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A voyage to Mars: Space radiation, aging, and nutrition

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Abstract. On exploratory class missions, such as a voyage to Mars, astronauts will be exposed to doses and types of radiation that are not experienced in low earth orbit where the space shuttle and International Space Station operate. Astronauts who participate in exploratory class missions outside the magnetic field of the earth will be exposed to galactic cosmic rays which are composed of alpha particles, protons and particles of high energy and charge. Exposure to cosmic rays produces changes in neuronal and behavioral functioning which are characteristic of aged organisms. As has been observed with aging, maintaining rats on antioxidant berry diets can prevent/ameliorate the radiation-induced changes in neural and behavioral function. As such, these diets have the potential to provide protection to astronauts from the deleterious effects of exposure to space radiation.

Keywords: Cosmic rays, oxidative stress, neuroinflammation, antioxidant diets

1. Space radiation

On exploratory class missions, such as a voyage to Mars, astronauts will be exposed to doses and types of radiation that are not experienced in low earth orbit (LEO) where the space shuttle and International Space Station operate [1–3]. For missions in LEO, astronauts are afforded some degree of protection from the types of radiation encountered in space by the magnetic field of the earth. Astronauts who participate in exploratory class missions outside the magnetic field of the earth will be exposed to galactic cosmic rays (GCR) which are composed of alpha particles, protons and particles of high energy and charge (HZE particles), such as ^{56}Fe, ^{48}Ti, ^{12}C and ^{16}O. The primary source of high energy protons are solar particle events ("solar flares"). HZE particles are of celestial origin and, while some may be given off as a consequence of solar particle events, most are free particles in space remaining from the formation of the universe [4].

The amount of energy deposited in tissue (and hence tissue damage) following irradiation is indicated by the linear energy transfer (LET) of the specific particle. LET varies inversely with the particle energy: the LET of 1000 MeV/n ^{56}Fe is $\approx$ 150 keV/μm; the LET of 600 MeV/n ^{56}Fe is $\approx$ 189 keV/μm. In general, the higher the LET of a particle the greater the relative effectiveness of the radiation in affecting physiological endpoints. While exposure to all types of radiation will lead to the development of cancer [5–8], exposure to higher doses of low LET X- and gamma rays are needed to produce cancers compared to the higher LET HZE particles. However, with regard to neurobehavioral performance, exposure to low doses of gamma- or X-rays do not affect central nervous system function in mature organisms. In contrast, low dose, non-lethal exposures to HZE particles produce changes in neuronal functioning [9] and a significant disruption of cognitive/behavioral performance [10–14].

The differences in the neurocognitive effects of exposure to low or high LET types of radiation may result from differences in how the different types of radiation interact with tissue [e.g., 15, 16]. X-rays and gamma rays exert diffuse effects on tissue, and the dose delivered to tissue decreases exponentially as a function of depth in tissue. In contrast, HZE particles deposit energy along a well-defined track, the length of which is determined by the energy of the particle.

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The dose deposited in the tissue is relatively constant, except at the point at which the particle stops, where there is a significant increase in energy deposition [17].

The neural mechanisms underlying the changes in neurocognitive function are not completely certain. One suggestion has been that the passage of HZE particles through the brain makes a series of microlesions [18, 19]. That is, as an HZE particle passes through neural tissue, cells that are along and adjacent to the track are destroyed or inactivated. Therefore, the subsequent loss of functioning neurons is responsible for the disruption of cognitive performance following exposure to HZE particles. Although the evidence of an actual loss of tissue along the particle track is weak, it is possible that neurons along the track are no longer functional [20].

A complementary/alternative hypothesis is that exposure to HZE particles produces oxidative stress and neuroinflammation. Oxidative stress occurs when endogenous and exogenous sources of reactive oxygen species (ROS) exceed the capacity of the endogenous antioxidant systems to remove them. A number of studies have shown an increase in reactive oxygen species and a decrease in antioxidant enzymes in the brains of organisms exposed to ionizing radiation [21–24]. The consequences of oxidative stress include aging [25], carcinogenesis [26] and a variety of neurodegenerative disorders such as Parkinson's and Alzheimer's diseases [27].

