Marijuana and its CD4 Receptors: A New HIV Treatment Strategy?

March 21, 2012 By Tim Horn

Drugs that target one of the two cellular receptors stimulated by the active ingredient in marijuana may prove to be effective at blocking a form of HIV that has been linked to faster disease progression during late stages of the infection. Though the PLoS One research report highlighting these findings—published March 20 by a team of scientists at Mt. Sinai School of Medicine in New York—stops short of concluding that marijuana is one of nature's best antiretrovirals, the authors suggest that further study of cannabinoids is needed to ultimately discover drugs with both antiviral and symptom-reducing properties.

Marijuana—purchased legally or illegally and either smoked or ingested—along with its synthetic counterpart Marinol (dronabinol) are used by many people living with HIV to manage various symptoms of illness, including pain, depression and weight loss.

The numerous effects of marijuana are the result of chemical interactions between the drug's active ingredient, tetrahydrocannabinol (THC), and two receptors on a variety of cells in the body: cannabinoid receptor 1 (CR1) and cannabinoid receptor 2 (CR2).

CR1 receptors are densely populated in the brain and, when stimulated by chemicals like THC, can have a variety of neurological effects. It is THC's interaction with CR1 in the brain and central nervous system that contributes to marijuana's "high"-like effects.

THC also interacts with CR2, which is not only found on some cells in the brain, but also on cells of the immune system, gastrointestinal tract and peripheral nervous system. It is THC's stimulation of CR2 in the latter two compartments that may account for the drug's positive therapeutic effects on nausea and neuropathic pain, to name a few important symptoms.

CR2 has also been found on a variety of immune system cells and is present on CD4 cells in abundance. While some studies have classified CR2 as a suppressor of CD4 cells and early trials indicated that marijuana use was associated with progression to AIDS, more recent analyses suggest that the drug isn't associated with significant immune suppression. In fact, both smoked marijuana and Marinol have been associated with increases in CD4 cell counts—along with a decrease in viral load—in at least one short-term study and laboratory experiments.

In effect, the mechanisms by which the interactions between THC and the cannabinoid receptors alter CD4 cell function remain unclear. One particular area of interest, though, is the connection between CR2 and CXCR4, another receptor on immune system cells. For example, CR2 activation

blocks CXCR4 from directing the movement of certain cells in the body (chemotaxis). CR2 also plays a role in moving white blood cells out of bone marrow (egress), a role previously attributed largely to CXCR4.

The apparent “cross talk” between CR2 and CXCR4, therefore, led the Mt. Sinai researchers—under the direction of Cristina Maria Costantino, PhD—to explore whether stimulation of CR2 can block the way CXCR4 interacts with a particular form of HIV: CXCR4-tropic virus.

During the early years of untreated HIV infection, HIV primarily targets—or is tropic for—cells with the CCR5 receptor. As HIV disease progresses, however, approximately 50 percent of people living with HIV see their virus develop preference for the CXCR4 receptor on CD4 cells. This particular form of the virus, research has shown, is associated with rapid disease progression, though it is unclear if the emergence of CXCR4-tropic virus is a cause or an effect of immune suppression.

Costantino’s test tube experiments proved encouraging. Using a cannabinoid receptor agonist—a THC-like compound—her team found that activation of CR2 inhibited CXCR4-tropic HIV infection. It did this, not by altering the number of CXCR4 receptors on CD4 cells—this is a therapeutic approach being explored by others—but rather by blocking the receptor’s “signaling process” and interaction with HIV.

According to the PLoS One report, activation of CR2 blocked the ability of CXCR4-tropic virus to infect other cells by 30 to 60 percent. “This inhibition is pronounced in resting cells,” the researchers explain, “which are a target of CXCR4-tropic HIV.”

“Developing a drug that triggers only [CR2] 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 in an accompanying news announcement.

As a result of this discovery, additional research at Mt. Sinai is being planned. Specifically, researchers there will be developing a mouse model of late-stage HIV infection in order to test the efficacy of a drug that triggers CR2, not in test tubes, but in living organisms.

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