

DIET AS A FACTOR IN BEHAVIORAL RADIATION PROTECTION FOLLOWING EXPOSURE TO HEAVY PARTICLES

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ABSTRACT

Major risks associated with radiation exposures on deep space missions include carcinogenesis due to heavy-particle exposure of cancer-prone tissues and performance decrements due to neurological damage produced by heavy particles. Because exposure to heavy particles can cause oxidative stress, it is possible that antioxidants can be used to mitigate these risks (and possibly some health risks of microgravity). To assess the capacity of antioxidant diets to mitigate the effects of exposure to heavy particles, rats were maintained on antioxidant diets containing 2% blueberry or strawberry extract or a control diet for 8 weeks prior to exposure to 1.5 or 2.0 Gy of accelerated iron particles at Brookhaven National Laboratory. Following irradiation rats were tested on a series of behavioral tasks: amphetamine-induced taste aversion learning, operant responding and spatial learning and memory. The results indicated that the performance of the irradiated rats maintained on the antioxidant diets was, in general, significantly better than that of the control animals, although the effectiveness of the diets ameliorating the radiation-induced deterioration in performance varied as a function of both the specific diet and the specific endpoint. In addition, animals fed antioxidant diets prior to exposure showed reduced heavy particle-induced tumorigenesis one year after exposure compared to the animals fed the control diet. These results suggest that antioxidant diets have the potential to serve as part of a system designed to provide protection to astronauts against the effects of heavy particles on exploratory missions outside the magnetic field of the earth.

INTRODUCTION TO SPACE RADIATION RISKS AND THEIR MANAGEMENT

The field of space radiation health has recently been singled out as one of two major initiatives within the research programs of the U. S. National Aeronautics and Space Administration (NASA, 2002). The goals of space radiation health research are to understand qualitatively and quantitatively the ionizing radiations present in the space environment, identify qualitatively and quantitatively the risks associated with these radiations, and discover countermeasures to mitigate these risks (Tobias and Todd, 1974). This article first introduces the basic science and definitions of quantities underlying

radiation health research and protection then summarizes recent research related[to a specific countermeasure (dietary antioxidants) to a specific risk (neurological performance decrement).

Many things come in threes. *Omnia homiliae in tres partes divisae sunt.*

In this section, briefly, we introduce

- Three kinds of space radiation
- Three space radiation risks
- Three forms of radiation risk management
- Three forms of biological countermeasures

THREE KINDS OF SPACE RADIATION

Space radiations consist of (1) energetic protons from the sun, (2) protons and electrons from the sun that are trapped in the earth's magnetic field, and (3) cosmic rays that include energetic nuclei of H, He, C, N, O and Fe atoms.

Solar Particles. When the sun is very active, such as just before and just after sunspot maxima (every 11 years) magnetohydrodynamic effects allow the escape of intense clouds of energetic protons that can deliver doses of 0.3 to 3.0 Gy over a period of about 3 days (Townsend et al., 1991; Parsons et al., 1999). Otherwise the sun is constantly releasing lower energy protons that pass from the solar magnetosphere to Earth's magnetosphere.

Trapped Radiations. Energetic electrons and protons arriving at Earth from the sun are trapped in Earth's magnetic flux lines, where they spiral back and forth between the north and south magnetic poles, in which case they are said to comprise "trapped radiation belts".

Galactic Cosmic Rays. The presumed celestial origin of the high-energy, high-charge particles causes them to be called "galactic cosmic rays", or GCR. They are also called "HZE" particles owing to their high charge and energy. A few such particles pass every cm² every few seconds above the Earth's atmosphere, but these are attenuated by the Earth's magnetic field and atmosphere and never reach sea level. All of these three categories of radiations produce secondary radiations such as neutrons and gamma rays when they interact with matter. This fact is relevant to problems of shielding spacecraft and their contents; not only is shielding heavy, it could generate more dangerous radiation.

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THREE SPACE RADIATION RISKS

The risks presented to space travelers by these radiations include (1) cancer due to chronic proton and cosmic-ray exposure, (2) immune and/or hematopoietic failure due to high-dose solar proton storms, and (3) possible neurological effects caused by single tracks of cosmic-ray heavy nuclei. Other well-known effects of heavy ions, such as cataracts and retinal flashes, are not considered mission- or life-threatening. Until more is known about the biological effects of chronic heavy-ion exposure it remains to be determined which of these is the most serious biological risk or whether these three risks need to be considered in parallel, independently.

