Researchers identify toehold for HIV's assault on brain

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Scientists have unraveled in unprecedented detail the cascade of events that go wrong in brain cells affected by HIV, a virus whose assault on the nervous system continues unabated despite antiviral medications that can keep the virus at bay for years in the rest of the body.

The new research reveals key steps taken in the brain by Tat, a protein that is central to HIV's attack on cells called neurons. Researchers discovered the receptor that Tat uses to attack neurons, and they were able to reverse the effects of Tat in the laboratory by blocking the receptor.

The discovery of a major molecular player in the process opens up a new avenue for researchers to explore in their efforts to prevent or treat HIV's neurological effects, for which there is no currently approved treatment. Researchers say that much of the molecular action that underlies HIV's attack on the brain also occurs in other diseases, such as Parkinson's and Alzheimer's diseases, and that the results spell progress for those conditions as well.

The team from the University of Rochester Medical Center and other institutions published its results online Nov. 13 in the journal *PloS One*.

The powerful antiviral drugs that keep many HIV patients healthy for years don't completely eradicate the virus from the body, and in the brain, even the very low levels of that remain cause relentless damage. Scientists have observed that a large percentage of HIV patients –

perhaps up to half – show evidence of neurologic disease from the virus,

"The current medications give many patients a new lease on life. But the virus is still taking a toll on the brain, even when the virus appears to be much less active elsewhere in the body," said the paper's corresponding author, neurologist Harris "Handy" Gelbard, M.D., Ph.D. of the University of Rochester Medical Center.

Gelbard was a newly minted pediatric neurologist embarking on his career when a good friend of his – a doctor with whom Gelbard had trained – became ill and died of AIDS in less than two years. His friend's struggle, and the severity of his neurological symptoms, touched Gelbard. Gradually, with the support of mentors, Gelbard came to focus on the neurological effects of HIV. He now leads a group of researchers funded by the National Institute of Mental Health that is trying to identify or create the first treatment for the neurological effects of HIV, known collectively as neuroAIDS or HIV dementia.

Scientists have known that Tat, which helps HIV operate, replicate, and infect cells, is at the forefront of HIV's attack on the brain, bringing about severe inflammation. Immune cells within the brain go into overdrive, churning out substances that attract more immune cells, and white blood cells from the body flood in and join the fray, all clumping together to form destructive entities known as multinucleated giant cells.

"Suddenly the brain environment turns from nurturing to toxic, and the brain has to work much harder to send messages. Cells are on overdrive, spending a lot more energy to do the same things they used to do easily," said Gelbard, who is director of the Center for Neural Development and Disease at Rochester.

Other changes occur throughout the brain as well. Neurons that normally reach throughout the brain by forming networks of far-reaching, delicate

extensions crucial for cell communication become damaged. Instead of sprouting healthy dendrites – projections that resemble tiny trees – neurons in the brain of an HIV patient have had parts of their dendrites abruptly torn off, in a process known as "synaptic pruning." The dendrites begin to look like a patch of severely damaged trees after a bad ice storm.

Such damage occurs in parts of the brain crucial for thinking, decision-making, and movement and memory. That accounts for symptoms like difficulties concentrating, forgetfulness, poor coordination, confusion, and gait disturbances. In later stages, neuroAIDS can cause outright dementia.

Gelbard's team discovered that Tat works through the ryanodine receptor to sicken neurons in two ways. Scientists have known that Tat makes vulnerable the mitochondria, organelles within neurons and other cells that are commonly considered the "power packs" or energy sources for cells. The team discovered that Tat destroys the ability of mitochondria to protect themselves from changes in levels of calcium.

The scientists discovered another effect of Tat as well. Tat has a dramatic effect on an organelle known as the endoplasmic reticulum, where proteins are actually assembled and folded. Gelbard's team discovered that it's Tat's effects on the ryanodine receptor that cause an "unfolded protein response" seen in the brains of HIV patients. Shape is everything for proteins, and they're nearly always useless or harmful when they are unfolded or misfolded. The problem in HIV patients is exacerbated because protein folding requires a great deal of energy – energy that cells whose mitochondria are petering out aren't likely to have.

The team also showed, in mice, that a single exposure to Tat has long-lasting effects on the brain, causing problems with mitochondria and

endoplasmic reticulum weeks later. Perhaps most striking, Gelbard says, is the observation that the exact same types of damage were seen in brain tissue of patients with HIV and neurologic disease but not in tissue from patients with HIV who did not have the neurologic disease.

The findings are in line with past findings from the team, which has shown that the central problem in HIV dementia is not that brain cells simply die. Rather, they become sick and lose their ability to communicate with each other. Because the cells are still alive, there is hope that the condition could be stopped or even reversed with proper treatment. Indeed, doctors commonly see patients who begin antiviral therapy and immediately are less confused and have improved brain functioning, but the effect generally fades as the disease progresses.

In their experiment, Gelbard's team was able to stop the harmful effects of Tat in neurons from mice by using the drug dantrolene, which blocks the ryanodine receptor. While the work offers a new target in the search for a drug that could be used in people to stop the effects of HIV dementia, Gelbard cautions that dantrolene has side effects and would not be appropriate.

"A lot of people are under the impression that HIV has been 'solved,' that somehow, it's no longer a problem. But the disease never went away, and it's a huge problem," said Gelbard, who is professor of Neurology, Pediatrics, and Microbiology and Immunology.

"There are a fair number of similarities between this brain disease and other diseases, such as Parkinson's or Alzheimer's," said Gelbard. "We hope that what we are learning can be applied to other diseases as well."

Source: University of Rochester