NEUROLOGICAL EFFECTS OF SPACE RADIATION
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ABSTRACT

In this brief review, several aspects of radiation effects on the central nervous system are considered. Low to moderate levels (~1 to 2 Gy) of charged particle radiation exposure will characterize the environment experienced by astronauts on long-term space missions. These doses are well below those associated with gross pathological changes and tissue breakdown; however, they may cause persistent functional changes. The intrinsic membrane properties of mature neurons appear to be stable to space-like radiation exposures but their connectivity and information processing properties are persistently altered. These alterations result in altered excitability with reductions in synaptic remodeling for many months post irradiation. Changes in information processing due to synaptic changes as well as depletion of neural precursor cells may in turn lead to reduced cognitive abilities. Supporting this idea, behavioral studies on irradiated rodents and human children have shown that performance decrements do occur in the space operations dose range. An analysis of charged particle track interactions with neuron structure suggests that nearly every nerve cell’s dendritic or axonal arborizations will be traversed by multiple cosmic rays during a long duration space mission. The functional changes observed experimentally are associated with the complex arborizations of nerve cells and their structural specializations. Although the data for charged particle radiation exposures are sparse, the available observations from all exposure regimens point to a credible risk of cognitive or performance decrements during long term space missions.

KEYWORDS

Central nervous system, hippocampus, neurogenesis, space radiation, synapse.

INTRODUCTION

The effects of radiation on the central nervous system (CNS) have been investigated for many years, but primarily in the context of radiotherapy. In this context, survival of cells is the key indicator as the emphasis is on tumor control, while minimizing side effects to normal tissue. Most of these studies have employed gamma rays or X-rays and typically, high doses (>20 Gy) are applied to local areas. This results in steep dose response curves for white matter degeneration in either cortex (leukencephalopathy) or the spinal cord (myelopathy) which appears after a substantial time lag of many months (Debus et al., 2003). This may be accompanied by edema, breakdown of the blood-brain barrier, swelling of vessels (telangiectasia), inflammatory reactions and sometimes necrosis. In this literature, there has been an active debate about whether vascular endothelial cells or parenchymal cells (especially oligodendrocytes) are the dose limiting cells of the tissue which is characterized overall by low rates of cell division and replacement. Three excellent reviews of this literature are: Wong and Van der Kogel, 2004; Tofilon and Fike, 2000; Schultheiss et al., 1995. Many of the mainstream opinions about CNS radiation responses are derived from results that result from high dose exposures. These may not extrapolate well to effects of the space environment in which the relevant exposures are in the dose range of <2 Gy delivered slowly to the whole body by mixed fields of charged particles. In this exposure regime there is much less known, and NASA’s interest is in establishing whether: 1) there are acute risks that could lead to mission compromising performance impairments, and 2) whether the severity and onset of neurodegenerative conditions later in life may be enhanced or accelerated. The following presentation will consider some selected studies that address this lower dose regime, with emphasis on charged particle effects if known.

Charged Particle Radiation

The unique properties of charged particles are associated with their track structure. Unlike X-rays and gamma rays which are absorbed in an exponential fashion with depth in tissue, charged particles have a defined range and deposit their energy at an increasing rate until they reach the end of their range. This rate of energy loss is termed the linear energy transfer or LET and is commonly used as a measure of the quality of the radiation or its ionization density. Charged particle interactions with electrons in the target material are primarily electrostatic rather than through processes such as Compton scattering. Because the particles have significant mass, they travel in relatively straight lines and about half of the energy they deposit is confined to a narrow cylinder (track core) about 20 nm in diameter along the track. The other half of their energy is deposited through radially scattered electrons around the track core. These properties tend to concentrate damage along the track rather than in the more diffuse damage patterns produced by X-ray and gamma ray exposures. Unique DNA damage, genotoxicity and tissue responses have been described for such densely ionizing radiation and many of these properties have been reviewed in volume 16 of this Bulletin (Nelson, 2003).

Cellular Level Responses

The first level of biological organization to explore is the neuron with its excitable membrane that is the basic
functional unit of the nervous system. It might be expected that radiation-induced lipid peroxidation reactions would compromise neuronal electrochemical gradients, membrane receptors and ion channels. Extensive studies of membrane fluidity, cell leakage and activities of Na+/K⁺ ATPases and acetylcholinesterases show that only doses in excess of 100 Gy are significantly deleterious, although lipid chain shortening is observed at lower dose (Benderitter et al., 2003; Krokosz and Szweda-Lewandowska, 2005). However, isolated rat synaptosomes show decreased ²²Na⁺ uptake after 1 Gy of gamma rays (Mullin et al., 1986) and some tissue culture cells exhibit alterations in Ca²⁺ transport after 1-4 Gy of electrons (Todd and Mikkelsen, 1994) suggesting sensitivity of ion channels. Direct measurements of charged particle-induced lipid peroxidation of liposomes shows that they are much less effective than X-rays (Ziegler & Wessels, 1998).

