

Geometrically and conformationally restrained cinnamoyl compounds as inhibitors of HIV-1 integrase: synthesis, biological evaluation, and molecular modeling.

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Various cinnamoyl-based structures were synthesized and tested in enzyme assays as inhibitors of the HIV-1 integrase (IN). The majority of compounds were designed as geometrically or conformationally constrained analogues of caffeic acid phenethyl ester (CAPE) and were characterized by a *syn* disposition of the carbonyl group with respect to the vinylic double bond. Since the cinnamoyl moiety present in flavones such as quercetin (inactive on HIV-1-infected cells) is frozen in an *anti* arrangement, it was hoped that fixing our compounds in a *syn* disposition could favor anti-HIV-1 activity in cell-based assays. Geometrical and conformational properties of the designed compounds were taken into account through analysis of X-ray structures available from the Cambridge Structural Database. The polyhydroxylated analogues were prepared by reacting 3,4-bis(tetrahydropyran-2-yloxy)benzaldehyde with various compounds having active methylene groups such as 2-propanone, cyclopentanone, cyclohexanone, 1,3-diacetylbenzene, 2, 4-dihydroxyacetophenone, 2,3-dihydro-1-indanone, 2,3-dihydro-1, 3-indandione, and others. While active against both 3'-processing and strand-transfer reactions, the new compounds, curcumin included, failed to inhibit the HIV-1 multiplication in acutely infected MT-4 cells. Nevertheless, they specifically inhibited the enzymatic reactions associated with IN, being totally inactive against other viral (HIV-1 reverse transcriptase) and cellular (RNA polymerase II) nucleic acid-processing enzymes. On the other hand, title compounds were endowed with remarkable antiproliferative activity, whose potency correlated neither with the presence of catechols (possible source of reactive quinones) nor with inhibition of topoisomerases. The SARs developed for our compounds led to novel findings concerning the molecular determinants of IN inhibitory activity within the class of cinnamoyl-based structures. We hypothesize that these compounds bind to IN featuring the cinnamoyl residue C=C-C=O in a *syn* disposition, differently from flavone derivatives characterized by an *anti* arrangement about the same fragment. Certain inhibitors, lacking one of the two pharmacophoric catechol hydroxyls, retain moderate potency thanks to nonpharmacophoric fragments (i.e., a *m*-methoxy group in curcumin) which favorably interact with an "accessory" region of IN. This region is supposed to be located adjacent to the binding site accommodating the pharmacophoric dihydroxycinnamoyl moiety. Disruption of coplanarity in the inhibitor structure abolishes activity owing to poor shape complementarity with the target or an exceedingly high strain energy of the coplanar conformation.

Effect of artemisinin/artesunate as inhibitors of hepatitis B virus production in an "in vitro" replicative system.

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The antiviral effect against hepatitis B virus (HBV) of artemisinin, its derivative artesunate and other compounds highly purified from traditional Chinese medicine remedies, were investigated. HBV production by permanently transfected HepG2 2.2.15 cells was determined by measuring the release of surface protein (HBsAg) and HBV-DNA after drug exposure (0.01-100 µM) for 21 days. The forms of HBV-DNA released were investigated by Southern-blotting. Neutral Red retention test was used to evaluate drug-induced toxicity on host cells. The compounds were classified according to their potential interest as follows: (i) none: they had no effect on viral production (daidzein, daidzin, isonardosinon, nardofuran, nardosinon, tetrahydronardosinon and quercetin); (ii) low: they were able to markedly reduce viral production, but also induced toxicity on host cells (berberine and tannic acid) or they had no toxic effect on host cells but only had a moderate ability to reduce viral production (curcumin, baicalein, baicalin, bufalin, diallyl disulphide, glycyrrhizic acid and puerarin); (iii) high: they induced strong inhibition of viral production at concentrations at which host cell viability was not affected (artemisinin and artesunate). Moreover,

artesanate in conjunction with lamivudine had synergic anti-HBV effects, which warrants further evaluation of artemisinin/artesanate as antiviral agents against HBV infection.

Herbal medicines for treating HIV infection and AIDS.

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BACKGROUND: HIV-infected people and AIDS patients often seek complementary therapies including herbal medicines due to reasons such as unsatisfactory effects, high cost, non-availability, or adverse effects of conventional medicines. **OBJECTIVES:** To assess beneficial effects and risks of herbal medicines in patients with HIV infection and AIDS. **SEARCH STRATEGY:** Electronic searches included the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, LILACS, Science Citation Index, the Chinese Biomedical Database, TCMLARS; plus CISCOM, AMED, and NAPRALERT; combined with manual searches. The search ended in December 2004. **SELECTION CRITERIA:** Randomized clinical trials on herbal medicines compared with no intervention, placebo, or antiretroviral drugs in patients with HIV infection, HIV-related disease, or AIDS. The outcomes included mortality, HIV disease progression, new AIDS-defining event, CD4 cell counts, viral load, psychological status, quality of life, and adverse effects. **DATA COLLECTION AND ANALYSIS:** Two authors extracted data independently and assessed the methodological quality of trials according to randomization, allocation concealment, double blinding, and drop-out. **MAIN RESULTS:** Nine randomized placebo-controlled trials involving 499 individuals with HIV infection and AIDS met the inclusion criteria. Methodological quality of trials was assessed as adequate in five full publications and unclear in other trials. Eight different herbal medicines were tested. A compound of Chinese herbs (IGM-1) showed significantly better effect than placebo in improvement of health-related quality of life in 30 symptomatic HIV-infected patients (WMD 0.66, 95% CI 0.05 to 1.27). IGM-1 appeared not to affect overall health perception, symptom severity, CD4 count, anxiety or depression (Burack 1996a). An herbal formulation of 35 Chinese herbs did not affect CD4 cell counts, viral load, AIDS events, symptoms, psychosocial measure, or quality of life (Weber 1999). There was no statistical difference between SPV30 and placebo in new AIDS-defining events, CD4 cell counts, or viral load (Durant 1998) although an earlier pilot trial showed positive effect of SPV30 on CD4 cell count (Durant 1997). Combined treatment of Chinese herbal compound SH and antiretroviral agents showed increased antiviral benefit compared with antiretrovirals alone (Sangkitporn 2004). SP-303 appeared to reduce stool weight ($p = 0.008$) and abnormal stool frequency ($p = 0.04$) in 51 patients with AIDS and diarrhoea (Holodniy 1999). Qiankunning appeared not to affect HIV-1 RNA levels (Shi 2003), Curcumin ineffective in reducing viral load or improving CD4 cell counts (Hellinger 1996), and Capsaicin ineffective in relieving pain associated with HIV-related peripheral neuropathy (Paice 2000). The occurrence of adverse effects was higher in the 35 Chinese herbs preparation (19/24) than in placebo (11/29) (79% versus 38%, $p = 0.003$) (Weber 1999). Qiankunning was associated with stomach discomfort and diarrhoea (Shi 2003). **AUTHORS' CONCLUSIONS:** There is insufficient evidence to support the use of herbal medicines in HIV-infected individuals and AIDS patients. Potential beneficial effects need to be confirmed in large, rigorous trials.

Active site binding modes of curcumin in HIV-1 protease and integrase.

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Structure models for the interaction of curcumin with HIV-1 integrase (IN) and protease (PR) were investigated using computational docking. Curcumin was found to bind preferentially in similar ways to the active sites of both IN and PR. For IN, the binding site is formed by residues Asp64, His67, Thr66, Glu92, Thr93, Asp116, Ser119, Asn120, and Lys159. Docked curcumin contacts the catalytic residues adjacent to Asp116 and Asp64, and near the divalent metal (Mg^{2+}). In the PR docking, the curcumin structure fitted well to the active site, interacting with residues Asp25, Asp29, Asp30, Gly27', Asp29', and Asp30'. The results suggest that o-hydroxyl and/or keto-enol structures are important for both IN and PR inhibitory actions. The symmetrical structure of curcumin seems to play an important role for binding to the PR protein, whereas the keto-enol and only one side of the terminal o-hydroxyl showed tight binding to the IN active site.

Design, synthesis and biological evaluation of heteroaryl diketohexenoic and diketobutanoic acids as HIV-1 integrase inhibitors endowed with antiretroviral activity.

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Highly active anti-retroviral therapy (HAART) using reverse transcriptase (RT) and protease (PR) inhibitors and, more recently, inhibitors of the fusion is currently the best clinical approach in combating acquired immunodeficiency syndrome (AIDS), caused by infection from human immunodeficiency virus type 1 (HIV-1). However, this therapy does not completely eradicate the virus, so that resistant strains easily emerge. The above problem calls urgently for research on inhibitors of further viral targets such as integrase (IN), the third enzyme produced by HIV. Recently, our research group was engaged in studies on conformationally restrained cinnamoyl compounds related to curcumin as anti-IN agents. Compounds containing both a 3,4,5-trihydroxyphenyl group and a carboxylic acid function were potent IN inhibitors active against viral replication. More recently, a promising new class of inhibitors synthesized by Merck Company has emerged, which contain aryl-diketoacid (ADK) functionality. The ADKs selectively inhibited the strand transfer (ST) step of integration and were proven to be effective IN inhibitors in vivo. Our interest in the field of IN inhibitors led us to design pyrrole and indole derivatives containing both a cinnamoyl moiety and a diketoacid group. A number of the cited derivatives were proven potent IN inhibitors, which selectively inhibited the ST step at submicromolar concentrations and were effective against virus replication in HIV-1 infected cells.

