Sodium MRI of chemotherapeutic response in a 9L rat glioma model

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Introduction

Diffusion mapping of brain tumors detects an early tumor response to the therapy, prior to shrinkage of the tumor, as an increase in ADC [1]. The underlying hypothesis of the changes in diffusion suggests the large changes in tumor cell integrity during tumor treatment and, correspondingly, the large variations in the Na MR signals. The goal of the present study was to investigate this relationship by detecting Na signals from 9L rat brain tumor in response to the known chemotherapeutic agent 1,3 bis(2-chloroethyl)-1-nitrosurea (BCNU). Evaluation of Na NMR, as a surrogate marker for cancer therapy, was previously discussed in several publications [2, 3, 4].

Materials and Methods

Rats with 9L brain tumors were studied when their tumor size reached ~50µl (n=6). At this point, a single dose of BCNU was injected (IP, 26.6 mg/Kg). Tumor development was monitored by T2-wt FSE proton imaging, and by diffusion mapping protocols using 13 axial slices (FOV 30x30 mm, slice thickness 1 mm). Three-D Na imaging was performed by a back-projection [5] pulse sequence with an echo time of 0.4 ms, TR = 100 ms, matrix 32x32x32, FOV 60 mm and acquisition time 30 min. TQ Na signals were also detected from the entire rat head by two pulse sequences: (a) classical three pulse sequence (TQF) and (b) its modification using simultaneous increment of inter-pulse interval and phase (TQTPPI). Amplitude of Na RF pulses were 5 KHz. All measurements were repeated every few days for several weeks after BCNU administration. Experiments were performed on a 9.4 T Varian system. Animal experiments were conducted according to the protocols approved by the University LARC.

Results

The BCNU intervention did not immediately halt the growth of the 9L brain tumor; it proceeded to grow continuously for 8 days after the injection before it began to shrink. The treatment of the tumor, however, produced a dramatic response in the brain which was clearly detectable on Na MRI two days after the injection. Na images showed a large increase in tumor Na content ~30% (Fig.1), which remained elevated even at a later time. The volume of the elevated Na matched the size of the tumor, which over seven days grew up to 250 µl followed by shrinkage then subsequent re-growth Diffusion mapping showed an increase of the average ADC in tumor from 1.0*10-3 mm2/sec to a peak value of 1.5*10-3 mm2/sec in three days. There was a decrease in TQ/SQ sodium signal observed in both TQ Na experiments following chemotherapy. TQTPPI pulse sequence gave TQ/SQ =28% in a rat head before treatment, while in BCNU treated animal it was ~ 22 % after seven days. Later when the tumor started shrinking, only a partial recovery of the TQ signals were observed.

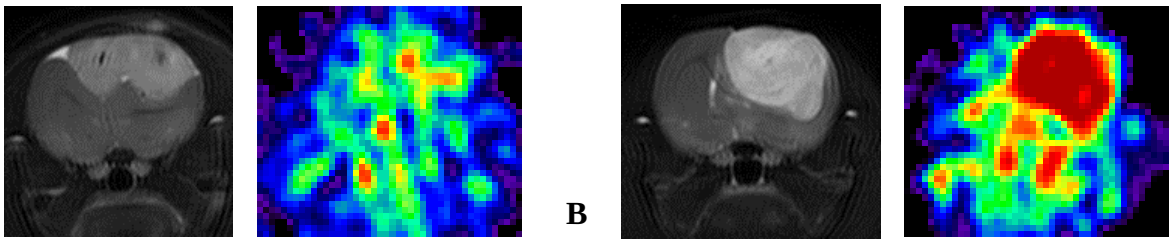

Fig. 1. Proton FSE (left) and Na back-projection images (right) for untreated L9 rat brain tumor (A). The corresponding MR images for a rat brain tumor taken five days after a single dose BCNU injection (B).

Discussion

BCNU chemotherapy increases the tumor Na content and decreases the total TQ signal. The initial rate of these changes is comparable with the elevation of ADC values simultaneously observed in the tumor. Both changes of the SQ and TQ Na signals correlate with the destructive BCNU effects on the integrity of tumor cells and ADC changes after chemotherapy. When tumor shrinkage occurred, the TQ/SQ ratio did not show a full recovery indicating an incomplete recuperation of the brain. The likelihood of the decreased Na TQ signals in tumor was also observed in some previous studies [3, 6]. TQTPPI pulse sequence is more efficient in detecting Na TQ signals. It does not use a spin-lock pulse thus decreasing an RF power deposition. Simultaneous detection of SQ and TQ, and a relatively error free setting for the RF pulse durations are advantages of this pulse sequence [7].

Conclusion

BCNU chemotherapy of 9L tumor in a rat brain increases the Na content and decreases Na TQ signals. Both facts correlate and have comparable kinetics with tumor diffusion mapping during tumor therapy. Na SQ and TQ signals changes in tumor may serve as a surrogate marker, as well as proton diffusion, for detecting early tumor response to anticancer therapies.

References

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