In early studies, the conduction velocities of compound action potentials along isolated frog and rabbit sciatic nerves was found to be very resistant to radiation, requiring in excess of 500 Gy to show conduction block (Gerstner et al., 1955). Recent studies using patch clamp recordings from mouse hippocampal slices indicate that intrinsic membrane properties of pyramidal neurons are resistant to change after 1-4 Gy of iron ions or 1-8 Gy of protons (NSCOR, unpublished). Together these results emphasize the stability of nerve functional properties to radiation exposure. By contrast, the survival of cultured NT2 human neural precursor cells is quite sensitive to charged particles and shows significant LET-dependent apoptosis and necrotic death at doses < 0.5 Gy (Guida et al. 2005). Growth of new processes (neuritogenesis) from neurons in chick retinal explants is also sensitive to iron ions at doses below 0.5 Gy (Vazquez et al., 1994). So, survival, growth and differentiative properties of neurons are radio-sensitive in the space radiation dose range while the functional integrity of fully differentiated neurons appears to be relatively stable.

**Electrical Output of Nerve Ensembles**

The primary function of systems of nerves is to generate output signals in response to input from other neurons and environmental cues. Early experiments using implanted microelectrodes in rabbits measured spontaneous electrical activity from a number of brain locations including hippocampus, thalamus and cortex. Significant decreases in the frequency and amplitude of spikes were observed in most brain regions after 4 – 5 Gy at times up to 6 hr, but the hippocampus exhibited hyperexcitability along with changes in spike train organization that may be associated with inhibitory neuron malfunction (Monnier and Krupp, 1962). At higher doses (9 Gy) all activity was suppressed. Visually-evoked potentials in mice irradiated with 20 MeV deuterons exhibited spike amplitude and firing pattern modifications after 5 Gy (Ordy et al., 1968) and the pedal-pleural ganglion of the sea slug *Aplysia* exhibited increased excitability after 10 Gy of ¹³⁷Cs gamma rays (Clatworthy et al., 1999). Pellmar and collaborators performed recordings on Guinea Pig hippocampal slices during or shortly after irradiation and demonstrated increases in synaptic efficacy (dendritic response) while population spikes (somatic response) were inhibited at gamma ray doses above 30 Gy (Pellmar et al., 1990; 1993). All of the above observations demonstrate that changes in output may occur within hours after > 4 Gy of low LET radiation but do not address late changes or responses to high LET radiation.

Recent field recording experiments conducted by Vlkolinsky et al. (2007) under NASA funding (NSCOR, unpublished) examined mouse hippocampal slices isolated from 1 to 18 months following 0 to 4 Gy of accelerated iron ions or protons. These demonstrated that synaptic efficacy was increased long after irradiation and led to hyperexcitability. However, in the simple long term potentiation (LTP) model of memory, synaptic remodeling between pyramidal neurons was inhibited months after 1-2 Gy of iron ions. LTP is correlated with hippocampus functions in spatial memory and learning using behavioral measures. These electrophysiological paradigms report alterations in the number and strength of synapses as well as glutamate receptor function and are mostly post-synaptic in their anatomical distribution. Observations on the important neural adhesion molecule NCAM, which regulates synaptic plasticity, show that it is down-regulated after doses of 2.5 Gy of 1 GeV/n iron ions in rats (Casadesus et al., 2005) and > 0.5 Gy of iron ions in mice (NSCOR, unpublished). These observations suggest that the output of systems of neurons (and their associated glia) is altered after irradiation at the level of connectivity between cells in the networks. Further, these systems are vulnerable to charged particle doses of the same order as predicted for long term space missions and exhibit defects in information processing that underlies all CNS functions. The observed hyperexcitability may also indicate an enhanced susceptibility to seizures.

