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Glutamate From Gliomas Sparks Seizures

BY JEFF EVANS

New evidence suggests that excessive glutamate released from glioma cells causes epileptic activity in peritumoral neurons, which may be stopped by a drug that blocks the release of glutamate from tumor cells.

Previous studies have suggested that tumor-associated seizures arise from increased levels of glutamate near areas of epileptiform activity in the peritumoral border where invading cells surround neurons, but this is the first study to establish that the activity is associated with glutamate release from the system x_c^- cystine-glutamate transporter that is expressed on tumor cells, according to Susan C. Buckingham, Ph.D., and her associates at the University of Alabama at Birmingham.

The investigators detected abnormal EEG activity in 37% of immunodeficient mice 1 week after they underwent intracranial implantation of human glioma cells, but not in any mice that underwent sham implantation. This abnormal activity manifested itself as subtle changes in behavior such as freezing, facial automatisms, and tremor. Tumor-bearing cortical slices from these mice revealed a time-dependent increase in glutamate concentration (Nat. Med. 2011 Sept. 11 [doi:10.1038/nm.2453]).

Sulfasalazine (SAS), a Food and Drug Administration–approved drug that is known to inhibit system x_c^-, blocked the release of glutamate from the tumor cells but not from sham slices, which suggested to the investigators "that system x_c^- does not contribute substantially to glutamate release in tumor-free brain." Electrode recordings revealed spontaneous paroxysmal discharges near tumor cells in 23% of the cortical slices, but not in sham slices. Patch-clamp recordings from neurons in these areas demonstrated increased excitability. When the researchers applied SAS to these neurons, the mean duration of epileptiform activity declined significantly. Mice with xenografted tumors that received intraperitoneal injections of SAS also showed decreased epileptic activity on EEG.

Patients with low-grade, slow-growing tumors that can become refractory to traditional antiepileptic drugs "would be most likely to benefit from SAS treatment," the investigators noted.

Based on the approved status and tolerable side effects of SAS, the investigators are planning a trial using it as an adjuvant treatment for peritumoral epilepsy in approximately 50 patients with gliomas. They also will undergo chemical shift MRI to determine the acute effect of oral SAS on glutamate release. Although the trial is open to patients with all grades of glioma, senior author Dr. Harald Sontheimer said in an interview that his team is "primarily interested in newly diagnosed patients with low-grade gliomas who present with seizures."

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ADVISER'S VIEWPOINT

New Avenue for Treating Seizures

Seizures are often a presenting symptom or sometimes a contributing factor in morbidity for patients with primary brain tumors. Dr. Buckingham and her colleagues demonstrated, through a commonly used mouse model, that glutamate is released from glioblastoma cells, thereby altering the surrounding neuronal resting membrane potential. This hyperexcitable state is ultimately responsible for epileptogenesis. Tumors release glutamate via a transporter mechanism called system x_c^-, which is a viable target for seizure treatment. In fact, this transporter mechanism has been downregulated through use of sulfasalazine (SAS), an FDA-approved drug for use in Crohn's disease.

In 32 of 86 mice, epileptogenic potentials were recorded. Only three experienced convulsions. The remaining mice had events that were characterized as freezing behavior, automatisms, and head tremor. Based on phenotype alone, these manifestations were not clearly epileptic. But activity seen by depth electrodes confirmed them as seizures. Once SAS was administered, the frequency of seizure activity was significantly decreased. This finding is exciting, given the prior dearth of data relating tumorigenesis and epilepsy. The subtle behavioral changes that were witnessed to correlate with epileptic activity may suggest that patients with glioblastoma are experiencing subclinical seizure activity and further morbidity that is often thought of as a direct result of tumor growth and/or sequelae of chemoradiation.

In vitro studies are needed to further assess feasibility and tolerability of SAS as an antiepileptic drug, given its short half-life and its impact on metabolism of chemotherapeutic agents. This drug has been looked at previously in patients with progressive glioblastoma in terms of activity against tumorigenesis, but not for antiepileptic activity.

