Marijuana-like chemicals inhibit human immunodeficiency virus in late-stage AIDS

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Mount Sinai School of Medicine researchers have discovered that marijuana-like chemicals trigger receptors on human immune cells that can directly inhibit a type of human immunodeficiency virus (HIV) found in late-stage AIDS, according to new findings published online in the journal *PLoS ONE*.

Medical marijuana is prescribed to treat pain, debilitating weight loss and appetite suppression, side effects that are common in advanced AIDS. This is the first study to reveal how the marijuana receptors found on immune cells—called cannabinoid receptors CB1 and CB2—can influence the spread of the virus. Understanding the effect of these receptors on the virus could help scientists develop new drugs to slow the progression of AIDS.

"We knew that cannabinoid drugs like marijuana can have a therapeutic effect in AIDS patients, but did not understand how they influence the spread of the virus itself," said study author Cristina Costantino, PhD, Postdoctoral Fellow in the Department of Pharmacology and Systems Therapeutics at Mount Sinai School of Medicine. "We wanted to explore cannabinoid receptors as a target for pharmaceutical interventions that treat the symptoms of late-stage AIDS and prevent further progression of the disease without the undesirable side effects of medical marijuana ."

HIV infects active immune cells that carry the viral receptor CD4, which makes these cells unable to fight off the infection. In order to spread, the

virus requires that "resting" immune cells be activated. In advanced AIDS, HIV mutates so it can infect these resting cells, gaining entry into the cell by using a signaling receptor called CXCR4. By treating the cells with a cannabinoid agonist that triggers CB2, Dr. Costantino and the Mount Sinai team found that CB2 blocked the signaling process, and suppressed infection in resting immune cells.

Triggering CB1 causes the drug high associated with marijuana, making it undesirable for physicians to prescribe. The researchers wanted to explore therapies that would target CB2 only. The Mount Sinai team infected healthy immune cells with HIV, then treated them with a chemical that triggers CB2 called an agonist. They found that the drug reduced the infection of the remaining cells.

"Developing a drug that triggers only CB2 as an adjunctive treatment to standard antiviral medication may help alleviate the symptoms of late-stage AIDS and prevent the virus from spreading," said Dr. Costantino. Because HIV does not use CXCR4 to enhance immune cell infection in the early stages of infection, CB2 agonists appear to be an effective antiviral drug only in late-stage disease.

As a result of this discovery, the research team led by Benjamin Chen, MD, PhD, Associate Professor of Infectious Diseases, and Lakshmi Devi, PhD, Professor of Pharmacology and Systems Therapeutics at Mount Sinai School of Medicine, plans to develop a mouse model of late-stage AIDS in order to test the efficacy of a drug that triggers CB2 in vivo. In 2009 Dr. Chen was part of a team that captured on video for the first time the transfer of HIV from infected T-cells to uninfected T-cells.

More information: Costantino CM, Gupta A, Yewdall AW, Dale BM, Devi LA, et al. (2012) Cannabinoid Receptor 2-Mediated Attenuation of CXCR4-Tropic HIV Infection in Primary CD4+ T Cells. PLoS ONE 7(3): e33961. doi:10.1371/journal.pone.0033961 .

www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0033961

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 (CB1R and CB2R) 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 CB2R, but not CB1R, 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 CB2R agonism on to CXCR4-induced signaling following binding of chemokine or virus to the co-receptor. We found that CB2R agonism decreased CXCR4-activation mediated G-protein activity and MAPK phosphorylation. Furthermore, CB2R agonism altered the cytoskeletal architecture of resting CD4+ T cells by decreasing F-actin levels. Our findings suggest that CB2R 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 CB2R 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.

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