Glioma, glutamate (SLC7A11) and seizures—a commentary

Vani Santosh[1], Palavalasa Sravya[2]

[1]Department of Neuropathology, [2]Department of Clinical Neurosciences, National Institute of Mental Health and Neurosciences, Bangalore, India

Correspondence to: Dr. Vani Santosh. Department of Neuropathology, National Institute of Mental Health and Neurosciences, Bangalore, India. Email: vani.santosh@gmail.com.

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Glioma, a common type of adult primary brain tumor and also the most dreaded, often presents to the clinic with seizures. These seizures are usually difficult to control with the standard anti-epileptics. Some of the patients presenting with medically refractory epilepsy due to a low grade glioma, achieve seizure control by surgical resection but some remain symptomatic despite surgery. Excitability in the human CNS is predominantly mediated by glutamate and recent compelling evidence points to the role of glutamate in excitotoxic damage resulting in seizures as well as maintenance and invasion of malignant glioma (1). Furthermore, recent studies have shown that excitotoxicity favours glioma preservation, progression and invasion in cases of malignant glioma (2-4). For instance, necrosis in glioblastoma was reported to result due to glutamate excitotoxicity through inhibition of system XC^- (SXC), which normally exchanges intracellular glutamate with extracellular cystine, causing deficient intracellular cystine or through change in calcium homeostasis eventually leading to cell death resulting from reactive oxygen species damage (5). Thus, targeting excitotoxicity in glioma patients not only helps in symptomatic management of the seizures but may, possibly, play a role in altering the underlying tumor pathogenesis.

Glutamate excitotoxicity is mainly a result of extracellular accumulation of glutamate which is regulated principally by a balance between glutamate secreting SXC and the glutamate reuptake through excitatory amino acid transporters (EAATs). Hence, an aberration in either can cause glutamate excitotoxicity (5). Though the notion that glioma cells secrete excitotoxic concentrations of glutamate has been in vogue for over a decade (6), direct evidence of the role of glutamate in causing seizures in malignant glioma has been lacking.

The article titled "*SLC7A11 expression is associated with seizures and predicts poor survival in patients with malignant glioma*" by Robert SM, Buckingham SC, Campbell SL, *et al*. and published in *Science Translational Medicine* in May 2015, has provided evidence that a glutamate transporter (SLC7A11) expression in glioma is associated with excitotoxicity and the article discusses the glutamate release via the SXC pathway in glioma and the clinical significance of SLC7A11 expression in malignant glioma.

This study focuses on the cystine/glutamate exchanger SXC pathway for glutamate release and demonstrates the role of the catalytic subunit of SXC, SLC7A11 in causing seizures and determining prognosis of patients with diffuse glioma (grades II to IV). This comprehensive study involves animal models of glioma developed through xenografts from the tumor tissue of patients with glioblastoma showing high SLC7A11 expression and low SLC7A11 expression, their seizure activity, the ability of sulfasalazine, an SXC inhibitor in curbing these seizures and a pilot study on nine patients with malignant glioma which monitors the change in glutamate levels in the peritumoral region after administration of sulfasalazine. The findings from this study indicate that (I) the excitotoxic damage predominates in the peritumoral region and there is hyper excitability of cortical neurons in the peritumoral region; (II) the expression of catalytic subunit of SXC, SLC7A11 correlates with glutamate release as well as the prognosis of the patients with glioma; (III) SLC7A11 expression correlates

with the incidence and onset of seizures in the animal models (IV) Sulfasalazine (SAS), an SXC inhibitor reduces glutamate excitotoxicity and causes changes in glutamate concentration in the peritumoral region in patients, as determined through MRS.

This study is a significant contribution to the evidence of glutamate excitotoxicity in gliomas for various reasons. Firstly, this study has stratified gliomas into two types based on the expression of SLC7A11 in paired tumor core and peripheral brain tissue sample from each patient. The authors have further shown that clinically, the patient survival data from REMBRANDT, when stratified into SLC7A11 high and low expression, showed that those with low expression survived an average of 9 months longer than those with high expression. This correlates well with existing literature which showed that SLC7A11 knockdown cell lines when implanted in mice, showed reduced peritumoral edema and neuronal death and increased overall survival compared to control mice (7). However, the grade of the glioma was not considered for this survival analysis and this may have been a major confounding factor. Also, as the author has mentioned, the study is based on high grade glioma essentially and further study involving lower grade glioma is warranted.

Another strength of this study is that it helps in establishing the animal model for studying tumor related epilepsy and includes meticulously designed experiments to examine mechanisms involved in tumor-related epileptogenesis both *in vitro* as well as *in vivo*. Through the study of calcium signaling in the cortical neurons harvested from rat brain and through co-culturing the glioma cells with cortical neurons in transwell system preventing any physical contact, they have proven that glutamate secreted by the glioma cells indeed causes excitotoxic damage to the cortical neurons. Using the *in vivo* model, the authors have successfully shown that only the cortical neurons but not the astrocytes in the peritumoral zone are susceptible to the excitotoxic damage caused by the SXC expression. The electrophysiological testing using whole-cell patch clamp experiments and pharmacologically (bicuculline and magnesium-free) induced excitability involving acute brain slices containing SXC expressing and non SXC expressing tumor have shown that indeed, seizures may be induced more easily in the SXC expressing tumors than the non SXC expressing tumors. Also, they have shown that nearly all glioma implanted mice showed spike and wave epileptic discharges but only the SXC expressing mice have developed seizures. However, the seizures in the experimental animals are not representative of the human seizures and with the exception of a very small proportion of subjects, interictal epileptic discharges also usually represent seizure disorder in humans (8).

The greatest strength of this study lies in that it includes a pilot study involving 9 glioma patients, 3 oligodendroglioma, 3 astrocytoma and 3 glioblastoma. This part of the study performed using glutamate MRS has shown that peritumoral glutamate responds to acute oral dosing of sulfasalazine, an SXC inhibitor and the authors have measured the change which they subsequently compared with SLC7A11 expression in the biopsy tissue from these patients. This comparison had thrown light on the fact that higher SLC7A11 expression corresponded to larger change in glutamate in response to sulfasalazine. Thus, they have shown that SAS penetrates the blood brain barrier and alters glutamate level acutely. Also, six of these patients were tested and were found to have an abnormal EEG. Though this part of the study greatly enhances the translational aspect of this study, it must be noted that the grades of glioma were either grade II or grade IV. There were no anaplastic grade III gliomas included in the study which would have completed the spectrum of adult diffuse gliomas. The SXC expression in different grades of glioma is different according to the Figure S11 in the article. Thus, the grade of the tumor may have influenced the results of the study. However since grade of glioma cannot be determined until after the biopsy, recruiting patients of all grades was out of scope for the clinical MRS pilot study. Since SAS has a short half life, the rebound increase as shown in the study is more likely and hence, other SXC inhibitors need to be investigated for the purpose.

On the whole, this well conducted study has investigated glutamate release in gliomas from multiple angles and has successfully shown that SXC inhibitors may be an important treatment modality in gliomas which so far depend heavily on temozolomide. Though clinically underpowered to make such a suggestion, the study goes in hand with recent studies using Sulfasalazine in glioma which have shown promise *in vitro* (9) as well as in clinical trials. These clinical trials demonstrated the benefit of sulfasalazine treatment in the form of seizure control in humans (10) and in the form of radio-sensitization for gamma knife radiosurgery in rats with human GBM xenografts (11). Thus, a search for SXC inhibitors with longer half life and better suited for administration to glioma patients may hold promise in the treatment of these dreaded tumors.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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