Sodium and Proton Diffusion MRI of Rodent Glioma Therapy at 21 T

V. D. Schepkin[1], C. W. Levenson[2], S. M. Figueiroa[3], W. W. Brey[1], P. L. Gor'kov[1], and K. K. Shetty[1]

[1]CIMAR, NHMFL/FSU, Tallahassee, FL, United States, [2]College of Medicine, Florida State University, Tallahassee, FL, United States, [3]College of Human Sciences, Florida State University, Tallahassee, FL, United States

Introduction

Detecting sodium and water diffusion in an untreated tumor, as well as during therapy, gives important insights into the role of sodium homeostasis during cancer progression. The value of sodium MRI is currently not well established. However, sodium has the potential to be more than an indicator of tumor response to therapy. Increased tumor sodium may be an early sign of apoptosis or a cell reaction directed to augment tumor cell proliferation, determined by excessive release of glutamate during glioma invasion. In time sodium homeostasis can be valuable in the fight against cancer (1-5). In the present study tumor sodium alterations and diffusion MRI have been investigated in non-treated and chemotherapeutically treated rodents 9L glioma. The observation that sodium in non treated tumors steadily increases over time was verified by using sodium MRI at 21T. The results give additional insights into the role of sodium and diffusion being more than simply a biomarker of an initial tumor therapeutic response. All experiments were performed for the first time in the record high magnetic field of 21.1 T built at the NHML in Tallahassee, FL.

Materials and Methods

Rat 9L gliosarcoma cells were implanted intra-cranially in male Fisher 344 rats (weight ~ 120 g). At ~14 days after tumor implantation, animals (total n = 12) were subjected to a single ip carmustin (BCNU) chemotherapy with two different doses (BCNU(1x)=13 mg/kg or BCNU(2x)=26 mg/kg). In the control group (n=4) tumors remained untreated. Each 1-3 days thereafter, tumor sodium, diffusion and tumor volume were detected. The experiments were performed in a 21T MRI scanner using proton (900 MHz) and sodium (237 MHz) signals (Bruker Avance console equipped with Micro 0.75 gradient set, GREAT60 amplifiers and operated by PV4.0 and TopSpin 1.5 software). Sodium 3D backprojection MRI scans had a duration of 27 min, TE =1 ms, TR=100 ms. Diffusion SE pulse sequence had flow/motion compensated diffusion gradients, two b values of 100 and 1000 (sec/mm2), TE=34 ms and 15 backprojection 2D slices. New RF probes were specifically developed for *in vivo* rat proton and sodium MR imaging at 21 T. All animal experiments were conducted according to the protocols approved by The Florida State University ACUC. Image processing was performed using Matlab 7.5 and Analyze 8.1.

Results and Discussion

The high sensitivity at 21T allowed sodium MRI in rat brain with resolution of 1 µL (Fig. 1). Two weeks after tumor implantation, a non treated glioma can bee seen as a sharply elevated area of sodium intensity with sodium content ~ 1.5 time larger than in a normal rat brain. The most important observation is that the sodium content in the non treated tumor is steadily increasing with a rate of ~ 5% per day (Fig. 2). During this time water diffusion in the tumor remains practically unchanged, suggesting that there are no changes in brain cell integrity. Sodium increase may be an early indicator of Na/K pump inhibition, possibly by the rising glutamate release during cancer progression. Time courses of ADC (Fig. 3) and sodium MRI (not shown) illustrate that the first day's responses during BCNU therapy show only that the therapy is working. The corresponding survival depends on how quickly tumor cell can re-grow after chemotherapy. Delay in tumor re-growth after more efficient BCNU(2x) therapy correlates with delays in ADC and sodium recovery. These effects can be seen only a couple of weeks after the therapy starting point (Fig. 3). Ideally, the best therapy would have the longest time delay for ADC and sodium recovery.

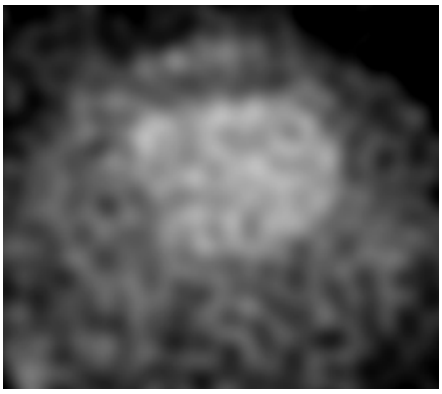

Fig. 1. Sodium MR image of rat 9L glioma, MRI resolution is 1 µL.

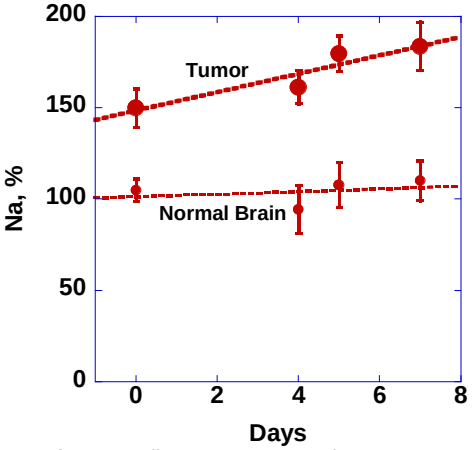

Fig. 2. Sodium tumor content in non-treated 9L rat glioma was steadily increasing at a rate of ~ 5%/day.

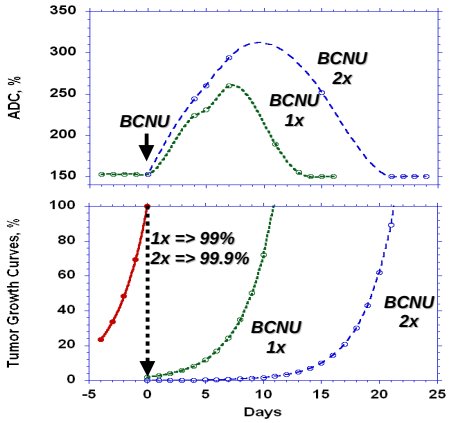

Fig. 3. Time course of changes in tumor diffusion and size during BCNU therapy.

Conclusion

The first proton and sodium MRI of large rodents has been performed at 21T. The rate of continuous increase of sodium content in non treated tumors was determined. It is important that there was no change in water diffusion at this time indicating the unchanged tumor cell integrity. A possible explanation for tumor sodium alterations may be an increase of intracellular Na during cancer proliferation. Results of sodium and diffusion MRI showed the first tumor response within a few days, but predict the outcome later, about two weeks after the initiation of therapy. The study supports the unique role of sodium homeostasis for tumor therapy and importance of sodium and diffusion MRI in evaluating and predicting efficacy of tumor therapy.

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