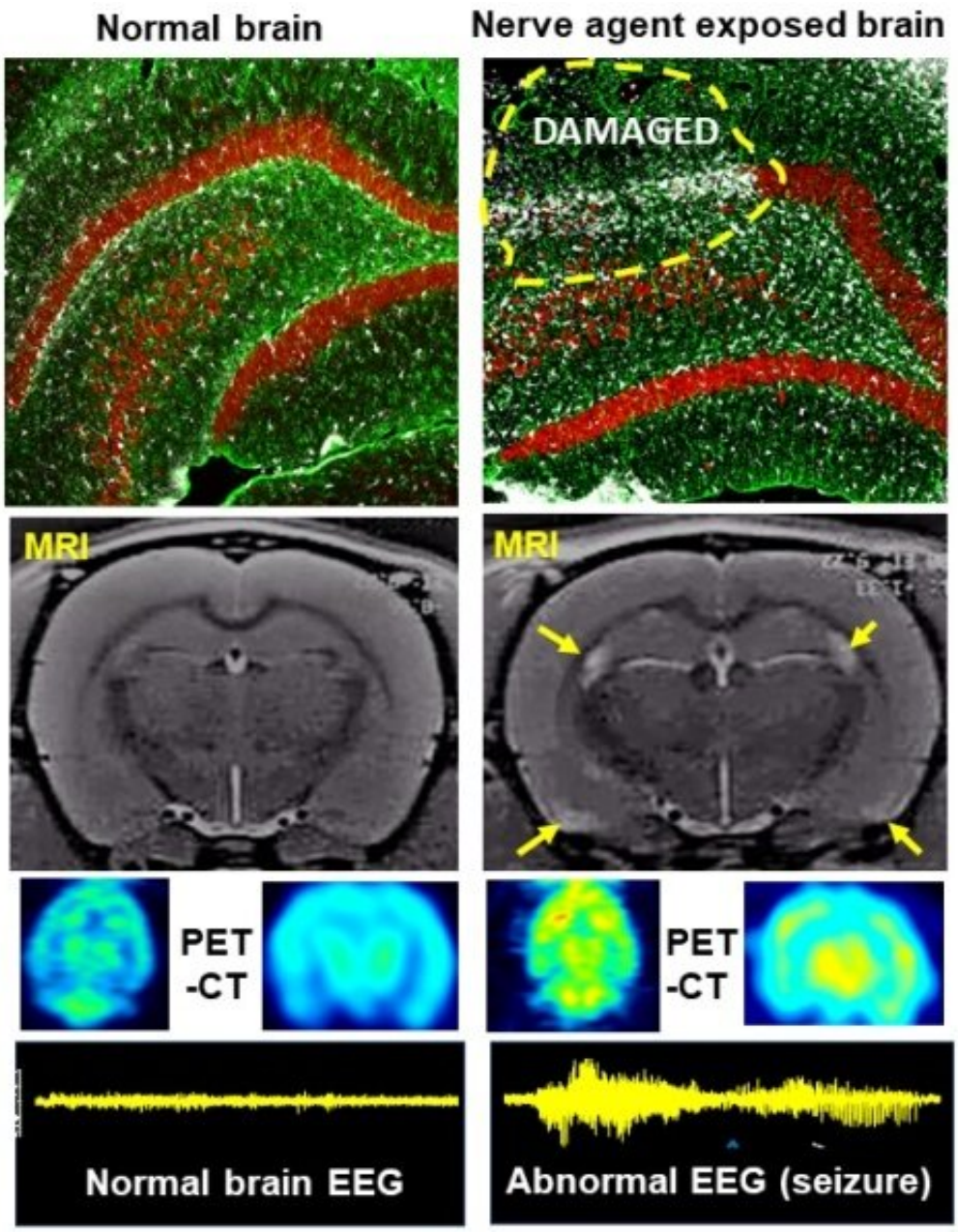
Treating long-term brain damage after exposure to nerve agents

December 17 2021



Nerve cells die gradually after nerve agent exposure, causing the brain to be swamped by misbehaving glia cells, which otherwise would serve as supporting cells in a healthy brain. A special staining for nerve cells (red cells in the picture) and misbehaving glial cells (white cells) in a nerve agent-exposed brain suggests damage. A brain MRI and PET-CT comparing a healthy versus nerve agent exposed individual is shown in the image. The arrows indicate damage to the parts of the brain that process learning, memory, anxiety and depression. These changes affect brain electrical activity and initiate seizures. Credit: Thippeswamy lab

Medical science has come up with few options to treat the long-term brain damage that results from exposure to chemical agents such as sarin gas, but an Iowa State University biomedical scientist aims to uncover new and better treatments.

Thimmasettappa Thippeswamy, a professor of biomedical sciences in the ISU College of Veterinary Medicine, is studying a pair of drugs that could reduce or prevent the harm done by nerve agents, which are organophosphate compounds such as sarin, tabun, soman and VX agent, that have been deployed as chemical weapons and disrupt the ability of brain cells to work together. Thippeswamy recently received a grant that could total as much as $3.75 million from the National Institutes of Health to test the treatments over five years. The research could shed light on other kinds of brain damage as well, such as the kind that results from severe epileptic seizures or head trauma that may cause epilepsy.

Thippeswamy said antidotes are available to fight some of the immediate symptoms caused by nerve agents, such as tremors, seizures and excessive salivation. But the chemicals also cause long-term negative effects on the brain, and no treatments have proven capable of countering them.

Nerve agents cause neurons, the nerve cells in the brain that send and receive electrical signals, to fire uncontrollably. This hyperexcited state triggers neighboring glial cells, which at first try to calm the neurons before switching to attack mode due to changes in chemical signals between cells. Exposure to chemical agents can permanently upset the balance between neurons and glial cells, and the researchers' goal is to correct this imbalance by using novel investigational drugs, Thippeswamy said.

"Misbehaving glial/supporting cells will cause long-term damage to the brain," he said. "We want to prevent that at the earliest, soon after nerve agent exposure."

New treatments show promise

Drugs like diazepam/midazolam can dampen the hyperexcitement of neurons for a short period of time, but when the drugs wear off, the neurons often begin firing again, causing the glial cells to attack the neurons.

Thippeswamy's lab is testing two treatments that have shown promise in staving off that long-term imbalance among brain cells in a surrogate nerve agent model. The researchers hope the treatments shut down the production of harmful chemicals to allow glial cells and neurons to work together.

One drug, saracatinib, has been patented by Thippeswamy for epilepsy. This drug is currently undergoing clinical trials to gauge its effects in fighting Alzheimer's disease and brain tumors. The other, known as 1400W, is an antioxidant drug and can protect nerve cells.

"Both drugs aim to prevent neurodegeneration, and both drugs may work on a synergistic principle, though their molecular targets are different,"

he said.

Researchers in Thippeswamy's lab will test both drugs separately and in concert to see if they have synergistic effects.

The research could lead to advances in the treatment of other neurological disorders as well, he said. For instance, brain damage caused by severe epileptic seizures is similar to damage caused by nerve agents. Around a third of people with epilepsy don't respond to currently available treatments. Testing the ability of saracatinib and 1400W to treat epileptic seizures could form the basis for future study, Thippeswamy said.

Provided by Iowa State University