**Neural Precursor Cells**

The most radiosensitive cells of the CNS are neural precursor cells (NPC). These astrocyte-like stem cells located in the linings of the ventricles and in the subgranular layer of the hippocampus continue to divide throughout life in mammals. They differentiate into astrocytes, oligodendrocytes and neurons which become incorporated into neuronal circuits and contribute to learning and memory. J.R. Fike and others have demonstrated that X-ray doses of 2-5 Gy cause substantial apoptosis of NPCs and continued reduction in the production of immature neurons (Mizamatsu et al., 2003; Rola et al., 2004). Lower doses of ~1 Gy iron ions result in similar elimination of NPCs (NSCOR, unpublished). Further, irradiation causes remodeling of the CNS microenvironment resulting in a state that inhibits differentiation of resident NPC descendents (or grafted unirradiated NPCs) and the continued elevated production of reactive oxygen species (Monje et al., 2002; Limoli et al., 2007) and chronic activation of microglia (Rola et al., 2004). Iron ions are much more effective than 250 MeV...
protons or X-rays (NSCOR, unpublished). The loss of NPC regenerative capacity may lead to accelerated learning and memory decline with age.

**Behavioral and Cognitive Effects**

Electrophysiological and neurogenesis experiments are consistent with behavioral observations on rats and mice irradiated with charged particles. Morris water maze and Barnes maze experiments indicate that spatial memory and learning are inhibited by doses as low as 0.1 Gy of iron ions (Shukitt-Hale et al., 2000; Raber et al., 2004). These behaviors are believed to be largely associated with the hippocampus. Conditioned taste aversion to amphetamine (but not lithium) in rats is inhibited at doses of >0.1 – 0.8 Gy iron ions in rats implicating dopamine pathways. Ascending scale operant conditioning studies (food reward after lever pressing) also indicate that, in rodents, cognitive abilities may be susceptible to low doses of charged particles (2 Gy iron ions) (Rabin et al., 2004).

But are humans susceptible to radiation in the low dose regime? Adult radiotherapy patients treated for head, neck and brain tumors have commonly reported depression, confusion and lethargy; but these are individuals receiving high localized doses and who have underlying medical conditions. There are, however, observations on human children that have shown sensitivity of still-developing nervous systems to low LET radiation. In Israel, a large cohort of children (~20,000 of average age 7 years) were treated with a mean dose of 1.3 Gy X-rays to cause depilation of the scalp in order to facilitate treatment of *tinea capitis* fungal infections. These children later showed poorer outcomes in high school aptitude and IQ performance and more frequent psychiatric disturbances in later life. (Ron et al., 1982). A group of 6-18 month-old Swedish children treated for cutaneous hemangioma (strawberry birthmarks) on the head were followed-up at the time of comprehensive testing prior to military enlistment (age 18 – 19 years). They showed cognitive impairments at doses above 0.1 Gy and up to 32% decreases in high school attendance (corrected for social influences) after frontal lobe X-ray doses > 0.25 Gy (Hall et al., 2004). So, human CNS tissue that is still undergoing growth and differentiation is susceptible to space-like doses of low LET radiation. Together with animal behavioral studies this suggests that low doses of charged particles may be of concern in adults, especially with respect to brain regions or processes dependent on continued neurogenesis.

**Fluence-Based Assessment of the Cellular Target**

In estimating risks from fields of charged particles, especially at low doses, it has been useful to consider the fluence of particles rather than the dose. The planar fluence is the number of particles that traverse a unit area and dose is proportional to fluence and LET. In this way the contributions from different particles expressed as the probability of exhibiting an endpoint (such as mutation or cell death) per particle type can be summed to estimate the total probability. Using this strategy, Curtis et al. have estimated the number of traversals of cell nuclei or soma in different CNS structures for a reference 3-year Mars mission (Curtis et al., 1998). They showed that approximately 46% of cell somas (areas from 180 – 486 $\mu m^2$) and 7.6% of cell nuclei (areas 40 – 100 $\mu m^2$) in human hippocampal cells would be traversed by at least one particle of atomic number $Z \geq 15$. By extension, 16,000 cells in the retinal macula, 2x10$^7$ cells of the hippocampus, and 850,000 cells of the thalamus would be “hit” by such heavy ions. These calculations were motivated by cell survival as the significant endpoint but experiments suggest that fully differentiated cells are radioresistant for survival. Extensive modeling of network failure modes in the hippocampus have shown that a very high proportion of cells in the hilar region must be lost before there are significant changes in connectivity (Dyhrfjeld-Johnsen et al., 2007). This suggests that minor cell loss would not lead to major functional changes. The situation may be different for radiosensitive NPCs, however. If they are preferentially incorporated into new memories, then lower fractions of cell loss may be significant.