Cancer and cellular effects due to heavy-ion exposure. It has been noted that (Curtis and Letaw, 1989; Setlow, 1999) on a round trip to Mars, the nuclei of about half of all of a crew member's cells will have been traversed by at least one energetic multiply charged cosmic-ray particle unless extraordinary shielding measures are implemented. The irradiation of cells *in vitro* with heavy ions has for several decades served as a model for studying the potential effects of cosmic-ray particles on cells. Most of our earliest understanding of high LET particle radiobiology was derived from studies of cell killing, carcinogenesis and mutagenesis *in vitro*. It has been amply demonstrated that surviving cells traversed by heavy particles are transformed to malignancy (Yang, 1985; Kronenberg, 1994) or mutated (Evans et al., 2001). Modern molecular methods of studying mutagenesis and *in vitro* and *in vivo* carcinogenesis are being applied to this problem with the discovery of interesting, previously unappreciated phenomena such as genome instability and "bystander effects" on non-hit cells (Deshpande et al., 1996). Delayed effects on the progeny of irradiated cells, such as mutation, carcinogenesis and impaired growth rate are not expected to be reflected in human responses during a deep space mission; these processes carry post-flight risks to individual health and constitute the most significant risk only if the other two risks are less important or less probable.

Immune/Hematopoietic System Failure due to High-Dose Proton Storms. The most efficient action of ionizing radiation is the killing of cells. A hit cell is typically 10,000 times as likely to undergo reproductive death as it is to be transformed to malignancy or to express an assayable mutation. The probability of cell death per unit dose increases with LET up to a maximum (Barendsen et al., 1960; Todd, 1967). Granulopoietic and lymphopoietic cells in the bone marrow are exquisitely sensitive to ionizing radiation, and the reduction of their progeny in the circulation to about 2% of normal cell counts is considered life threatening (Bond et al., 1965). In this context, a proton dose as low as 2.0 Gy could be life threatening, and, considering the compromising effects of space flight, including low gravity, on the immune system (Konstantinova, 1991), even lower doses should be considered dangerous (Todd et al., 1999).

Neurological Effects of Heavy Ions. The earliest biological studies with cyclotron beams targeted neural tissue damage and the accompanying physiological effects (Malis et al., 1957). The general thought was that heavy ions, due to the geometry of their energy loss, were capable of directly killing non-dividing neurons and vital glial cells whereas only very large doses of x or gamma rays had this capability (Zeman et al., 1961). A wide variety of morphological and physiological changes in neural systems have been reported following heavy-ion irradiation, usually at rather high doses, typically exceeding 1 Gy (Joseph et al., 1998). Recalling that about half of all cells are hit by at least one cosmic ray in a 2-3-year deep-space mission although the dose is only a few cGy, it is still necessary to ask if the neurological functioning of crew members will be impaired to such an extent as to jeopardize a mission and/or the lives of the crew members. Critical switchyards in the central nervous system, sparsely populated with neurons (hippocampus, corpus callosum, etc.) are particularly vulnerable points for the induction of behavior decrements due to the destruction of a small number of cells. Laboratory animal studies are now underway to determine, via quantitative neurochemistry and behavior analysis, the nature and level of effects of nervous function (Rabin et al., 2000), since functional effects constitute end-points of relevance to mission performance while morphological effects may or may not relate to critical functions. This risk is the subject of this article.

THREE FORMS OF RADIATION RISK MANAGEMENT

With three categories of radiation and three categories of biological response radiation health in space is more complicated than that on Earth; therefore, one of the goals of space radiation health research is the reduction of uncertainties. However, there are predictable (trapped protons, galactic cosmic rays) and stochastic (solar event protons) radiation sources. Likewise the biological responses include stochastic (carcinogenesis, neurological effects) and those with predictable dose-response curves. These combine to create risk management dilemmas (Todd, 2003).

Potential countermeasures have been classified into three categories (Cucinotta et al., 2001). These are (1) *operations* (which establish flight schedules and orbital strategies), (2) *shielding* (which increases spacecraft up-mass), and (3) *biological*, such as medication consisting of radical scavengers (that must be taken immediately before exposure), anti-oxidant consumption (which must be maintained continuously), cytokines (which may ameliorate immune and hematological effects specifically after exposure), and cell transplants (which should be isologous).