Curcumin, a novel p300/CREB-binding protein-specific inhibitor of acetyltransferase, represses the acetylation of histone/nonhistone proteins and histone acetyltransferase-dependent chromatin transcription.

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Acetylation of histones and non-histone proteins is an important post-translational modification involved in the regulation of gene expression in eukaryotes and all viral DNA that integrates into the human genome (e.g. the human immunodeficiency virus). Dysfunction of histone acetyltransferases (HATs) is often associated with the manifestation of several diseases. In this respect, HATs are the new potential targets for the design of therapeutics. In this study, we report that curcumin (diferuloylmethane), a major curcumanoid in the spice turmeric, is a specific inhibitor of the p300/CREB-binding protein (CBP) HAT activity but not of p300/CBP-associated factor, in vitro and in vivo. Furthermore, curcumin could also inhibit the p300-mediated acetylation of p53 in vivo. It specifically represses the p300/CBP HAT activity-dependent transcriptional activation from chromatin but not a DNA template. It is significant that curcumin could inhibit the acetylation of HIV-Tat protein in vitro by p300 as well as proliferation of the virus, as revealed by the repression in syncytia formation upon curcumin treatment in SupT1 cells. Thus, non-toxic curcumin, which targets p300/CBP, may serve as a lead compound in combinatorial HIV therapeutics.

Curcumin inhibits ultraviolet light induced human immunodeficiency virus gene expression.

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Recently, we reported that the herbal drug St. John's Wort is a potent inhibitor of UV-induced HIV-LTR activation in stably transfected HIVcat/HeLa cells. Our previous studies have demonstrated that the activation of p38 MAP kinase (stress-activated protein kinase-2) and NF-kappaB are both required for a full UV-induced HIV gene expression response. In this study we have investigated the mechanism by which curcumin inhibits UV-activated HIV-LTR gene expression. We found that treatment of HIVcat/HeLa cells with micromolar concentrations of curcumin completely abolished UV activation of HIV gene expression. Curcumin treatment at similar doses as those used to inhibit HIV gene expression also effectively blocked UV activation of NF-kappaB, as demonstrated by electrophoretic mobility shift assay. In contrast, curcumin did not inhibit UV-induced phosphorylation of p38 MAP kinase. This observation was also supported by findings that curcumin did not inhibit UV-induced phosphorylation of CREB/ATF-1 and ATF-2. Although curcumin was ineffective in preventing UV-induced p44/42 MAP kinase phosphorylation, the JNK (1 and 2) and AP-1 activation were efficiently blocked by curcumin in HeLa cells. We conclude that the mechanism by which curcumin modulates UV activation of HIV-LTR gene expression mainly involves the inhibition of NF-kappaB activation.

Design and development of integrase inhibitors as anti-HIV agents.

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A review is presented on different categories of compounds that have been studied for the inhibition of the HIV-1 integrase to develop anti-HIV agents. These compounds are: oligonucleotides (double-stranded, triplex, and G-quartet), curcumin analogues, polyhydroxylated aromatic compounds, diketo acids, caffeoyl- and galloyl - based compounds, hydrazides and amides, tetracyclines, and depsides and depsidones. For all these compounds, the important structural features essential for the inhibition of the integrase are pointed out.

Current lead natural products for the chemotherapy of human immunodeficiency virus (HIV) infection.

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A large variety of natural products have been described as anti-HIV agents, and for a portion thereof the target of interaction has been identified. Cyanovirin-N, a 11-kDa protein from Cyanobacterium (blue-green alga) irreversibly inactivates HIV and also aborts cell-to-cell fusion and transmission of HIV, due to its high-affinity interaction with gp120. Various sulfated polysaccharides extracted from seaweeds (i.e., *Nothogenia fastigiata*, *Aghardhiella tenera*) inhibit the virus adsorption process. Ingenol derivatives may inhibit virus adsorption at least in part through down-regulation of CD4 molecules on the host cells. Inhibition of virus adsorption by flavanoids such as (-)-epicatechin and its 3-O-gallate has been attributed to an irreversible interaction with gp120 (although these compounds are also known as reverse transcriptase inhibitors). For the triterpene glycyrrhizin (extracted from the licorice root *Glycyrrhiza radix*) the mode of anti-HIV action may at least in part be attributed to interference with virus-cell binding. The mannose-specific plant lectins from *Galanthus*, *Hippeastrum*, *Narcissus*, *Epipactis helleborine*, and *Listera ovata*, and the N-acetylglucosamine-specific lectin from *Urtica dioica* would primarily be targeted at the virus-cell fusion process. Various other natural products seem to qualify as HIV-cell fusion inhibitors: the siamycins [siamycin I (BMV-29304), siamycin II (RP 71955, BMV 29303), and NP-06 (FR901724)] which are tricyclic 21-amino-acid peptides isolated from *Streptomyces* spp that differ from one another only at position 4 or 17 (valine or isoleucine in each case); the betulinic acid derivative RPR 103611, and the peptides tachyplesin and polyphemusin which are highly abundant in hemocyte debris of the horseshoe crabs *Tachyplesus tridentatus* and *Limulus polyphemus*, i.e., the 18-amino-acid peptide T22 from which T134 has been derived. Both T22 and T134 have been shown to block T-tropic X4 HIV-1 strains through a specific antagonism with the HIV coreceptor or CXCR4. A number of natural products have been reported to interact with the reverse transcriptase, i.e., baicalin, avarol, avarone, psychotrine, phloroglucinol derivatives, and, in particular, calanolides (from the tropical rainforest tree, *Calophyllum lanigerum*) and inophyllums (from the Malaysian tree, *Calophyllum inophyllum*). The natural marine substance illimaquinone would be targeted at the RNase H function of the reverse transcriptase. Curcumin (diferuloylmethane, from turmeric, the roots/rhizomes of *Curcuma* spp), dicaffeoylquinic and dicaffeoyl tartaric acids, L-chicoric acid, and a number of fungal metabolites (equisetin, phomasetin, oteromycin, and integrin acid) have all been proposed as HIV-1 integrase inhibitors. Yet, we have recently shown that L-chicoric acid owes its anti-HIV activity to a specific interaction with the viral envelope gp120 rather than integrase. A number of compounds would be able to inhibit HIV-1 gene expression at the transcription level: the flavonoid chrysin (through inhibition of casein kinase II, the antibacterial peptides melittin (from bee venom) and cecropin, and EM2487, a novel substance produced by *Streptomyces*. (ABSTRACT TRUNCATED)

Enhanced apoptosis mediates inhibition of EBV-transformed lymphoblastoid cell line proliferation by curcumin.

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BACKGROUND: Epstein-Barr virus (EBV)-associated B-cell lymphomas occur more frequently in immunodeficient states such as organ transplantation and HIV infection. We have previously reported that B cell immortalization with EBV was promoted by cyclosporin A (CyA) and that curcumin (Cur), a natural phenol with known antioxidant and antitumor properties, blocked EBV-induced B cell immortalization. In the following experiments we show that Cur inhibits the proliferation of EBV-transformed lymphoblastoid cell lines (LCL) via enhanced apoptosis.

METHODS: LCL were generated by infecting freshly isolated human B cells with EBV (B95-8) for 12 h and coculturing with predetermined optimal concentrations of CyA (500 ng/ml) for 4 weeks. LCL were then either frozen for future use or propagated for immediate experiments. These cells were then plated in 96-well plates with 20 microM Cur or 0.1% DMSO (vehicle control). The number of immortalized colonies/well, cell count, and (3)H uptake were used as an index of immortalization. To assess apoptosis rate LCL were cultured with 0.1% DMSO or Cur (20 microM) for 0, 18, and 42 h in culture flasks and then stained with MC540 and H33342, as markers for apoptosis, and analyzed by FACS.

RESULTS: A profound inhibition of proliferation was seen in the LCL with 20 microM curcumin compared to 0.1% DMSO control. The colony count reduced from 34.5 +/- 3.4 to 0/well (P = 0.005), cell number reduced from 101,250 +/- 12,093 to 3750 +/- 1500/well (P = 0.002), and (3)H uptake reduced from 40,889 +/- 3669 to 70 +/- 5.2/well (P = 0.001). The apoptosis rate of LCL in the DMSO control at 24.07 and 16.87% increased significantly with 20 microM Cur to 76.4 and 95.1% at 18 and 42 h, respectively (P = 0.02).

