PROTON AND HZE RADIATION AFFECTS HIPPOCAMPAL FUNCTIONS IN APP/PSEN1 TRANSGENIC MICE

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ABSTRACT

In space, protons and high-energy, high-charge particle (HZE) radiation may impair neuronal functions at relatively low doses. Decrements in synaptic transmission and plasticity have been reported in irradiated brains and they are similar to those commonly observed in Alzheimer's disease (AD). In this study we tested whether proton (p^+, 150 MeV), ^{28}Si (250 MeV/n) and ^{56}Fe (600MeV/n) radiation exacerbates the AD-like pathology in double transgenic (TG) APP/PSEN1 mice.

Methods: We irradiated 2.5 month old male TG mice at doses 0, 0.1, 0.5, 1 Gy (whole body) and 6 to 9 mo later performed *in vitro* electrophysiological recordings of excitatory synaptic transmission in CA1 neurons in hippocampal slices. We evaluated field excitatory post-synaptic potentials (fEPSPs) and population spikes (PS) evoked with increasing stimulation intensities. Paired pulse facilitation (PPF) and long-term potentiation (LTP) were used to measure short- and long-term plasticity. Behavioral testing was performed pre- and 3 and 6 months post-irradiation in the water maze (WM) to assess hippocampal functions. In p^+-irradiated mice we performed immunohistochemical (IHC) evaluation of amyloid-β (Aβ) plaque load by staining with 6E10-antibody to evaluate the effects of radiation on Aβ deposition in the dorsal cortex and the hippocampus.

Results: Our electrophysiological recordings in TG mice indicated that the earliest changes in p^+-irradiated mice were observed at 6 months post irradiation as reduced PPF at 1 Gy, indicating increased probability of presynaptic glutamate release. At 9 months, in TG mice 0.5 Gy p^+ reduced the synaptic excitability, but it increased this response in wild-type (WT) mice. These effects were not observed at 1 Gy. In TG mice at 9 months, the p^+ radiation at 0.1, 0.5, and 1 Gy reduced the size of the population spikes (PS), which is suggestive of impaired generation of action potentials and reduced neuronal output in CA1 neurons. We found no significant impairments of LTP in mice irradiated with p^+. Some of the functional decrements in TG mice may be associated with significantly increased Aβ-deposition detected by IHC analyses in the dorsal cortex at 1 Gy. Interestingly, in WT mice only the p^+ significantly reduced the epileptiform activity in CA1 neurons evoked by perfusion with Mg-free media. These spontaneous waveforms (SW) are reminiscent of sharp-wave/ripple complexes that have been associated with memory consolidation in the hippocampus. The incidence of SW was not affected in TG mice by either p^+, ^{28}Si or ^{56}Fe radiation. In p^+-irradiated WT mice at 0.5 Gy we observed impaired reversal learning in the WM at 6 months post irradiation. Interestingly, in these mice we also found a significant negative correlation between the incidence of SW and increased swim distance in the WM. Irradiation of TG mice with ^{28}Si caused temporary impairment in WM at 3 months, while irradiation with ^{56}Fe improved their performance at 6 months post-irradiation.

Summary: Our electrophysiological data indicate that irradiation with protons and HZE at low doses may differently affect excitatory synaptic transmission and hippocampus-dependent behavior in WT and APP/PSEN1 TG mice. Thus, different neurological or cognitive decrements may be expected in normal subjects relative to those prone to AD-like pathology.

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