HIV

Human Immunodeficiency Virus

Excerpt from aids.gov

HIV stands for human immunodeficiency virus. If left untreated, HIV can lead to the disease AIDS (acquired immunodeficiency syndrome).

Unlike some other viruses, the human body can't get rid of HIV completely. So once you have HIV, you have it for life.
HIV attacks the body's immune system, specifically the CD4 cells (T cells), which help the immune system fight off infections. If left untreated, HIV reduces the number of CD4 cells (T cells) in the body, making the person more likely to get infections or infection-related cancers. Over time, HIV can destroy so many of these cells that the body can't fight off infections and disease. These opportunistic infections or cancers take advantage of a very weak immune system and signal that the person has AIDS, the last state of HIV infection.

No effective cure for HIV currently exists, but with proper treatment and medical care, HIV can be controlled. The medicine used to treat HIV is called antiretroviral therapy or ART. If taken the right way, every day, this medicine can dramatically prolong the lives of many people with HIV, keep them healthy, and greatly lower their chance of transmitting the virus to others. Today, a person who is diagnosed with HIV, treated before the disease is far advanced, and stays on treatment can live a nearly as long as someone who does not have HIV.

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Cannabinoid Inhibition of Macrophage Migration to the Trans-Activating (Tat) Protein of HIV-1 Is Linked to the CB2 Cannabinoid Receptor

Erinn S. Raborn and Guy A. Cabral

Macrophages and macrophage-like cells are important targets of HIV-1 infection at peripheral sites and in the central nervous system. After infection, these cells secrete a plethora of toxic factors, including the viral regulatory trans-activating protein (Tat). This protein is highly immunogenic and also serves as a potent chemoattractant for monocytes. In the present study, the exogenous cannabinoids δ-9-tetrahydrocannabinol (THC) and (−)-*cis*-3-[2-hydroxy-4-(1,1-dimethylheptyl)phenyl]-trans-4-(3-hydroxypropyl) cyclohexanol (CP55940) were shown to significantly inhibit migration of human U937 macrophage-like cells to the Tat protein in a concentration-related manner. The CB1 receptor-selective agonist *N*-(2-chloroethyl)-5*Z*,8*Z*,11*Z*,14*Z*-eicosatetraenamide (ACEA) had no effect on Tat-mediated migration. In contrast, the CB2 receptor-selective agonist (1*R*,3*R*)-1-[4-(1,1-dimethylheptyl)-2,6-dimethoxyphenyl]-3-methylcyclohexanol (O-2137) exerted a concentration-related inhibition of U937 cell migration in response to Tat. Pharmacological blockage of CB1 receptor signaling using the antagonist 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-*N*-(1-piperidyl)pyrazole-3-carboxamide hydrochloride (SR141716A) had no effect on CP55940-mediated inhibition of macrophage migration to Tat, whereas treatment with the CB2 receptor antagonist (1*S*-endo)-5-(4-chloro-3-methylphenyl)-1-((4-methylphenyl)methyl)-*N*-(1,3,3-trimethylbicyclo(2.2.1)hept-2-yl)-1*H*-pyrazole-3-carboxamide (SR144528) reversed the CP55940-mediated inhibition of migration. In addition, THC had no inhibitory effect on U937 migration to Tat after small interfering RNA knockdown of the CB2 receptor. Collectively, the pharmacological and biochemical knockdown data indicate that cannabinoid-mediated modulation of macrophage migration to the HIV-1 Tat protein is linked to the CB2 cannabinoid receptor. Furthermore, these results suggest that the CB2 cannabinoid receptor has potential to serve as a therapeutic target for ablation of HIV-1-associated untoward inflammatory response.

Ann Intern Med. 2003 Aug 19;139(4):258-66.

Short-term effects of cannabinoids in patients with HIV-1 infection: a randomized, placebo-controlled clinical trial.

Abrams DI1, Hilton JF, Leiser RJ, Shade SB, Elbeik TA, Aweeka FT, Benowitz NL, Bredt BM, Kosel B, Aberg JA, Deeks SG, Mitchell TF, Mulligan K, Bacchetti P, McCune JM, Schambelan M.

Abstract

BACKGROUND:
Cannabinoid use could potentially alter HIV RNA levels by two mechanisms: immune modulation or cannabinoid-protease inhibitor interactions (because both share cytochrome P-450 metabolic pathways).

OBJECTIVE:
To determine the short-term effects of smoked marijuana on the viral load in HIV-infected patients.

DESIGN:
Randomized, placebo-controlled, 21-day intervention trial.

SETTING:
The inpatient General Clinical Research Center at the San Francisco General Hospital, San Francisco, California.

PARTICIPANTS:
67 patients with HIV-1 infection.

INTERVENTION:
Participants were randomly assigned to a 3.95%-tetrahydrocannabinol marijuana cigarette, a 2.5-mg dronabinol (delta-9-tetrahydrocannabinol) capsule, or a placebo capsule three times daily before meals.

