Methamphetamine increases susceptibility to deadly fungal infection

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Methamphetamine use can make a person more susceptible to the lung infection cryptococcosis, according to a study published in *mBio*, the online open-access journal of the American Society for Microbiology.

Researchers found that injected methamphetamine (METH) significantly enhanced colonization of the lungs by *Cryptococcus neoformans* and accelerated progression of the disease and the time to death in mouse models. *C. neoformans* is usually harmless to healthy individuals, but METH causes chinks in the blood-brain barrier that can permit the fungus to invade the central nervous system, where it causes a deadly brain infection.

"The highest uptake of the drug is in the lungs," says corresponding author Luis Martinez of Long Island University-Post, in Brookville, New York and of Albert Einstein College of Medicine in The Bronx. "This may render the individual susceptible to infection. We wanted to know how METH would alter *C. neoformans* infection."

Thirteen million people in the US have abused METH in their lifetimes, and regular METH users numbered approximately 353,000 in 2010, the most recent year for which data are available. A central nervous system stimulant that adversely impacts immunological responses, recent studies show that injected METH accumulates in various sites in the body, but the lungs seem to accumulate the highest concentrations, says Martinez, which could well impact how the lung responds to invading pathogens.

To study the impact this accumulation might have on pulmonary infection, Martinez and his colleagues injected mice with doses of METH over the course of three weeks, then exposed those mice to the *C. neoformans* fungus. In humans, *C. neoformans* initially infects the lungs but often crosses the blood-brain barrier to infect the central nervous system and cause meningitis. In their experiments, METH significantly accelerated the speed with which the infected mice died, so that nine days after infection, 100% of METH treated mice were dead, compared to 50% of the control mice.

Using fluorescent microscopy to examine lung tissue in METH-treated and control mice, the researchers found that METH enhanced the interaction of *C. neoformans* with epithelial cells in the lining of the lung. Seven days after exposure to the fungus, the lungs of METH-treated mice showed large numbers of fungi surrounded by vast amounts of gooey polysaccharide in a biofilm-like arrangement. METH-treated mice also displayed low numbers of inflammatory cells early during infection and breathed faster than controls, a sign of respiratory distress.

Martinez says this greater ability to cause disease in the lung may be due in part to simple electrical attraction. Their analysis shows that METH imparts a greater negative charge on the surface of the fungal cells, possibly lending them a greater attraction to the surface of the lung and an enhanced ability to form a biofilm that can protect its members from attack by the immune system. The fungus also releases more of its capsular polysaccharide in METH-treated mice, which can help the organism colonize and persist in the lung.

"When the organism senses the drug, it basically modifies the polysaccharide in the capsule. This might be an explanation for the pathogenicity of the organism in the presence of the drug, but it also tells you how the organism senses the environment and that it will modify the way that it causes disease," Martinez says.

But the fungus doesn't stop in the lungs. "The drug stimulates colonization and biofilm formation in the lungs of these animals," says Martinez. "And this will follow to dissemination to the central nervous system by the fungus."

C. neoformans in the lung moved on to the bloodstream and then into the central nervous system. The brains of METH-treated mice had higher numbers of *C. neoformans* cells, greater quantities of the fungus' polysaccharide, and larger lesions than control mice, indicating that METH has a detrimental effect on the blood-brain barrier, permitting the pathogen to cross more easily from the bloodstream to infect the central nervous system.

"METH-induced alterations to the molecules responsible to maintain the integrity of the blood-brain barrier provide an explanation for the susceptibility of METH abuser to brain infection by HIV and other pathogens," write the authors.

Martinez and his colleagues plan to follow up on the work by investigating how aspects of the immune system might be involved in changes the drug causes to the blood-brain barrier.

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