



Tumors Generate Excitement: The Role of Glutamate in Tumor-Related Epilepsy

Glutamate Release by Primary Brain Tumors Induces Epileptic Activity.

Buckingham SC, Campbell SL, Haas BR, Montana V, Robel S, Ogunrinu T, Sontheimer H. *Nat Med* 2011;17:1269–1274.

Epileptic seizures are a common and poorly understood comorbidity for individuals with primary brain tumors. To investigate peritumoral seizure etiology, we implanted human-derived glioma cells into severe combined immunodeficient mice. Within 14–18 d, glioma-bearing mice developed spontaneous and recurring abnormal electroencephalogram events consistent with progressive epileptic activity. Acute brain slices from these mice showed marked glutamate release from the tumor mediated by the system x_c^- cystine-glutamate transporter (encoded by *Slc7a11*). Biophysical and optical recordings showed glutamatergic epileptiform hyperexcitability that spread into adjacent brain tissue. We inhibited glutamate release from the tumor and the ensuing hyperexcitability by sulfasalazine (SAS), a US Food and Drug Administration–approved drug that blocks system x_c^- . We found that acute administration of SAS at concentrations equivalent to those used to treat Crohn’s disease in humans reduced epileptic event frequency in tumor-bearing mice compared with untreated controls. SAS should be considered as an adjuvant treatment to ameliorate peritumoral seizures associated with glioma in humans.

Commentary

One of the biggest fears that immediately arises in people presenting with their first seizure is the worry that they have a brain tumor. While fortunately the majority of patients with epilepsy do not have brain tumors, about 4% of all patients with epilepsy have seizures caused by brain tumors. Conversely, approximately 30% of patients with brain tumors have epilepsy (1). The risk of developing seizures depends on the type of tumor, with low-grade tumors typically having the highest incidence of epilepsy. For example, low-grade astrocytomas, gangliogliomas, and dysembryoplastic neuroepithelial tumors have a seizure incidence of about 75 percent, 80 to 90 percent, and 100 percent, respectively (1). Furthermore, while seizure medications are standard treatment for tumor-related epilepsy, these tumors represent common causes of medically refractory epilepsy (2–4). Although surgical resection of the tumor has a relatively high success rate in eliminating seizures, a substantial proportion of patients continue to have seizures or suffer a seizure relapse despite tumor resection (3, 4). Furthermore, some tumors cannot be completely resected, and risk of tumor recurrence is high. Thus, tumor-induced epilepsy significantly increases morbidity in patients, adding to the direct detrimental effects of brain tumors themselves.

Developing more effective therapies for tumor-related epilepsy depends on understanding the underlying mechanisms

of epileptogenesis. However, while a number of mechanistic hypotheses exist about tumor-related epilepsy, the specific cellular and molecular mechanisms involved in epileptogenesis related to brain tumors are incompletely understood. One important issue is whether seizures originate within the tumors themselves or from the areas surrounding the tumors. Most studies indicate that tumors are electrically relatively quiescent, and seizures are more likely triggered in the peritumoral region surrounding the tumor (5, 6). Regardless of where seizures are generated, an important related issue is whether tumors directly cause seizures via intrinsic physical or biochemical properties of the tumors themselves or whether tumors induce secondary changes in the surrounding tissue, which then mediate epileptogenesis. Abnormalities observed within tumors or in the peritumoral region that have been hypothesized to promote epilepsy include inflammation, hypoxic-ischemic injury, metabolic changes, blood-brain barrier disruption, and alterations of neurotransmitter receptor systems (7).

A leading mechanistic hypothesis about tumor-mediated epileptogenesis involves abnormal glutamate homeostasis. In other types of epilepsy, glutamate levels are elevated in epileptic brains and may directly trigger seizures by increasing neuronal excitability or promote epileptogenesis by inducing neuronal death (8). Glutamate concentrations have also been found to be abnormally increased in the peritumoral regions surrounding gliomas compared with uninvolved brain regions (9, 10). However, direct proof for a primary role of glutamate excitation in tumor-related epilepsy has been lacking.

