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Researchers to explore ability of compounds to protect brain against HIV infection

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Antiretroviral drugs can greatly increase life expectancy for patients infected with HIV, the AIDS-causing virus, but one thing the drugs cannot do is completely eliminate the virus from the body. Hidden away in cells, latent HIV eventually gains access to the brain, causing a debilitating syndrome known as HIV-associated neurocognitive disorder (HAND). Remarkably, however, a group of compounds known as cannabinoid receptor type 2 (CB2) agonists may be able to stop HAND from developing, and now, thanks to new funding from the National Institute on Alcohol Abuse and Alcoholism (NIAAA), researchers at the Lewis Katz School of Medicine at Temple University are poised to investigate that possibility.

The Principal Investigator on the new study is Yuri Persidsky, MD, PhD, Chair of the Department of Pathology and Laboratory Medicine at the Lewis Katz School of Medicine (LKSOM). According to Dr. Persidsky, "The major aim with our new grant is to test novel compounds that activate CB2 and show that the compounds are safe and effective based on experiments in cell models and mice with HIV infection."

The novel CB2 agonists that Dr. Persidsky is studying have been developed only recently, and none of them have been investigated specifically in the cell and animal models that are being used in his laboratory. Moreover, according to Dr. Persidsky, "The novel compounds are clinically promising, so the refinements we'll be studying could bring us closer to eventually being able to use the compounds to treat HIV patients affected by HAND and alcoholism."

Dr. Persidsky is partnering on the new work with researcher Pal Pacher, MD, PhD, from the NIAAA as part of the National Institutes of Health (NIH) Program for Extramural/Intramural Research Collaborations. While Dr. Persidsky's team investigates the effects of the novel CB2 agonists in the central nervous system in the context of alcohol exposure and HIV infection, Dr. Pacher is working to characterize the pharmacological and pharmacokinetic properties of the compounds.

The new award, which provides $1.755 million in funding over five years, enables Dr. Persidsky to continue studies that he began in 2010 with a previous NIAAA grant, the Method to Extend Research in Time (MERIT) award. MERIT is an honorific NIH award given to investigators who have demonstrated superior competence and outstanding productivity during their previous research endeavors and who are likely to continue to perform in an outstanding manner in the future.

In that work, Dr. Persidsky and colleagues were able to show that CB2 activation protects neurons in the brain in a mouse model. Neuroprotection was mediated by the effects of CB2 activation on certain immune cells, including HIV-infected macrophages, and on the blood brain barrier, which normally prevents viral toxins and inflammatory substances from entering the central nervous system but is compromised by alcohol exposure and HIV infection.

But while activation of CB2 receptors is a promising means of treating or even preventing alcohol- and HIV-associated neurotoxicity, whether recently developed synthetic CB2 agonists can safely and effectively shield the brain from that damage remains unknown. The previous generation of compounds was unsuitable for use in patients affected by HIV and alcoholism, owing to poor solubility and gut absorption, toxicological issues, and off-target effects, particularly on psychoactive CB1 receptors in the brain.

Both CB1 and CB2 receptors serve as key binding sites for tetrahydrocannabinol (THC), the active compound in marijuana (cannabis). The CB1 receptor occurs mainly on neurons in the brain, where its activation mediates the psychoactive response to THC. CB2, on the other hand, is located on the outer surface of macrophages and B lymphocytes, where it appears to be involved primarily in blocking inflammation in the central nervous system.

With a new generation of CB2 agonists available for study, the challenge now lies in finding a compound that specifically targets CB2 to safely produce the desired anti-inflammatory response in the HIV-infected brain, avoiding CB1 activation and psychoactive side effects.

"We want to identify selective CB2 agonists that have optimal pharmacological properties and a safe toxicology profile," Dr. Persidsky explained. "By first testing the chosen compounds in cell models, we'll be able to determine which agonists are most effective at decreasing HIV replication in macrophages while also protecting the endothelial cells that make up the blood brain barrier against inflammation and alcohol exposure. The most promising compounds will then be tested in a humanized mouse model of HIV infection, where we'll be able to thoroughly evaluate pharmacological effects and toxicities."

If the novel CB2 agonists work and have good toxicology profiles, Dr. Persidsky hopes to eventually be able to develop the compounds into drugs that could be used in patients. Hence, though clinical trials would be years away, the studies carried out under the new grant could prove critical to the future care of patients affected by HAND.

Provided by Temple University