestion.

CONCLUSION: NAC treatment for 8 weeks safely replenishes whole blood GSH and T cell GSH in HIV-infected individuals. Thus, NAC offers useful adjunct therapy to increase protection against oxidative stress, improve immune system function and increase detoxification of acetaminophen and other drugs. These findings suggest that NAC therapy could be valuable in other clinical situations in which GSH deficiency or oxidative stress plays a role in disease pathology, e.g. rheumatoid arthritis, Parkinson's disease, hepatitis, liver cirrhosis, septic shock and diabetes.

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<http://herzenberg.stanford.edu/Publications/Reprints/LAH448.pdf> FREE

[Curr Opin Clin Nutr Metab Care](#). 1999 Nov;2(6):493-8.

N-acetyl-cysteine in the therapy of HIV-positive patients.

[Dröge W](#), [Breitkreutz R](#).

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Abstract

Randomly selected asymptomatic HIV-positive persons reveal, on average, a massive daily loss of sulphur, which appears to represent in first approximation the mean loss throughout the asymptomatic stage, and may explain the widely observed decrease in cyst(e)ine and glutathione levels. This sulphur loss is reasonably expected to lead, within a few years, to a life-threatening condition and may, therefore, contribute decisively to disease progression. Importantly, the rate of sulphur loss is not ameliorated by highly active antiretroviral therapy and may contribute to antiretroviral treatment failure. Several clinical trials on N-acetyl-cysteine treatment of HIV-positive patients have revealed various therapeutic effects, but did not meet the rigorous standards for approval by the health authorities.

PMID: 10678679 [PubMed - indexed for MEDLINE]

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[Blood](#). 1998 Jul 1;92(1):59-67.

The redox state as a correlate of senescence and wasting and as a target for therapeutic intervention.

[Hack V](#), [Breitkreutz R](#), [Kinscherf R](#), [Röhler H](#), [Bärtsch P](#), [Taut F](#), [Benner A](#), [Dröge W](#).

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Abstract

The loss of body cell mass (bcm) in senescence and wasting is poorly understood. We now show that the plasma cystine/acid soluble thiol ratio, ie, an indicator of the redox state, is increased in old age and cancer patients and correlated with a decrease in bcm and plasma albumin. A cause/effect relationship was suggested by two independent studies with N-acetylcysteine (NAC). NAC caused an increase in the bcm of healthy persons with high plasma cystine/thiol ratios, and treatment of cancer patients with NAC plus interleukin-2 caused an increase in bcm, plasma albumin, and functional capacity. Albumin levels below 680 micromol/L were associated with an increase in body water. Our studies suggest that the shift in the redox state may contribute to the loss of bcm and may provide a quantitative guideline for therapeutic intervention. Treatment of cancer patients with thiol-containing antioxidants may improve the quality of life.

PMID: 9639500 [PubMed - indexed for MEDLINE]Free Article

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[FASEB J.](#) 1997 Nov;11(13):1077-89.

Role of cysteine and glutathione in HIV infection and other diseases associated with muscle wasting and immunological dysfunction.

[Dröge W](#), [Holm E](#).

Division of Immunochemistry, Deutsches Krebsforschungszentrum, Heidelberg, Germany.

Abstract

The combination of abnormally low plasma cystine and glutamine levels, low natural killer (NK) cell activity, skeletal muscle wasting or muscle fatigue, and increased rates of urea production defines a complex of abnormalities that is tentatively called "low CG syndrome." These symptoms are found in patients with HIV infection, cancer, major injuries, sepsis, Crohn's disease, ulcerative colitis, chronic fatigue syndrome, and to some extent in overtrained athletes. The coincidence of these symptoms in diseases of different etiological origin suggests a causal relationship. The low NK cell activity in most cases is not life-threatening, but may be disastrous in HIV infection because it may compromise the initially stable balance between the immune system and virus, and trigger disease progression. This hypothesis is supported by the coincidence observed between the decrease of CD4+ T cells and a decrease in the plasma cystine level. In addition, recent studies revealed important clues about the role of cysteine and glutathione in the development of skeletal muscle wasting. Evidence suggests that 1) the cystine level is regulated primarily by the normal postabsorptive skeletal muscle protein catabolism, 2) the cystine level itself is a physiological regulator of

nitrogen balance and body cell mass, 3) the cyst(e)ine-mediated regulatory circuit is compromised in various catabolic conditions, including old age, and 4) cysteine supplementation may be a useful therapy if combined with disease-specific treatments such as antiviral therapy in HIV infection.

