Magnetic Resonance Imaging of Acute Alterations in the Rat Brain following Simulated Space Radiation

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Introduction

The biological effects of the high energy charged particles (HZE) that encompass space radiation are largely uncertain. Emerging evidence has shown that the vulnerability of hippocampus to HZE exposure, such as ^{56}Fe, results in cognitive impairment. From our perspective, the development of biomarkers would be advantageous for monitoring ^{56}Fe radiation-induced brain injury *in vivo*. In this study, we applied for the first time multi-modal MRI to assess the hippocampus and entorhinal cortex at 1 week after ^{56}Fe exposure with simulated doses of space radiation. The acute molecular disturbances in the two important memory-related regions can be sensitively assayed by quantitative protocols which may easily translate to the clinical context.

Methods

Total 24 Sprague-Dawley rats weighing approximately 290g were studied. Whole brain-only ^{56}Fe radiation (0, 1, 2, 4 Gy) was performed as previously described[1] with 6 animals per group. One week after irradiation, MRI scans were performed using T2-weighted imaging (T2WI), diffusion weighted imaging (DWI) and contrast enhanced T1WI (CET1). T2 relaxation time (T2) and apparent diffusion coefficient (ADC) maps were generated for quantitative MRI analysis[1]. T2 and ADC values were quantified and averaged from bilateral hippocampus and entorhinal cortices. In addition, pre- and postcontrast CET1 images were compared to evaluate the local damage to blood brain barrier (BBB). Histopathology was examined in corresponding brain sections.

Results

No overt abnormalities were visualized in T2W, DW or CET1 images at 1 week after radiation exposure. Compared to the 0 Gy, however, there were significantly prolonged T2 values in the hippocampus and entorhinal cortex of brains exposed to radiation, suggestive of the increased tissue water. Within the hippocampus, the increase of T2 was maximal in the 2 Gy group; alternately, a dose dependent elevation was noted within the entorhinal cortex (Fig. 1). A reduction of ADC revealed significantly more restricted water mobility in the irradiated-brains compared to 0 Gy controls (Fig. 2). The hippocampal ADCs were significantly reduced with no dose-dependency. Within the entorhinal cortex, the decrease of ADC was reverse dose-dependent, reflective of the differential neuropathology in microstructure evolving with the radiation dose increment. No neuronal pathology was evident on cresyl violet stained sections with the principal cell layers in the hippocampus and entorhinal cortex being intact. Glial fibrillary astrocytic protein (GFAP) staining revealed astrocytic activation in 50% of the 4 Gy animals but not in either the 1 or 2 Gy groups. Microglial staining is currently being conducted to assay inflammatory activation.

Conclusion

At 1 week after whole brain-only ^{56}Fe exposure, quantitative analysis of T2WI and DWI were sensitive to detect different patterns of alteration within brain structures critical to memory. The radioresponse including initial molecular and subsequent cellular disturbances was revealed using quantitative MRI. In consideration of the feasibility of the current protocol in the clinical setting, this approach may provide an opportunity for *in vivo* assessment of radiation injury following protons or helium radio-therapy.

1.Obenaus A, et al. Magnetic resonance imaging and spectroscopy of the rat hippocampus 1 month after ^{56}Fe radiation. Radiat. Med. 2007

Fig.1 T2 analysis: A) In the hippocampus, 2 Gy irradiation resulted in the most significant increase in T2 values compared to 0 Gy controls. T2 in both 1 Gy and 4 Gy also were significantly longer than 0 Gy. There was no dose-dependent change in T2 within the hippocampus. B) In entorhinal cortex, there was a significant dose-dependent increase of T2 when compared to 0 Gy controls, resulting in the most prolonged T2 values in 4 Gy group. *p<0.05,**p<0.01 vs 0Gy;$^{\#\#}$p<0.01vs 2Gy; $^{\&}$p<0.05, $^{\&\&}$p<0.01 vs 4Gy

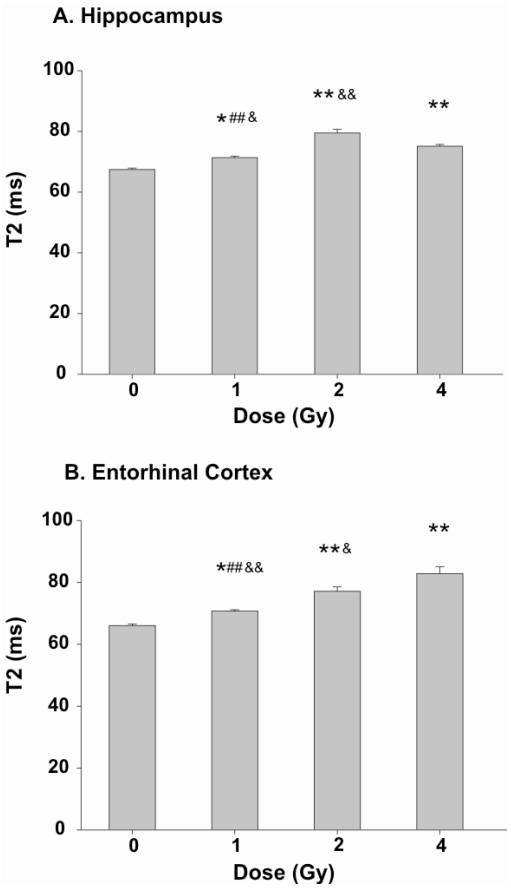

Fig.2 ADC analysis: ^{56}Fe radiation dose (Gy) versus average ADC value (mm^2/s). A) In the hippocampus, ADCs were significantly decreased in animals receiving 1, 2 and 4 Gy irradiation compared to 0 Gy controls. B) Within entorhinal cortex, the significant decreases in ADC were associated with irradiated groups in reversed dose-dependent manner. One Gy had lowest ADC compared to controls. *p<0.01 vs 0 Gy; $^{\#\#}$p<0.01 vs 2Gy, $^{\&\&}$p<0.01 vs 4Gy