Charged particle radiation, reactive oxygen species, and CNS function

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Exposure to radiation in the space environment may impact brain function during the mission and also at later times when slow-developing adverse effects could finally become apparent. In the CNS, exposure to space radiation may directly affect structure/function within the brain, e.g. cognitive performance. The involved mechanisms are elusive but may involve reductions in neurogenesis or in the expression of the plasticity-related immediate early gene *Arc* in the dentate gyrus of the hippocampus. *Arc* is rapidly induced in response to synaptic activity and Arc protein is essential for synaptic plasticity and memory consolidation, and correlates temporally and spatially with the stimulus that induced its transcription. Inhibition of Arc expression impairs hippocampus-dependent memory and long-term potentiation and ionizing irradiation significantly reduces the numbers of granule neurons that express *Arc* mRNA and Arc protein in a time-dependent manner. Recently, we showed that following cranial ^{56}Fe irradiation (600 MeV, 1 Gy), changes in Arc expression in the dentate gyrus correlated with cognitive performance in a hippocampus-dependent task (*Radiat Res*, 80, 567-573).

We started to determine the effects of whole body irradiation with Si (600 MeV, 0, 0.25, or 1 Gy), protons (150 MeV, 0, 0.1, 0.5 or 1 Gy), and ^{56}Fe (600 MeV, 1 Gy) on hippocampus-dependent contextual fear conditioning, neurogenesis, neuroinflammation (activated microglia), and Arc-positive cell in the dentate gyrus. Compared to sham irradiation, Si irradiation enhanced contextual freezing 3 months following irradiation at a dose of 0.25 but not 1 Gy. In the same animals, Si irradiation dose-dependently reduced neurogenesis. There was no correlation between freezing, Arc positive cells in the dentate gyrus, activated microglia, or neurogenesis. One month following irradiation with protons, there was an increase in contextual freezing. This was significant at a dose of 0.1 Gy, with a trend towards an increase following 0.5 and 1 Gy. There was no correlation between freezing, Arc positive cells in the dentate gyrus, activated microglia, or neurogenesis. Together, these data indicate that low dose whole body space irradiation causes hippocampus-dependent cognitive changes and changes in neurogenesis in the dentate gyrus. However, there does not seem a simple relationship between radiation-induced changes in cognition and neurogenesis. The data three months following whole body irradiation with protons or ^{56}Fe are being analyzed and will be presented as well.

Space radiation increases reactive oxygen species (ROS) levels, which may contribute to radiation-induced cognitive changes. Although ROS are involved in learning and memory, a prolonged increase in ROS can be detrimental. Alterations in ROS levels are in part linked to the capability of charged particle irradiation to perturb redox homeostasis at the mitochondrial level. The availability of mice overexpressing human catalase targeted to the mitochondria (MCAT) provide the capability to address specific mechanistic questions concerning the role of oxidative stress as it relates to the radioresponse of the CNS. To assure that MCAT mice and the cognitive paradigm selected are suitable for planned space radiation studies, we behaviorally phenotyped 5-6 month-old MCAT and wild-type male mice. MCAT mice show reduced measures of anxiety in the elevated zero maze and enhanced hippocampus-dependent contextual fear conditioning. These data indicate that MCAT mice and the fear conditioning paradigm are appropriate for planned space radiation studies.

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