Scientists weaken HIV infection in immune cells using synthetic agents

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HIV, the virus that causes AIDS, is notorious for hiding within certain types of cells, where it reproduces at a slowed rate and eventually gives rise to chronic inflammation, despite drug therapy. But researchers at Temple University School of Medicine's Department of Pathology and Laboratory Medicine and Center for Substance Abuse Research (CSAR) recently discovered that synthetic anti-inflammatory substances distantly related to the active ingredient of marijuana may be able to take the punch out of HIV while inside one of its major hideouts – immune cells known as macrophages.

The breakthrough comes at a crucial time in the HIV/AIDS pandemic. "Powerful antiretroviral drug cocktails have allowed many HIV patients to live longer," explained Servio H. Ramirez, PhD, Assistant Professor of Pathology and Laboratory Medicine at Temple University School of Medicine (TUSM), and first author on the study. But living longer with HIV means extended exposure to low levels of HIV replication and associated inflammation. In the central nervous system (CNS), this inflammatory process is thought to be the underlying cause of HIV-associated neurocognitive disorder (HAND), a spectrum of conditions that is on the rise again after more than a decade of decline following the advent of antiretroviral therapy.

To better understand the connection between inflammation and neurocognitive conditions linked to long-term exposure to HIV, Ramirez and colleagues looked specifically at the CB2 receptor, a protein located on the surface of macrophages. CB2 is a binding site for substances

called cannabinoids, the primary active compounds of *cannabis* (marijuana), and it may play a role in blocking inflammation in the CNS. Unlike its counterpart, the CB1 receptor, which is found primarily on neurons in the brain, CB2 does not mediate the psychoactive effects for which *cannabis* is popularly known.

Ramirez explained that there has been much pharmacological interest in developing agents that selectively target CB2. Ideally, these compounds would help limit chronic inflammatory responses and would not bind to CB1. The most promising compounds are those derived from THC (tetrahydrocannabinol), the main active substance in cannabis.

The development of such drugs, however, hinges largely on knowing which cells harbor HIV. Earlier studies suggested that T cells, central components of the immune system, are HIV reservoirs. The Temple team, however, chose to focus on macrophages, which are a type of white blood cell that engulfs and destroys foreign agents.

According to Ramirez and the study's senior investigator, Yuri Persidsky, MD, PhD, Chair of the Department of Pathology and Laboratory Medicine at TUSM, macrophages likely are the primary reservoir for HIV. They are among the first cells to become infected following sexual transmission of the virus, and they are found in every organ of the human body and circulate in the blood. It is currently thought that macrophages may be responsible for introducing HIV into the brain, ultimately initiating HIV-associated cognitive decline.

The scientists landed on their discovery by conducting a series of experiments in a well-established, non-clinical HIV macrophage cell model. They began by treating the HIV-infected cells with one of three different synthetic CB2-activating compounds. The cells were then sampled periodically to measure the activity of an enzyme called reverse transcriptase, which is essential for HIV replication. After seven days,

the team found that all three compounds had successfully attenuated HIV replication. The experiments and findings are detailed in the May issue of the *Journal of Leukocyte Biology*.

The results suggest that selective CB2 agonists could potentially be used in tandem with existing antiretroviral drugs, opening the door to the generation of new drug therapies for HIV/AIDS. The data also support the idea that the human immune system could be leveraged to fight HIV infection.

"Our study suggests that the body's own natural defenses can be made more powerful to fight some of the worst symptoms of HIV," Persidsky explained. He also noted that stimulating CB2 receptors in white blood cells could produce similar benefits against other viral infections.

The new research further highlights the important work being carried out at Temple's Center for Substance Abuse Research (CSAR). "The compounds we had available through CSAR formed an important aspect of this research," Ramirez said.

Persidsky added, "From our perspective we were in a better position for in vitro research. We have interesting models and were able to take advantage of our colleagues' knowledge of receptors and cannabinoids to make a unique contribution."

The team plans next to perform further screening studies using other novel CB2 agonists in parallel with studies that can help uncover the molecular events within the cell that regulate the effect of CB2 on HIV.

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