Is AIDS Dementia Due to Increases in Calcium?

An HIV protein increases calcium in neurons—and may be responsible for the neurological damage seen in AIDS patients

As many as two-thirds of AIDS patients suffer from dementia and a host of other neurological disorders. Researchers have recognized for some time that much of the significant damage seems to occur in their patients' neurons. Yet HIV, though found in some types of brain cells, is not found in the neurons. What's going on here? Neuropathologist Clayton Wiley of the University of California, San Diego, calls this the "$60-million question."

Now a team at the Harvard Medical School may have uncovered an important clue—one that could lead to a new treatment for the neurological aspects of AIDS. On page 364 of this issue, Stuart A. Lipton, Evan B. Dreyer, Peter K. Kaiser, and Jeffrey T. Offermann report that gp120, HIV's envelope glycoprotein, may be the culprit. On the basis of in vitro work with rat neurons, they conclude that gp120 increases the amount of free calcium inside the neurons and that the increased calcium is responsible for the cellular damage. A drug that blocks calcium channels might reverse the effect, the authors say, and they argue for human trials soon.

"The work is important because it opens up new ways of looking at how the virus accomplishes neurological damage," says Samuel Broder, director of the National Cancer Institute, who was instrumental in bringing AZT, the only drug approved by the Food and Drug Administration for treating AIDS, into clinical use. But that doesn't mean it will be universally accepted. On the contrary, it has already been met with some skepticism. While the group's finding isn't implausible—free calcium is known to cause neural damage in a number of diseases, including stroke—the finding that it might also be responsible for some of the neurological damage seen in AIDS is unexpected.

That surprising result was obtained from an in vitro system based on retinal ganglion cells and hippocampal neurons from the rat. Lipton's team applied both native gp120 prepared from AIDS patients' serum and a pure recombinant form of gp120 to the outside of these nerve cells. Calcium ion within the cells was then detected with digital imaging microscopy, which is sensitive to fluorescent light emitted by a calcium-sensitive dye.

Within 7 minutes of the application of a picomolar solution of the HIV glycoprotein to the neurons, the amount of free calcium in the cells increased by a remarkable 33-fold. The increase in calcium depended directly on how strong a dose of gp120 was applied, although even very low concentrations produced an effect. Neurons exposed to both high and low doses of gp120 died within one day.

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The researchers prevented the rise in calcium inside the neurons by reducing the amount of free calcium in the solution around the cells. Intriguingly, they also were able to protect the neurons from damage by adding nimodipine, one of a family of calcium channel antagonists, which is used to stop the destruction caused by vasospasms after bleeding from cerebral aneurysms.

And that was enough to suggest to Lipton and others that human trials of nimodipine as a treatment for AIDS-related neurological damage are in order; he is already speaking with members of the National Institute of Allergy and Infectious Diseases' division of AIDS about further in vitro work and whether to set up clinical trials in Boston with volunteers infected with HIV.

Other scientists, however, warn that, although the work by Lipton's group is interesting, a huge gap separates in vitro work from success in treating human patients. "You can't take it as a promissory note that there will be new treatments," says Broder. "It's very important to keep in mind that this is not a clinical observation."

And Lipton would be the first to agree. "To put this in perspective," he says, "this is in rodents' neurons instead of humans', and it's in the dish instead of in the brain."

Some of the skepticism lies in the fact that the mechanism whereby gp120 could lead to increased levels of intracellular calcium is unknown. In infecting lymphocytes, the gp120 on HIV interacts with a cell-surface molecule called CD4—but neurons have no CD4. In their paper the authors say it is unclear whether gp120 somehow directly alters the electrical properties of the cell membrane, thereby opening calcium channels, or whether it acts indirectly, perhaps through intermediate molecules.

"The mechanisms involved here are still uncertain," says Richard W. Price, chairman of the neurology department at the University of Minnesota. "This [work] still does not prove that gp120 is the cause of the damage. There may be other mechanisms that are more relevant or important."

Others agree that there are many significant unanswered questions. "Is this truly caused by gp120 or by a breakdown product of gp120 or some other contaminant in the preparation?" asks Michael A. Rogawksi, chief of the neural excitability section of the National Institute of Neurological Disorders and Stroke, who also expressed surprise that nimodipine would be protective.

Given these uncertainties, some workers think it's too soon for tests in human beings. Richard Johnson, director of the department of neurology at Johns Hopkins, says it would be hard to set up a good trial in human beings. Patients, he says, would have to be free of the effects of AZT, which can temporarily improve the neurological symptoms seen in AIDS. Instead, Johnson suggests a first test in macaques against SIV, which causes simian AIDS.

But Lipton counters that macaques and other animals don't show the same signs of dementia as humans. He argues that there's little to lose by testing nimodipine in human beings, because the drug has already been approved for other clinical uses and has been found to have few side effects. He points to the many AIDS patients whose lives are being extended by treatment with new drugs, but who still suffer from dementia.

Lipton would like to start trials within the next few months, but that may have to wait as the debate continues. "This will eventually come to study in people," says Price. "But you have to remember we have no clues about the benefit [of administering nimodipine] to humans. And it's my personal opinion that further experiments should be done in vitro, perhaps at the same time as human studies." ■ **Ann Gibbons**

Ann Gibbons has just joined the staff of the Science *News Department.*