CONCLUSION: Cur is a potent inhibitor of EBV-transformed LCL. This effect appears to be mediated through enhanced apoptosis. A further investigation of this effect may be useful in prevention and therapy of B-cell lymphoma in immunodeficient patients. Copyright 1999 Academic Press.

Curcumin and curcumin derivatives inhibit Tat-mediated transactivation of type 1 human immunodeficiency virus long terminal repeat.

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The transcription of HIV1 provirus is regulated by both cellular and viral factors. Various evidence suggests that Tat protein secreted by HIV1-infected cells may have additional action in the pathogenesis of AIDS because of its ability to also be taken up by non-infected cells. Curcumin [diferuloylmethane or 1,7-bis-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione] is the yellow pigment in turmeric *Curcuma longa* (Linn). It exhibits a variety of pharmacological effects including antiinflammatory and antiretroviral activities. Here, we demonstrated that curcumin used at 10 to 100 nM inhibited Tat transactivation of HIV1-LTR lacZ by 70 to 80% in HeLa cells. In order to develop more efficient curcumin derivatives, we synthesized and tested in the same experimental system the inhibitory activity of reduced curcumin (C1), which lacks the spatial structure of curcumin; allyl-curcumin (C2), which possesses a condensed allyl derivative on curcumin that plays the role of metal chelator; and tocopheryl-curcumin (C3), which enhances the antioxidant activity of the molecule. Results obtained with C1, C2 and C3 curcumin derivatives showed a significant inhibition (70 to 85%) of Tat transactivation. Despite the fact that tocopheryl-curcumin (C3) failed to scavenge O₂·, this curcumin derivative exhibited the most activity; 70% inhibition was obtained at 1 nM, while only 35% inhibition was obtained with the curcumin.

Plant-derived leading compounds for chemotherapy of human immunodeficiency virus (HIV) infection.

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Many compounds of plant origin have been identified that inhibit different stages in the replication cycle of human immunodeficiency virus (HIV): 1) virus adsorption: chromone alkaloids (schumannificine), isoquinoline alkaloids (michellamines), sulphated polysaccharides and polyphenolics, flavonoids, coumarins (glycocoumarin, licopyranocoumarin) phenolics (caffeic acid derivatives, galloyl acid derivatives, catechinic acid derivatives), tannins and triterpenes (glycyrrhizin and analogues, soyasaponin and analogues); 2) virus-cell fusion: lectins (mannose- and N-acetylglucosamine-specific) and triterpenes (betulinic acid and analogues); 3) reverse transcription; alkaloids (benzophenanthridines, protoberberines, isoquinolines, quinolines), coumarins (calanolides and analogues), flavonoids, phloroglucinols, lactones (protolichesterinic acid), tannins, iridoids (fulvoplumierin) and triterpenes; 4) integration: coumarins (3-substituted-4-hydroxycoumarins), depsidones, O-caffeoyl derivatives, lignans (arctigenin and analogues) and phenolics (curcumin); 5) translation: single chain ribosome inactivating proteins (SCRIP's); 6) proteolytic cleavage (protease inhibition): saponins (ursolic and maslinic acids), xanthones (mangostin and analogues) and coumarins; 7) glycosylation: alkaloids including indolizidines (castanospermine and analogues), piperidines (1-deoxynojirimicin and analogues) and pyrrolizidines (australine and analogues); 8) assembly/release: naphthodianthrone (hypericin and pseudohypericin), photosensitisers (terthiophenes and furoisocoumarins) and phospholipids. The target of action of several anti-HIV substances including alkaloids (O-demethyl-buchenavianine, papaverine), polysaccharides (acemannan), lignans (intheriotherins, schisantherin), phenolics (gossypol, lignins, catechol dimers such as peltatols, naphthoquinones such as conocurvone) and saponins (celasdin B, Gleditsia and Gymnocladus saponins), has not been elucidated or does not fit in the proposed scheme. Only a very few of these plant-derived anti-HIV products have been used in a limited number of patients suffering from AIDS viz. glycyrrhizin, papaverine, trichosanthin, castanospermine, N-butyl-1-deoxynojirimicin and acemannan.

Curcumin analogs with altered potencies against HIV-1 integrase as probes for biochemical mechanisms of drug action.

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We have previously reported the inhibitory activity of curcumin against human immunodeficiency virus type one (HIV-1) integrase. In the present study, we have synthesized and tested analogs of curcumin to explore the structure-activity relationships and mechanism of action of this family of compounds in more detail. We found that two curcumin analogs, dicaffeoylmethane (6) and rosmarinic acid (9), inhibited both activities of integrase with IC₅₀ values below 10 µM. We have previously demonstrated that lysine 136 may play a role in viral DNA binding. We demonstrated equivalent potencies of two curcumin analogs against both this integrase mutant and wild-type integrase, suggesting that the curcumin-binding site and the substrate-binding site may not overlap. Combining one curcumin analog with the recently described integrase inhibitor NSC 158393 resulted in integrase inhibition which was synergistic, reflective of drug-binding sites which may not overlap. We have also determined that these analogs can inhibit binding of the enzyme to the viral DNA but that this inhibition is independent of divalent metal ion. Furthermore, kinetic studies of these analogs suggest that they bind to the enzyme at a slow rate. These studies can

provide mechanistic and structural information which may guide the future design of integrase inhibitors.

Arylamide inhibitors of HIV-1 integrase.

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Based on data derived from a large number of HIV-1 integrase inhibitors, similar structural features can be observed, which consist of two aryl units separated by a central linker. For many inhibitors fitting this pattern, at least one aryl ring also requires ortho bis-hydroxylation for significant inhibitory potency. The ability of such catechol species to undergo in situ oxidation to reactive quinones presents one potential limitation to their utility. In an effort to address this problem, a series of inhibitors were prepared which did not contain ortho bishydroxyls. None of these analogues exhibited significant inhibition. Therefore an alternate approach was taken, whose aim was to increase potency rather than eliminate catechol substructures. In this latter study, naphthyl nuclei were utilized as aryl components, since a previous report had indicated that fused bicyclic rings may afford higher affinity relative to monocyclic phenyl-based systems. In preliminary work with monomeric units, it was found that the 6,7-dihydroxy-2-naphthoic acid (17) (IC₅₀ = 4.7 microM) was approximately 10-fold more potent than its 5,6-dihydroxy isomer 19 (IC₅₀ = 62.4 microM). Of particular note was the dramatic difference in potency between free acid 17 and its methyl ester 21 (IC₅₀ > 200 microM). The nearly total loss of activity induced by esterification strongly indicates that the free carboxylic -OH is important for high potency of this compound. This contrasts with the isomeric 5,6-dihydroxy species 19, where esterification had no effect on inhibitory potency (23, IC₅₀ = 52.7 microM). These data provide evidence that the monomeric 6,7- and 5,6-dihydroxynaphthalenes may be interacting with the enzyme in markedly different fashions. However, when these naphthyl nuclei were incorporated into dimeric structures, significant enhancements in potencies each relative to the monomeric acids were observed, with bis-6,7-dihydroxy analogue 49 and bis-5,6-dihydroxy analogue 51 both exhibiting approximately equal potencies (IC₅₀ values of 0.81 and 0.11 microM, respectively).

Inhibition of HIV-1 Tat-mediated transactivation by quinacrine and chloroquine.

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The replication of human immunodeficiency virus type 1 (HIV-1) requires cellular components to interact with regulatory elements located in the long terminal repeat (LTR) as well as viral proteins Tat and Rev. Several well known signaling transduction inhibitors were tested to determine their effects on the Tat-mediated transactivation using a transfection assay with the bacterial chloramphenicol acetyltransferase gene under the control of the HIV-1 LTR. The protein kinase C inhibitors curcumin and staurosporine, but not a tyrosine kinase inhibitor herbimycin A, inhibited Tat-mediated LTR-driven transactivation. Two antimalarial drugs quinacrine and chloroquine, that are also arachidonic acid metabolism inhibitors, were found to inhibit the Tat-mediated LTR-driven gene expression. Another inhibitor of arachidonic acid metabolism 4-bromophenacyl bromide was also found to inhibit Tat-mediated gene expression driven by HIV-1 LTR. However, the antimalarial

drug quinine elicited no effects on Tat-mediated transactivation. These results suggest that the anti-arachidonic acid metabolism properties of quinacrine and chloroquine may be responsible for their ability to inhibit Tat-mediated LTR-regulated gene expression.

Antiretroviral agents as inhibitors of both human immunodeficiency virus type 1 integrase and protease.

