

This article was downloaded by: [University of Calgary]

On: 28 May 2015, At: 15:58

Publisher: Taylor & Francis

Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Channels

Publication details, including instructions for authors and subscription information:
<http://www.tandfonline.com/loi/kchl20>

Do BK channels mediate glioma hypoxia-tolerance?

Matthew E Pamerter^a & Gabriel G Haddad^{bcd}

^a Department of Zoology; University of British Columbia; Vancouver, BC Canada

^b Department of Pediatrics; Section of Respiratory Medicine; University of California San Diego; La Jolla, CA USA

^c Department of Neuroscience; University of California San Diego; La Jolla, CA USA

^d The Rady Children's Hospital-San Diego; San Diego, CA USA

Published online: 09 May 2014.



[Click for updates](#)

To cite this article: Matthew E Pamerter & Gabriel G Haddad (2014) Do BK channels mediate glioma hypoxia-tolerance?, Channels, 8:3, 176-177, DOI: [10.4161/chan.28994](https://doi.org/10.4161/chan.28994)

To link to this article: <http://dx.doi.org/10.4161/chan.28994>

PLEASE SCROLL DOWN FOR ARTICLE

Taylor & Francis makes every effort to ensure the accuracy of all the information (the "Content") contained in the publications on our platform. Taylor & Francis, our agents, and our licensors make no representations or warranties whatsoever as to the accuracy, completeness, or suitability for any purpose of the Content. Versions of published Taylor & Francis and Routledge Open articles and Taylor & Francis and Routledge Open Select articles posted to institutional or subject repositories or any other third-party website are without warranty from Taylor & Francis of any kind, either expressed or implied, including, but not limited to, warranties of merchantability, fitness for a particular purpose, or non-infringement. Any opinions and views expressed in this article are the opinions and views of the authors, and are not the views of or endorsed by Taylor & Francis. The accuracy of the Content should not be relied upon and should be independently verified with primary sources of information. Taylor & Francis shall not be liable for any losses, actions, claims, proceedings, demands, costs, expenses, damages, and other liabilities whatsoever or howsoever caused arising directly or indirectly in connection with, in relation to or arising out of the use of the Content.

This article may be used for research, teaching, and private study purposes. Terms & Conditions of access and use can be found at <http://www.tandfonline.com/page/terms-and-conditions>

It is essential that you check the license status of any given Open and Open Select article to confirm conditions of access and use.

Do BK channels mediate glioma hypoxia-tolerance?

Matthew E Pamerter^{1,*} and Gabriel G Haddad^{2,3,4}

¹Department of Zoology; University of British Columbia; Vancouver, BC Canada; ²Department of Pediatrics; Section of Respiratory Medicine; University of California San Diego; La Jolla, CA USA; ³Department of Neuroscience; University of California San Diego; La Jolla, CA USA;

⁴The Rady Children's Hospital–San Diego; San Diego, CA USA

Like all tumors, human gliomas are remarkably tolerant of hypoxia. Conversely, hypoxia rapidly activates cell death pathways in healthy brain cells. Therapies aimed at reversing the hypoxia-tolerance of cancerous cells offer considerable promise in the treatment of brain tumors; however, the underlying cellular mechanisms that permit tumor cells to tolerate prolonged hypoxia are poorly understood. Key to normal cellular responses to hypoxia are a number of ion channels whose expression or activity are modified by changes in oxygen. Such changes in ion channel function alter cellular ion gradients that control downstream signaling cascades, which in turn mediate a wide variety of intra- and inter-cellular 2nd messenger systems that are critical to cellular viability, growth, and proliferation. Therefore, the ability of ion channels to respond to hypoxia and beneficially regulate these downstream cellular pathways plays a key role in determining cellular tolerance to low oxygen stress. As such, differences in the oxygen-sensitivity of ion channels between healthy vs. cancerous cells are excellent candidates to contribute to the hypoxia-tolerance of tumor cells. Of particular interest in the search for treatments of human glioma is one particular family of ion channels, the Ca²⁺-activated and voltage-dependent K⁺ (BK) channels, which are found in both the plasmalemmal and mitochondrial inner membranes.

