

Fiscal Year:	FY 2006	Task Last Updated:	FY 07/05/2006
PI Name:	Raber, Jacob Ph.D.		
Project Title:	Neurogenesis and cognition in human apoE transgenic mice following 56Fe radiation		
Division Name:	Human Research		
Program/Discipline:	HUMAN RESEARCH		
Program/Discipline--Element/Subdiscipline:	HUMAN RESEARCH--Radiation health		
Joint Agency Name:	TechPort:	No	
Human Research Program Elements:	(1) SR :Space Radiation		
Human Research Program Risks:	(1) BMed :Risk of Adverse Cognitive or Behavioral Conditions and Psychiatric Disorders		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
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Zip Code:	97239-3011	Congressional District:	1
Comments:			
Project Type:	GROUND	Solicitation / Funding Source:	2004 Radiation Biology NNH04ZUU005N
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No. of PhD Candidates:	1	No. of Master' Degrees:	0
No. of Master's Candidates:	0	No. of Bachelor's Degrees:	0
No. of Bachelor's Candidates:	0	Monitoring Center:	NASA JSC
Contact Monitor:	Contact Phone:		
Contact Email:			
Flight Program:			
Flight Assignment:	End date changed to 9/30/2009 per JSC update info (10/06)		
Key Personnel Changes/Previous PI:	0		
COI Name (Institution):	Fike, John R (UCSF)		
Grant/Contract No.:	NNJ05HE63G		
Performance Goal No.:			
Performance Goal Text:	Of the major human isoforms of apolipoprotein E (E), E4 is associated with age-related cognitive decline and increased risk to develop Alzheimer's disease (AD). The space radiation environment contains 56Fe. 56Fe radiation exposure causes cognitive injury and might predispose E4 subjects to cognitive injury and an earlier onset or more severe extent of AD. The pathogenesis of this injury may involve loss or injury to neural precursor cells in the dentate subgranular zone (SGZ) of the hippocampus, which is involved in complex learning requiring the ability to learn about multiple relationships among stimuli. Disturbances in hippocampal functioning reduce spatial learning and memory. The granule cells of the dentate gyrus are involved in spatial memory and their radiation-induced depletion implicated in cognitive deficits. Our data show reduced numbers of proliferating cells and immature neurons and spatial learning and memory impairments in wild type mice x-irradiated at 2 months and behaviorally tested 3 months later. Treatments that damage		

Task Description:	<p>neuronal precursor cells or their progeny might reduce neurogenesis and impair hippocampus-dependent cognitive functions in an E isoform-dependent fashion. Our data indicate that neuronal expression of E3 protects immature neurons against radiation injury and that E3 is more potent than E4 in supporting neuronal proliferation. After irradiation, SGZ precursor cells undergo rapid apoptotic cell death, which might involve oxidative stress. Oxidative stress might also play a critical role in later reductions in hippocampal neurogenesis. E isoforms differ in their ability to protect against neurotoxicity and apoptosis and oxidative stress. Isoform-specific effects of E on 56Fe radiation-induced oxidative stress, apoptosis, and loss of proliferating SGZ cells rapidly after 56Fe-irradiation or oxidative stress later after irradiation might contribute to their effects on cognitive injury later in life. We hypothesize that human E isoforms are associated with different levels of 56Fe-induced loss of neural precursor cells and hippocampus-dependent cognitive injury, and that these effects can be ameliorated by antioxidants. The Specific Aims are: 1A. Determine if E isoform is associated with radiation-induced apoptosis of neural precursor cells in the dentate SGZ; 1B. Determine the role of E isoform in the development of radiation-induced cognitive deficits and whether the severity of these deficits are associated with apoptosis of neural precursor cells in the dentate SGZ. Mice will be tested 3 months following radiation; 1C. Determine how E isoform affects neurogenesis following 56Fe- irradiation, and determine if this effect is related to the severity of radiation-induced cognitive deficits; 2A. Determine if the presence of a specific E isoform is associated with markers of oxidative stress following radiation injury; and 2B. Determine if the antioxidant a-lipoic acid enhances cognitive function and reduces radiation-induced cognitive impairments and whether this ability is E isoform-dependent. Mice will be irradiated with 56Fe ions (0 to 3 Gy). We will assess cognitive impairments using behavioral tests that require hippocampal functioning and quantify of radiation-induced changes using immunohistochemistry.</p>