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The human immunodeficiency virus type one integrase (HIV-1 integrase) is required for integration of a double-stranded DNA copy of the viral RNA genome into a host chromosome and for HIV replication. We have previously reported that phenolic moieties in compounds such as flavones, caffeic acid phenethyl ester (CAPE), tyrphostins, and curcumin confer inhibitory activity against HIV-1 integrase. We have investigated the actions of several recently described protease inhibitors, possessing novel structural features, on HIV-1 integrase. NSC 158393, which contains four 4-hydroxycoumarin residues, was found to exhibit antiviral, antiprotease, and antiintegrase activity. Both the DNA binding and catalytic activities (3'-processing and strand transfer) of integrase were inhibited at micromolar concentrations. Disintegration catalyzed by an integrase mutant containing only the central catalytic domain was also inhibited, indicating that the binding site for these compounds resides in the central 50-212 amino acids of HIV-1 integrase. Binding at or near the integrase catalytic site was also suggested by a global inhibition of the choice of attacking nucleophile in the 3'-processing reaction. NSC 158393 inhibited HIV-2, feline, and simian immunodeficiency virus integrases while eukaryotic topoisomerase I was inhibited at higher concentrations, suggesting selective inhibition of retroviral integrases. Molecular modeling studies revealed that the two hydroxyls and two carbonyl moieties in NSC 158393 may represent essential elements of the pharmacophore. Antiviral efficacy was observed with NSC 158393 derivatives that inhibited both HIV protease and integrase, and the most potent integrase inhibitors also inhibited HIV protease. Hydroxycoumarins may provide lead compounds for development of novel antiviral agents based upon the concurrent inhibition of two viral targets, HIV-1 integrase and protease.

Effects of tyrphostins, protein kinase inhibitors, on human immunodeficiency virus type 1 integrase.

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Efficient replication of HIV-1 requires establishment of the proviral state, i.e., the integration of a DNA copy of the viral genome, synthesized by reverse transcriptase, into a chromosome of the host cell. Integration is catalyzed by the viral integrase protein. We have previously reported that phenolic moieties in compounds such as naphthoquinones, flavones, caffeic acid phenethyl ester (CAPE), and curcumin confer inhibitory activity against HIV-1 integrase. We have extended these findings by examining the effects of tryphostins, tyrosine kinase inhibitors. The catalytic activities of HIV-1 integrase and the formation of enzyme-DNA complexes using photocross-linking were examined. Both steps of the integration reaction, 3'-processing and strand transfer, were inhibited by tyrphostins at micromolar concentrations. The DNA binding activity of integrase was inhibited at

higher concentrations of tyrphostins. Disintegration, an apparent reversal of the strand transfer reaction, catalyzed by an integrase mutant lacking the N-terminal zinc finger and C-terminal DNA binding domains is also inhibited by tyrphostins, indicating that the binding site for these compounds resides in the central catalytic core of HIV-1 integrase. Binding of tyrphostins at or near the integrase catalytic site was also suggested by experiments showing a global inhibition of the choice of attacking nucleophile in the 3'-processing reaction. None of the tyrphostins tested inhibited eukaryotic topoisomerase I, even at 100 microM, suggesting selectivity for integrase inhibition. Molecular-modeling studies have revealed that, after energy minimization, several tyrphostins may adopt folded conformations. The similarity of the tyrphostin family to other families of inhibitors is discussed. Tyrphostins may provide lead compounds for development of novel antiviral agents for the treatment of acquired immunodeficiency syndrome based upon inhibition of HIV-1 integrase.

Hydroxylated aromatic inhibitors of HIV-1 integrase.

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Efficient replication of HIV-1 requires integration of a DNA copy of the viral genome into a chromosome of the host cell. Integration is catalyzed by the viral integrase, and we have previously reported that phenolic moieties in compounds such as flavones, caffeic acid phenethyl ester (CAPE, 2), and curcumin confer inhibitory activity against HIV-1 integrase. We now extend these findings by performing a comprehensive structure-activity relationship using CAPE analogues. Approximately 30 compounds have been prepared as HIV integrase inhibitors based on the structural lead provided by CAPE, which has previously been shown to exhibit an IC₅₀ value of 7 microM in our integration assay. These analogues were designed to examine specific features of the parent CAPE structure which may be important for activity. Among the features examined for their effects on inhibitory potency were ring substitution, side chain length and composition, and phenyl ring conformational orientation. In an assay which measured the combined effect of two sequential steps, dinucleotide cleavage and strand transfer, several analogues have IC₅₀ values for 3'-processing and strand transfer lower than those of CAPE. Inhibition of strand transfer was assayed using both blunt-ended and "precleaved" DNA substrates. Disintegration using an integrase mutant lacking the N-terminal zinc finger and C-terminal DNA-binding domains was also inhibited by these analogues, suggesting that the binding site for these compounds resides in the central catalytic core. Several CAPE analogues were also tested for selective activity against transformed cells. Taken together, these results suggest that the development of novel antiviral agents for the treatment of acquired immune deficiency syndrome can be based upon inhibition of HIV-1 integrase.

Inhibition of human immunodeficiency virus type-1 integrase by curcumin.

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Curcumin (diferuloylmethane) is the yellow pigment in turmeric (*Curcuma longa* L.) that is widely used as a spice, food coloring (curry) and preservative. Curcumin exhibits a variety of pharmacological effects including antitumor, anti-inflammatory, and anti-infectious activities and is currently in clinical trials for AIDS patients. The effects of curcumin have been determined on purified human immunodeficiency virus type 1 (HIV-1) integrase. Curcumin has an inhibitory concentration₅₀ (IC₅₀) for strand transfer of 40 microM. Inhibition of an integrase deletion mutant containing only amino acids 50-212 suggests that curcumin interacts with the integrase catalytic core. Two structural analogs, methyl cinnamate and chlorogenic acid, were inactive. Energy minimization studies suggest that the anti-integrase activity of curcumin could be due to an intramolecular stacking of two phenyl rings that brings the hydroxyl groups into close proximity. The present data suggest that HIV-1 integrase inhibition may contribute to the antiviral activity of curcumin. These observations suggest new strategies for antiviral drug development that could be based upon curcumin as a lead compound for the development of inhibitors of HIV-1 integrase.

Inhibition of the HIV-1 and HIV-2 proteases by curcumin and curcumin boron complexes.

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Curcumin, a relatively non-toxic natural product isolated from *Curcuma longa*, is a modest inhibitor of the HIV-1 (IC₅₀ = 100 microM) and HIV-2 (IC₅₀ = 250 microM) proteases. Simple modifications of the curcumin structure raise the IC₅₀ value but complexes of the central dihydroxy groups of curcumin with boron lower the IC₅₀ to a value as low as 6 microM. The boron complexes are also time-dependent inactivators of the HIV proteases. The increased affinity of the boron complexes may reflect binding of the orthogonal domains of the inhibitor in intersecting sites within the substrate-binding cavity of the enzyme, while activation of the alpha, beta-unsaturated carbonyl group of curcumin by chelation to boron probably accounts for time-dependent inhibition of the enzyme.

Three inhibitors of type 1 human immunodeficiency virus long terminal repeat-directed gene expression and virus replication.

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Transcription of type 1 human immunodeficiency virus (HIV-1) provirus is governed by the viral long terminal repeat (LTR). Drugs can block HIV-1 replication by inhibiting activity of its LTR. We report that topotecan, beta-lapachone, and curcumin are potent and selective inhibitors of HIV-1 LTR-directed gene expression, at concentrations that have minor effects on cells. At these concentrations, each drug inhibited p24 antigen production in cells either acutely or chronically infected with HIV-1. Their target is transcriptional function of the LTR.

An antimalarial extract from neem leaves is antiretroviral.

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An acetone-water neem leaf extract with antimalarial activity was evaluated in vitro at 5 microg/ml for inhibition of adhesion of malaria parasite-infected erythrocytes and cancer cells to endothelial cells, and at 10 microg/ml for protection of lymphocytes against invasion by HIV. The extract was also evaluated in 10 patients with HIV/AIDS at 1000 mg daily for 30 d. The mean binding of infected erythrocytes and cancer cells per endothelial cell was 15 and 11 respectively in the absence of the extract, and 0 and 2 respectively in with the extract. In the absence and presence of the extract, 0% and 75%, respectively, of lymphocytes were protected. In the treated patients, haemoglobin concentration, mean CD4+ cell count and erythrocyte sedimentation rate, which were initially 9.8 g/dl, 126 cells/microl and 90 mm/h respectively, improved to 12.1 g/dl, 241 cells/microl and 49 mm/h. Mean bodyweight and platelet count, initially 57 kg and $328 \times 10(3)/\text{mm}^3$ respectively, increased to 60 kg and $359 \times 10(3)/\text{mm}^3$. No adverse effects were observed during the study. The extract showed antiretroviral activity with a mechanism of action that may involve inhibition of cytoadhesion. The results may help in the development of novel antiretroviral and antimalarial drugs.

Bactericidal activity of organic extracts from *Flourensia cernua* DC against strains of *Mycobacterium tuberculosis*.

