Protease Inhibitors Appear to Cause Damage to Neurons

Findings suggest that the older class of HIV drugs may contribute to HIV-associated neurocognitive disorders.

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The protease inhibitor class of HIV antiretrovirals (ARVs) may contribute to HIV-associated neurocognitive disorders (HAND), leading to symptoms such as forgetfulness, confusion and behavioral and motor changes. This is according to research conducted in primates, mice and cell cultures.

Publishing their findings in the American Journal of Pathology, researchers first studied a population of macaque monkeys, some of which were infected with SIV, HIV's simian cousin.

Compared with the untreated SIV-positive monkeys, those treated with protease inhibitors had increased expression of what is known as the amyloid precursor protein (APP) in their neurons, a sign of damage to neurons. The protease inhibitor–treated animals also had greater levels of a so-called beta amyloid known as BACE1, an enzyme responsible for neuronal damage.

The investigators then gave the protease inhibitors Norvir (ritonavir) and Invirase (saquinavir) to uninfected mice. The fact that they saw significant increases in BACE1 confirmed that protease inhibitors were indeed contributing to a similar effect in the SIV-infected primates.

Next, the scientists conducted research in cell cultures, administering Norvir or Invirase at doses equivalent to those seen in the blood of humans on HIV treatment. This led to dramatic increases in likely indicators of an unfolded-protein response (UPR), a process that when chronically activated, can lead to cellular damage or death. They also saw increases in BACE1 and found that increases in its expression led directly to an increase in the processing of APP.

On the bright side, the investigators found that applying an agent that inhibited BACE1 to a culture of rat brain cells prevented the cellular damage caused by Norvir.

"It appears that [protease inhibitors] are triggering oxidative stress that is damaging proteins and inducing the unfolded protein response," Cagla Akay Espinoza, MD, a research scientist in the lab at the University of Pennsylvania that conducted the study and a coauthor of the paper, said in a press release. "The virus itself provides a stress, but the drugs are causing additional stress and

damage to neurons, in part by BACE1 leading to downstream processing of amyloid precursor protein."

In their last set of experiments, the researchers found that an enzyme known as PERK, which contributes significantly to the cell-damaging UPR effect, played a role in helping increase the protease inhibitor–triggered expression of BACE1 in neurons. The scientists believe that targeting PERK , BACE1 or both could yield a treatment for HIV treatment–associated cognitive disorders.

For a list of all approved protease inhibitors, click here. Note that Norvir is often used as a "booster" to raise the levels of other ARVs in the bloodstream. Protease inhibitors, including Norvir, are not included in any of the single-tablet combination HIV regimens.

To read the study abstract, click here.

To read a press release about the study, click here.
