INDIVIDUAL DIFFERENCES IN NEUROBEHAVIORAL DEFICITS FOLLOWING PROTON IRRADIATION ARE RELATED TO DIFFERENTIAL BRAIN PROTEIN AND CYTOKINE EXPRESSION

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INTRODUCTION

We have previously reported individual differences in the effects of low-dose proton, ^{56}Fe, and ^{28}Si exposure on rats' performance of the rat psychomotor vigilance task (rPVT), which is an animal analog of the human PVT, a highly sensitive and standardized assay, currently employed in a variety of operational settings as a "fitness-for-duty" self-test. Approximately 50% of the rats were behaviorally "radiation-sensitive" and also displayed changes in dopamine (DA) protein levels. The current work further examines the effect of proton radiation on brain protein expression in two inbred strains of rats, the Fischer 344 (F344) and Lewis (LEW) rats with differences in dopamine function that are characterized by a lower density of dopamine-transporter (DAT) levels in the striatum, nucleus accumbens, and olfactory tubercle of LEW rats compared to F344 rats, a lower density of DA D_2 receptor levels in the striatum and nucleus accumbens of LEW rats, and a slower *in vivo* clearance of DA, all of which suggests lower basal DAT function in LEW rats. Thus these two strains were used as subjects in order to test the importance of differences in DA system function in the behavioral and molecular responses to radiation.

METHODS

The rPVT tracks the same general performance variables as the human PVT (e.g., motor function, speed, inhibitory control or "impulsivity", selective attention). Cohorts of F344 and LEW rats were trained on the rPVT, exported to BNL for head-only radiation exposure (0, 25, or 100 cGy protons, 150 MeV/n), then returned to Johns Hopkins for follow-up behavioral testing. Once the post-irradiation testing period was complete, brain tissue was collected from all rats for further protein and cytokine analyses. Brain areas collected include: frontal cortex, nucleus accumbens, parietal cortex, caudate-putamen, and hippocampus.

RESULTS

Only the F344 rats exposed to 25 cGy protons displayed performance deficits in accuracy and increases in impulsive responding on the rPVT. In contrast, the F344 rats exposed to 100 cGy protons and the LEW rats exposed to 25 or 100 cGy protons continued to display rPVT performance similar to sham-irradiated animals. Several proteins important for dopamine neurotransmission (e.g., dopamine transporter, D_2 receptor, tyrosine hydroxylase) and cell survival (e.g., Akt, p-Akt, CREB), in addition to various cytokines (e.g., TNF-α, Il-1α, Il-6, GM-CSF), were examined in the areas described above and data from these analyses will be presented.

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