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BACKGROUND: Tuberculosis is a chronic disease caused mainly by *Mycobacterium tuberculosis*. The emergence of antibiotic-resistant strains of this species underscores the need for novel effective drugs against resistant mycobacteria as first-line antituberculosis medications. **METHODS:** Crude aqueous (obtained by decoction, in accordance with the traditional mode of preparation), methanol, acetone, and hexane extracts from aerial parts of *Artemisia ludoviciana* Nutt., *Chenopodium ambrosioides* L., *Marrubium vulgare* L., *Mentha spicata* L., and *Flourensia cernua* DC were assessed for their ability to either inhibit the growth of or kill *M. tuberculosis* strains H37Rv and CIBIN:UMF:15:99, the former being sensitive to, and the latter resistant to, streptomycin, isoniazide, rifampin, ethambutol, and pyrazinamide. These five plant species are used in Mexico to treat respiratory disorders. **RESULTS:** *Flourensia cernua* was the uniquely active plant among those evaluated. Its hexane and acetone extracts not only inhibited the growth of but killed *M. tuberculosis*. The hexane extract showed a minimal inhibitory concentration (MIC) of 50 and 25 microg/mL against sensitive and resistant strains, respectively; the acetone extract was active against only CIBIN:UMF:15:99 (MIC = 100 microg/mL). **CONCLUSIONS:** The hexane extract from *F. cernua* leaves could be an important source of bactericidal compounds against multidrug-resistant *M. tuberculosis*.

Activity against multidrug-resistant *Mycobacterium tuberculosis* in Mexican plants used to treat respiratory diseases.

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The increase of multidrug-resistant *Mycobacterium tuberculosis* (MDR-TB) demands the search for alternative antimycobacterial drugs. The aim of this study was to evaluate plants used in Mexican traditional medicine to treat respiratory diseases for activity against MDR-TB. A group of 22 plants was screened for activity against *Mycobacterium tuberculosis* H37Rv and *Mycobacterium avium* at concentrations from 50 to 200 microg/mL. The antimycobacterial effect was determined by a microcolorimetric assay with Alamar blue dye. None of the aqueous extracts had antimycobacterial activity. Hexane extracts from *Artemisia ludoviciana*, *Chamaedora tepejilote*, *Lantana hispida*, *Juniperus communis* and *Malva parviflora*, and methanol extracts from *Artemisia ludoviciana* and *Juniperus communis* inhibited the growth of *Mycobacterium tuberculosis*. *Mycobacterium avium* was inhibited by *Juniperus communis* hexane extract and by *Malva parviflora* methanol extract. The active extracts were tested against mono-resistant variants of *Mycobacterium tuberculosis* H37Rv (isoniazid, rifampin, streptomycin and ethambutol resistant) and the hexane extract of *Lantana hispida* showed the best activity. *Lantana hispida* hexane extract was also active against a group of MDR-TB clinical isolates. In contrast, it did not inhibit the growth of non-tuberculous mycobacteria. The hexane extract of *Lantana hispida* was fractionated by column chromatography and one of its fractions (FVI) inhibited the growth of all the MDR-TB clinical isolates at concentrations up to 25 microg/mL. This study supports the fact that selecting plants by ethnobotanical criteria enhances the probability of finding species with activity against mycobacteria, and our results point to *Lantana hispida* as an important source of potential compounds against MDR-TB. Copyright 2003 John Wiley & Sons, Ltd.

Nitric oxide synthase and cytokines gene expression analyses in *Leishmania*-infected RAW 264.7 cells treated with an extract of *Pelargonium sidoides* (Eps 7630).

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A modern aqueous-ethanolic formulation of the roots of *Pelargonium sidoides* (Eps 7630), elaborated from the traditional herbal medicine used in areas of southern Africa, is effectively employed for the treatment of ENT and respiratory tract infections in modern phytotherapy. Previous studies have demonstrated antibacterial and immunomodulatory activities. To gain insight into the mode of action at the molecular level, gene expression analyses for the inducible nitric oxide synthase and the cytokines interleukin (IL)-1, IL-12, IL-18, tumour necrosis factor (TNF)-alpha, interferon (IFN)-alpha, and IFN-gamma, were performed using reverse transcription-polymerase chain reaction (RT-PCR). The experiments were carried out in parallel in non-infected and in *Leishmania major*-infected RAW 264.7 cells and the expression profiles were compared with those mediated by IFN-gamma+LPS. Eps 7630 induced low mRNA levels in non-infected cells, and it considerably up-regulated the transcript expressions in parasitised cells. Interestingly, and in contrast

to activation by IFN-gamma+LPS, Eps 7630 also stimulated infected cells to produce IFN-gamma mRNA. A similar expression profile was observed for the methanol-insoluble fraction (MIF) of Eps 7630 and gallic acid, a trace constituent of the extract, while the methanol-soluble fraction and umckalin, an exclusive and representative member of the occurring coumarins, proved to be devoid of any remarkable gene-inducing capabilities. The present results provide not only convincing support for the improvement of immune functions as previously demonstrated in functional bioassays, but also evidence for activation at the transcriptional level and suggest that the underlying inducing principle is located in the MIF.

In vitro activity of extracts and constituents of Pelargonium against rapidly growing mycobacteria.

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Extracts of the roots of plants of the Geraniaceae family have been used for many years in South Africa as native herbal remedies and there is circumstantial evidence for efficacy in the treatment of pulmonary tuberculosis. We have examined dried roots of *Pelargonium reniforme* and *P. sidoides* for antibacterial activity against rapidly growing mycobacteria. Fractions with activity against *Mycobacterium aurum* and *M. smegmatis* were obtained from both plant species by bioassay-guided fractionation of n-hexane extracts and were found to contain mixtures of straight-chain fatty acids. Analysis by gas chromatography-mass spectrometry (GC-MS) of the corresponding fatty acid methyl esters revealed structures with chain lengths ranging from C12 to C26. Unsaturated compounds were analysed as the corresponding dimethyl disulfide adducts to determine double-bond positions. Active mixtures differed in the relative abundance of their components, but all contained 16:0 (palmitic), Delta9-18:1 (oleic) and Delta9,12-18:2 (linoleic acid) as the major components. When tested against *M. aurum*, *M. smegmatis* and other rapidly growing mycobacteria (*M. fortuitum*, *M. abscessus* and *M. phlei*), all saturated compounds except 12:0 were devoid of antimycobacterial activity, whereas unsaturated compounds showed antimycobacterial activity related to their degree of unsaturation, their chain length and the bacterial species tested. The most potent compound was linoleic acid, with MIC of 2 mg/l against *M. aurum*. Copyright 2004 Elsevier B.V.

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Immunomodulatory principles of Pelargonium sidoides.

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Extracts and isolated constituents (coumarins and phenols) of *Pelargonium sidoides* DC, a plant species used in folk medicine by the Southern African native population, were evaluated for their effects on nonspecific immune functions. Although this herbal medicine is also successfully employed in modern phytotherapy in Europe to cure infectious

diseases of the respiratory tract, the scientific basis of its remedial effects is still unclear. Thus, functional bioassays including an in vitro model for intracellular infection with Leishmania parasites, an extracellular Leishmania growth assay, a fibroblast-virus protection assay (IFN activity), a fibroblast-lysis assay (TNF activity) and a biochemical assay for inorganic nitric oxides (iNO) were employed. None of the test samples revealed significant activity against extracellular, promastigote Leishmania donovani, the causative agent of human visceral leishmaniasis. In contrast, apart from the coumarin samples, all the Pelargonium extracts (EC(50) <0.1-3.3 microg/mL), gallic acid (EC(50) 4.4 microg/mL) and its methyl ester (EC(50) 12.5 microg/mL) significantly reduced the intracellular survival of L. donovani amastigotes within murine macrophages. These data indicate that the samples acted indirectly on Leishmania parasites, possibly by activating leishmanicidal macrophage functions. Macrophage activation was confirmed by detection of tumour necrosis factor (TNF-alpha) and inorganic nitric oxides (iNO) in supernatants of sample-treated macrophage cultures. Synthesis of iNO is a well-known effector mechanism of macrophages against microorganisms such as Leishmania. Interestingly, blocking iNO-synthase with L-NMMA had no substantial effect on sample-induced intracellular Leishmania kill. From bioassay-guided fractionation, gallic acid and its methyl ester present in large amounts in P. sidoides and in its active extracts, were identified as the prominent immunomodulatory principle for this herbal medicine. The results, when taken together with recent reported antibacterial activity, provide a rational basis for both the traditional and the present utilization of P. sidoides in the claimed conditions. Copyright 2001 John Wiley & Sons, Ltd.

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Antibacterial activity of extracts and constituents of Pelargonium sidoides and Pelargonium reniforme.