Operations. It is unwise to be in the wrong place at the wrong time if this can be avoided. Scheduling deep-space missions to miss periods of solar proton storm activity

and choosing trajectories and spacecraft orientations are examples of risk management by operations.

Shielding. In the case of shielding, several approaches have been considered, some very creative. In addition to the skin of a spacecraft the normal contents of space vehicles (water tanks, waste containers, avionics instruments) also constitute shielding. Active shielding, such as with a plasma or strong magnetic fields, has been entertained for several years.

Biological Countermeasures. In the case of biological countermeasures, all of the alternatives mentioned below are under exploration.

THREE FORMS OF BIOLOGICAL COUNTERMEASURES

Biological countermeasures against near-term and late effects of ionizing radiations consist of (1) radical scavengers, (2) cytokine treatment and (3) pharmacological and nutritional countermeasures against reactive oxygen species (ROS). At least 2 of these categories might also mitigate microgravity effects.

Radical scavengers. These consist of compounds, typically alcohols and sulfhydryls that function at the moment of irradiation to chemically react with free radical species produced in the radiation's path. Most radical scavengers have been tested in vitro, and most of them have been found toxic in vivo.

Cytokine treatment. The radiosensitive leukopoietic and hematopoietic systems are known to be responsive to interleukins and hematopoietic factors. These are relevant in managing both space-flight stress (low gravity) and radiation damage (cell killing and carcinogenesis)

Pharmacological and Nutritional countermeasures against persistent ROS. Research over the past several years has been conducted to discover biological countermeasures to the above three risks: carcinogenesis by HZE particles, immune system effects due to high doses plus life in low gravity, and subtle neurological and behavioral effects that might jeopardize a deep-space mission. The general findings to date indicate that dietary antioxidants can constitute a line of defense against all of these radiation risks.

NEUROBEHAVIORAL EFFECTS OF EXPOSURE TO HZE PARTICLES

Exposing rats to HZE particles can affect performance on a variety of neurobiological and behavioral endpoints. Following exposure to ⁵⁶Fe particles rats show a reduction in potassium-stimulated dopamine release and in the behaviors that are dependent upon the integrity of the dopaminergic system (Joseph et al., 1992).

Deficits have been observed in both motor and cognitive behaviors. The effect of exposure on motor behavior is shown as a decrease in upper body strength, measured by

the length of time rats can maintain their grip on a wire suspended above the ground (Joseph et al., 1992). Similarly, exposure to low doses of HZE particles will prevent the acquisition of a conditioned taste aversion (CTA) produced by the dopamine agonist amphetamine (Rabin et al., 1998). A CTA is produced by pairing a novel taste solution (10% sucrose) with an unconditioned stimulus (amphetamine). As a result of this pairing the rat will avoid ingestion of the solution at a subsequent presentation. Because amphetamine is a dopamine agonist, the development of an amphetamine-induced CTA requires an intact dopamine system. In this regard, the effects of exposure to ⁵⁶Fe particles are similar to those produced by the dopamine antagonist haloperidol (Rabin et al., 1998) in that both treatments disrupt dopaminergic function and interfere with the acquisition of an amphetamine-induced CTA.

Exposure to HZE particles can also affect cognitive performance (Shukitt-Hale et al., 2000). The Morris water maze is a standard test of cognitive ability in which rats are required to use spatial cues to locate a platform placed just below the surface of the water. There are no differences in performance between the non-irradiated controls and the irradiated rats in the initial acquisition of the task. However, when the platform is moved to a different location in the maze the irradiated rats show significantly poorer performance than the control rats. Similarly, when the platform is absent during probe trials, the irradiated rats spend significantly less time in the quadrant in which the platform had been located than do the non-irradiated control rats. These results indicate that the irradiated rats are deficient in their ability to perform a task requiring the use of spatial cues.

A second cognitive behavior which is affected by exposure to HZE particles is operant conditioning (Rabin et al., 2002), in which the organism learns to make a response in order to obtain reward or avoid punishment. Operant conditioning is broadly construed to include all forms of complex learning. The specific task that was utilized was responding on a fixed-ratio (FR) reinforcement schedule. On an FR schedule, a rat is required to make a fixed number of responses (level presses) in order to secure a reinforcement (45 mg food pellet). On an FR-1 schedule, the rat is rewarded for every lever press, while on an FR-35 reinforcement schedule the rat is required to make 35 responses in order to be rewarded with a single food pellet. When tested 3 months following exposure to ⁵⁶Fe particles, only the rats exposed to 2.0 Gy (but not 1.0 or 1.5 Gy) showed a disruption of responding at schedules of reinforcement of FR-20 or greater. There were no effects of irradiation at schedules less than FR-15. When tested 8 months later (11 months post-irradiation) all irradiated groups showed significantly decreased performance compared to the non-irradiated controls.

