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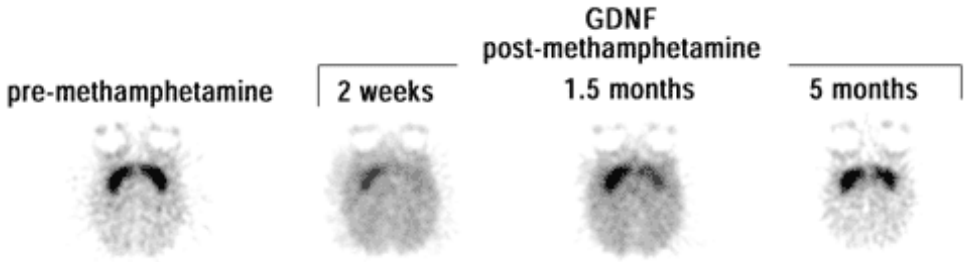
NIDA Pursues Many Approaches to Reversing Methamphetamine's Neurotoxic Effects

By Robert Mathias, NIDA NOTES Staff Writer

NIDA-supported scientists are pursuing a number of promising approaches to blocking or reversing some of the brain damage wreaked by chronic abuse of methamphetamine. Research has shown that methamphetamine can damage blood vessels and nerve endings in the brain and cause changes in brain chemicals. These effects put chronic methamphetamine abusers at risk for cognitive impairment and early onset of movement disorders associated with aging. (See "Methamphetamine Brain Damage in Mice More Extensive Than Previously Thought")

In January, NIDA's Division of Treatment Research and Development (DTR&D) convened a "Methamphetamine Addiction Treatment Think Tank." The meeting brought together preclinical and clinical researchers to set up a new program within NIDA's Medications Development Program to develop methamphetamine medications. The program now is selecting and setting up five sites to conduct clinical pharmacology and outpatient studies of medications proposed to treat different aspects of methamphetamine abuse, beginning with methamphetamine addiction. Overdose, neurodegeneration and cognitive impairment, psychoses, and movement disorders will be secondary targets.



These PET images show brain activity of a chemical messenger called dopamine (shown by dark color) in a monkey that was pretreated with glial-derived neurotrophic factor (GDNF) 1 week before being administered a neurotoxic dose of methamphetamine. Later images showed that the treated monkey had significantly greater recovery of dopamine function than an untreated monkey, at all time points following methamphetamine administration. (Brain images by Dr. William P. Melega.)

"The first priority of the methamphetamine medications development program is to develop medications to treat methamphetamine addiction," says Dr. Ahmed Elkashef of DTR&D, who heads the program. Such medications are aimed at

stopping or reducing methamphetamine abuse and not at directly reversing cognitive impairment or other clinical manifestations of methamphetamine's neurotoxic effects when they already have occurred in drug abuse treatment patients, Dr. Elkashef says. However, by reducing drug use, this approach could stop additional neurotoxic damage that might occur with continuing drug use, he says.

In addition to preventing new brain damage, addiction treatment medications may also help treat some of the clinical manifestations of methamphetamine neurotoxicity. "We will assess cognitively impaired patients to see if medications that stop or reduce methamphetamine abuse also improve cognitive functioning," Dr. Elkashef says. Program scientists also plan to test a long list of promising medications that may be able to reverse cognitive impairment caused by methamphetamine abuse, Dr. Elkashef says.

One of the first compounds the program will test-selegiline-is a medication that has the potential to treat both methamphetamine addiction and its associated cognitive impairment. NIDA has been testing selegiline, an approved treatment for some symptoms of Parkinson's disease, as a cocaine treatment medication. Selegiline's neuroprotective effects counter several possible mechanisms of methamphetamine neurotoxicity, Dr. Elkashef says. "This medication has been shown to reduce cognitive impairments among HIV-positive patients, and we expect it to help treat that aspect of methamphetamine abuse," he says.

Methamphetamine may damage the brain in many ways, including impairment of blood flow, production of harmful free radicals, and killing of brain cells. Thus, the methamphetamine medications development program also is considering using medications that have the potential to improve cognitive function by countering these effects. Potential cognitive enhancers, such as Hydergine, are thought to improve overall brain function by increasing blood flow and brain metabolism. Free radical scavengers, such as vitamin E, boost natural protective chemicals and processes that reduce brain damage caused by free radicals. Hydergine has shown modest success in improving alertness and short-term memory in stroke patients and individuals with Alzheimer's disease. Vitamin E administered with selegiline has slowed progression of Parkinson's disease and reduced severity of abnormal movements in tardive dyskinesia patients.

One possible strategy to address cognitive impairment in methamphetamine-addicted patients would be to add potential cognitive enhancers to drug addiction treatment medications, Dr. Elkashef says. However, the first step with each potential medication will be to assess whether clinical pharmacology interaction studies are needed to make sure it is safe to give it to outpatients who may continue to abuse methamphetamine, he stresses.

Developing Future Treatments

At a much earlier stage of treatment development, NIDA-supported researchers are conducting preclinical studies that could lead to the development of more sophisticated approaches to repairing methamphetamine-induced brain damage. Among the approaches that have shown promising results in animal studies are:

- DADLE ([D-Ala2,D-Leu5] enkephalin), a synthetic brain chemical and known tissue-protective agent. DADLE has been shown to block and reverse one type of methamphetamine-induced brain damage in mice;
- Neurotrophic factors, proteins produced by the body that nourish and maintain nerve cells. One of these factors, glial-derived neuro-trophic factor, has been shown to reduce methamphetamine's neurotoxic effects in monkeys;
- Genetic factors and natural anti-oxidants that promote cell survival. Boosting production of these genes and antioxidants in the brains of mice has been shown to prevent or moderate methamphetamine's neurotoxic effects.

Much additional research is needed to design safe and effective formulations of these treatments and ways to get them into the brain before researchers can begin testing in humans. However, these basic studies are increasing understanding of toxic reactions and protective mechanisms in the brain. This understanding should lead to the development of new medications that advance the goals of enabling patients to stop abusing methamphetamine and recover from at least some of the brain damage caused by the drug.

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