Neuroinflammatory responses also occur as a response to exposure to toxic treatments, including both high and low LET ionizing radiation [28–31]. Toxic treatments can affect central nervous system function directly through the release of peripheral cytokines into the circulatory system [32] or indirectly through the mediation of the vagus nerve [33]. The consequences of neuroinflammation may include the development of neurodegenerative disorders such as Parkinson's and Alzheimer's diseases [32]. Behaviorally the effects of neuroinflammation may include depression, anxiety, psychomotor slowing and cognitive dysfunction [34].

2. Aging

Aging is characterized by changes in central nervous system (CNS) functioning compared to young adult and middle-aged organisms. Exposure to space radiation also produces changes in CNS functioning compared to non-irradiated controls. Aging-related changes have been reported in a variety of neurotransmitter systems including dopaminergic [35, 36], glutamatergic [35, 37] and muscarinic acetylcholine [38] systems. Changes have also been reported in hippocampal proteome [39] and in protein kinase C activity in the prefrontal cortex [40] as a function of age. There are also age-related changes in hippocampal neurogenesis [41–43] and in autophagy [44]. Similar changes have been reported following exposure to HZE particles (see below).

Behaviorally, aging is characterized by deficits in dopamine-mediated motor function [45] and by an increase in the frequency of occurrence of cognitive dysfunction. Although the cognitive performance of some rats remains unimpaired compared to young organisms, other rats show a reduction in their ability to perform a variety of cognitive tasks [e.g., 35, 37, 39, 46, 47]. Performance decrements have been reported in spatial learning and memory using the Morris water maze [35, 37, 46, 47] and the radial arm water maze [48]; in object location memory [49]; in executive function using attentional set shifting [38, 50]; and in novel object recognition [51–53].

Current theories propose a role for both oxidative stress [54–58] and neuroinflammation [59–61] in the aging process. While the free radical theory of aging may not be able to account for all aspects of aging [62], it is generally accepted that oxidative stress is a key component of the aging process. The deficits in cognitive performance that accompany the aging process have been linked to the effects of oxidative stress [63–65] and neuroinflammation [66–68] on brain function. Complementary research using diets which reduce oxidative stress and neuroinflammation show an amelioration of the cognitive deficits that accompany the aging process [69–72].

Heavy particle radiation, like other toxic stimuli, produces oxidative stress [21, 23, 73, 74] and neuroinflammation [28, 75–77] resulting in changes in neuronal function. Given that both exposure to HZE particles and aging produce oxidative stress and neuroinflammation, similar changes in neuronal function should also occur. As observed in aged animals, exposure to HZE particles causes changes in dopaminergic [78] and muscarinic acetylcholine [79, 80] activity in the striatum, in hippocampal neurogenesis [75, 81, 82] and in autophagy [77]. In effect, exposure to HZE particles accelerates the aging process [78, 79] in terms

of changes in neuronal functioning. As a result of accelerating neuronal aging, there is a corresponding effect on behavioral performance.

Exposing rats to low doses (<100 cGy) of the types of radiation encountered in space (protons and HZE particles) disrupts behaviors that are dependent upon the integrity of the dopaminergic system, including motor performance [83]; startle responses [84]; amphetamine-induced conditioned taste aversion learning [10, 11, 85]; and operant responding on an ascending fixed-ratio schedule [12, 86]. Similarly, exposure to low doses of HZE particles disrupts spatial learning and memory measured using the Morris water maze [14, 87] and the radial arm water maze [22]. Performance on the novel object recognition task is also disrupted [88] as is executive function using the attentional set shifting task [89]. Overall, these studies indicate that exposure to low doses of the types of radiation encountered in space affect cognitive performance on a wide range of tasks, including spatial learning and memory, motivation, anxiety and executive function.

In addition to accelerating the aging process, research has shown that there is an interaction between age and exposure to HZE particles such that exposing subjects to doses of ^{56}Fe particles that do not affect the performance of younger rats do produce a significant disruption in performance in these same animals at older ages [90]. Also, lower doses of ^{56}Fe HZE particles are needed to produce neurocognitive deficits in subjects that are exposed at older ages [91]. The interaction between age and susceptibility to the neurocognitive effects of exposure to space radiation may result from the fact the neurocognitive effects of both the aging process and exposure to HZE particles are mediated by oxidative stress and neuroinflammation and exposure to HZE particles accelerates the decline in cognitive performance.