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Low Pregabalin Dosing Clouds Partial Seizures Trial

BY DIANA MAHONEY

FROM LANCET NEUROLOGY

Monotherapy with lamotrigine might be more effective than with pregabalin in providing freedom from seizures for patients with newly diagnosed partial seizures, according to a randomized study, but the results could be attributable to nonequivalent dosing of the drugs in the trial.

Lead investigator Dr. Patrick Kwan of the Chinese University of Hong Kong and his colleagues may have selected too low of a starting dose of pregabalin, biasing the study against patients who were unresponsive to the drug at the low dose and leaving too little time in the trial's primary end point of freedom from seizures at 6 months or more for patients to experience greater seizure control at higher doses.

Patients with newly diagnosed partial seizures also often have low seizure frequency and could have had a partial response to pregabalin but then had a breakthrough seizure around 6 months, thereby not leaving enough time for 6 months of seizure freedom, according to Dr. Jacqueline French of the comprehensive epilepsy center at New York University.

The fact that approximately 70% of pregabalin patients were on the lowest two doses of the drug at the end of the trial suggests the possibility that "the seizures were too infrequent to allow more than one or two dosage increases during the 52 weeks of the trial," Dr. French wrote in an editorial accompanying the study. "Longer trials of pregabalin versus lamotrigine and other pairs of antiepileptic drugs are essential, and every methodological detail, as well as its consequences, needs to be scrutinized before a true winner can be declared" (Lancet Neurol. 2011 Sept. 1 [doi:10.1016/S1474-4422(11)70191-0]).

Pregabalin has not been approved by the Food and Drug Administration as monotherapy for partial seizures.

Dr. Kwan and his associates conducted a double-blind, parallel-group noninferiority study in which 660 patients at 105 centers were randomized during 2006-2009 to oral pregabalin titrated to 75 mg twice daily or oral lamotrigine titrated to 50 mg twice daily during a 4-week dose-escalation phase. This was followed by a 52-week efficacy assessment phase during which the daily dose could be increased to a maximum 600 mg of pregabalin and 500 mg of lamotrigine (Lancet Neurol. 2011 Sept. 1 [doi:10.1016/S1474-4422(11)70154-5]).

In the intention-to-treat population, 162 of the 314 pregabalin patients (52%) were seizure free for 6 or more continuous months at any time during the efficacy assessment phase, compared with 209 of the 308 lamotrigine patients (68%), the authors reported. With respect to secondary end points, 19 (6%) of the initial 330 patients receiving pregabalin withdrew because of lack of efficacy compared with 3 (1%) of the 330 patients initially randomized to lamotrigine, and time to first seizure and time to 6-month seizure freedom after the dose-escalation phase favored lamotrigine.

Because there was no previous monotherapy study of pregabalin, the investigators referenced adjunctive trials to select the daily dose range. By extrapolating from the results of previous trials, however, the authors speculated that "pregabalin 150 mg/day could have been too low as the initial dose in our study. Lack of equivalence might have selected against patients who were unresponsive to low does of pregabalin, and might explain the reduced times to first seizure in the pregabalin group."

The overall incidence of adverse events was similar in both treatment groups, and the adverse event profiles were consistent with those reported in the prescribing information, according to the authors. The most common adverse events were headache, dizziness, somnolence, fatigue, and weight increase – the latter four of which were numerically more common in the pregabalin group. Specifically, in the pregabalin group, there were 211 adverse events, including 131 (40%) that were treatment related, and there were 36 serious adverse events of which 6 (2%) were treatment related. Similarly, 125 (38%) of the 207 adverse events reported in the lamotrigine group were treatment related, and 1 of the 24 serious adverse events in this group (less than 1%) were treatment related. None of the four deaths – two in each group – were considered to be treatment related, they said.

The study authors disclosed financial relationships with Pfizer, Eisai, Johnson & Johnson, UCB Pharma, GlaxoSmithKline, Novartis, Valeant Pharmaceuticals International, Sierra Neuropharmaceuticals, Neuronex, and Medtronic. Dr. French disclosed performing work for multiple pharmaceutical companies, noting that all of the money from those relationships is paid to the nonprofit Epilepsy Study Consortium, of which she serves as president. ■