Research points to potential therapy for tumor-associated epilepsy

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Glioma, one of the most deadly and common types of brain tumor, is often associated with seizures, but the origins of these seizures and effective treatments for them have been elusive. Now a team funded by the National Institutes of Health has found that human gliomas implanted in mice release excess levels of the brain chemical glutamate, overstimulating neurons near the tumor and triggering seizures.

The researchers also found that sulfasalazine, a drug on the market for treating certain inflammatory disorders, can reduce seizures in mice with glioma.

About 80 percent of people with glioma will experience at least one seizure during their illness, often as the first symptom. About one-third of patients will develop recurring seizures, known as tumor-associated epilepsy. Sen. Ted Kennedy, D-Mass., whose death was caused by a malignant glioma in August 2009, was diagnosed after having a seizure 15 months earlier.

"Seizures are a frequent symptom of glioma and are often poorly controlled by epilepsy medications," said Jane Fountain, Ph.D., a program director at NIH's National Institute of Neurological Disorders and Stroke (NINDS). "Understanding why the seizures occur and how to counteract them could help us substantially improve the quality of life for people with glioma."

"People have assumed that tumors cause seizures by irritating the brain,

but that really isn't a scientific explanation. We have now shown that the seizures are caused by glutamate release from the tumor," said Harald Sontheimer, Ph.D., a professor of neurobiology and director of the Center for Glial Biology in Medicine at the University of Alabama Birmingham (UAB). Dr. Sontheimer and his team published their results in Nature Medicine.

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Glutamate serves as a chemical relay within the brain. Its release from one neuron can stimulate other neurons to fire electrical impulses. However, excess glutamate can cause abnormal electrical activity in the brain – which is the basis for epileptic seizures. In particular, excess release of glutamate from non-neuronal cells called glia appears to play a role in some types of epilepsy. Because gliomas result from an overgrowth of glia, researchers had theorized that glutamate produced by the tumors might cause seizures, but no one had established a causal link.

Dr. Sontheimer's team tested the theory by studying mice whose brains were seeded with human glioma cells. They found that about one-third of the animals with gliomas developed abnormal brain activity and behavioral signs consistent with seizures. They also investigated whether or not the tumors affect brain activity in response to stimulation. When they delivered electrical pulses near a tumor, they saw a pattern of activity that spread outward from the tumor and was more prolonged and widespread than the responses to stimulation seen in normal brain tissue. Brain tissue containing the tumors also released higher levels of glutamate compared to normal brain tissue.

Next, the researchers sought to determine if the drug sulfasalazine could correct these abnormalities. Sulfasalazine is an anti-inflammatory sometimes prescribed for ulcerative colitis and rheumatoid arthritis. It

also targets a protein complex called the system Xc(-) transporter. System Xc(-) acts like a commodities broker within glioma cells, importing the essential amino acid cystine into the cells in exchange for exporting glutamate.

Dr. Sontheimer's team found that by inhibiting the system Xc(-) transporter, sulfasalazine can reduce glutamate release from gliomas. The drug also reduced seizure activity in the glioma-bearing mice, cutting the frequency of epileptic bursts nearly fivefold in the first hour after treatment. After four hours, the effects of the drug wore off unless it was re-administered. The likely reason is that most of the drug is broken down into a form that does not affect system Xc(-), according to Dr. Sontheimer.

A clinical trial is planned at UAB to determine if sulfasalazine can reduce seizures in people with slow-growing gliomas. Meanwhile, Dr. Sontheimer's lab is working with medicinal chemists to develop a form of the drug that is more stable in the bloodstream and brain, and more active against system Xc(-).

"There is hope that in addition to reducing seizures, sulfasalazine might reduce the growth of glioma cells," Dr. Sontheimer said. The cystine molecules imported by system Xc(-) are used to manufacture vital proteins that help tumor cells grow stronger, he explained. In a 2005 study, he found that sulfasalazine delays glioma growth in mice.

Whether these promising results with sulfasalazine in animal studies will translate into improved outcome in patients with brain tumors remains to be tested. Indeed, caution was raised by a small trial of 10 patients with advanced stage gliomas treated with varying doses of sulfasalazine. No beneficial effects were established, and safety concerns arose about whether treatment worsened brain swelling near the tumor. That trial was terminated early.

"It is worth examining whether or not the drug can help patients with newly diagnosed, slow-growing gliomas as opposed to patients with advanced disease," Dr. Sontheimer said.

More information: Buckingham SC et al. "Glutamate Release by Primary Brain Tumors Induces Epileptic Activity." *Nature Medicine*, published online September 11, 2011.

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