Tricking rats into liking cats

The blood–brain barrier is highly effective at protecting the central nervous system of mammals from infiltration by most pathogens. One pathogen, however, is capable of crossing this barrier in order to manipulate the brain, and influence the behavior, of its host.

Toxoplasma gondii is a parasite that infects ground-dwelling rats. Its eventual goal is to make its way to the cat gastrointestinal system, which is the only environment in which it is able to reproduce. In order to get from the rat to the cat, *T. gondii* uses its access to the rat brain to manipulate the rat's behavior to its advantage.

Robert Sapolsky and researchers at Stanford University (CA) report that the parasite settles in the rat's amygdala, the 'emotional' region of the brain involved in both fear responses and sexual attraction (*PLoS One* **6**, e23277; 2011). There, it seems to rewire the rat's neural circuitry so that the rat responds to cat odor not with the typical fear response, but with sexual attraction. The researchers compared rats' neural responses to cat urine odor with their neural responses to a female rat in estrous. They found that in infected rats, both stimuli elicited similar activity in the 'reproductive' area of the amygdala. Additionally, activity in the 'defensive' area of the amygdala during exposure to the cat urine was dampened in comparison with uninfected rats. The result was that infected rats spent more time exploring cat urine than uninfected rats.

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How exactly *T. gondii* achieves this change in behavior remains unclear. The authors hypothesize that the parasite releases its own store of a common brain chemical in order to enhance the activity of circuitry underlying sexual attraction. The parasite likely developed this ability as an adaptive means of increasing its chance of reproduction by gaining access to cats. Interestingly, other researchers have reported that the alteration in behavior of rats infected with *T. gondii* is specific to the cat urine odor, as the rats retain normal defensive responses to non-feline predator odors as well as normal performance on fear-related behavioral tasks.

The occurrence of such manipulation of host behavior by a parasite is alarming and may have implications for human infection by such parasites. Indeed, the authors of the study point out that a connection has been found between *Toxoplasma* infection and increased risk of mental disorders in humans. The mechanisms by which the parasite alters its host's behavior are, therefore, of particular interest to human medicine.

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NEUTRALIZING HOSPITAL-ACQUIRED INFECTIONS

Hospital-acquired infections (HAIs) afflict as many as 5% of hospital patients, particularly those receiving antibiotic therapy. The antibiotics are thought to damage normal gut microflora, allowing pathogens to flourish. *Clostridium difficile* is one of the most common pathogens, causing diarrhea, intestinal inflammation (colitis) and even death in infected patients. Management of *C. difficile* incurs an estimated $3.5 billion in health care costs in the US annually, and costs are expect to increase with the emergence of new, more virulent strains of *C. difficile*.

C. difficile is resistant to many antibiotics and is normally treated with one of two potent antibiotics (metronidazole or vancomycin). Such treatment carries two key drawbacks: relapses are common, and the treatment may contribute to increasing antibiotic resistance among bacteria. Effective alternatives to antibiotics are greatly needed. To address this need, recent research has explored a new treatment strategy for *C. difficile* that relies on the body's own defenses against infection. The results may lead to development of new approaches for treating *C. difficile* infection as well as other bacterial diseases.

The new research first examined the process by which *C. difficile* causes disease. *C. difficile* releases toxins into the gut that must be cleaved in order to enter gut epithelial cells. Cleavage is carried out by a cysteine protease that requires the presence of a cofactor, inositol hexakisphosphate ($InsP_6$). After cleavage, the toxins can enter the gut epithelium, where they trigger inflammation. But they also trigger the host system to release chemicals that effectively neutralize *C. difficile*'s 'cleaver' cysteine protease, preventing further toxin entry (*Nat. Med.* doi:10.1038/nm.2405; published online 21 August 2011).

Tor Savidge (University of Texas Medical Branch, Galveston) and colleagues found a way to induce this toxin neutralization process, called S-nitrosylation, using S-nitrosoglutathione (GSNO) in mice infected with *C. difficile*. Infected mice treated with GSNO became less ill and were more likely to survive infection than were untreated mice. The survival rate at 4 days after *C. difficile* infection was ~85% in mice given GSNO plus the cofactor $InsP_6$ compared with ~25% in untreated mice. The GSNO treatment was less effective than conventional treatment with vancomycin, however, which had a 100% survival rate at 4 days after infection.

"Our study suggests a novel therapeutic approach for treating *Clostridium difficile* infection by exploiting a newly discovered defense mechanism that has evolved in humans to inactivate microbial toxins," Savidge said in a press release.

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