BK channels are critical signaling intermediates that detect changes in local oxygen availability and coordinate cellular responses to hypoxia in healthy brain cells.^{1,2} The function of BK channels in

cancerous cells is less well understood; however, in biopsies from human gliomas, BK channel expression is upregulated relative to in healthy tissue and this change correlates with the malignancy grade of tumors.³ Perhaps more importantly, pharmacologically activating plasma membrane BK (_{plasma}BK) channels activates apoptotic cell death pathways in a human glioma cell line.⁴ Together, these studies suggest a strong correlation between _{plasma}BK-channel activity and glioma cell viability and tumor proliferation. In combination with their role as cellular oxygen sensors in healthy brain tissue, this putative connection between BK channel function and glioma viability suggests that there may be a link between the function of _{plasma}BK channels in glioma cells and their tolerance to hypoxia. It is therefore reasonable to hypothesize that differences in the expression or function of _{plasma}BK channels between healthy brain cells and glioma contribute to the divergent hypoxia-tolerance of these 2 cell types. Experiments designed to elucidate functional differences between _{plasma}BK channels in healthy vs. glioma cells may thus inform the development of treatments for hypoxia-tolerant tumors.

In a recent study, we employed electrophysiological approaches to examine the oxygen-sensitivity and channel kinetics of mitochondrial and plasmalemmal BK channels in a human glioma cell line (LN229 cells).⁵ We found that unlike in healthy neurons and glia, _{plasma}BK channels in human glioma are not sensitive to hypoxia. Furthermore, we found that activating _{plasma}BK channels (but not mitochondrial BK channels)

Keywords: tumor, calcium, LN229, IP₃, cancer

*Correspondence to: Matthew E Pamerter; Email: pamerter@zoology.ubc.ca

Submitted: 03/05/2014

Accepted: 03/09/2014

Published Online: 05/09/2014

<http://dx.doi.org/10.4161/chan.28994>

Commentary to: Gu XQ, Pamerter ME, Siemen D, Sun X, Haddad GG. Mitochondrial but not plasmalemmal BK channels are hypoxia-sensitive in human glioma. *Glia* 2014; 64:504-13; PMID: 24446243; <http://dx.doi.org/10.1002/glia.22620>

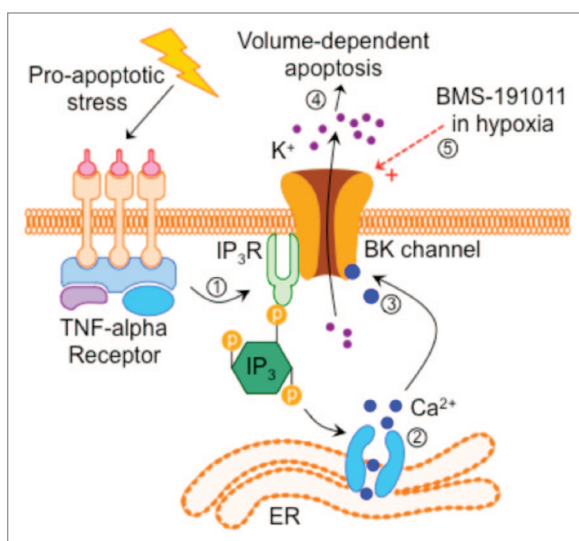


Figure 1. Model of $_{\text{plasma}}$ BK channel-mediated cell death in human glioma cells. (1) Pharmacological activation of apoptosis induces cytosolic Ca²⁺ accumulation via (2) inositol triphosphate (Ins(1,4,5) P₃)-mediated stimulation of ER Ca²⁺ release. (3) Elevated cytoplasmic [Ca²⁺] chronically activates $_{\text{plasma}}$ BK channels, which permit K⁺ efflux, leading to (4) volume-dependent apoptosis. (5) During hypoxia, pharmacological activation of $_{\text{plasma}}$ BK channels may induce glioma cell death via a similar mechanism.