RELATIONSHIP TO AGING AND OXIDATIVE STRESS

The neurochemical and behavioral deficits detailed above are also observed in old rats. As a result, it has been proposed that exposing rats to HZE particles produces “accelerated aging” (Joseph et al., 1992). Specifically, old rats show deficits in potassium-stimulated dopamine release and related deficits in motor behavior (Joseph et al., 1978). Similarly there are significant decreases in the performance of old rats on the Morris water maze, indicating decreased ability to utilize spatial cues in a learning task (Shukitt-Hale et al., 1999). In addition, the partial loss of dopaminergic neurons produced by treatment with the neurotoxin 6-hydroxydopamine which does not affect the performance of young rats on an ascending fixed-ratio schedule does cause a significant impairment in the performance of older rats (Lindner et al., 1999).

Previous research has shown that maintaining rats on antioxidant diets containing blueberry or strawberry extract can ameliorate the neurochemical and behavioral changes that are characteristic of the aging process. This observation is consistent with current theories which suggest that oxidative stress and the production of reactive oxygen species (ROS) are key factors in the aging process (Finkel and Holbrook, 2000).

Oxidative stress occurs when endogenous and exogenous sources of ROS exceed the capacity of the antioxidant systems to remove them. In addition to the production of ROS by endogenous sources, such as the aerobic metabolism of mitochondria and the destruction of dopamine by monoamine oxidase, oxidative stress can also be produced by exogenous sources such as exposure to ionizing radiation, including exposure to HZE particles (Denisova et al., 2002). Acting to mitigate the effects of oxidative stress are a variety of endogenous antioxidant defense systems (superoxide dismutase and glutathione peroxidase) and exogenous sources of antioxidants (vitamins and flavonoid antioxidants). Where the production of ROS exceeds the antioxidant capacity of these systems, the consequences of oxidative stress include aging (Finkel and Holbrook, 2000), carcinogenesis (Oberly, 2002) and a variety of neurodegenerative disorders such as Parkinson’s and Alzheimer’s diseases (Halliwell, 2001).

One treatment that has been effective in ameliorating the neurobehavioral effects of aging has been the use of dietary antioxidants, such as are found in fruits and berries. Measured as Oxygen Radical Absorbance Capacity, the free radical scavenging capacity of blueberries and strawberries is much higher than that of vitamin E (Prior et al., 1998; Wang et al., 1996). Research using old animals has shown that maintaining rats on diets containing 2% blueberry or strawberry extract prevents the age-related changes in potassium-stimulated dopamine release and in the behaviors that

depend upon the integrity of the dopaminergic system (Bickford et al., 2000; Joseph et al., 1998, 1999).

DIETARY COUNTERMEASURES AGAINST SPACE RADIATION RISKS

To the extent that oxidative stress mediates the neurobehavioral effects of exposure to HZE particles, then antioxidant treatments may function to ameliorate the effects of irradiation. Given the similarity in the neurobehavioral effects of aging and irradiation, it is possible that maintaining rats on diets containing flavonoid antioxidants may also counteract the effects of exposure to HZE particles.

Blueberries and strawberries contain a variety of compounds which may function as antioxidants. The polyphenolics contained in fruits include the hydroxycinnamates and the flavonoids such as the anthocyanins and flavonols. As indicated by HPLC analysis (Joseph, unpublished), the relative amounts of these compounds in different fruits vary, which may account for differences in the antioxidant capacity. Additional work will be needed in order to determine the active compounds and their effects on specific neurobehavioral endpoints. Nonetheless, as summarized below, maintaining rats on diets containing either blueberry or strawberry extract can ameliorate the effects of exposure to HZE particles on specific neurochemical and behavioral endpoints.

When rats are maintained on diets containing 2% blueberry or strawberry extract for two months prior to exposure to ^{56}Fe particles (1.5 Gy, 1 GeV/n), the radiation-induced decrease in potassium-stimulated dopamine release in the striatum is prevented (Joseph et al., unpublished). These results are similar to those obtained with aged rats maintained on identical diets (Joseph et al., 1998, 1999).

