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# NIDA NOTES

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## Research Advances

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## Opioid Analogue May Slow Spread of HIV in Brain

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By Neil Swan, NIDA NOTES Staff Writer

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Synthetic compounds, or analogues, related to the opiates morphine and heroin can limit the growth of HIV - the virus that causes AIDS - in the brain, according to NIDA-funded research findings. The study with human cell culture suggests that a synthetic compound that binds to the brain's kappa opioid receptors (KOR) may curtail a virus subtype called HIV-1 from spreading in the brains of people infected with the AIDS virus. A drug analogue is a chemical compound that differs slightly from another drug.

Although the study was performed in cell culture, the results suggest the possibility that a medication could be developed to prevent a particularly destructive aspect of AIDS - the loss of intellectual capacity. This research is part of a broad range of NIDA-supported studies of the complex relationship between drugs of abuse and AIDS, including studies of the effects of drug use on the body's immune system and, subsequently, on infection and disease progression. The study also provides an example of how research on drugs of abuse can have benefits in other areas of medicine.

In some HIV-infected patients, HIV-1 infection in the brain leads to a disease syndrome called "AIDS dementia complex," which results in apathy, difficulties in muscle control and movement, and problems in performing complex tasks. The mental capacity of patients with dementia complex may deteriorate until they are incapable of voluntary acts.

When HIV-1 involves the brain, the infection occurs in microglial cells, found throughout the nervous system, which are the principal sites for HIV growth in the brain.

The study was conducted by Drs. Chun C. Chao and Phillip K. Peterson and their colleagues at the Minneapolis Medical Research Foundation and the University of Minnesota Medical School. It builds on research by Dr. Jean Bidlack of the University of Rochester Medical School in New York and the late Dr. Sydney Archer of Rensselaer Polytechnic Institute in Troy, New York. Dr. Chao says the collaboration developed at a NIDA-supported symposium on interactions between drugs of abuse and the immune function.

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To learn more about these interactions, the Minnesota scientists first treated microglial cell cultures with two KOR agonists - compounds that mimic actions of the body's natural kappa opioids - for 24 hours and then infected the treated cells with HIV-1 for another 24 hours. When the researchers examined the cell culture after 14 days, they found that pretreatment with the KOR agonists U50,488 and U69,593 prevented the growth of HIV-1. Currently, they are testing other synthetic KOR compounds for their potential for treating AIDS dementia complex.

The next step will be to conduct similar studies on the effect of KOR compounds on the spread of HIV in living animals, says Dr. Chao. Some of these studies likely will examine the growth of simian immunodeficiency virus (SIV) infections. SIV is an HIV-like virus found in monkeys. "One possibility is to treat SIV-infected monkeys with kappa opioid compounds, such as those we used in the human cell culture study, to test whether these KOR compounds have therapeutic value in monkeys with SIV," Dr. Chao says.

Dr. Chao presented his findings at the Fourth Annual Symposium on AIDS, Drugs of Abuse, and the Neuro-Immune Axis held in conjunction with the annual meeting of the College on Problems of Drug Dependence in San Juan, Puerto Rico, in June. Scientists at the symposium concentrated on both human and animal data to study the relationships among drug abuse, immune function, and infectious diseases.

Both human and animal studies show that different drugs and different classes of opiates regulate the immune system function in different ways. For example, earlier findings by Dr. Chao and his colleagues show that in human cell culture morphine, unlike the KOR agonists, may stimulate growth of HIV in microglia.

Likewise, a particular drug may regulate the human immune system differently than it does an animal's immune system. Sometimes drug-induced influences on immune function increase the death rate of animals with infectious disease.

A study by Dr. M.P. Yeager at Dartmouth-Hitchcock Medical Center in Lebanon, New Hampshire, on the acute effects of morphine on humans did show that morphine caused marked immune suppression. But epidemiologic research has provided only limited evidence of similar findings.

While some epidemiologic studies indicate that injecting drug users (IDUs) are at increased risk for infection with tuberculosis and HIV, natural history studies can find no evidence that HIV infection progresses more rapidly among IDUs than among other risk groups, including people who do not abuse drugs: both homosexuals and heterosexuals. Other research also suggests that some drug abusers may be more susceptible than are people who do not abuse drugs to "opportunistic" infectious diseases, such as pneumonia, that may arise after physiological damage or weakening of the immune system by AIDS. The basis of this apparent susceptibility is not clear.

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"You can find drug-induced effects in test-tube experiments and in animals that you can't duplicate in humans," says Dr. John Madden of Emory University in Atlanta, cochair of the symposium. "In the test tube and in animals, researchers are usually testing the short-term, acute effects of drugs on the immune system and disease progression. But in humans addicted to heroin, they are more often dealing with long-term, chronic drug effects. It appears that addicts build up a state of homeostasis in which the immune system over time adapts to the effects of the drugs and returns to an apparent state of normalcy." He notes that this state of apparent normalcy can be disturbed, however, by stresses such as drug withdrawal, infectious diseases, or poor nutrition.

Researchers are seeking to develop a research model in monkeys that more closely resembles the chronic effects found in human addicts, says Dr. Madden. They are also focusing more on other variables, such as the effects on the immune system of stress induced by drug withdrawal, and the relationship between drug use and disease susceptibility in the early stages of addiction.

Inconsistencies between laboratory animal findings and epidemiologic data on the effect of drugs of abuse on the progression of AIDS in humans may result from a number of other factors, researchers say. These include the overall health status of drug-abusing individuals, which can vary significantly among different drug-using groups; difficulty in tracking injecting drug users over time; and the possibility that the death or serious illnesses of some study subjects may go unreported when they are instead counted as study "dropouts." In addition, polydrug abuse may have compounding or even conflicting effects since there is evidence some drugs of abuse may actually counteract the immune system effects of other drugs. Researchers have noted that many HIV-infected people studied use both heroin and cocaine, which may have opposing or conflicting effects on immune system regulation and, perhaps, on AIDS disease progression.

### **Sources**

Chao, C.C.; Gekker, G.; Hu, S.; Sheng, W.S.; Shark, K.B.; Bu, D-F.; Archer, S.; Bidlack, J.M.; and Peterson, P.K. Kappa opioid receptors in microglia downregulate human immunodeficiency virus-1 expression. *Proceedings of the National Academy of Sciences* 93:8051-8056, 1996.

Yeager, M.P.; Colacchio, T.A.; Yu, C.T.; Hildebrandt, L.; Howell, A.L.; Weiss, J.; and Guyre, P.M. Morphine inhibits spontaneous cytokine-enhanced natural killer cell cytotoxicity in volunteers. *Anesthesiology* 83(3):500-508, 1995.

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