PMID: 9367343 [PubMed - indexed for MEDLINE]Free Article

Supplemental Content



[FASEB J](#). 1997 Jan;11(1):84-92.

Cystine levels, cystine flux, and protein catabolism in cancer cachexia, HIV/SIV infection, and senescence.

[Hack V](#), [Schmid D](#), [Breitkreutz R](#), [Stahl-Henning C](#), [Drings P](#), [Kinscherf R](#), [Taut F](#), [Holm E](#), [Dröge W](#).

Department of Immunochemistry, Deutsches Krebsforschungszentrum, Heidelberg, Germany.

Abstract

Patients with skeletal muscle catabolism (cachexia) fail to conserve the skeletal muscle protein and release large amounts of nitrogen as urea. Previous studies suggest that the threshold for the conversion of amino acids into other forms of chemical energy and the concomitant production of urea are regulated by the plasma cystine level and hepatic cysteine catabolism. Studies of plasma amino acid exchange rates in the lower extremities now show that healthy young subjects regulate their plasma cystine level in a process that may be described as controlled constructive catabolism. The term controlled describes the fact that the release of cystine and other amino acids from the peripheral tissue is negatively correlated with (certain) plasma amino acid levels. The term constructive describes the fact that the release of cystine is correlated with an increase of the plasma cystine level. The regulation of the plasma cystine level is disturbed in conditions with progressive skeletal muscle catabolism including cancer, HIV infection, and old age. These conditions show also a low plasma glutamine:cystine ratio indicative of an impaired hepatic cystine catabolism. In HIV+ patients and SIV-infected macaques, a decrease of the plasma cystine level was found to coincide with the decrease of CD4+ T cells.

PMID: 9034170 [PubMed - indexed for MEDLINE]Free Article

Supplemental Content



[Proc Natl Acad Sci U S A](#). 1997 Mar 4;94(5):1967-72.

Glutathione deficiency is associated with impaired survival in HIV disease.

[Herzenberg LA](#), [De Rosa SC](#), [Dubs JG](#), [Roederer M](#), [Anderson MT](#), [Ela SW](#), [Deresinski SC](#), [Herzenberg LA](#).

Department of Genetics, Stanford University Medical School, CA 94305-5125, USA.

Abstract

Glutathione (GSH), a cysteine-containing tripeptide, is essential for the viability and function of virtually all cells. In vitro studies showing that low GSH levels both promote HIV expression and impair T cell function suggested a link between GSH depletion and HIV disease progression. Clinical studies presented here directly demonstrate that low GSH levels predict poor survival in otherwise indistinguishable HIV-infected subjects. Specifically, we show that GSH deficiency in CD4 T cells from such subjects is associated with markedly decreased survival 2-3 years after baseline data collection (Kaplan-Meier and logistic regression analyses, $P < 0.0001$ for both analyses). This finding, supported by evidence demonstrating that oral administration of the GSH prodrug N-acetylcysteine replenishes GSH in these subjects and suggesting that N-acetylcysteine administration can improve their survival, establishes GSH deficiency as a key determinant of survival in HIV disease. Further, it argues strongly that the unnecessary or excessive use of acetaminophen, alcohol, or other drugs known to deplete GSH should be avoided by HIV-infected individuals.

PMID: 9050888 [PubMed - indexed for MEDLINE]PMCID: PMC20026Free PMC Article

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[FASEB J](#). 1994 Nov;8(14):1131-8.

Functions of glutathione and glutathione disulfide in immunology and immunopathology.

[Dröge W](#), [Schulze-Osthoff K](#), [Mihm S](#), [Galter D](#), [Schenk H](#), [Eck HP](#), [Roth S](#), [Gmünder H](#).

Department of Immunochemistry, Deutsches Krebsforschungszentrum, Heidelberg, Germany.

Abstract

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.

PMID: 7958618 [PubMed - indexed for MEDLINE]Free Article

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[FASEB J](#). 1994 Apr 1;8(6):448-51.