MEASUREMENTS:
HIV RNA levels, CD4+ and CD8+ cell subsets, and pharmacokinetic analyses of the protease inhibitors.

RESULTS:
62 study participants were eligible for the primary end point (marijuana group, 20 patients; dronabinol group, 22 patients; and placebo group, 20 patients). Baseline HIV RNA level was less than 50 copies/mL for 36 participants (58%), and the median CD4+ cell count was 340 x 109 cells/L. When adjusted for baseline variables, the estimated average effect versus placebo on change in log10 viral load from baseline to day 21 was -0.07 (95% CI, -0.30 to 0.13) for marijuana and -0.04 (CI, -0.20 to 0.14) for dronabinol. The adjusted average changes in viral load in marijuana and dronabinol relative to placebo were -15% (CI, -50% to 34%) and -8% (CI, -37% to 37%), respectively. Neither CD4+ nor CD8+ cell counts appeared to be adversely affected by the cannabinoids.

CONCLUSIONS:
Smoked and oral cannabinoids did not seem to be unsafe in people with HIV infection with respect to HIV RNA levels, CD4+ and CD8+ cell counts, or protease inhibitor levels over a 21-day treatment.

Cannabinoid Receptor 2-Mediated Attenuation of CXCR4-Tropic HIV Infection in Primary CD4+ T Cells

Cristina Maria Costantino,
Achla Gupta,
Alice W. Yewdall,
Benjamin M. Dale,
Lakshmi A. Devi ,
Benjamin K. Chen

Abstract

Agents that activate cannabinoid receptor pathways have been tested as treatments for cachexia, nausea or neuropathic pain in HIV-1/AIDS patients. The cannabinoid receptors (CB_1R and CB_2R) and the HIV-1 co-receptors, CCR5 and CXCR4, all signal via Gαi-coupled pathways. We hypothesized that drugs targeting cannabinoid receptors modulate chemokine co-receptor function and regulate HIV-1 infectivity. We found that agonism of CB_2R, but not CB_1R, reduced infection in primary CD4+ T cells following cell-free and cell-to-cell transmission of CXCR4-tropic virus. As this change in viral permissiveness was most pronounced in unstimulated T cells, we investigated the effect of CB_2R agonism on to CXCR4-induced signaling following binding of chemokine or virus to the co-receptor. We found that CB_2R agonism decreased CXCR4-activation mediated G-protein activity and MAPK phosphorylation. Furthermore, CB_2R agonism altered the cytoskeletal architecture of resting CD4+ T cells by decreasing F-actin levels. Our findings suggest that CB_2R activation in CD4+ T cells can inhibit actin reorganization and impair productive infection following cell-free or cell-associated viral acquisition of CXCR4-tropic HIV-1 in resting cells. Therefore, the clinical use of CB_2R agonists in the treatment of AIDS symptoms may also exert beneficial adjunctive antiviral effects against CXCR4-tropic viruses in late stages of HIV-1 infection.

http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0033961

The cannabinoid CB2 receptor agonist AM1241 enhances neurogenesis in GFAP/Gp120 transgenic mice displaying deficits in neurogenesis

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Abstract

Background and Purpose

HIV-1 glycoprotein Gp120 induces apoptosis in rodent and human neurons *in vitro* and *in vivo.* HIV-1/Gp120 is involved in the pathogenesis of HIV-associated dementia (HAD) and inhibits proliferation of adult neural progenitor cells (NPCs) in glial fibrillary acidic protein (GFAP)/Gp120 transgenic (Tg) mice. As cannabinoids exert neuroprotective effects in several model systems, we examined the protective effects of the CB2 receptor agonist AM1241 on Gp120-mediated insults on neurogenesis.

Experimental Approach

We assessed the effects of AM1241 on survival and apoptosis in cultures of human and murine NPCs with immunohistochemical and TUNEL techniques. Neurogenesis in the hippocampus of GFAP/Gp120 transgenic mice *in vivo* was also assessed by immunohistochemistry.

Key Results

AM1241 inhibited *in vitro* Gp120-mediated neurotoxicity and apoptosis of primary human and murine NPCs and increased their survival. AM1241 also promoted differentiation of NPCs to neuronal cells. While GFAP/Gp120 Tg mice exhibited impaired neurogenesis, as indicated by reduction in BrdU+ cells and doublecortin+ (DCX+) cells, and a decrease in cells with proliferating cell nuclear antigen (PCNA), administration of AM1241 to GFAP/Gp120 Tg mice resulted in enhanced *in vivo* neurogenesis in the hippocampus as indicated by increase in neuroblasts, neuronal cells, BrdU+ cells and PCNA+ cells. Astrogliosis and gliogenesis were decreased in GFAP/Gp120 Tg mice treated with AM1241, compared with those treated with vehicle.

Conclusions and Implications

The CB2 receptor agonist rescued impaired neurogenesis caused by HIV-1/Gp120 insult. Thus, CB2 receptor agonists may act as neuroprotective agents, restoring impaired neurogenesis in patients with HAD.