How might efavirenz affect the brain?

Researchers are not certain precisely why efavirenz or the compounds into which it is broken down by the body affect the brain. In part, this problem arises because the action of efavirenz on the brain, at least at the molecular level, is disputed by some researchers.

However, clues about how efavirenz interacts with brain cells are emerging from laboratory experiments with cells and animals. We now present some findings from lab research on cells and animals. Until this information is confirmed in studies in people, it should be considered preliminary.

The benzo link

Valium and chemically related drugs belong to a class of drugs commonly called benzodiazepines (benzos). Efavirenz belongs to the class of anti-HIV medicines called non-nukes. These drugs are somewhat similar in shape to benzos. This is an advantage because benzos can penetrate the brain and, not surprisingly, so can efavirenz.

Getting drugs inside the brain is important because this organ plays host to visiting cells of the immune system that can be infected with HIV. In other words, the brain can act as a reservoir or sanctuary for HIV. Efavirenz, as part of combination anti-HIV therapy, can help reduce the amount of HIV in the blood and brain.

Not all non-nukes cause identical side effects. For instance, other non-nukes such as nevirapine (Viramune), rilpivirine (Edurant) and etravirine (Intelence) can penetrate the brain and can cause side effects, but they are generally not associated with the same degree of neuropsychiatric side effects as efavirenz.

Cannabinoids

Many of the natural chemicals in marijuana responsible for its effect on the brain are called cannabinoids. These chemicals stimulate the body’s receptors for cannabinoids. Efavirenz or the compounds into which the body breaks it down may also stimulate the body’s receptors for cannabinoids. The evidence for this is indirect, as follows:

- There are reports that people taking efavirenz sometimes falsely test positive for marijuana use.
- Studies with cancer cells in the lab suggest that efavirenz interacts with them via cannabinoid receptors.

LSD

Recently, researchers in Texas conducted extensive lab experiments with rats, trying to identify receptors that these animals have that could be affected by efavirenz. The researchers found that efavirenz had the potential to stimulate the receptors used by several substances when they entered the brain, including the following:

- Valium-type drugs
- barbiturates
- cocaine
- LSD (acid)
- methamphetamine

However, efavirenz did not cause addiction in these experiments with rats. This suggests that efavirenz’s effects may be somewhat different from the substances tested.

Although efavirenz can stimulate receptors for several substances, at least in rats, the Texas researchers found that the drug’s main effect on the behaviour of rats occurs though a receptor called 5-HT2A. This is the same receptor used by LSD and related compounds. The Texas researchers found that the behaviour of rats that were fed
Efavirenz seemed similar to when they were fed LSD. They suspected that the interaction between efavirenz and the receptor 5-HT\textsubscript{2A} might in part be responsible for some of the side effects—hallucinations, psychosis, flashbacks and nightmares—reported by some efavirenz users.

Abuse

A recent report by researchers in South Africa has documented that some substance users likely make use of efavirenz by crushing it and mixing it with other substances and then smoking the mixture to get high.

Brain cells

Researchers in Spain have conducted lab experiments with human and rat brain cells and efavirenz. They found that in some cases efavirenz can impair the parts of the cell used to generate energy (called mitochondria). This occurs because efavirenz has apparently injured brain cells in lab experiments. Researchers suspect that this effect of efavirenz may help to explain some of the neuropsychiatric side effects reported.

Bear in mind

For now, all of these different research findings we presented are just that. Scientists have not been able to prove that any of the molecular mechanisms discussed here are indeed the source of efavirenz-related problems that can occur in people.

Doctors have found that efavirenz can be a very useful part of combination anti-HIV therapy when used in the right patients. However, earlier in the summer, a trio of leading researchers in Canada, France and the U.K. reviewed clinical data on efavirenz. Due to a combination of factors—side effects, reduced overall effectiveness compared to newer drugs, concern about the potential for birth defects, and the presence of efavirenz-resistant HIV—they suggested that the time has come to reconsider “the routine use of efavirenz” in high-income countries.

As many HIV treatment options are now available in Canada and other high-income countries, it will be interesting to see if efavirenz will still be widely used five years from now.

REFERENCES:


Disclaimer

Decisions about particular medical treatments should always be made in consultation with a qualified medical practitioner knowledgeable about HIV- and hepatitis C-related illness and the treatments in question.

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