

Researchers reveal potential cause of HIV-associated dementia

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Researchers at Georgetown University Medical Center appear to have solved the mystery of why some patients infected with HIV, who are using antiretroviral therapy and show no signs of AIDS, develop serious depression as well as profound problems with memory, learning, and motor function. The finding might also provide a way to test people with HIV to determine their risk for developing dementia.

They say the answer, published in the July 11 issue of the *Journal of Neuroscience*, may ultimately lead to a therapeutic solution that helps these patients as well as others suffering from [brain](#) ailments that appear to develop through the same pathway, including those that occur in the aged.

"We believe we have discovered a general mechanism of neuronal decline that even explains what happens in some elderly folks," says the study's lead investigator, Italo Mocchetti, Ph.D., professor and vice chair of the department of neuroscience at Georgetown University Medical Center. "The [HIV](#)-infected patients who develop this syndrome are usually quite young, but their brains act old."

The research team found that even though HIV does not infect neurons, it tries to stop the brain from producing a [protein](#) growth factor — mature brain derived neurotrophic factor (mature BDNF) — that Mocchetti says acts like "food" for brain neurons. Reduced mature BDNF results in the shortening of the axons and their branches that neurons use to connect to each other, and when they lose this

communication, the neurons die.

"The loss of neurons and their connections is profound in these patients," Mocchetti says. HIV-associated [dementia](#) occurs in two to three percent of HIV-infected patients using retroviral therapies, all of who appear to be otherwise healthy, and in 30 percent of HIV-positive patients who are not on medication.

Mocchetti believes that HIV stops production of mature BDNF because that protein interferes with the ability of the virus to attack other brain cells. It does this through the potent gp120 envelope protein that sticks out from the viral shell – the same protein that hooks on to brain macrophages and microglial cells to infect them. "In earlier experiments, when we dumped gp120 into neuronal tissue culture, there was a 30-40 percent loss of neurons overnight. That makes gp120 a remarkable neurotoxin."

This study is the product of years of work that has resulted in a string of publications. It began when Mocchetti and his colleagues were given a grant from the National Institutes on Drug Abuse to determine whether there was a connection between the use of cocaine and morphine, and dementia. (A substantial number of HIV-positive patients have been or currently are intravenous drugs users.)

They found that it was the virus that was responsible for the dementia, not the drugs, and so they set out to discover how the virus was altering neuronal function.

Their scientific break came when the researchers were able to study the blood of 130 women who were enrolled in the 17 year-old, nationwide WIHS (Women's Interagency HIV Study, directed at Georgetown by Mary Young, M.D.), which has focused on the effects of HIV in infected females. In one seminal discovery, Mocchetti and colleagues

found that when there was less BDNF in the blood, patients were at risk of developing brain abnormalities. He published this finding in 2011 in the May 15 issue of [AIDS](#).

In this study, Mocchetti, Alessia Bachis, Ph.D., and their colleagues studied the brains of HIV-positive patients who had died, and who had developed HIV-associated dementia. They also found that neurons had shrunk, and that mature BDNF had substantially decreased.

He and his colleagues then worked out the mechanism responsible for this destruction of neurons.

Normally, neurons release a long form of BDNF known as proBDNF, and then certain enzymes, including one called furin, cleave proBDNF to produce mature BDNF, which then nurtures brain neurons. When uncut, proBDNF is toxic, leading to "synaptic simplification", or the shortening of axons. It does this by binding to a receptor, p75NTR, that contains a death domain.

"HIV interferes with that normal process of cleaving proBDNF, resulting in neurons primarily secreting a toxic form of BDNF," Mocchetti says. The same imbalance between mature BDNF and proBDNF occurs as we age, he says, although no one knows how that happens. "The link between [depression](#) and lack of mature BDNF is also known, as is the link to issues of learning and [memory](#). That's why I say HIV-associated dementia resembles the aging brain."

Loss of mature BDNF has also been suggested to be a risk factor in chronic diseases such as Parkinson's and Huntington's diseases, Mocchetti says.

The findings suggest a possible therapeutic intervention, he adds. "One way would be to use a small molecule to block the p75NTR receptor that

proBDNF uses to kill [neurons](#). A small molecule like that could get through the blood-brain barrier.

"If this works in HIV-dementia, it may also work in other brain issues caused by proBDNF, such as aging," Mocchetti adds.

The finding also suggests that measuring proBDNF in HIV-positive [patients](#) may provide a biomarker of risk for development of dementia, he adds.

"This finding is extremely important for both basic scientists and physicians, because it suggests a new avenue to understand, and treat, a fairly widespread cause of dementia," Mocchetti says.

Provided by Georgetown University Medical Center

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