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The antibacterial activity of extracts and isolated constituents (scopoletin, umckalin, 5,6,7-trimethoxycoumarin, 6,8-dihydroxy-5,7-dimethoxycoumarin, (+)-catechin, gallic acid and its methyl ester) of Pelargonium sidoides and Pelargonium reniforme (Geraniaceae), plant species used in folk medicine by the Southern African native population, was evaluated against 8 microorganisms, including 3 Gram-positive (Staphylococcus aureus, Streptococcus pneumoniae, and beta-hemolytic Streptococcus 1451) and 5 Gram-negative bacteria (Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Haemophilus influenzae). Minimum inhibitory concentrations (MICs) varied with the preparation of the extracts and microorganisms tested, from about 0.6 mg/ml for aqueous phases to over 10 mg/ml for crude Pelargonium extracts. With the exception of the ineffective (+)-catechin, all the potentially active compounds exhibited antibacterial activities with MICs of 200-1000 micrograms/ml. The results provide for a rational basis of the traditional use of the titled Pelargonium species.

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

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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.

Glutathione deficiency is associated with impaired survival in HIV disease.

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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.

1: Proc Natl Acad Sci U S A 1998 Mar 17;95(6):3071-6

Glutathione levels in antigen-presenting cells modulate Th1 versus Th2 response patterns.

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Current thinking attributes the balance between T helper 1 (Th1) and Th2 cytokine response patterns in immune responses to the nature of the antigen, the genetic composition of the host, and the cytokines involved in the early interaction

between T cells and antigen-presenting cells. Here we introduce glutathione, a tripeptide that regulates intracellular redox and other aspects of cell physiology, as a key regulatory element in this process. By using three different methods to deplete glutathione from T cell receptor transgenic and conventional mice and studying in vivo and/or in vitro responses to three distinct antigens, we show that glutathione levels in antigen-presenting cells determine whether Th1 or Th2 response patterns predominate. These findings present new insights into immune response alterations in HIV and other diseases. Further, they potentially offer an explanation for the well known differences in immune responses in "Th1" and "Th2" mouse strains.

1: 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

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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 &mgr;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.

.....Glutamine-antioxidant supplementation increases body cell mass in AIDS patients with weight loss: a randomized, double-blind controlled trial.

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Loss of body cell mass, the active functioning tissue of the body, commonly occurs in patients with human immunodeficiency virus (HIV) infection, and the extent of wasting is related to the length of survival. We evaluated the anabolic role of the

amino acid L-glutamine (GLN) and antioxidants in a double-blind, placebo-controlled trial in 26 patients with > 5% weight loss since disease onset. Subjects received GLN-antioxidants (40 g/d) in divided doses or glycine (40 g/d) as the placebo for 12 wk. Throughout the study, the subjects were seen weekly by a nutritionist, and body weight, bioelectric impedance assessment, and nutritional counselling were performed. Twenty-one subjects completed the study, and the groups were well matched.

The 5 patients excluded from analysis all met a priori exclusion criteria. Over 3 mo, the GLN-antioxidant group gained 2.2 kg in body weight (3.2%), whereas the control group gained 0.3 kg (0.4%, $P = 0.04$ for difference between groups). The GLN-antioxidant group gained 1.8 kg in body cell mass, whereas the control group gained 0.4 kg ($P = 0.007$). Intracellular water increased in the GLN-antioxidant group but not in the control group. In conclusion, GLN-antioxidant nutrient supplementation can increase body weight, body cell mass, and intracellular water when compared with placebo supplementation. GLN-antioxidant supplementation provides a highly cost-effective therapy for the rehabilitation of HIV+ patients with weight loss.

L-carnitine deficiency in AIDS patients.

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OBJECTIVE: To evaluate carnitine (3-hydroxy-4-N-trimethyl-ammonibutanoate) deficiency in AIDS patients by measuring serum total, free and short-chain carnitine concentrations.

DESIGN: We conducted an open study. **SETTING:** All patients were seen at the Infectious Diseases Clinic, Universita 'La Sapienza', Rome, Italy. **PATIENTS, PARTICIPANTS:**

Twenty-nine AIDS patients, aged 27-41 years, with a previous history of drug use; and 14 healthy age- and sex-matched controls were studied. **INTERVENTIONS:** Study subjects were administered 500-800 mg zidovudine daily for 2 to 28 months (8 +/- 6 months). **MAIN OUTCOME MEASURES:** Carnitine deficiency was suspected in study participants prior to data collection because of previously reported cardiac symptoms, muscle weakness, hypometabolism and/or cachexia. **RESULTS:** A marked decrease in total and free carnitine was observed in 21 (72%) subjects. Nine of these patients also had low levels of short-chain carnitine. **CONCLUSIONS:** AIDS patients may become carnitine-depleted and therefore at risk for alterations in fatty-acid oxidation and energy supply.

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

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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 cysteine 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.

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Abnormal glutathione and sulfate levels after interleukin 6 treatment and in tumor-induced cachexia.

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Excessive urea excretion associated with a negative nitrogen balance and massive loss of skeletal muscle mass (cachexia) is a frequent life threatening complication in malignancies and HIV infection. As these patients have often elevated interleukin-6 (IL-6) and abnormally low cystine levels, we have now determined the intracellular levels of glutathione and other cysteine derivatives in the liver and muscle tissue of IL-6-treated or tumor-bearing C57BL/6 mice. IL-6 treatment or inoculation of the MCA-105 fibrosarcoma caused a significant increase in hepatic gamma-glutamyl-cysteine synthetase activity and a decrease in the sulfate level, glutamine/urea ratio, and glutamine/glutamate ratio, suggesting that a decrease of the proton generating cysteine catabolism in the liver may increase carbamoyl-phosphate synthesis and urea formation at the expense of net glutamine synthesis. Treatment with cysteine, conversely, caused an increase in sulfate, glutamine/urea ratios, and glutamine/glutamate ratios and may thus be a useful therapeutic tool in clinical medicine. In contrast to the liver, muscle tissue of tumor-bearing mice showed decreased glutathione and increased sulfate levels, suggesting that the cysteine pool may be drained by an increased cysteine catabolism in this tissue. The findings indicate that tumor cachexia is triggered initially by IL-6 and is later sustained by processes driven by an abnormal cysteine metabolism in different organs. -Hack, V., Gross, A., Kinscherf, R., Bockstette, M., Fiers, W., Berke, G., and Droge, W. Abnormal glutathione and sulfate levels after interleukin 6 treatment and in tumor-induced cachexia.

The possible role of glutamine in some cells of the immune system and the possible consequence for the whole animal.

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Glutamine is important for the function of lymphocytes and macrophages. A role for the high rate of glutamine utilisation by these cells is presented. Since muscle synthesises, stores and releases glutamine, this tissue may play a role in the immune response. Since the number of immune cells utilising glutamine may be large, the demand for glutamine from muscle, especially during trauma, sepsis or burns, may be very high. A speculative suggestion is put forward that this requirement for glutamine from muscle may play a role in cachexia under some of these conditions.

Dehydroepiandrosterone sulfate (DHEAS) and testosterone: relation to HIV illness stage and progression over one year.

Ferrando SJ, Rabkin JG, Poretsky L.

Department of Psychiatry, Cornell University Medical College, New York, New York, USA.

This study explored associations between serum dehydroepiandrosterone sulfate (DHEAS), free and total testosterone levels, and HIV illness markers, including viral load, and the behavioral problems of fatigue and depressed mood. Subjects were 169 HIV-positive men evaluated at baseline, 6, and 12 months for levels of DHEAS, total and free testosterone, HIV RNA, CD4, HIV symptoms, opportunistic illnesses, fatigue, and depression. Men with AIDS (N = 105), compared with men with less advanced illness, had lower mean levels of DHEAS. Baseline DHEAS was positively correlated with CD4 count, HIV symptom severity, and was inversely correlated with HIV RNA. Baseline DHEAS below the laboratory reference range (96 microg/dl) was associated with history of opportunistic infections and malignancies (adjusted odds ratio [OR], 4.4; 95% confidence interval [CI], 1.9-10.4) and with incidence of these complications or death over 1 year (adjusted OR, 2.6; 95% CI, 1-7.2). Initiating protease inhibitor combination therapy was associated with an increase in DHEAS over 6 months. Free testosterone was inversely correlated with HIV RNA, but there were no other significant associations between testosterone and HIV illness markers. No hormone was related to fatigue or depression. This study confirms that low serum DHEAS is associated with HIV illness markers, including viral load, and carries negative prognostic value. Further, protease inhibitor therapy may result in increased circulating DHEAS.

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The Th1-Th2 hypothesis of HIV infection: new insights.

Clerici M, Shearer GM

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In their earlier, much quoted, viewpoint article, Mario Clerici and Gene Shearer examined the role of T helper 1 (Th1)- and Th2-type responses in immune dysregulation associated with human immunodeficiency virus (HIV) infection. In this article, they consider the complications of a Th1-Th2 model raised by the nomenclature, discuss the issue of cytokine production by non-T cells, and compare data obtained from T-cell clones with heterogeneous populations of leukocytes from patients. They define Th-cell responses and cytokine profiles as 'type 1' and 'type 2', and reemphasize the importance of strong cellular immune responses, along with the cytokines that augment and maintain such responses, in protective immunity against HIV infection and AIDS progression. Finally, they present a model of activation-induced, cytokine-modulated, programmed cell death as a major factor in the pathogenesis of HIV infection and AIDS.

