Methamphetamine Enters Brain Quickly and Lingers

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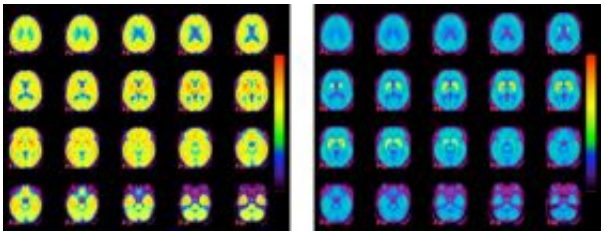

These PET scans show a comparison of the distribution of methamphetamine (left) and cocaine (right) in the human brain using a rainbow scale (red indicating the highest concentration of drug, purple the lowest). Methamphetamine binds all over the brain and stays a long time while cocaine binds only in the striatum (the reward center) and leaves the brain quickly.

(PhysOrg.com) -- Using positron emission tomography (PET) to track tracer doses of methamphetamine in humans' brains, scientists at the U.S. Department of Energy's (DOE) Brookhaven National Laboratory find that the addictive and long-lasting effects of this increasingly prevalent drug can be explained in part by its pharmacokinetics — the rate at which it enters and clears the brain, and its distribution. This study in 19 healthy, non-drug-abusing volunteers includes a comparison with cocaine and also looked for differences by race. It will appear in the November 1, 2008, issue of *Neuroimage.*

"Methamphetamine is one of the most addictive and neurotoxic drugs of abuse," said Brookhaven chemist Joanna Fowler, lead author on the

study. “It produces large increases in dopamine, a brain chemical associated with feelings of pleasure and reward — both by increasing dopamine’s release from nerve cells and by blocking its reuptake.”

Studies by Fowler and others have shown that drugs that produce greater elevations in brain dopamine tend to be more addictive. But other factors, including the speed with which a drug enters and clears the brain and its distribution within the brain, can also be important in determining its addictive and toxic potential.

In undertaking this first study of methamphetamine pharmacokinetics, the researchers also wanted to know if there were differences between Caucasians and African Americans. “Reports that the rate of methamphetamine abuse among African Americans is lower than for Caucasians led us to question whether biological or pharmacokinetic differences might explain this difference,” Fowler said.

The scientists measured brain uptake, distribution, and clearance of methamphetamine by injecting 19 normal healthy men (9 Caucasian, 10 African American) with a radioactively tagged form of the drug in “trace” doses too small to have any psychoactive effects. They used PET scanning cameras to monitor the concentration and distribution of the tagged methamphetamine in the subjects’ brains. On the same day, the same subjects were injected with trace doses of cocaine and scanned for comparison. The scientists also used PET to measure the number of dopamine reuptake proteins, known as dopamine transporters, available in each research subject’s brain.

Like cocaine, methamphetamine entered the brain quickly, a finding consistent with both drugs’ highly reinforcing effects. Methamphetamine, however, lingered in the brain significantly longer than cocaine, which cleared quickly. In fact, some brain regions, particularly white matter, still showed signs of tracer methamphetamine

at the end of the 90-minute scanning session, by which time all cocaine had been cleared. The distribution of methamphetamine in the brain was remarkably different from that of cocaine. Whereas cocaine was concentrated only in the 'reward' center and cleared rapidly, methamphetamine was concentrated all over the brain, where it remained throughout the study.

"This slow clearance of methamphetamine from such widespread brain regions may help explain why the drug has such long-lasting behavioral and neurotoxic effects," Fowler said. Methamphetamine is known to produce lasting damage not only to dopamine cells but also to other brain regions, including white matter, that are not part of the dopamine network.

Surprisingly, the researchers found significant differences in cocaine pharmacokinetics between African Americans and Caucasians, with the African Americans exhibiting higher uptake of cocaine, a later rise to peak levels, and slower clearance. In contrast, the scientists found no differences in methamphetamine pharmacokinetics between these groups.

"This suggests that variables other than pharmacokinetics and bioavailability account for the lower prevalence of methamphetamine abuse in African Americans," Fowler said. "The differences observed for cocaine pharmacokinetics are surprising considering there are no differences in cocaine abuse prevalence between these two ethnic groups." These differences may merit further study, and also suggest the need to match subjects by ethnic group in future studies to avoid interference from this potentially confounding variable.

Another interesting finding was that across all research subjects, the level of dopamine transporters was directly related to the level of methamphetamine taken up by the brain. This finding suggests that

transporter proteins somehow play a role in regulating the brain's uptake of this drug.

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