Behavioral Effects of 1 GeV/n Fe ions and Gamma Rays
Marcelo Vazquez, John Gatley, Magalie Bruneus, Adele Billups and Stacy Koslovsky
Brookhaven National Laboratory, Medical Department, Upton, New York 11973, US

Space travel beyond the Earth’s protective magnetic field will involve exposure of astronauts to irradiation by high-energy nuclei such as $^{56}$Fe, which are a component of galactic cosmic rays. These particles have high linear energy transfer (LET) and are expected to irreversibly damage cells they traverse. Exposure to HZE radiation may therefore cause progressive deterioration of brain function, adding to other inescapable damage involved in normal aging. We propose a study of the hypothesis that long-term behavioral alterations are induced after exposure of the brain to 1 GeV/n iron and silicon particles with fluences of 1 to 8 particles/cell targets. Previous studies support this notion but are not definitive, especially with regard to long-term effects. Our principal goal is to examine the neurological effects of high-LET radiation on C57BL/6 mice using a series of behavioral tests to unveil the temporal expression of altered behaviors in the radiation response, as well as the means, which can modulate these responses.

In April 2002 we exposed C57 mice to 1 GeV/n $^{56}$Fe radiation (head only) at doses of 0, 15, 30, 60, 120 and 240 cGy (16 mice per group). The ability of animals to increase locomotor activity in response to an intraperitoneal injection of cocaine were measured at 1, 4, 8, 12, 16, 20, 24 and 28 weeks. Cocaine-stimulated locomotor activity was chosen in part because it is a behavioral assay with which we have considerable experience. More importantly, the ability to respond to cocaine is a complex behavior involving many neurotransmitter systems and brain circuits. Therefore, the probability of alteration of this behavior by HZE particles was considered high. However, the central circuit is the nigrostriatal dopamine system, in which dopamine is released in striatum from nerve terminals whose cell bodies are located in the substantia nigra. Dopamine activates receptors on striatal GABAergic cells that project to the thalamus. Activation of the motor cortex by projections from the thalamus leads ultimately to increased locomotion. Cocaine activates behavior by blocking dopamine transporters in striatum and therefore elevating the concentration of dopamine in the synapse. Although we have not yet conducted a detailed statistical analysis of our data (in fact, the experiments are still proceeding), it is apparent from the database that the exposure to $^{56}$Fe particles did reduce cocaine-stimulated locomotor activity at 120 and 240 cGy. The 240 cGy and 120 cGy mice were less active than unexposed controls at all time-points after 1 wk. Differences achieved significance (p<0.05) for 240 cGy at all time-points with the exception of 24 wk. The 120 cGy mice were significantly different from controls at 4, 8, 20 and 28 wk. There was, however, no suggestion in the data of an effect at 60 cGy, and no significant differences were found between 0, 15, 30 and 60 cGy groups between 4 and 28 weeks. It does not appear as though the decrements in locomotor activity first observed at 4 wk are resolving by 28 wk.

In the same experiment, we have exposed groups of mice to $^{60}$Co gamma radiation at doses of 0, 15, 30, 60, 120, 240 and 480 cGy. Spontaneous and cocaine-stimulated locomotor activity was measured in the same way as for the $^{56}$Fe radiation. Cocaine stimulated locomotion appears to decrease in a dose-related manner at all time-points up to 20 weeks. Statistically significant reductions were observed at both 240 and 480 cGy at 4, 8 and 12 weeks post irradiation, and significant reductions were also seen at 16 and 20 weeks for the 480 cGy animals. For the 480 cGy group, the data as a whole show a progressive decrease in cocaine stimulated activity to a minimum at 8 weeks, followed by a progressive increase at later times. The overall picture is thus one of resolution of the impairment in locomotion induced by gamma radiation, whereas the impairment induced by HZE radiation does not appear to be resolving. The data at 1 week for gamma radiation share the trend towards dose dependent reduction in activity with the later time-points. This is unlike the situation with HZE radiation, where the 1 week data show increased cocaine stimulated locomotion in the irradiated animals.