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	<p>Our research impacts life on earth as it determines whether genetic risk factors for age-related cognitive decline are also risk factors for radiation-induced cognitive impairments. In case the anti-oxidant dietary supplement is able to antagonize these impairments, the impact would also constitute of a potential intervention against these challenges.</p>
Task Progress:	<p>This month (June 2006) was the first time the beam at BNL was available to our research. As the animals will be tested behaviorally three months following irradiation, these data are not available yet. However, we generated data using Cesium irradiation. These data, which are summarized in more detail below, indicate that the isoform-dependent effects of apoE on cognitive function are sex-dependent with female mice being more susceptible to radiation-induced cognitive impairments than male mice. While our proposals only included studies of male mice, we believe that these results are very important and bring up new critical path questions concerning the role of sex in the effects of irradiation on cognitive function, particularly in the context of apoE. Importantly, the risk to develop Alzheimer’s disease (AD) in people carrying apoE4 is sex-dependent. Women are at higher risk to develop AD than men, and particularly women carrying apoE4. There is an synergistic interaction between female sex and apoE4 in risk to develop AD. It is conceivable that radiation might increase the risk of age-related cognitive decline and development of AD in a sex- and apoE isoform-dependent fashion.</p> <p>To determine the potential effects of apoE isoform and sex on radiation-induced cognitive impairments, we irradiated, using Cesium irradiation at 10 Gy, two-month-old apoE2, apoE3, and apoE4 male and female mice and assessed their cognitive performance three months later. When hippocampus-dependent spatial learning and memory was assessed in the water maze, sham-irradiated apoE2, apoE3 and apoE4 and irradiated apoE2 female mice showed spatial memory retention, but irradiated apoE3 and apoE4 female mice did not. Compared to sham-irradiated apoE4 female mice, irradiated apoE4 female mice also required more trials to reach criterion in the hippocampus-dependent passive avoidance test. Irradiation had no effects on water maze or passive avoidance learning and memory of male apoE2, apoE3, or apoE4 mice, indicating that the effects of radiation on cognitive performance are sex- and apoE isoform-dependent. These results show that brain irradiation induces sex- and apoE isoform-dependent cognitive impairments. The lack of effects of irradiation on spatial memory retention of apoE2 female mice is consistent with the relative protection of apoE2 carriers in risk to develop AD. While irradiation affected passive avoidance learning of apoE4, but not apoE3, female mice, it affected water maze performance of both apoE3 and apoE4 female mice. A differential susceptibility of apoE3 and apoE4 female mice to irradiation-induced cognitive-impairments in the water maze might be revealed at a lower or higher irradiation dose. In addition, in contrast to the effects of irradiation on the water maze learning curves in this study stronger effects of irradiation on water maze learning curves might have been detected at higher irradiation doses and/or at longer follow-up times. Deficits in water maze performance were detected following higher irradiation doses (21-25 Gy) and longer follow-up times.</p> <p>These result show higher anxiety levels in 5-month-old apoE4 than age-matched apoE3 mice expressing apoE under control of the mouse apoE promoter. These data are consistent with the higher anxiety levels of 6-month-old ApoE^{-/-} male mice expressing apoE4 in neurons or astrocytes than those expressing apoE3 in neurons or astrocytes and with the higher anxiety levels of probable AD patients with only apoE4 than those with only apoE3. ApoE4 female and male mice moved less than sex-matched apoE3 mice in the open field, light-dark, and elevated zero maze. In the elevated plus maze, apoE4 female mice moved less than apoE3 female mice but this genotype difference did not reach significance in the genotype-matched male mice. Taken together, these data indicate that apoE4 mice move less than apoE3 mice in novel environments. This could be related to increased measures of anxiety and/or reduced exploratory drive in the context of apoE4.