Quantifying Potassium Channel-mediated Regulation of Brain Tumor Permeability by DCE-MRI

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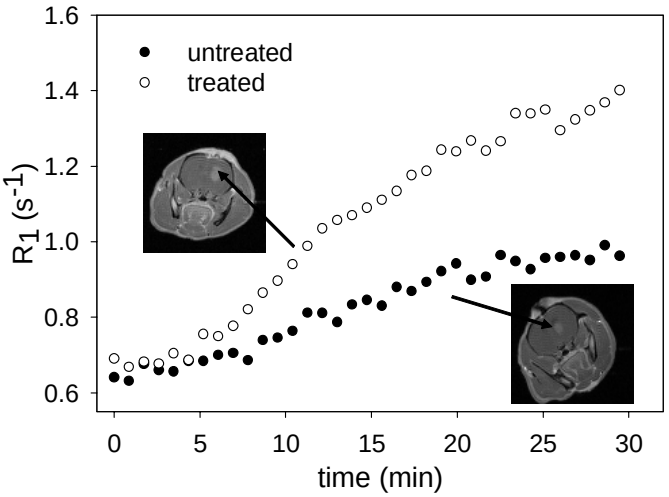
INTRODUCTION Dynamic contrast enhanced MRI (DCE-MRI) may be used to assess tumor perfusion, microvascular vessel wall permeability, and extravascular extracellular volume fraction (1,2). In a standard DCE-MRI analysis the parameters returned are K^{trans} (vessel perfusion permeability index) and v_e (extravascular extracellular volume fraction). These methods have been applied to many pathologies, including brain tumors. A significant number of brain cancer patients who respond well to anti-cancer agents for the primary tumor, however, develop CNS metastasis. This is most likely due to the inability of anti-cancer agents to cross the blood-brain barrier (BBB) and blood-brain tumor barrier (BTB) to reach cancer cells in the brain in effective quantities. It has recently been shown that calcium-activated potassium (K_{CA}) channels regulate both BTB permeability and tumor cell proliferation in metastatic brain tumors (3). Here we compare the permeability of C6 brain tumors in rats that received a K_{CA} channel-mediated BTB opening (with K_{Ca} channel agonists) to C6 brain tumors in rats that did not receive the permeabilizing agent.



METHODS Eight Female Wistar rats weighing about 180-200 gms were implanted with 2×10^5 C6 glioma cells obtained from ATCC, Manassas, VA. Briefly, an incision of about 5-mm was made on the head of the anesthetized rat. A hole was drilled using a dentist's drill with a 2-mm drill bit at a distance of 2-mm to the right from the bregma. Tumor cells were drawn up into a Hamilton syringe and the needle was inserted into the drilled hole to a depth of 4.5 mm and then pulled back 0.5mm. The cells were slowly released and the needle was pulled back up another 0.5 mm. This creates enough space for the cells to lodge and settle down. The needle was slowly pulled out after 5 minutes and the hole was closed using bone-wax. The incision was closed using a wound clip and the animals were allowed to recover. The rats were imaged 2 days later using a Varian 4.7 T scanner equipped with a 63 mm quadrature birdcage coil one week post injection. Prior to scanning each rat they received either 1ml of saline (control, n=4), or 1 ml of NS1619 (treatment, n=4) over 15 minutes. A variable flip angle gradient echo approach was employed to produce a R_1 ($\equiv 1/T_1$) map. The DCE-MRI protocol employed a standard T_1-weighted, gradeient echo sequence to obtain 35 serial images for each of 8 axial oriented planes in 45 min of imaging. The parameters were: TR = 200 ms, TE = 3.0 ms, flip angle = 30^o, FOV = $(30 \text{ mm})^2$,acquisition matrix = 128^2, slice thickness = 1.0 mm, and NEX = 2. A bolus of 0.2 mmol/kg Magnevist was delivered within 30 s *via* a tail vein catheter. DCE-MRI data analysis was performed via the reference region model as previously described (3); this analysis returns K^{trans} and v_e, the extravascular extracellular volume fraction.

Rat	K^{trans}	v_e	K^{trans}	v_e
#1	1.00	0.25	3.90	0.25
#2	2.30	0.11	9.40	0.11
#3	1.80	0.10	20.00	0.10
#4	2.20	0.19	3.50	0.19

RESULTS **Figure 1** displays typical results from this study: axial views of the tumor from a central slice of mouse 2 (control, filled circles) and mouse 6 (treated, open circles). The increased level of enhancement in the treated rat can be quantified by DCE-MRI analysis. The results from the study are summarized in the Table. The control group K^{trans} mean was 1.83 +/- 0.59 min^{-1}, while the treatment group was 9.20 +/- 7.69 min^{-1}; this difference is significant at the $P<0.05$ level. (K^{trans} units are in mL (blood)/[mL(tissue)·min].) The control group v_e mean was 0.16 +/- 0.07, while the treatment group was 0.19 +/- 0.07; this difference is not significant.

DISCUSSION We have shown that the noninvasive, clinically relevant DCE-MRI metric of tissue vessel perfusion-permeability (as assessed by the reference region model) is sensitive to changes in blood vessel permeability following administration of NS1619. It is anticipated that these experiments will provide a basis for targeting metastatic brain cancer cells that overexpress K_{CA} channels with therapeutic agents that open K_{CA} channels to permit more effective drug targeting. Monitoring the outcome of increased RTK inhibitor delivery in patients with metastatic brain tumor should lead to beneficial clinical results.

REFERENCES 1. Tofts. JMRI 1997;7:91-101. 2. Choyke, Dwyer, Knopp. JMRI 2003;17:509-520. 3. Ningaraj, Rao, Black. Cancer Res 2003;63:8899-8911. 4. Yankeelov, Niermann, Lepage, Price, Gore.12th Annual ISMRM meeting, p. 1974.

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