

## Space Radiation and the Central Nervous System: Potential Risks

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### Overview of the Central Nervous System

The central nervous system (CNS), comprised of the brain and spinal cord, is a complex organ with characteristics that set it apart from other parts of the body. One of these characteristics is that the CNS is made up of many cell types with unique interdependencies. Neurons represent the principal substrate for neural signaling; they dictate our perception of the outside world (senses) and how we respond to it (behavior). The myriad functions of neurons are reflected in a multitude of neuron types with different shapes, sizes, signaling properties, transmitter systems, and connectivity. A unifying feature of neurons is their ability to rapidly propagate signals to each other across relatively large distances through specialized axons and synapses. The signaling capability of neurons is dependent on high-energy maintenance of membrane potentials and a stable microenvironment that maintains ionic and energy balance.

Collectively, CNS cells involved in microenvironmental control are known as glia and include two cell types arising from the same neuroectodermal origin as neurons: astrocytes and oligodendrocytes. The third type of glial cell is the microglia, which arise from myeloid precursors. Astrocytes, which outnumber neurons by about 10 fold, are major workhorses in maintaining the CNS microenvironment. Their activities include rapid uptake of ions and neurotransmitters, provision of substrates for neuronal generation of energy and neurotransmitters, and maintenance of the blood-brain barrier (BBB)—a unique property of CNS vasculature that depends on interactions between astrocytes and brain endothelial cells. Recently, astrocytes have been recognized to have their own signaling systems and ability to propagate signals through intercellular channels; these properties and their intimate association with blood vessels and neuronal synapses organized in domains underlies their critical and active involvement in neural signaling [1]. Oligodendroglia are highly specialized cells that act to segregate neural signals by insulating individual axons. For larger neurons, oligodendrocytes wrap axons with multiple lipid-rich membranes known as myelin. The specialized properties of myelin increase the rapidity by which signals can be propagated along axons and makes the process more energy efficient. Microglia represent the third major type of glia and are often considered to be resident CNS macrophages. Microglia are of myeloid cell origin and participate in phagocytosis as part of normal processes (e.g.

synapse turnover) and in response to injury. Interestingly, microglia have recently been shown to sample the CNS by continual extension and retraction of fine processes. Thus they function as CNS sensors and are positioned to respond to changes in the microenvironment arising from injury, infection, or disease by producing signals (e.g. cytokines and other inflammation-associated molecules) that alert other cells and drive changes in microglial and astrocyte phenotypes to contend with the changes. Collectively, this innate immune response of the brain is called neuroinflammation.

Endothelial cells and the specialized vasculature of the CNS represent an additional unique component that cannot be ignored. Because of its continuous need for energy to maintain ionic gradients, the brain is highly vascularized. As already mentioned, the interface between the brain and vasculature depends on astrocyte-endothelial interactions that induce tight junctions between endothelial cells to form the BBB. Along with specialized transport systems these tight junctions limit exchange across the barrier to maintain the unique CNS intercellular environment.

In contrast to many tissues, a second characteristic of the adult CNS is that most cells are post-mitotic. In particular, the vast majority of neurons are terminally differentiated and though rare populations continue to divide postnatally and neural precursor cells can be isolated from CNS tissues, there is little evidence for functional regeneration of neuronal cell populations in mammals following injury or loss from degenerative diseases. Astrocytes and oligodendrocytes are also generally considered to be post-mitotic; however, microglia do have the capacity to divide in response to injury and evidence exists for recruitment of peripheral myeloid populations to replace microglia, particularly following insult.

## **Radiation Injury in the CNS**

The complex interdependencies of CNS cell types and their post-mitotic status provides a unique substrate for radiation injury. Unlike more radiosensitive tissues such as bone marrow and gut, CNS radiation effects may not manifest for many months or even years following exposure. This is not to say that acute CNS effects are not observed following high doses of radiation (e.g. radiotherapy), but that potential space-radiation effects most likely fall in the general category of late degenerative risks, which also includes tissues such as lens epithelium (manifest as cataract), bone, and the cardiovascular system. An important consideration for CNS is that radiation effects on any specific target cell (neurons, glial populations or endothelial cells) will significantly impact functioning of the entire system.

After a brief consideration of possible acute CNS effects, this remainder of this article will highlight several mechanisms that contribute to late CNS radiation injury. Although accumulating work, performed largely with NASA support at the NSRL, is beginning to shed light on specific space radiation CNS effects, most of our knowledge comes from studies of conventional photon radiation.

## **Acute CNS Effects**

Although radiation doses associated with examples of acute CNS radiation toxicity (e.g. accidental exposure or radiotherapeutic applications) are many-fold higher than will be experienced by space travelers, possible effects of high-dose proton exposure arising from a solar flare might include somnolence, confusion, and vomiting. Mechanistically, these effects are thought to arise from BBB dysfunction and tissue edema. Based on clinical experience and some experimental evidence, anti-inflammatory agents may provide some symptomatic relief. Though such effects might jeopardize specific mission objectives, from a CNS standpoint a greater concern is the long-term effects of such doses. Challenges arising from acute radiation exposure in space are highlighted in a recent review [2].

### **Delayed CNS Effects**

Very high doses of radiation, such as those achieved in radiosurgery, can lead to delayed normal tissue injury called radiation necrosis, which is typified by hemorrhagic necrosis and frank demyelination. Radiation necrosis can occur months to years after radiation treatment and manifests as increasing brain dysfunction. Although the doses of radiation that space travelers will be exposed to are not sufficient to cause frank radiation necrosis, the hypothesized mechanisms underlying its emergence, namely impaired tissue repair due to loss of endothelial and oligodendroglial precursors, may contribute to more subtle delayed effects.