Concordant with the neurochemical effects, antioxidant diets also ameliorate the cognitive/behavioral deficits produced by exposure to HZE particles, although the effectiveness of the blueberry and strawberry diet varies as a function of the specific endpoint. For CTA learning, the rats maintained on either the blueberry or strawberry diet failed to show the ^{56}Fe particles-induced disruption of an amphetamine-induced CTA (Rabin et al., 2002). Following exposure to either 1.5 Gy or 2.0 Gy the irradiated rats maintained on either diet for two months prior to exposure showed the acquisition of a CTA following injection of the dopamine agonist amphetamine. As shown previously (Rabin et al., 1998, 2000), the irradiated rats fed a control diet failed to acquire an amphetamine-induced taste aversion.

Similar results were obtained in the initial test of spatial learning and memory using the Morris water maze (Shukitt-Hale, unpublished). The irradiated rats maintained on either the blueberry or strawberry diets showed a significant reduction in the latency to find the

location of the submerged platform on the probe trial on Day 2 compared to the irradiated rats fed a control diet. By Day 3, however, the performance of the irradiated rats fed the strawberry diet was not significantly different from that of irradiated rats fed the control diet, whereas the irradiated rats fed the blueberry diet continued to show a reduced latency compared to the irradiated rats fed the control diet.

The effects of antioxidant diets on operant responding also varied as a function of the specific diet. Seven months following exposure to 1.5 Gy of ⁵⁶Fe particles, there was no effect of irradiation on operant responding. When the rats were tested eleven months following irradiation, the animals fed either the control or blueberry diets showed significantly poorer performance on an ascending fixed-ratio reinforcement schedule than the non-irradiated rats (Rabin et al., in press). The performance of the rats fed the strawberry diet was not significantly different from that of the non-irradiated controls and significantly better than that of the irradiated rats fed the blueberry diet. Similar results were obtained following exposure to 2.0 Gy of ⁵⁶Fe particles, except that the effects of irradiation and diet were observed when the rats were first tested five months following irradiation (Rabin et al., submitted).

As indicated above, exposure to HZE particles can produce cancer. Current theories ascribe a role for oxidative stress in carcinogenesis (Oberly, 2002). To the extent that oxidative stress does play a role in tumor development, the use of antioxidant diets should reduce the development of tumors following irradiation. Because the rats that were tested on the operant conditioning task were observed for up to 12 months following exposure to 1.5 Gy or 2.0 Gy of ⁵⁶Fe particles, data were also collected on the effects of diet on tumor development. Preliminary analyses indicate that both blueberry and strawberry diets significantly reduced the occurrence of radiation-induced tumors (Joseph, in preparation).

CONCLUSIONS

Overall, the observations presented in this review indicate that exposing the heads of laboratory animals to doses of HZE particles can have deleterious effects on cellular and systemic functioning. On a cellular level, irradiation can produce mutagenesis or cell death. On a systemic level, there are changes in signal transduction processes in the central nervous system and related decrements of motor and cognitive performance which have the potential to affect the capacity of astronauts to successfully meet mission requirements. There are a number of strategies that may be used to counteract the effects of exposure to HZE particles. These include scheduling missions during times of reduced GCR flux or increasing the level of shielding. An alternative approach which may hold promise involves using dietary manipulations to reduce the levels of oxidative stress produced by exposure to HZE particles. By reducing oxidative stress and the

generation of ROS, diets containing blueberry or strawberry extract may provide necessary protection against the deleterious effects of exposure to GCR, while also potentially mitigating other space flight stresses, and enabling astronauts to successfully fulfill mission requirements.

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NOMENCLATURE AND GLOSSARY

GCR	Galactic Cosmic Rays, high energy nuclei from outer space
Gy	Gray, the SI unit of absorbed ionizing radiation dose (1 J/kg)
HZE	High-charge, high energy particles (GCR)
LET	Linear Energy Transfer, energy deposited per unit distance in particle track
QF	Quality factor, for adjusting dose to equivalent dose based on radiation quality (LET)
rad	Radiation absorbed dose, cgs units (100 erg/g; 0.01 Gy)
rem	Biological equivalent cgs dose unit, rad x RBE (0.01 Sv)
RBE	Relative Biological Effectiveness
ROS	Reactive Oxygen Species
Sv	Sievert, the SI unit of biologically equivalent dose (Gy x RBE)

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