From the discussion above on functional output, it can be argued that dendritic and axonal arboreizations may be the more relevant cellular targets, so a re-examination of the impact of fluence is in order. Neuroanatomical studies have characterized the number and topology of neuronal processes; from these studies, the properties of hippocampal CA1 (subfield cornu ammonis I) pyramidal neurons are summarized below for the rat (Pyapali et al., 1998; The Hippocampus Book, 2007):

- Cell soma diameter: 15 $\mu m$ with cross sectional area = 193 $\mu m^2$
- Total dendritic length per cell: 1.2 – 1.3 cm at 1.0 to 2.5 $\mu m$ diameter.
- Total axon length per cell: ~ 0.2 cm and diameter < 1 $\mu m$.
- Total dendritic spines per cell: ~30,000.
- Total spine synapses per cell: 10,000 – 30,000 (of which only 16-26 need to fire synchronously to generate action potentials).

From these dimensions and three dimensional reconstructions of cells it was possible to calculate the cross sectional area of a typical pyramidal cell at 11,800 +/- 3,200 $\mu m^2$ (N=11) and the number density of synapses at between 1 and 2 per $\mu m^3$. Using these areas and the estimated Mars mission fluences from Curtis et al. (1998), Poisson distribution calculations yield the following. At solar minimum, with a fluence for $Z \geq 15$ ions of 10,700/cm$^2$, each cell body would be traversed, on average, by 0.21 particles (1 out of 5 cells) whereas each arbor area would be traversed by 12.8 particles (a 128-fold greater value). At solar maximum, with a $Z \geq 15$ fluence of 59,300/cm$^2$, the values are 0.14 hits per soma and 7.1 hits per arbor (a 71-fold greater value). Thus, essentially every cell will be traversed multiple times and...
the high interconnectivity of neurons is likely to spread
the influence of each traversal to many cells.

Another estimate can be made from the track structure of
the particles. Chatterjee and collaborators (Chatterjee and
Schaefer, 1976) employed a model for particle tracks that
describes the local dose as a function of radial distance
from the track axis. Applying their model to 600 MeV/n
iron ions or 250 MeV/n protons (which are relevant
energies for accelerator experiments, cosmic rays and
solar particle events) one may estimate that cylindrical
regions within 4.5 µm of an iron ion track axis will
receive ≥ 1 cGy dose and regions within 2 µm will receive
at least 5 cGy. For protons the corresponding radial
distances are 0.32 and 0.05 µm. At 2 synapses per µm^3
this means that for iron ions, 25,132 synapses per
millimeter track length receive ≥ 5 cGy dose and
127,235/mm receive ≥ 1 cGy. For protons the values are
16/mm and 643/mm, respectively. If only 16-26 synapses
must be activated to initiate an action potential (The
Hippocampus Book, 2007), and if 5 cGy has a 10%
chance of activating a synapse, then for each millimeter of
iron track length, approximately 2500 synapses could be
activated and could, in turn, result in 100 action potentials
in interconnected neurons participating in the same
pathway or local circuit. Sufficient activation might mimic the effects of high frequency (tetanic) stimulation
to neuron ensembles leading to persistent changes in their
synaptic strengths and efficacies. Perhaps the light
flashes perceived by astronauts during to the passage of
charged particles through their retinas reflect such
activation processes.

**SUMMARY**

In this brief review, several aspects of radiation effects on
the central nervous system were considered. It was
shown that although major necrotic and demyelinating
changes are not expected from exposures to space
radiation, there may still be enduring functional
consequences. While the excitability properties of mature
neurons are expected to be stable, their connectivity and
information processing properties may be persistently
altered. These alterations result in hyperexcitability,
perhaps with attendant seizure risks. Changes in
information processing due to synaptic changes and/or
depletion of newly-born neurons may also lead to reduced
cognitive abilities. Radiation-induced alterations in the
CNS microenvironment could stabilize an unfavorable
milieu for cell function and replacement possibly through
oxidative stress and inflammatory mechanisms.
Behavioral studies on young adult rodents exposed to
charged particles and observations of human children
exposed to photons have shown that performance
decrements can occur in the dose range associated with
space operations. Finally, a reconsideration of how
charged particle tracks interact with neuron structure
suggests that nearly every nerve cell’s dendritic or axonal
arborizations will be traversed by multiple cosmic rays
during a long duration space mission. Thus, earlier
estimates focusing on cell survival alone may
underestimate the potential for deleterious functional
changes.

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