</p> <p>In the first two visible sessions of visible platform training, irradiated apoE2 female mice performed less than sham-irradiated apoE2 female mice. These data indicate that in apoE2 female mice irradiation impaired initial task learning. In the elevated zero maze, there was a trend towards lower measures of anxiety in irradiated than sham-irradiated apoE2 female mice. Therefore, it is possible that irradiated apoE2 female mice showed this initial task learning deficit in the water maze as they might have been slightly less motivated to learn how to escape the water.</p> <p>While anxiety can influence performance in the water maze probe trials, differences in anxiety levels did not contribute to the spatial memory retention deficits in irradiated apoE3 and apoE4 female mice. Irradiation or sex had no effects on measures of anxiety in the anxiety tests used or on time spent in the outer zone of the water maze. In addition, while apoE2 mice showed higher measures of anxiety than apoE3 mice, apoE3, but not apoE2, female mice showed spatial memory retention deficits following irradiation. Finally, the isoform-dependent effects of apoE on measures of anxiety were more pronounced in males than females but the radiation-induced impairments in water maze performance were</p>

	<p>only seen in females. In contrast to the water maze, isoform-dependent effects of apoE on measures of anxiety might have contributed to the better passive avoidance learning of apoE4 than apoE3 or apoE2 mice. Trials to reach criterion in the passive avoidance test correlated with measures of anxiety in the elevated zero maze, elevated plus maze, and light-dark tests. When sensorimotor function was assessed on the rotarod, apoE3 mice showed lower fall latencies than sex-matched apoE2 or apoE4 mice but irradiation had no effect on rotarod performance. In addition, female mice, which showed increased susceptibility to radiation-induced cognitive impairments, showed higher fall latencies than male mice. These data indicate that potential alterations in sensorimotor function did not contribute to the observed radiation-induced alterations in cognitive performance in apoE3 and apoE4 female mice. In summary, these data show sex- and apoE isoform-dependent effects of Cesium irradiation on water maze and passive avoidance performance. Both tests are hippocampus-dependent and the mechanisms underlying these effects might involve alterations in neurogenesis in the subgranular zone of the hippocampal dentate gyrus and in subsequent migration of newly born cells into the dentate granule cell layer. As the effects of radiation on cognitive injury are not transient and observed in rodents one year after irradiation, radiation exposure might predispose to age-dependent cognitive decline and an earlier onset or more severe extent of neurodegenerative diseases such as AD in a sex- and apoE isoform-dependent fashion.</p>
Bibliography Type:	Description: (Last Updated: 10/30/2023)
Abstracts for Journals and Proceedings	<p>Villasana L, Acevedo S, Poage C, Raber J. "Effects of Cesium Irradiation on Cognitive Function: Role of Sex- and Apolipoprotein E Isoform. " 4th Intl 17th Annual NASA Space Radiation Investigators' Workshop 2006, Moscow-St. Petersburg, Russia, June 2006.</p> <p>4th Intl 17th Annual NASA Space Radiation Investigators' Workshop 2006, June 2006. , Jun-2006</p>
Abstracts for Journals and Proceedings	<p>Villasana L, Acevedo S, Poage C, Raber J. "Sex- and ApoE Isoform-dependent effects of radiation on cognitive function. " Society for Neuroscience Oregon Chapter Annual Meeting, Salishan, Oregon, 2006.</p> <p>Society for Neuroscience Oregon Chapter Annual Meeting, 2006. , Jun-2006</p>
Abstracts for Journals and Proceedings	<p>Villasana L, Acevedo S, Poage C, Raber J. "Sex- and ApoE Isoform-dependent effects of radiation on cognitive function. " Society for Neuroscience Annual Meeting 2006, Atlanta, GA, October 2006.</p> <p>Society for Neuroscience Annual Meeting, October 2006. , Oct-2006</p>
Awards	<p>Villasana L, Acevedo S, Poage C, Raber J. "Awarded Best Poster , Student Research Forum OHSU 2006, Oregon."</p> <p>Mar-2006</p>