3. Nutrition

To the extent that oxidative stress plays a role in the cognitive decline that accompanies the aging process, then treatments that reduce oxidative stress should reduce the aging-induced performance decrement. Within the last 15 years, a large number of studies have been conducted evaluating the effects of antioxidant diets (i.e., diets with antioxidant activities) to ameliorate the age-induced deficit in cognitive performance [92, 93]. While the antioxidant capacity of many different compounds has been explored, including vitamins C [94] and E [95], caffeine [96], resveratrol [97, 98], and folic acid [99] by far the most research has been concerned with the effectiveness of flavonoid-containing fruits and vegetables to reverse the age-induced increase in oxidative stress and the corresponding decline in cognitive function [69, 70, 72, 100–103]. Research suggests that phytochemical compounds contained in colorful fruits and vegetables exhibit potent antioxidant and anti-inflammatory activities [104]. These effects may be due to the types, quantities, and combinations of dietary antioxidants and anti-inflammatories found in them. Moreover, recent work also suggests that the polyphenolic compounds found in berry fruits may actually have direct effects on the brain, which may also contribute to their beneficial effects with respect to cognitive and motor behaviors. Specifically, berry fruits mediate signaling pathways involved in inflammation and cell survival in addition to enhancing neuroplasticity, neurotransmission, and calcium buffering, all of which lead to attenuation of age- and pathology-related deficits in behavior [105]. Overall, the general finding has been that treatments that reduce oxidative stress and neuroinflammation also reduce or prevent the disruption of cognitive function that occurs in the aged organism. Specifically, inclusion of antioxidant extracts in the food of aged rats results in improved performance on object recognition [96, 100, 103]; spatial learning and memory [69, 70, 94]; and in plus-maze and avoidance tasks [99, 101].

Historically, little attempt has been paid to issues related to the development of cognitive deficits following exposure to space radiation. As a consequence of this approach, attempts to develop radioprotectors have been concerned with the role of antioxidant treatments on biological endpoints [23]. Within this category, there have been tests of chemical antioxidant compounds as potential radioprotectants, including selenomethionine [106, 107], alpha-tocopheral [108]; tamoxifen [109], melatonin [110], alpha-lipoic acid [111], DSMO [112] and an inhibitor of pro-inflammatory cytokines [76]. These studies have shown that treatment with a variety of free radical scavenging compounds is effective in preventing/ameliorating the biological consequences of exposure to radiation.

In as much as exposure to HZE particles and protons produces oxidative stress and neuro-inflammation

leading to decrements in cognitive performance that are characteristic of the aged organism, antioxidant diets should be equally effective in mitigating the deleterious effects of exposure to the types of radiation encountered in space. In contrast to the studies cited above, attempts to ameliorate the cognitive effects of exposure to space radiation have utilized the same compounds that have been shown effective for the treatment of aging-induced cognitive deficits. The majority of these studies of have utilized blueberry and strawberry extract added to the diet of rats prior to exposure to ^{56}Fe particles.

Maintaining rats on diets containing 2% blueberry or strawberry extract for two months prior to exposure to ^{56}Fe particles (1.5 Gy, 1 GeV/n) prevented the radiation-induced decreases in potassium-stimulated dopamine release in the striatum [113]. Exposure to 2.5 Gy of 1 GeV/n ^{56}Fe particles alters gene expression in the hippocampus related to the regulation of oxidative and inflammatory signals. When rats were maintained on strawberry and blueberry diets the radiation-induced changes in gene expression were ameliorated [114].

Concordant with the effects of berry diets on neuronal function, antioxidant diets also ameliorate the cognitive/behavioral deficits produced by exposure to HZE particles, although the effectiveness of the blueberry or strawberry diet varies as a function of the specific behavioral endpoint. For dopamine-dependent conditioned taste aversion learning, rats maintained on either the blueberry or strawberry diet failed to show the ^{56}Fe particle-induced disruption of an amphetamine-induced CTA [115]. In contrast, the irradiated rats fed a control diet failed to acquire an amphetamine-induced taste aversion, which is consistent with previous research [10, 11]. Similarly, rats maintained on either a 2% or 4% strawberry or blueberry diet for two weeks prior to exposure to 150 cGy 1000MeV/n ^{56}Fe particles did not show a disruption of novel object recognition performance compared to irradiated rats maintained on a control diet [88]. As with conditioned taste aversion learning, there were no differences in the degree of protection as a function of the diet (blueberry or strawberry).