increases glioma cell death in both normoxia and hypoxia (1% O₂), and that cell viability decreases by > 50% following 24 h of hypoxia when $_{\text{plasma}}$ BK channels are activated. Conversely, untreated LN229 cells tolerate 24 h of hypoxia without significant mortality. The exact mode via which $_{\text{plasma}}$ BK channel activation killed glioma cells in our study is unclear but another recent study from Sontheimer's group demonstrated that $_{\text{plasma}}$ BK channel activation is central to the execution of volume-dependent apoptosis in a different human glioma cell line.⁶ Although this study did not investigate hypoxia, these authors reported that TNF- α -induced apoptosis is dependent upon the activation of $_{\text{plasma}}$ BK channels via a Ca²⁺-dependent mechanism. Specifically, Ca²⁺ release from endoplasmic reticulum (ER)

stores leads to the activation of $_{\text{plasma}}$ BK channels, which permits the large-scale K⁺ efflux that is the key mediator of volume-dependent apoptosis (Fig. 1).

Plasmalemmal BK channels are particularly well suited to a role in this mechanism as they (1) are unusually sensitive to local changes in cytosolic [Ca²⁺] relative to BK channels in healthy glia,⁷ and (2) are located in close proximity to the intracellular point of Ca²⁺ release from the ER: $_{\text{plasma}}$ BK channels co-localize with, and are connected via lipid rafts to inositol-triphosphate receptors, which are the primary receptors that mediate intracellular Ca²⁺ release from ER stores.⁸ It remains to be determined whether a similar mechanism is involved in the loss of cellular viability in hypoxic glioma cells in which $_{\text{plasma}}$ BK channels are pharmacologically

activated; however, based on our findings and previous work in the field, we propose that the muted or absent hypoxic response of glioma $_{\text{plasma}}$ BK channels might represent a strategic adaptation to hypoxia that permits tumor cells to survive in otherwise deleterious hypoxic environments by preventing the execution of volume-dependent apoptosis. Tumor cells are generally known to tolerate hypoxic environments but the mechanism of their hypoxic resistance is unknown. Enhancing $_{\text{plasma}}$ BK channel activity or "re-activating" the sensitivity of these channels to hypoxia may offer therapeutic potential in the treatment of cancers; however, the data currently available is largely correlative and further studies that directly investigate the putative link between altered $_{\text{plasma}}$ BK channel function and the hypoxia-tolerance of glioma cells are required to determine if there is a causative link between these 2 phenomenon.

References

1. Liu H, Moczydlowski E, et al. J Clin Invest 1999; 104:577-88; PMID:10487772; <http://dx.doi.org/10.1172/JCI17291>
2. Cheng Y, et al. Cell Physiol Biochem 2008; 22:127-36; PMID:18769039; <http://dx.doi.org/10.1159/000149790>
3. Sontheimer H. Exp Biol Med (Maywood) 2008; 233:779-91; PMID:18445774; <http://dx.doi.org/10.3181/0711-MR-308>
4. Debska-Vielhaber G, et al. J Physiol Pharmacol 2009; 60:27-36; PMID:20065494
5. GuXQ, et al. Glia 2014; 62:504-13; PMID:24446243; <http://dx.doi.org/10.1002/glia.22620>
6. McFerrin MB, et al. Am J Physiol Cell Physiol 2012; 303:C1070-8; PMID:22992678; <http://dx.doi.org/10.1152/ajpcell.00040.2012>
7. Ransom CB, et al. Glia 2002; 38:281-91; PMID:12007141; <http://dx.doi.org/10.1002/glia.10064>
8. Weaver AK, et al. J Biol Chem 2007; 282:31558-68; PMID:17711864; <http://dx.doi.org/10.1074/jbc.M702866200>