As might be expected, neuroinflammation can be observed following CNS exposure to radiation. For instance, *in vivo* studies reveal acute and sustained (out to 6 months) astrocytic and microglial activation following brain irradiation in mice that is accompanied by proinflammatory cytokine expression [3-5]. These changes are accompanied by acute induction of prostaglandin synthesis, which contributes to radiation-induced vascular activation and brain edema, based on studies with cyclooxygenase-2 inhibitors [6,7].

Initial radiation injury in biological tissues includes immediate generation of free radical species with subsequent oxidative damage. Importantly, the ensuing response to tissue damage includes long-term generation of reactive oxygen and nitrogen species by enzyme systems upregulated as part of the neuroinflammatory response. These species arise from many sources, including superoxide from NADPH oxidase activation and nitric oxide from nitric oxide synthase activity. These reactive species lead to further tissue damage and neuroinflammatory responses, resulting in a cycle of damage/repair that has been hypothesized to play a major role in delayed CNS radiation injury [8]. A similar cumulative mechanism appears to be important for generation of cataracts, a known sequelae of space radiation [9].

## Neurogenesis and Neurocognitive Sequelae

Recent literature has focused on the radiosensitivity of neuronal precursor cells destined to populate the dentate gyrus of the hippocampus. These cells are born from the subgranular zone (SGZ) of the dentate gyrus throughout life and migrate into the dentate gyrus granular layer where they assume functional neuron morphologies and characteristics. Ionizing radiation at doses of 1 Gy and higher has the interesting effects of not only eliciting apoptosis and decreasing division of these precursors, but also of influencing their cellular fate away from neurons towards glia [10]. Importantly, the effects of radiation on cell proliferation and neurogenesis appear to persist for months following exposure [11,12], indicating long-lasting effects on the precursor pool and/or the CNS microenvironment. High linear energy transfer (LET) radiation also inhibits hippocampal neurogenesis in a dose-dependent fashion. For example, 3 months after irradiation with 1 GeV/u  $^{56}\text{Fe}$ , C57BL/6 mice showed dose dependent decreases in proliferation and immature neurons over a range of 1 to 3 Gy [13]. The effect was even greater 9 months following irradiation.

Hippocampal neurogenesis occurs in many mammalian species, including humans. There is much speculation about the role of these particular cells in cognitive function since the dentate gyrus serves as the entry point for most signals destined for the hippocampus, a structure critical for learning and memory formation. In support of this contention is evidence from many rodent studies showing a correlation between effects of moderate radiation doses (e.g. 5 Gy) on neurogenesis and on deficits in hippocampal-dependent learning tasks [11,12]. High LET radiation ( $^{56}\text{Fe}$ ) has been shown to impair contextual fear conditioning in irradiated female C57BL/6 mice at a dose of 3 Gy [14], though no measures of hippocampal neurogenesis were made in this study. Although it is not clear that inhibition of adult neurogenesis is directly responsible for functional deficits observed in patients receiving brain radiotherapy, the idea is compelling, particular for pediatric populations where such sequelae are common. Regardless of the role of defective neurogenesis in explaining cognitive changes associated with radiation exposure, accumulating evidence suggests an association between neuroinflammation and decreased neurogenesis. In particular, numbers of activated microglia have been shown to correlate with a dose-dependent decline in neurogenesis, starting with doses as low as 2 Gy of low LET radiation and 1 Gy of particles of high energy and charge (HZE particles), such as  $^{56}\text{Fe}$  [15,16]. Moreover, neuroinflammation induced by peripheral LPS injection alone is sufficient to inhibit neurogenesis, and the non-steroidal anti-inflammatory drug (NSAID) indomethacin partially restored hippocampal neurogenesis following irradiation [17]. Oxidative stress appears to be an important factor in the radiosensitivity of neurogenic cells since mice deficient in any of the SOD enzymes show alterations in this measure [18,19]. An association between radiation exposure, oxidative stress and cell proliferation/differentiation has also been demonstrated in cultured neural precursor cells [20].

## Can Radiation Promote Neurodegenerative Disease?

Neuroinflammation and oxidative injury are widely recognized as playing important roles in neurodegenerative diseases such as Alzheimer's, Parkinson's, and amyotrophic lateral sclerosis (ALS) (for review, see [21]). Moreover, there is ample evidence, particularly for Alzheimer's and Parkinson's disease, that neuronal damage and brain pathology start decades before clinical symptoms become manifest. This raises the critical question as to whether radiation injury might contribute to or promote neurodegenerative disease in susceptible individuals. Precedent exists for this possibility based on data that Alzheimer's patients with systemic inflammation may suffer from a greater decline in cognitive capacity [22]. Moreover, exposure to bacterial lipopolysaccharide in young adult mice, which models acute bacterial infections, leads many months later to degeneration of the same dopaminergic neurons lost in Parkinson's disease [23].

### Conclusion

Delayed radiation effects in the CNS appear to arise from cycles of oxidative injury and neuroinflammatory responses, which alter the normal microenvironment and impede repair, ultimately becoming manifest as cognitive dysfunction. Open questions include whether such effects occur at the very low dose rates expected in space, whether HZE particles elicit unique CNS effects, and how to best model the human brain, which is structurally quite different from the rodent. For examples, white matter comprises 50% of brain volume in humans compared to 14% in rodents. A question of particular importance is whether space radiation promotes neurodegenerative disease in susceptible individuals. Clearly, further study will be required to ascertain CNS risks for future space travelers.

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