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

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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.

The 1996 Albert Lasker Medical Research Awards. The discovery of endothelium-derived relaxing factor and its importance in the identification of nitric oxide.

Furchgott RF.

Department of Pharmacology, State University of New York, Health Science Center at Brooklyn, NY 11203, USA.

The discovery of endothelium-derived relaxing factor (EDRF) and its importance in the identification of nitric oxide (NO) originated with studies using rabbit aorta to examine drug-receptor interactions in vascular smooth muscle. Smooth muscle relaxation by acetylcholine and a number of other agonists was found to be dependent on the presence of endothelial cells, which, when stimulated by the agonist, released a diffusible, very labile, nonprostanoid substance, termed EDRF, that acted on vascular smooth muscle cells to activate relaxation. The characteristics of EDRF, when released from endothelial cells, were similar to the characteristics of NO. It is now established that EDRF, either as NO or some related nitrosyl substance, has a major role in a variety of important biological processes, including the regulation of vascular tone, local blood flow, and blood pressure, inhibition of platelet aggregation and adhesion, and involvement in postischemic reperfusion, memory function, and central nervous system degenerative diseases.

1: Annu Rev Pharmacol Toxicol 1995;35:1-27

A research trail over half a century.

Furchgott RF.

Department of Pharmacology, State University of New York Health Science Center at Brooklyn 11203, USA.

The author describes his major research activities from the time of his PhD thesis work (1937-1940) on properties of erythrocyte membranes to the present. His involvement in research on circulatory shock during World War II led to a continuing interest in the physiology and pharmacology of smooth muscle and cardiac muscle. From 1956 to 1978, his

main areas of research were photorelaxation of blood vessels, factors influencing contractility of cardiac muscle, peripheral adrenergic mechanisms, and receptor theory. The major findings of his and his collaborators in these areas are described. He then recounts how an accidental finding in an experiment in 1978 on preparations of rabbit aorta eventually led to the discovery of endothelium dependent relaxation and the endothelium-derived relaxing factor (EDRF); and how additional findings led him to propose in 1986 that EDRF is nitric oxide.

Nitric oxide donors and cardiovascular agents modulating the bioactivity of nitric oxide: an overview.

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Nitric Oxide Research Group (L.J.I.), Molecular and Medical Pharmacology, Center for the Health Sciences, University of California, Los Angeles.

Nitric oxide (NO) mediates multiple physiological and pathophysiological processes in the cardiovascular system. Pharmacological compounds that release NO have been useful tools for evaluating the pivotal role of NO in cardiovascular physiology and therapeutics. These agents constitute two broad classes of compounds, those that release NO or one of its redox congeners spontaneously and those that require enzymatic metabolism to generate NO. In addition, several commonly used cardiovascular drugs exert their beneficial action, in part, by modulating the NO pathway. Here, we review these classes of agents, summarizing their fundamental chemistry and pharmacology, and provide an overview of their cardiovascular mechanisms of action.

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Glutamine-antioxidant supplementation increases body cell mass in AIDS patients with weight loss: a randomized, double-blind controlled trial.

Shabert JK, Winslow C, Lacey JM, Wilmore DW.

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Loss of body cell mass, the active functioning tissue of the body, commonly occurs in patients with human immunodeficiency virus (HIV) infection, and the extent of wasting is related to the length of survival. We evaluated the anabolic role of the amino acid L-glutamine (GLN) and antioxidants in a double-blind, placebo-controlled trial in 26 patients with > 5% weight loss since disease onset. Subjects received GLN-antioxidants (40 g/d) in divided doses or glycine (40 g/d) as the placebo for 12 wk. Throughout the study, the subjects were seen weekly by a nutritionist, and body weight, bioelectric impedance assessment, and nutritional counseling were performed. Twenty-one subjects completed the study, and the groups were well matched. The 5 patients excluded from analysis all met a priori exclusion criteria. Over 3 mo, the GLN-antioxidant group gained 2.2 kg in body weight (3.2%), whereas the control group gained 0.3 kg (0.4%, $P = 0.04$ for difference between groups). The GLN-antioxidant group gained 1.8 kg in body cell mass, whereas the control group gained 0.4 kg ($P = 0.007$). Intracellular water increased in the GLN-antioxidant group but not in the control group. In conclusion, GLN-antioxidant nutrient supplementation can increase body weight, body cell mass, and intracellular water when compared with placebo supplementation. GLN-antioxidant supplementation provides a highly cost-effective therapy for the rehabilitation of HIV+ patients with weight loss.

Abnormal glutathione and sulfate levels after interleukin 6 treatment and in tumor-induced cachexia.

Hack V, Gross A, Kinscherf R, Bockstette M, Fiers W, Berke G, Droge W.

Division of Immunochemistry, Deutsches Krebsforschungszentrum, Heidelberg, Germany.

Excessive urea excretion associated with a negative nitrogen balance and massive loss of skeletal muscle mass (cachexia) is a frequent life threatening complication in malignancies and HIV infection. As these patients have often elevated interleukin-6 (IL-6) and abnormally low cystine levels, we have now determined the intracellular levels of glutathione and other cysteine derivatives in the liver and muscle tissue of IL-6-treated or tumor-bearing C57BL/6 mice. IL-6 treatment or inoculation of the MCA-105 fibrosarcoma caused a significant increase in hepatic gamma-glutamyl-cysteine synthetase activity and a decrease in the sulfate level, glutamine/urea ratio, and glutamine/glutamate ratio, suggesting that a decrease of the proton generating cysteine catabolism in the liver may increase carbamoyl-phosphate synthesis and urea formation at the expense of net glutamine synthesis. Treatment with cysteine, conversely, caused an increase in sulfate, glutamine/urea ratios, and glutamine/glutamate ratios and may thus be a useful therapeutic tool in clinical medicine. In contrast to the liver, muscle tissue of tumor-bearing mice showed decreased glutathione and increased sulfate levels, suggesting that the cysteine pool may be drained by an increased cysteine catabolism in this tissue. The findings indicate that tumor cachexia is triggered initially by IL-6 and is later sustained by processes driven by an abnormal cysteine metabolism in different organs.- Hack, V., Gross, A., Kinscherf, R., Bockstette, M., Fiers, W., Berke, G., and Droge, W. Abnormal glutathione and sulfate levels after interleukin 6 treatment and in tumor-induced cachexia.

Lymphocyte function in anergic patients.

Rode HN, Christou NV, Bubenik O, Superina R, Gordon J, Meakins JL, MacLean LD.

The lymphocyte function of anergic surgical patients who are at increased risk for sepsis and mortality was studied. In vitro lymphocyte responses appear to be normal in most instances, in that over 80% of patients showed a normal response in a standardized mixed leucocyte culture reaction. Similarly, 56% of the lymphocytes from anergic patients showed a positive in vitro proliferative response with PPD. The ability of in vitro-activated lymphocytes to elicit a skin reaction was determined by culturing the cells of anergic patients with PPD and then reinjecting the lymphocytes or their supernatants intradermally into the original donor. When there was a positive proliferative response to PPD in vitro, the reinjected cells or supernatant elicited a positive skin reaction in 79% of the anergic patients. In contrast, a skin reaction was obtained in less than 20% of the instances when there was no in vitro proliferation to PPD or when the cells were cultured without antigen. These results suggest that one of the acquired immune defects in these anergic patients is an in vivo block of lymphocyte activation.

The possible role of glutamine in some cells of the immune system and the possible consequence for the whole animal.

Newsholme EA. Department of Biochemistry, University of Oxford, United Kingdom.

Glutamine is important for the function of lymphocytes and macrophages. A role for the high rate of glutamine utilisation by these cells is presented. Since muscle synthesises, stores and releases glutamine, this tissue may play a role in the immune response. Since the number of immune cells utilising glutamine may be large, the demand for glutamine from muscle, especially during trauma, sepsis or burns, may be very high. A speculative suggestion is put forward that this requirement for glutamine from muscle may play a role in cachexia under some of these conditions.

Dehydroepiandrosterone sulfate (DHEAS) and testosterone: relation to HIV illness stage and progression over one year.

Ferrando SJ, Rabkin JG, Poretsky L. Department of Psychiatry, Cornell University Medical College, New York, New York, USA.

