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PI Name:	Vose, Linnea Ph.D.		
Project Title:	Protection of Neurogenesis as a Neuroprotectant Strategy for Low-Dose Space Radiation Exposure		
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Program/Discipline--Element/Subdiscipline:	NSBRI--Radiation Effects Team		
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Comments:			
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No. of Bachelor's Candidates:	0	Monitoring Center:	NSBRI
Contact Monitor:	Contact Phone:		
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COI Name (Institution):	Stanton, Patric Ph.D. (MENTOR/ New York Medical College)		
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Performance Goal No.:			
Performance Goal Text:	<p>POSTDOCTORAL FELLOWSHIP</p> <p>Transcranial exposure to simulated galactic cosmic radiation (GCR) is known to impact learning and memory, synaptic plasticity, neuronal physiology, and neurogenesis. The brain is particularly susceptible to GCR-induced damage, likely due to the highly specialized cells, complex functions, and plasticity required for cognition, learning, and memory. Neurogenesis persists throughout adulthood in the hippocampus, a specialized structure in the temporal lobe required for memory formation. Since neural progenitor cells are very susceptible to damage from radiation, GCR could cause both subtle alterations in the function of mature neurons, and alter the ability of the brain to replace these cells. Understanding the interactions between GCR and neurogenesis, and the effects of these on cognition, mood, and executive function, is critical for rational assessment of long-term CNS risk and efficient development of effective countermeasures for in-mission risks from GCR in long-duration space travel.</p>		

Task Description:

Since impaired neurogenesis is correlated with impaired cognition, we expected that preservation of neurogenesis has the potential to rescue cognitive impairments associated with GCR exposure. Thyroid hormone (TH) is required for normal neurogenesis, and hypothyroid humans and rodents exhibit decreased cognitive function and depression-like behavior which can be rescued by TH supplementation. Repeated exposure to neural insults (such as ischemia or medical radiation) can result in activation of compensatory mechanisms over a period of days or weeks and reduce damage upon subsequent exposure. The central hypotheses of this proposal were 1) the brain can become resistant to damage from repeated GCR exposures, and 2) TH supplementation may be a novel and effective therapeutic strategy to protect neurogenesis from GCR with an FDA approved compound (thyroxine).

For each neuroprotective method, we proposed to expose mice to ^{56}Fe in doses of 0, 5+45, 25+25, and 50 cGy, with dual irradiations spaced 4 days apart. One group of mice receiving 50 cGy also received daily treatment with thyroxine (TH) for one week before and after irradiation. Mice from each group were subjected to a battery of behavioral tests (learning, memory, anxiety, and depression-like behavior), analysis of synaptic plasticity and neuronal function, and quantification of newborn neurons. These experiments were performed at both 4 and 8 months after exposure to ^{56}Fe , to determine the long-term consequences of each intervention. Behavioral and electrophysiological data has been collected for the 4 month time point. Interestingly, TH treatment rescued radiation-induced changes in anxiety, but increased depression-like behavior in male and female mice. Dual, spaced radiation exposure enhanced synaptic plasticity (in females) and learning acquisition, but not memory (in males and females). These findings suggest that our interventions were, in fact, altering hippocampal function.

Future experiments in progress include quantification of neurogenesis at the 4 month time point. Biochemical analysis of samples collected immediately after GCR exposure will quantify serum TH levels and activity levels of brain enzymes involved in TH metabolism. In addition, all behavior, synaptic plasticity, and neurogenesis experiments will also be performed on the cohorts of mice 8 months post-GCR exposure (Spring 2017).

Rationale for HRP Directed Research:**Research Impact/Earth Benefits:**

A better understanding of the brain's natural mechanisms to prevent or compensate for radiation induced cognitive impairment is relevant for patients undergoing cancer treatment. Although the type of radiation is different from that experienced by astronauts, it is likely the brain employs similar protective mechanisms in response to a range of high-energy radiation challenges. Our findings may help prevent cognitive impairment in patients undergoing radiation therapy, either by exposing patients to a very small dose of radiation prior to high dose treatments, or by concurrent treatment with thyroxine. Exposing rodents to simulated galactic cosmic radiation (GCR) impacts learning and memory, long-term activity-dependent synaptic plasticity (changes in the strength of connections between neurons) that is thought to underlie memory storage, and neurogenesis (production of newborn neurons). Neural progenitor cells, because they are still dividing, are particularly susceptible to damage from radiation, and GCR may cause both subtle alterations in the function of mature neurons, and simultaneously alter the ability of the brain to grow new replacements for these cells. Since impaired neurogenesis is correlated with impaired cognition, we predicted that preservation of neurogenesis could prevent cognitive impairments associated with GCR exposure. Repeated exposure to a wide range of neural insults (from ischemic reduction of blood flow to medical radiation) can activate compensatory mechanisms to reduce damage upon subsequent exposure. Thyroid hormone (TH) is required for normal neurogenesis. Patients undergoing radiation treatment for cancer often show lowered thyroid hormone levels. Hypothyroid humans and rodents exhibit decreased cognitive function and depression-like behavior, which can be rescued by TH supplementation with thyroxine, an FDA approved compound. This project will improve our understanding of the effects of dual, spaced radiation exposure on cognitive function, learning and memory, long-term synaptic plasticity, and the production of newborn neurons. This project will also address whether TH supplementation during radiation exposure can prevent reduction of newborn neurons, and impairment of cognitive function and synaptic plasticity, towards development of treatments that may help protect individuals exposed to radiation in both terrestrial and space environments.

Task Progress:

We utilized dual, temporally spaced exposures to GCR, which offer the potential to activate compensatory neurogenic mechanisms and be a closer approximation to modeling reactive changes that may occur during long-term space exploration than single GCR exposure protocols. We hypothesize that, after a brief, low dose GCR-exposure, surviving neurons, and perhaps stem cells, will be altered at the cellular level to be more resistant to future insults. Treatment with thyroxine during radiation exposure may prevent impairment of neurogenesis and subsequent cognitive deficits. We are now testing our compensation hypothesis and the effectiveness of thyroxine using behavioral tests for learning and anxiety, histological quantification of newborn neurons, and electrophysiological techniques to determine functional properties of newborn neurons. These measurements are being acquired 4 and 8 months after radiation exposure to determine the long-term effects of radiation and our proposed countermeasures. Following the application process of Brookhaven National Labs for radiation beam time, mice were irradiated in June 2016, and behavioral and electrophysiological tests have been completed for the 4 month post-GCR time point. Histological experiments are commencing now. Experiments at the 8 month time point will be completed by spring 2017.

Bibliography Type:

Description: (Last Updated: 03/01/2017)

Abstracts for Journals and Proceedings

Vose LR, Miry O, Gopaul KR, Subah G, Stanton PK. "Effect of thyroxine on neurogenesis following galactic cosmic radiation." Neuroscience 2016, San Diego, CA, November 12-16, 2016. Neuroscience 2016, San Diego, CA, November 12-16, 2016. , Nov-2016

Abstracts for Journals and Proceedings

Vose LR, Miry O, Zhang X-L, Stanton PK. "Effect of thyroxine on synaptic function and neurogenesis following galactic cosmic radiation." 2016 NASA Human Research Program Investigators' Workshop, Galveston, TX, February 8-11, 2016. 2016 NASA Human Research Program Investigators' Workshop, Galveston, TX, February 8-11, 2016. , Feb-2016