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Jefferson immunology researchers halt lethal rabies infection in brain

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While rabies, an ancient scourge that still kills 70,000 every year in developing countries worldwide can be combated with a series of vaccines today, it nearly is always fatal when it reaches the brain.

But now, immunology researchers at the Kimmel Cancer Center at Jefferson have shown how a type of bat rabies infection can be prevented in mice – even after the virus reaches the brain, when it is most lethal. They found that by opening the central nervous system's (CNS) protective blood-brain barrier, powerful infection fighting substances can swarm in, essentially driving off the invading virus. A better understanding of the process, they say, may lead to improved treatment for late-stage rabies infections in humans.

"The findings indicate that delivering immune system 'effector cells' – T and B cells – to the CNS can reverse an otherwise lethal rabies infection even after the virus has reached the brain," says D. Craig Hooper, Ph.D., associate professor of cancer biology at Jefferson Medical College of Thomas Jefferson University in Philadelphia, who led the work. "While that's not a practical way to help infected humans, finding a method to open the blood brain barrier may be crucial to saving a person who is already showing clinical signs of rabies infection, where a vaccine is useless." They report their work in the *Journal of Virology*.

In earlier work in mice, Jefferson doctoral candidate Anirban Roy found evidence suggesting that despite an immune system response, cells that are responsible for clearing the rabies virus from the CNS never cross

the brain barrier. The researchers wanted to know why the barrier fails to open, and if mice were dying because the infection didn't get cleared, then would opening the barrier result in the animals surviving.

The scientists compared silver-haired bat rabies infections in two strains of mice: PLSJL mice and 129/SvEv mice. They found that the PLSJL mice, which genetically produce less inflammatory-regulating hormone, were less likely to die from the rabies infection, possibly because they are more prone to develop a stronger inflammatory response and more likely to have opened brain barriers. Conversely, they also found that despite a strong immune response, the rabies-infected 129/SvEv mice died and were less likely to have open barriers.

When they gave the PLSJL mice the anti-inflammatory steroid hormone DHEA, the brain inflammation decreased, the barrier's permeability lessened, and the death rate more than doubled.

The researchers thought that if some rabies-infected PLSJL mice died because the virus overwhelms the immune system T and B cells already in the brain and CNS, then opening the barrier even more would enable more immune cells to reach CNS tissue and fight the virus. They subsequently gave animals experimental autoimmune encephalitis (EAE), which causes an inflammatory response and the barrier to open. As a result, a higher percentage of animals survived the infection.

"In the future, one of the things we want to do is tone down the inflammatory response caused by EAE and minimize the pathogenesis, yet deliver immune cells to the CNS," says Dr. Hooper, who is also associate director of Jefferson's Center for Neurovirology. "The trick to survival might be to open the barrier and deliver effectors to the CNS.

"The data suggest that the CNS cells are developing T and B cells effectively, but that delivery to the CNS is impaired," Dr. Hooper

explains. “It might mean that the communication between the CNS and the immune system is somehow blocked. Perhaps when the disease gets further along, it triggers certain hormones that prevent the brain barrier from opening in response to immune signals. We’re trying to develop a better way to open the barrier and let these immune cells in.”

While they would like to try to understand the mechanism of the blockage, he notes, the work has larger implications. “Such studies should tell us a lot about more fundamental problems. Barrier integrity is important in Alzheimer’s, Parkinson’s, MS, and delivering immune factors in brain cancer.”

Source: Thomas Jefferson University