This study explored associations between serum dehydroepiandrosterone sulfate (DHEAS),

free and total testosterone levels, and HIV illness markers, including viral load, and the behavioral problems of fatigue and depressed mood. Subjects were 169 HIV-positive men evaluated at baseline, 6, and 12 months for levels of DHEAS, total and free testosterone, HIV RNA, CD4, HIV symptoms, opportunistic illnesses, fatigue, and depression. Men with AIDS (N = 105), compared with men with less advanced illness, had lower mean levels of DHEAS. Baseline DHEAS was positively correlated with CD4 count, HIV symptom severity, and was inversely correlated with HIV RNA. Baseline DHEAS below the laboratory reference range (96 microg/dl) was associated with history of opportunistic infections and malignancies (adjusted odds ratio [OR], 4.4; 95% confidence interval [CI], 1.9-10.4) and with incidence of these complications or death over 1 year (adjusted OR, 2.6; 95% CI, 1-7.2). Initiating protease inhibitor combination therapy was associated with an increase in DHEAS over 6 months. Free testosterone was inversely correlated with HIV RNA, but there were no other significant associations between testosterone and HIV illness markers. No hormone was related to fatigue or depression. This study confirms that low serum DHEAS is associated with HIV illness markers, including viral load, and carries negative prognostic value. Further, protease inhibitor therapy may result in increased circulating DHEAS.

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Circadian variations in plasma levels of hypophyseal, adrenocortical and testicular hormones in men infected with human immunodeficiency virus.

Villette JM, Bourin P, Doinel C, Mansour I, Fiet J, Boudou P, Dreux C, Roue R, Debord M, Levi F

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Alterations in the circadian time structure of the secretion of several hormones were investigated in 13 male patients infected with human immunodeficiency virus (HIV). Seven were asymptomatic (classified CDC II, according to the criteria of the Atlanta Centers for Disease Control), and 6 had acquired immunodeficiency syndrome (CDC IV). Ten healthy males volunteered as controls. Plasma levels of dehydroepiandrosterone (DHEA) and its sulfate (DHEA-S), cortisol, testosterone, ACTH, and beta-endorphin were determined by RIA in blood samples obtained every 4 h from 0830-0830 h the next morning. Data were analyzed both by two-way analysis of variance and the cosinor method. Circadian rhythms were statistically validated for each of the six hormones in each of the three groups of subjects. Compared with the control subjects, mesors (24-h adjusted means) were significantly higher for cortisol and lower for DHEA, DHEA-S, and ACTH (P less than 0.001 for all four hormones) in all HIV-infected patients. Plasma testosterone mesors were similar in controls and CDC II patients, but decreased significantly in the CDC IV patient group (P less than 0.05). Analysis of the circadian rhythms of plasma hormone levels clearly indicated an altered adrenal hormonal state in HIV-infected male patients, even during the asymptomatic period of the infection. For instance, plasma cortisol at 0430 h was more than twice as high in HIV-infected patients as it was in time-qualified controls. Although patients already had elevated plasma cortisol and lowered adrenal androgen levels at this stage, hypogonadism was not observed, as gauged by plasma testosterone concentrations. We speculate that the primary hormonal defect in HIV-infected patients is increased cortisol secretion resulting from circadian-varying stimulation of the adrenal cortex by a factor other than pituitary ACTH. This factor might be a stimulating substance secreted primarily by infected immune cells. Excess cortisol would lower adrenal androgen secretion by shifting adrenal steroid biosynthesis toward glucocorticoids and decreasing pituitary ACTH secretion via a negative feedback mechanism.

1: Am J Psychiatry 1995 Apr;152(4):543-50

Stress-associated reductions of cytotoxic T lymphocytes and natural killer cells in asymptomatic HIV infection.

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OBJECTIVE: Previous research has documented a possible relation of stress and depression to cell-mediated immunity. The authors examined how stressful events and depression may affect key parameters of cellular immunity in subjects with and without HIV infection. **METHOD:** Data were collected on 99 asymptomatic HIV-positive and 65 HIV-negative homosexual men as part of an ongoing, longitudinal study. Criticisms of previous studies of psychoimmunity were addressed by 1) using a comprehensive, semistructured interview to measure the objective context of stressful events, 2) double labeling of lymphocytes with monoclonal antibodies to measure subsets of cytotoxic/suppressor T lymphocytes and natural killer (NK) cells, and 3) controlling for circadian effects and methodological factors. **RESULTS:** In the HIV-positive men, severe stress was significantly associated with reductions in NK cell populations and a subset of T cells thought to represent cytotoxic T effector cells, particularly the CD8+ T cells expressing the CD57 antigen. In the HIV-negative men, no clear and consistent relation between stress and immune system measures was found. Depression was not correlated with any variables in either of the groups, perhaps due to the low levels of depressive symptoms. **CONCLUSIONS:** The findings suggest that stress is associated with reductions in killer lymphocytes (decreased NK cell and cytotoxic T lymphocyte phenotypes). The data provide evidence that stress may alter cell populations that provide cytotoxic defense against infection in HIV-positive men and indicate that the clinical significance of stress-related changes in cytotoxic T lymphocytes and NK cells in HIV infection warrants further study.

1: Am J Med Sci 1993 Feb;305(2):79-83

The relationship of serum DHEA-S and cortisol levels to measures of immune function in human immunodeficiency virus-related illness.

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Human immunodeficiency virus (HIV) is a major cause of immunoincompetence. Whether the virus, itself, accounts for all the deficiency remains in question. Steroids can also influence immune function; glucocorticoids cause immunoincompetence while dehydroepiandrosterone (DHEA) enhances immune function. Changes in the levels of such hormones during the course of HIV illness might result in significant changes in immune competence. The purpose of this study is to investigate whether dehydroepiandrosterone-sulphate (DHEA-S) or cortisol levels correlate with absolute CD4 lymphocyte levels. Plasma for cortisol and DHEA-S was drawn from 98 adults with HIV. Of these, 67 had simultaneous CD4 levels. Cortisol levels were 12.4 +/- 4.6 micrograms/dl, DHEA-S 262 +/- 142 micrograms/dl, and CD4 levels were 308 +/- 217/mm³ (mean +/- SD). Correlational analysis revealed a significant relationship between DHEA-S and CD4 levels ($r = 0.30$; $p = 0.01$) but not between CD4 levels and cortisol ($r = 0.11$; $p = 0.36$) or cortisol/DHEA-S ratios ($r = 0.17$; $p = 0.16$). When analyzed by clinical subgroups, significant differences were also found with a decrease in DHEA-S levels seen in persons with more advanced illness. The data exhibit a positive relationship between the immune status of patients with HIV-related illness and DHEA, leading to the hypothesis that DHEA deficiency may worsen immune status.

1: Immunol Today 1994 May;15(5):209-13

Oxidative stress and apoptosis in HIV infection: a role for plant-derived metabolites with synergistic antioxidant activity.

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The cascade of events resulting from 'oxidative stress' is markedly similar to that which can initiate apoptosis, a possible mechanism of immune-cell loss in patients with HIV infection and AIDS. Since primary and secondary metabolites found in plants can act as synergistic antioxidants, and can prevent oxidation-induced cell death, Howard Greenspan and Okezie Aruoma ask whether or not these compounds can be useful in inhibiting viral activation and the death of immune cells in HIV/AIDS.

1: J Leukoc Biol 1992 Jul;52(1):111-4
Related Articles, Books, LinkOut

The role of oxidative stress in disease progression in individuals infected by the human immunodeficiency virus.

Baruchel S, Wainberg MA

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This review describes the potential role of oxidative stress as a cofactor of disease progression from asymptomatic human immunodeficiency virus (HIV) infection to the acquired immunodeficiency syndrome (AIDS). Oxidative stress is a known activator of HIV replication in vitro through the activation of a factor that binds to a DNA-binding protein, NF-kappa B, which in turn stimulates HIV gene expression by acting on the promoter region of the viral long terminal repeat. Tumor necrosis factor alpha (TNF-alpha), an essential cytokine produced by activated macrophages, is also involved in the activation of HIV infection through similar mechanisms. TNF-mediated cytotoxicity of cells exposed to this substance is related to the generation of intracellular hydroxyl radicals. An indirect argument in favor of the role of oxidative stress in HIV-associated disease progression is the consumption of glutathione (GSH), a major intracellular antioxidant, during HIV infection and progression. GSH is known to play a major role in regulation of T cell immune functions. Oxidative stress may also play an important role in the genesis of cellular DNA damage and, in this context, may be related to HIV-associated malignancies and disease progression. Finally, the role of antioxidants as components of therapeutic strategies to combat HIV disease progression is discussed.

1: Immunol Today 1995 Apr;16(4):187-91

Immune activation is a dominant factor in the pathogenesis of African AIDS.

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The AIDS epidemic in Africa is very different from the epidemic in the West. As suggested here by Zvi Bentwich, Alexander Kalinkovich and Ziva Weisman, this appears to be primarily a consequence of the over-activation of the immune system in the African population, owing to the extremely high prevalence of infections, particularly helminthic, in Africa. Such activation shifts the cytokine balance towards a T helper 0/2 (Th0/2)-type response, which makes the host more susceptible to infection with human immunodeficiency virus (HIV) and less able to cope with it.