LETTER TO THE EDITOR

In Reference to Fu et al. (Neuro-Oncology 2008;10:139–152)

Dear Editor,

We read with interest the article “Tetramethylpyrazine inhibits activities of glioma cells and glutamate neuro-excitotoxicity: Potential therapeutic application for treatment of gliomas” by Fu et al. (Neuro-Oncology 2008;10:139–152).1 We were surprised that the authors did not examine or discuss the possible role of the N-methyl-D-aspartate (NMDA) type of ionotropic glutamate receptor in mediating glutamate-induced [Ca^{2+}] increase in glioma cells and glioma cell-induced neurotoxicity. In fact, the NMDA receptor was not mentioned anywhere in the article, although it has been implicated in mediating both glutamate excitotoxicity and glioma growth. There are a number of reasons why the involvement of NMDA receptors should have been investigated, or at least discussed.

The study by Fu et al. indicated that tetramethylpyrazine inhibited glioma growth and protected neurons against glioma-induced excitotoxicity. The involvement of non-NMDA glutamate receptors in some glutamate-induced responses was investigated by using the non-NMDA receptor antagonist CNQX. Although a role for non-NMDA glutamate ionotropic receptors in excitotoxicity has been demonstrated, the NMDA receptor is still recognized as the key molecule mediating glutamate-induced excitotoxicity. In fact, the “source-specificity” hypothesis of excitotoxicity proposes that Ca^{2+}-induced neurotoxicity is triggered more efficiently when influx of Ca^{2+} occurs through the NMDA receptor, due to complex protein-protein interactions that link NMDA receptor-mediated Ca^{2+} entry to downstream neurotoxic signaling pathways. Thus, the NMDA receptor together with its associated submembrane proteins gives rise to a protein complex specialized in mediating excitotoxicity.2

Fu et al. mention previous work by Takano et al.3 showing that glioma cells release glutamate, thus leading to neuronal damage through excitotoxicity, and correctly state that Takano et al. “have thus described a novel property of experimental tumors that might provide insight into why glioma cells grow so quickly and, more important, provided new clues for possible therapeutic intervention.” Fu et al. go on to refer to other work suggesting that non-NMDA receptors may play crucial roles in the proliferation and migration of glioblastoma, suggesting that a blockade of these Ca^{2+}-permeable receptors may be a useful therapeutic strategy for suppression of glioblastoma invasion.”1 However, in the study by Takano et al., the NMDA receptor was shown to play a major role in the observed effects. Thus, the growth of glutamate-secreting gliomas was inhibited by the NMDA receptor channel blockers MK-801 and memantine.3

The possibility that NMDA receptors are involved in the effects observed by Fu et al. might help to interpret some of their findings. For instance, the authors mention that pre-incubation with CNQX “reduced but did not abrogate” the increase of intracellular free calcium concentration [Ca^{2+}], by glutamate in C6 glioma cells. It is possible that CNQX did not completely block the [Ca^{2+}] increase because Ca^{2+} influx was partially mediated by NMDA receptors. Also, the authors raise the possibility that other ion channels might contribute to the prolonged Ca^{2+} influx observed when neuronal-conditioned medium was used, and mention that previous studies “have confirmed metabotropic glutamate receptors and voltage-gated Ca^{2+} channels were expressed in human glioma cells.” However, it was not mentioned that C6 glioma cells have been shown to respond to NMDA and NMDA receptor antagonists, suggesting that NMDA receptors might also be involved in glutamate-induced Ca^{2+} influx in these cells.4 These issues could have been examined by Fu et al. by including additional experimental groups verifying whether NMDA receptor antagonists such as aminophosphono-pentanoic acid (AP5), MK-801, or memantine could reduce the glutamate-induced Ca^{2+} influx and glioma cell-induced excitotoxicity.

Understanding the role of the NMDA receptor and the effects of NMDA receptor antagonists on excitotoxicity associated with gliomas has obvious clinical implications. Fu et al. correctly state that ideal therapeutic agents for the treatment of gliomas should inhibit Ca^{2+} influx into glioma cells and protect neurons against excitotoxicity.1 These are characteristics that apply to NMDA receptor antagonists. Moreover, at least one NMDA receptor antagonist that inhibits the growth of experimental gliomas,4 memantine, has proven clini-

Received August 26, 2008; accepted September 23, 2008.

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cally useful and well tolerated. NMDA receptor antagonists might provide the most promising novel therapeutic strategy for reducing glioma growth and neuronal damage associated with glioma-induced excitotoxicity.

Sincerely,
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