The present study by Buckingham and colleagues provides evidence that abnormal glutamate release pro-



motes tumor-related epilepsy through a specific glutamate transporter system. The x_c^- glutamate-cysteine transporter is found in multiple organs, including the brain, and typically exports glutamate extracellularly in exchange for cysteine. In this study, intracranial implantation of human glioma cell lines into mice results in the development of seizures within a couple of weeks. Cortical slices from these mice exhibit abnormally increased glutamate release, which is reversed by an inhibitor of the x_c^- glutamate-cysteine transporter. Inhibition of the x_c^- glutamate-cysteine transporter also reduces the frequency of seizures in these mice, indicating that glutamate release from tumor cells stimulates seizures in this model of tumor-related epilepsy.

This study is significant for several reasons. First of all, the study helps to establish and characterize an animal model of tumor-related epilepsy. Although animal models of brain tumors have been utilized extensively for neuro-oncologic applications, there have been few such studies focusing on epileptogenesis. The current study has carefully documented tumor-related epilepsy using video-EEG monitoring. Almost 40% of mice implanted with glioma cells developed seizures within a couple of weeks, which is comparable to the frequency of tumor-related epilepsy in people. However, the types of seizures elicited in this model may not be typical for human epilepsy. While a very small subset of mice had tonic-clonic seizures, most documented seizures consisted of brief freezing behavior associated with high-frequency EEG activity lasting only 0.5 to 1 second, which does not seem to resemble most tumor-related seizures in people. Longer-term monitoring and more detailed EEG recordings with better anatomic localization should reveal more information about the characteristics and clinical relevance of tumor-related epilepsy in this mouse model.

Secondly, perhaps the greatest strength of this model is the ability to examine mechanisms involved in tumor-related epileptogenesis in carefully controlled studies and reduced preparations. The use of an acute slice preparation was critical in demonstrating the elevated glutamate concentration and testing its dependence on the x_c^- glutamate-cysteine transporter with inhibitors. Although the studies performed indicate that overactivity of glutamate-cysteine transporter is a key component in inducing epilepsy in this model, a number of alternative or complementary mechanisms were not tested in this study and could be investigated further. For example, elevated glutamate levels could also result from impaired astrocyte uptake of glutamate by the abnormal glioma cells. Thus, abnormal astrocyte function could represent the primary defect, which becomes apparent secondary to overload from normal glutamate release through the glutamate-cysteine transporter. Even if overactivity of glutamate-cysteine transporters is the primary defect, the biochemical mechanism driving this defect remains to be determined. Furthermore, independent of glutamate homeostasis, there could also be other parallel mechanisms of epileptogenesis that could be investigated in this model. While the present study also examined a potential abnormality in GABAergic inhibition in this model, the contribution of other metabolic, ischemic, inflammatory, or morphologic changes in neurons or glia in or

around the area infiltrated by tumor could be the subject of future studies.

Finally, of the most clinical relevance, this study is also important in identifying a novel, rational therapeutic strategy for treating tumor-related epilepsy. The decrease in seizure activity following administration of the x_c^- glutamate-cysteine transporter inhibitor, sulfasalazine, in the mouse model raises the possibility of inhibiting glutamatergic systems as a treatment for tumor-related epilepsy in people. However, the effects were short-lived, being most prominent for the first 2 hours following treatment, which likely reflects the short half-life of sulfasalazine. This rapidly reversible effect of sulfasalazine suggests that the mechanism involves direct reduction in neuronal excitability by inhibition of glutamate release, but sulfasalazine could also have other actions, such as anti-inflammatory effects. Alternative therapeutic approaches that would also decrease glutamate stimulation, but have longer lasting effects, might include upregulation of astrocyte glutamate transporters or direct antagonism of glutamate receptors. Future mechanistic studies may lead to the development of a variety of unique therapeutic approaches specifically targeting tumor-related epilepsy.

by Michael Wong, MD, PhD

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