Similarly, rats exposed to ^{56}Fe particles maintained on either the blueberry or strawberry diet showed improved performance on the Morris water maze compared to irradiated rats maintained on the control diet [113, 116]. Although the irradiated rats showed improved performance on both diets, there were differences in the pattern of responding as a function of the specific diet (blueberry or strawberry). The improved performance of the rats fed the strawberry diet may have reflected better ability to retain place information which is mediated by the hippocampus; whereas the rats maintained on the blueberry diet showed better performance on the striatal-dependent reversal task.

The effects of antioxidant diets on operant responding on an ascending fixed-ratio schedule also varied as a function of the specific diet. Following exposure to 150 or 200 cGy of ^{56}Fe particles, 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 [117, 118]. 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, which did not differ from that of the irradiated rats fed the control diet.

While for some cognitive tasks both blueberry and strawberry diets are equally effective in preventing/ameliorating HZE particle-induced disruption of cognitive performance (e.g., taste aversion learning; novel object recognition), for other cognitive tasks the effectiveness of the diets differs (e.g., spatial learning and memory; operant responding on an ascending fixed-ratio schedule). The factors that might account for the differing effectiveness of the different diets on different cognitive tasks following exposure to HZE particles remain to be determined. It is possible that the differences in effectiveness result from a differential sensitivity to oxidative stress and the effects of free radical scavengers in the specific tissue that mediates the behavior. For the most part, spatial learning and memory depends upon the integrity of the hippocampus whereas the operant responding on an ascending fixed-ratio schedule depends upon the integrity of the striatum. An alternative factor influencing the differential effectiveness of the two diets is that neurocognitive endpoints may be related to the chemical composition of the diets, which could influence or affect their antioxidant capacity and their ability to cross the blood-brain barrier. While all berries contain bioactive chemicals including phenolics, anthocyanins, hydroxycinnamates and flavonols, the relative amounts of these constituents varies as a function of the specific berry: blueberries have more proanthocyanins whereas strawberries have more ellagitannins. This, in turn

may affect the antioxidant capacity of strawberries and blueberries as well as their ability to cross the blood-brain barrier [119–121].

In addition to the capacity of antioxidant berry diets to prevent or ameliorate the effects of exposure to space radiation on cognitive performance, maintaining rats on these diets also prevents the development of radiation-induced tumors. Rats maintained on a diet containing 2% strawberry or blueberry extract for 4 weeks prior to and up to 1 week after exposure to ^{56}Fe particles (150 cGy, 1 GeV/n) developed significantly fewer tumors than rats given the control diet [122]. The reduction in the frequency of occurrence of tumors only required that the enhanced diet-induced antioxidant capacity be functional at the time of exposure and not throughout the remaining life of the organisms. Both strawberry and blueberry diets were equally effective in reducing the frequency of development of HZE particle-induced tumors.

The human equivalents of the animal research cited above is 1-2 cups of blueberries or strawberries. This translates into 12–24 g/day of freeze dried powder. On a spacecraft for long-duration exploratory class missions, much of the food will be freeze-dried. For a 900-day Mars mission, approximately 21 kg of powder would be needed for each astronaut to provide significant protection against the deleterious effects of exposure to cosmic rays. Given the proven benefits, it seems reasonable to propose that freeze-dried blueberries or strawberries should constitute one component of the astronauts' diet.

4. Conclusions

On exploratory class missions to other planets, astronauts will be exposed to types and doses of radiation (cosmic rays) which are not experienced in low earth orbit. Exposure to low, non-lethal doses of space radiation can produce changes in neuronal function and in neurocognitive performance that resemble those seen in aged organisms: exposure to space radiation produces accelerated aging. The disruption of neurocognitive performance by exposure to space radiation may affect the ability of an astronaut to perform critical tasks during a mission or affect the quality of life of an astronaut after the conclusion of a mission by accelerating the aging process, perhaps leading to the development of Alzheimer's or Parkinson's diseases. It is therefore necessary to reduce the exposure of astronauts to HZE particles, either by increasing the shielding of the space capsule or by other means. However, shielding is not always an effective means of protecting astronauts, both because of the energy of the HZE particles and because particles striking the shielding material give rise to secondary particles [123–125]. This means that some other means must be found to provide the necessary degree of protection to permit an astronaut to successfully meet mission requirements and not produce a premature degradation in the quality of life after the conclusion of the mission. The data summarized in this review suggest that dietary supplements can meet this goal.

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