SODIUM MRI CAN GRADE PRE-NECROTIC DEVELOPMENT IN ANIMAL TUMOR MODELS

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Introduction

In-vivo MRI biomarkers of cellularity are essential for drug development and tailoring of individualized therapy. Sodium MRI and Proton Diffusion demonstrate strong potential for assessing of cell structural changes inside tumors. For the first time high resolution sodium MRI (voxel $\leq 1 \mu$L) was implemented together with proton Diffusion MRI. It was shown in previous experiments, using rat glioma models, that both methods have excellent correlation between each other during successful tumor therapy. These results were expanded here using high resolution sodium MRI. The present experiments revealed that in non-treated tumors sodium MRI and proton diffusion are different. Sodium concentration exhibited a consistent increase in time, reflecting the rising metabolic stress during tumor growth. Increases in sodium preceded any changes in tumor diffusion, demonstrating the unique ability of sodium MRI to grade tumor pre-necrotic development.

Experimental

Male Fisher 344 rats with 9L glioma were subjects for MRI study when their tumor size reached ~50µl (n=6). Tumor treatments were performed by chemotherapeutic agent 1,3 bis(2-chloroethyl)-1-nitrosurea (BCNU). Single IP injections of BCNU (26.6 mg/kg) were applied ~ 14 days after tumor implantation. Animals in the control group (n=3) remained untreated. Tumor alterations were observed in-vivo by both high resolution sodium MRI and proton diffusion mapping. Data were collected on Varian MRI scanner 9.4T (UM, Ann Arbor). Three-D sodium images were acquired by a back-projection GE pulse sequence with an echo time of 1 ms, TR = 100 ms, matrix 64x128x128, FOV 64 mm and acquisition time of 2 h. For proton diffusion mapping the isotropic DW SE pulse sequence was used with “high-$b$” ($b$=1082 s/mm$^2$) and “low-$b$” (117 s/mm$^2$), 15 axial slices, FOV 30x30 mm, slice thickness 1.0 mm, TR/TE = 3000/40 ms. All measurements were repeated every 2-3 days. MR images were co-registered in 3 dimensions in order to monitor the same area of the tumor over time.

Results and Discussion

During tumor growth, diffusion in untreated gliomas remained unchanged at $(1.1 \pm 0.05)*10^3$ mm$^2$/s, which was above the values in normal contra-lateral brain $(0.78 \pm 0.02) * 10^3$ mm$^2$/s. Sodium MRI, performed simultaneously with diffusion, showed elevated and consistently increasing Na content in tumor relative to a normal brain especially in central area of tumors. Furthermore, sodium increase was accelerating with tumor progression. The glioma response to BCNU treatment was dramatic, exhibiting a reliable correlated increase of Na and ADC. The moment of the largest values for tumor sodium and diffusion correlated with intensive tumor cell destruction. Tumor sodium T1 relaxation time was considerably increased at this time (57 ± 6 ms) while in normal contra-lateral brain it remained at the level of $30 \pm 3$ ms. It is important to note that a persistent increase of tumor sodium was taking place without any changes in diffusion. Level of tumor sodium can serve as predictive marker of future tumor necrosis. Necrosis, itself, was usually observed in the areas where both Na and diffusion were dramatically and simultaneously increased. During tumor therapy, the alteration of tumor sodium over time correlated with proton diffusion, and both were predictive of future tumor shrinking. The near doubling of sodium T1 relaxation time represents a significant decrease in sodium binding and indicates large structural changes in the brain tumor during therapy.

Conclusions

High resolution Na MRI in non-treated rat gliomas reflects pre-necrotic cancer development well in advance of any changes in tumor diffusion. Simultaneous use of both imaging modalities in rodent gliomas will be further investigated using advanced ability of 21T MRI scanner at NHMFL (Tallahassee).

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