EFFECTS OF COMBINED PROTON AND ^{56}FE IRRADIATION ON HIPPOCAMPAL FUNCTION

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The space radiation environment contains protons and ^{56}Fe, which could pose a significant hazard to space flight crews during and after the mission(s). With regard to the brain, the hippocampus and cortex might be particularly susceptible to space irradiation-induced changes. We first assessed the effects of proton irradiation (150 MeV) on hippocampus-dependent contextual fear conditioning 1 and 3 months following irradiation. At 1 month after 0.1 Gy of proton irradiation, there was enhanced contextual freezing as compared to sham-irradiated mice, suggesting improved hippocampal function. This effect was less pronounced and did not reach significance at a dose of 0.5 or 1 Gy. This effect was transient and not seen 3 months after proton irradiation. There were no effects of proton irradiation on immunohistochemical markers assessing neurogenesis, inflammation, or the percentage of neurons expressing the plasticity-related immediate early gene *Arc* in the dentate gyrus, suggesting the involvement of other mechanisms. Although at 3 months following proton irradiation, contextual fear conditioning was not affected other cognitive functions such as novel object recognition might be affected. In addition, the exposure in the space environment will involve exposures more complex than protons alone, such as a priming proton dose followed by a secondary or challenge dose with ^{56}Fe. To determine if there is an interaction or an additive effect between proton and ^{56}Fe irradiation, we exposed mice to protons alone (150 MeV, 0.1 Gy), ^{56}Fe alone (600 MeV, 0.5 Gy), or a combination (protons first) with the two exposures separated by 24 hrs. Mice irradiated with either protons or both protons and ^{56}Fe showed impaired novel object recognition 3 months after irradiation that was not seen in mice irradiated only with ^{56}Fe. The mechanisms involved in these impairments might involve inflammation. In mice irradiated with protons or ^{56}Fe, there was a negative correlation between novel object recognition and the density of newly born activated microglia in the free and enclosed blade, respectively. When cytokine and chemokine levels were assessed in the hippocampus of the cognitively tested mice, there were effects of irradiation on marcrophage-derived chemokine (MDC) and eotaxin. Compared to sham-irradiated mice, the levels of these factors were lower in mice receiving both types of radiation exposures. The levels of MDC and eotaxin correlated and the levels of MDC, but not eotaxin, correlated with the percentage of BrdU/CD68-positive cells in the blades of the dentate gyrus. Finally, hippocampal IL-6 levels were higher in mice receiving both types of irradiation compared to mice receiving only ^{56}Fe irradiation. These data show that novel object recognition is sensitive to detect cognitive injury 3 months following proton only and combined proton and ^{56}Fe irradiation exposure and that newly-born activated microglia and inflammation might be involved in this injury.

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