Blocking an enzyme prevents HIV infection

In an unusual twist to the understanding of how HIV infection occurs, researchers at Boston University School of Medicine have discovered that an enzyme found on the surface of some cells breaks certain chemical bonds in the AIDS-causing virus' outer coat. This sets off a chain of events that enables the virus to enter the cell.

Inhibiting this enzyme — protein disulfide-isomerase, or PDI — prevents HIV from infecting cells grown in the laboratory, Hugues J.-P. Ryser and his colleagues report in the May 10 PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES.

Since 1984, scientists have known that HIV binds to the CD4 protein found on the surfaces of some immune cells. However, binding to the CD4 receptor isn't sufficient to trigger infection. Some cells that carry CD4 and bind to the virus remain resistant to HIV. Ryser believes he has found a second factor necessary for HIV infection. By breaking the disulfide bonds that help form the shape of HIV's surface, he suggests, PDI allows the virus to fuse with the cell membrane.

"[Ryser's work] is intriguing," says pathologist Jonathan Braun of the University of California, Los Angeles, School of Medicine. "It's certainly a plausible and somewhat functionally defined mechanism for HIV entrance into the cell."

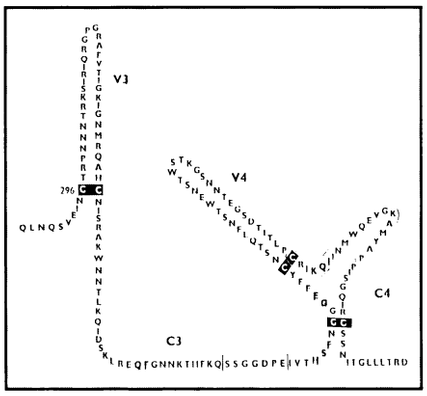
Ryser's team inhibited the effects of PDI by using three different classes of drugs. One, a nonspecific agent called DTNB, blocks all enzymes at the cell surface, including PDI, that contain a hydrogen-sulfur group. The other two, the antibiotic bacitracin and antibodies against PDI, specifically inhibit PDI's activity. All prevented HIV infection of cells but did not affect the replication of HIV in previously infected cells.

Few researchers have investigated the first steps of HIV infection, says Ryser, especially since the disulfide bonds in HIV were thought to be inaccessible to enzymes.

PDI is normally found inside cells and has only recently been shown to exist on the surface of some. Most anti-HIV drugs have tried to stop replication of the virus inside the cell, Ryser adds. He believes his work suggests promising new targets for therapeutic intervention.

Other scientists are not so sanguine, since many drugs that have blocked HIV in laboratory tests have not proved as successful in people.

This research may have implications beyond preventing HIV infection, says Dennis T. Brown, a molecular biologist at the University of Texas at Austin who has studied the Sindbis virus. This virus normally does not affect humans but can be deadly when it does. The same chemicals that block HIV's entry into the cell block the Sindbis virus, he says.



The position of disulfide bonds (highlighted) in relation to the CD4 binding domains (circled) on the gp120 segment of HIV. Each letter is a code for a different amino acid.

PDI's role in breaking viral disulfide bonds, Brown adds, "may be an emerging motif for many viruses that enter cell membranes by cell fusion."

His work may be unexpected, says Ryser, "[but] I'm very eager to see other people look into the implications. After all, we have a big problem on our hands with AIDS and every avenue should be explored. This is a very intriguing and unusual avenue." *— D. Christensen*

Brain images delve into hyperactivity

Two new brain-scan studies, both published in the May AMERICAN JOURNAL OF PSYCHIATRY, offer a mix of puzzling and intriguing evidence about the biology of hyperactivity.

Adults suffering from hyperactivity, dubbed attention-deficit hyperactivity disorder (ADHD) by psychiatrists, improve after treatment with stimulant medication but display no accompanying changes in brain activity, report John A. Matochik of the National Institute of Mental Health (NIMH) in Bethesda, Md., and his colleagues.

The ways in which these drugs affect the brains of people with ADHD remain elusive, the researchers add.

However, areas at the front of the brain implicated in the control of relatively automatic motor responses may malfunction in ADHD, NIMH psychiatrist Jay N. Giedd and his coworkers assert in the second study. An inability to rein in such behaviors at appropriate times, rather than inattention, may lie at the core of the disorder, they propose.

Matochik's group administered one of two stimulants to 21 men and 16 women, all diagnosed with ADHD. Each participant received two positron emission tomography (PET) scans, the first before drug treatment began and the second after 6 to 15 weeks of daily medication. PET scans measured glucose metabolism, which indicates how hard various parts of the brain are working.

At the end of the trial, two-thirds of the volunteers showed markedly less restlessness and much improved attention, the investigators say. Yet PET scans revealed no differences in glucose metabolism between those helped by medication and the remainder, whose condition stayed about the same.

"These findings may strengthen the voice of those who have taken the position that adult ADHD is an important cause of unrecognized and untreated distress," writes David Shaffer, a psychiatrist at the New York State Psychiatric Institute in New York City, in the same journal.

But Shaffer emphasizes caution in diagnosing and treating adult ADHD. Other studies suggest that symptoms of childhood ADHD often decrease sharply by adulthood (SN: 7/31/93, p.70). Hyperactive adults also tend to suffer from other mental disorders, such as substance abuse, that may wreak the greatest havoc on their lives, Shaffer maintains.

Most studies of stimulant treatment for adult ADHD — including the new report — fail to use placebo controls, involve small numbers of volunteers, and measure only concentration and physical activity rather than broader aspects of social functioning, he adds.

Giedd and his colleagues used magnetic resonance imaging (MRI) scans to examine the corpus callosum — a bundle of nerve fibers that runs between the brain's two hemispheres — in 18 boys with ADHD and 18 boys free of neurological and psychiatric problems.

Two regions at the front of the corpus callosum were markedly smaller in the ADHD group, the scientists report. Fibers in these areas connect to parts of the brain involved in suppressing automatic bodily responses that create problems in certain situations, they argue. For instance, these structures may mediate a young student's ability to quell the impulse to fidget during class so that he can play at recess.

A smaller corpus callosum may also reflect communication problems between brain hemispheres, Giedd's group adds.

Further imaging studies of people with ADHD should look throughout the brain, they say, with a focus on regions linked to the front of the corpus callosum.

"It is doubtful that a single 'lesion' will be found to account for all of the complicated and varied symptoms of ADHD," the researchers note. *— B. Bower*