In Vivo Visualization of Brain Tumour Angiogenesis using 3D ΔR2-Based Microscopic MR Angiography (3DΔR2-mMRA)

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Synopsis

Tumor-associated microvascular changes offer important new insight into how tumors grow and respond to treatment. This study was aimed to simultaneously assess the changes of microvascular morphology and function on ethylnitrosourea(ENU)-induced rat brain tumor model at different stages using 3D ΔR2-Based Microscopic MR Angiography (3DΔR2-mMRA).

Introduction

Tumour angiogenesis has been recognized as a key element in the pathophysiology of tumor growth and metastasis. The abnormality of microvascular morphology has been used to distinguish benign from malignant brain tumors (1), whereas blood flow and blood volume information are important for understanding the tumor physiology and can be valuable in selecting and evaluating therapies. Therefore, simultaneously monitoring functional and structural changes to tumor microvasculature might provide an effective means of assessing both tumor aggressiveness and treatment efficacy. Many studies have been reported to assess the vascular structure and function in brain tumor (2) using either MRA techniques to visualize the vasculature or MR perfusion method to measure the hemodynamic parameters of cerebral blood volume (CBV), blood flow, and permeability. However, there is currently no available method can determine both information simultaneously. Furthermore, current MRA method such as time-of-flight and contrast enhanced MRA are excellent for evaluating larger arteries and vein but not the microvasculature of tumors. Recently, 3D ΔR2-based microscopic MR angiography has been proposed to assess the microvascular function and structure in both normal and ischemia rats (3). The aim of this study is to simultaneously characterize the relationship between tumor growth, and the changes of vascular morphology and CBV on ENU-induced rat brain tumor model (4) using high resolution 3DΔR2-mMRA method.

Material and Methods

All images were performed on a 4.7-T Biospec 47/40 MR scanner with an active shielding gradient. Brain tumor model was created by chemical induction. Pregnant Sprague-Dawley (SD) rat were placed in a restrainer and injected i.p. with 50 mg/kg ENU (Sigma, St Louis, MO, USA) at gestation day18 to day19 using a 26-gauge needle. Pups were housed two per cage (same sex) after weaning and observed weekly for signs of illness. An offspring of ENU-injected pregnant SD rat underwent imaging at postnatal day 72, 145, and 199. The rat was initially anesthetized with 5% isoflurane at 1L/min air flow. When fully anesthetized, the animal was placed in a prone position and fitted with a custom-designed head holder inside the magnet. Isoflurane was then maintained with 1~1.2% at 1L/min air flow throughout the experiments. Images were acquired using a 72-mm birdcage transmitter coil and a separate quadrature surface coil for signal detection. To determine ΔR_2, T2-weighted images (T2WI) were performed before and after an injection of iron oxide (Resovist, Schering AG, Berlin, Germany) at a dose of 30 mg Fe/kg. The post-contrast image acquisition was delayed by 1-2 minutes for ensuring a steady state distribution of contrast agent in the vascular network. T2WI were acquired using 3D RARE sequence with a TR of 1500 ms, TEeff of 82 ms, ETL of 32, 4 averages, FOV = 2.8 cm × 2.8 cm × 1.4 cm, acquisition matrix = 256×256×96 (zero-padded to 512×512×192). The in-plane resolution and slice thickness were 54.68 and 72.91 μm, respectively. ΔR_2 map was calculated pixel-by-pixel using an in-house software written by Matlab (MathWorks, Natick, MA, USA). 3D view of microvasculature was constructed with 3D ΔR2 map using a volume-rendering utility (TGS, Amira, San Diego, CA).

Results and Discussion

Figures 1A–C show the temporal changes in T2WI, ΔR2, and normal and magnified views of 3DΔR2-mMRA. The hyperintensity of T2WI indicated tumor region. Tumor location, growth, and heterogeneity can be observed by T2WI. The hypointensity area within tumor in T2WI at the late stage (P199) may be due to tumor hemorrhage. Tumor volume was substantially increased after P145 as shown in Fig. 1D. The vessels appear bright signal in ΔR2 map owing to the signal difference around the vessels prior to and after the injection of contrast agent. It reflects the physiological status of the microvascular CBV. Quantitative analysis demonstrated that a substantial increase in ΔR2 within tumor area was observed after P145 (Fig. 1E). Interesting, the signal enhancement was mainly located in tumor core region at P199 (Fig. 1B). In order to observe the change of microvasculature within tumor, the volume rendering of whole tumor was constructed by outlining the tumor region form entire 3D T2WI and fused with 3DΔR2-mMRA. A gradually increase in vessel size and density from P72 to P199 was observed, suggesting high angiogenic activity.

Conclusion

3DΔR2-mMRA can simultaneously monitor the changes of microvascular structure and function associated with tumor angiogenesis at different stages that could provide new insights into the tumor growth and metastasis.

Reference

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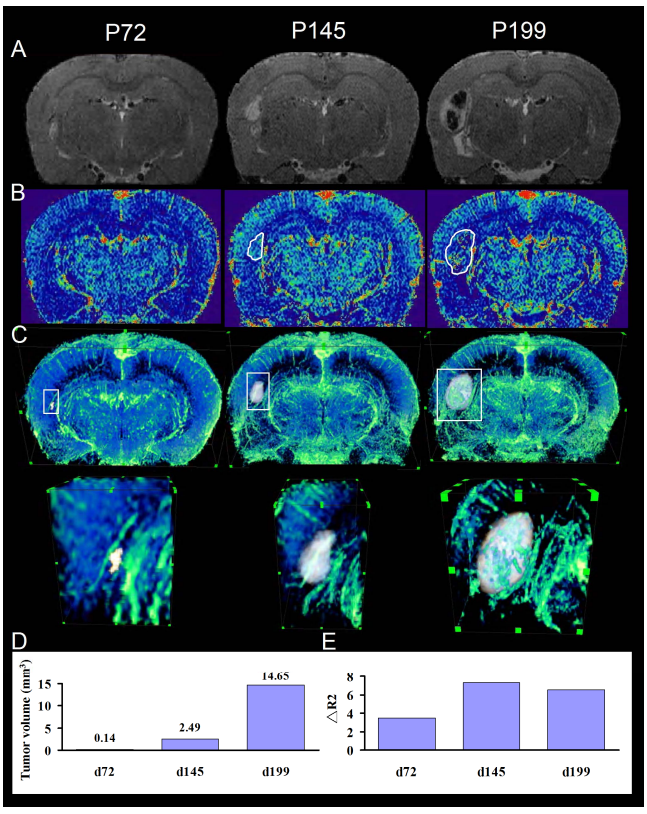

Fig.1 T2WI (A), ΔR2 (B), 3DΔR2-mMRA in normal and magnified view (C), of a section of rat brain in the tumor area as a function of time. Quantitative analysis of tumor volume (D) and ΔR2 value (E) of whole tumor.