Effect of glutathione depletion and oral N-acetyl-cysteine treatment on CD4+ and CD8+ cells.

[Kinscherf R](#), [Fischbach T](#), [Mihm S](#), [Roth S](#), [Hohenhaus-Sievert E](#), [Weiss C](#), [Edler L](#), [Bärtsch P](#), [Dröge W](#).

Department of Immunochemistry, Deutsches Krebsforschungszentrum, Heidelberg, Germany.

Abstract

HIV-infected individuals and SIV-infected rhesus macaques have, on the average, decreased plasma cysteine and cystine concentrations and decreased intracellular glutathione levels. We show that the cysteine supply and the intracellular glutathione levels have a strong influence on the T cell system. A study of healthy human subjects revealed that persons with intracellular glutathione levels of 20-30 nmol/mg protein had significantly higher numbers of CD4+ T cells than persons with either lower or higher glutathione levels. Persons who moved

during a 4-week observation period from the optimal to the suboptimal range (10-20 nmol/mg) experienced, on the average, a 30% decrease in CD4+ T cell numbers. This decrease was prevented by treatment with N-acetyl-cysteine (NAC). NAC caused this relative increase of CD4+ T cell numbers in spite of decreasing glutathione levels and not by increasing the glutathione level. Our studies suggest that the immune system may be exquisitely sensitive not only against a cysteine and glutathione deficiency but also against an excess of cysteine.

PMID: 7909525 [PubMed - indexed for MEDLINE]Free Article

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[Pharmacology](#). 1993;46(2):61-5.

Cysteine and glutathione deficiency in AIDS patients: a rationale for the treatment with N-acetyl-cysteine.

[Dröge W.](#)

Division of Immunochemistry, Deutsches Krebsforschungszentrum, Heidelberg, BRD.

Abstract

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)

[Immunol Today](#). 1992 Jun;13(6):211-4.

HIV-induced cysteine deficiency and T-cell dysfunction--a rationale for treatment with N-acetylcysteine.

[Dröge W](#), [Eck HP](#), [Mihm S](#).

Division of Immunochemistry, Deutsches Krebsforschungszentrum, Heidelberg, FRG.

Abstract

Markedly decreased plasma cystine and cysteine concentrations have been found in HIV-infected patients at all stages of the disease and in SIV-infected rhesus macaques. The elevated glutamate levels found in the same patients aggravate the cysteine deficiency by inhibiting the membrane transport activity for cystine. The intact immune system appears to require a delicate balance between pro-oxidant and antioxidant conditions, maintained by a limited and well-regulated supply of cysteine. This balance is obviously disturbed in HIV infection and may contribute to the pathogenesis of AIDS.

[Klin Wochenschr](#). 1991 Dec 15;69(21-23):1118-22.

Requirement for prooxidant and antioxidant states in T cell mediated immune responses.--Relevance for the pathogenetic mechanisms of AIDS?

[Dröge W](#), [Eck HP](#), [Gmünder H](#), [Mihm S](#).

Abteilung Immunchemie, Deutsches Krebsforschungszentrum, Heidelberg.

Abstract

The discovery of decreased plasma cysteine and cystine levels and elevated plasma glutamate levels in HIV-infected patients has led to intense investigations into the role of cysteine in T cell-mediated immune responses. A large body of evidence indicates that certain aspects of the T cell response require the action of active oxygen derivatives while other aspects of the response require the action of antioxidants such as cysteine and glutathione (GSH). The prooxidant and antioxidant states may be required sequentially at different times during T cell activation. The extremely weak cystine transport activity of T cells together with oxidizing metabolites from inflammatory microenvironments appear to be important factors that support the prooxidant state. The relatively high cystine transport activity of the antigen-presenting macrophages, in contrast, provides these cells with a "cysteine pumping" function that allows the antigen binding T cells in their vicinity to shift to the antioxidant state. The difference

between the membrane transport activities for cysteine of T cells and macrophages thus appears to be the key element of a mechanism that facilitates both, the prooxidant state of T cells and their regulated shift to the antioxidant state. When T cells do not receive sufficient amounts of cysteine, the intracellular GSH levels and rates of DNA synthesis activity decrease, and the cells may suffer from various manifestations of oxidative damage. (ABSTRACT TRUNCATED AT 250 WORDS)

[AIDS](#). 1991 May;5(5):497-503.

Inhibition of HIV-1 replication and NF-kappa B activity by cysteine and cysteine derivatives.

[Mihm S](#), [Emnen J](#), [Pessara U](#), [Kurth R](#), [Dröge W](#).

Institute of Immunology and Genetics, German Cancer Research Center, Heidelberg.

Abstract

HIV-1 proviral DNA contains two binding sites for the transcription factor NF-kappa B. HIV-1-infected individuals have, on average, abnormally high levels of tumour necrosis factor alpha (TNF alpha) and abnormally low plasma cysteine levels. We therefore investigated the effects of cysteine and related thiols on HIV-1 replication and NF-kappa B expression. The experiments in this report show that cysteine or N-acetylcysteine (NAC) raise the intracellular glutathione (GSH) level and inhibit HIV-1 replication in persistently infected Molt-4 and U937 cells. However, inhibition of HIV-1 replication appears not to be directly correlated with GSH levels. Cysteine and NAC also inhibit NF-kappa B activity as determined by electrophoretic mobility shift assays and chloramphenicol acetyl-transferase (CAT) gene expression under control of NF-kappa B binding sites in uninfected cells. This suggests that the cysteine deficiency in HIV-1-infected individuals may cause an over-expression of NF-kappa B-dependent genes and enhance HIV-1 replication. NAC may be considered for the treatment of HIV-1-infected individuals.

[Biol Chem Hoppe Seyler](#). 1989 Feb;370(2):101-8.

Low concentrations of acid-soluble thiol (cysteine) in the blood plasma of HIV-1-infected patients.

[Eck HP](#), [Gmünder H](#), [Hartmann M](#), [Petzoldt D](#), [Daniel V](#), [Dröge W](#).

Institut für Immunologie und Genetik Deutsches Krebsforschungszentrum, Heidelberg.

Abstract

Blood plasma samples from HIV-1-infected persons contain elevated glutamate concentrations up to 6-fold the normal level and relatively low concentrations of acid-soluble thiol (i.e. decreased cysteine concentrations). The intracellular glutathione concentration in peripheral blood-mononuclear cells (PBMC) and monocytes from HIV antibody-positive persons are also significantly decreased. Therapy with azidothymidine (AZT) causes a substantial recovery of the plasma thiol levels; but glutamate levels remain significantly elevated and intracellular glutathione levels remain low. Cell culture experiments with approximately physiological amino-acid concentrations revealed that variations of the extracellular cysteine concentration have a strong influence on the intracellular glutathione level and the rate of DNA synthesis [(3H)thymidine incorporation) in T cell clones and human and murine lymphocyte preparations even in the presence of several-fold higher cysteine and methionine concentrations. Cysteine cannot be replaced by a corresponding increase of the extracellular cysteine or methionine concentration. These experiments suggest strongly that the low cysteine concentration in the plasma of HIV-infected persons may play a role in the pathogenetic mechanism of the acquired immunodeficiency syndrome.

[Biol Chem Hoppe Seyler](#). 1988 Mar;369(3):143-8.

Abnormal amino-acid concentrations in the blood of patients with acquired immunodeficiency syndrome (AIDS) may contribute to the immunological defect.

[Dröge W](#), [Eck HP](#), [Näher H](#), [Pekar U](#), [Daniel V](#).

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Abstract

The acquired immunodeficiency syndrome (AIDS) is accompanied by a metabolic disturbance. Serum samples from persons with antibodies against the AIDS associated human immunodeficiency virus (HIV/LAV/HTLV III) including persons without overt symptoms, patients with lymphadenopathy syndrome (LAS) and patients with AIDS or AIDS-related complex (ARC) contain on the average significantly elevated concentrations of arginine and glutamate. The serum from patients with overt AIDS contains also, on the average, significantly reduced concentrations of methionine and cysteine. In vitro experiments revealed that the [3H]thymidine incorporation by mitogenically stimulated murine lymphocytes and cloned T cells is inhibited by an elevation of the extracellular glutamate concentration and augmented by the addition of cysteine. This suggests the possibility that the abnormal concentrations of glutamate and cysteine in the blood of HIV-infected persons may contribute to the defect in the lymphoid system.