Simulated space radiation and weightlessness: vascular-bone coupling mechanisms to preserve skeletal health

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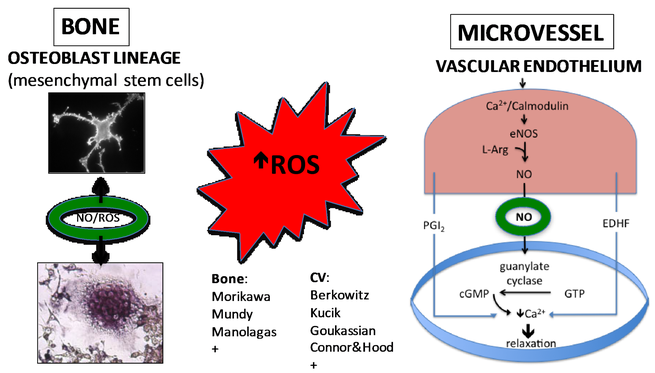
INTRODUCTION

Spaceflight, bone and oxidative stress

• Astronauts may develop bone loss in space as a result of environmental challenges, such as exposure to both weightlessness and ionizing radiation.

• Oxidative stress results from an imbalance between production of free radicals and the ability of cells to counteract their harmful effects at the molecular level.

Endogenous ROS/RNS signaling for adaptive responses



Together, defining bone structure

Together, defining vessel function

Published findings from the final grant year

This last year, published papers from our groups describe experimental findings with mice testing various aspects of our hypothesis[1-3], and related reviews of ionizing radiation[4] and simulated weightlessness[5].

[1] Delp MD et al. Apollo Lunar Astronauts Show Higher Cardiovascular Disease Mortality: Possible Deep Space Radiation Effects on the Vascular Endothelium. Sci Rep. 2016 Jul 28;6:29901.
[2] Schreurs AS et al. Dried plum diet protects from bone loss caused by ionizing radiation. Sci Rep. 2016 Feb 11;6:21343.
[3] Ghosh P et al. Effects of High-LET Radiation Exposure and Hindlimb Unloading on Skeletal Muscle Resistance Artery Vasomotor Properties and Cancellous Bone Microarchitecture in Mice. Radiat Res. 2016 Mar;185(3):257-66.
[4] Hendry JH et al. ICRP Publication 131: Stem cell biology with respect to carcinogenesis aspects of radiological protection. Ann ICRP. 2016 Jun;45(1 Suppl):239-52.
[5] Globus RK, Morey-Holton E. Hindlimb unloading: rodent analog for microgravity. J Appl Physiol (1985). 2016 May 15;120(10):1196-206. Review.

PURPOSE OF THE STUDIES

To define the mechanisms and risks of bone loss in space and to develop effective ways to prevent that bone loss.

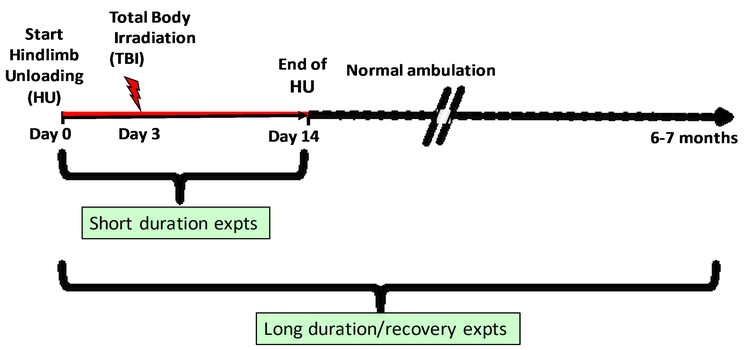
HYPOTHESES

Weightlessness and radiation cause oxidative stress, adversely affecting both bone and the blood vessels that feed muscle and bone.

METHODS

Animals: Adult (4 mo old at start), male C56Bl/6J mice
-Hindlimb unloading by tail traction to simulate weightlessness
-Irradiation with either ^{137}Cs, Protons, or ^{56}Fe

Experimental design



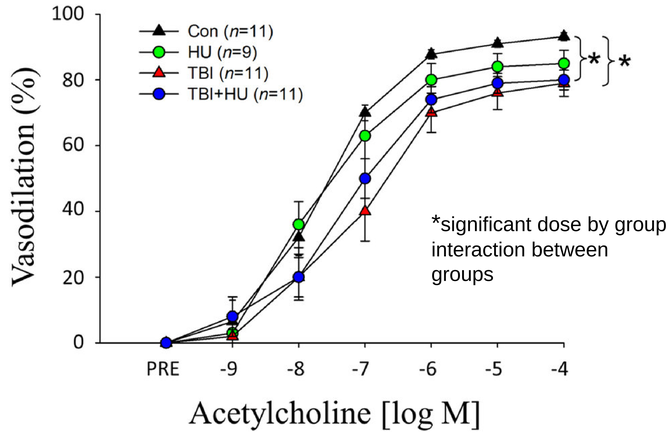
Experimental Groups: 2X2
Normally loaded (NL)
Hindlimb Unloaded (HU)
Irradiated (TBI)
Hindlimb Unloaded + Irradiated

Total body irradiation:
Gamma ^{137}Cs (1-2Gy)
HZE ^{56}Fe (0.5-2Gy, 600meV/n)
Dual: ^{1}H (0.5Gy)/^{56}Fe (0.5Gy)

RESULTS

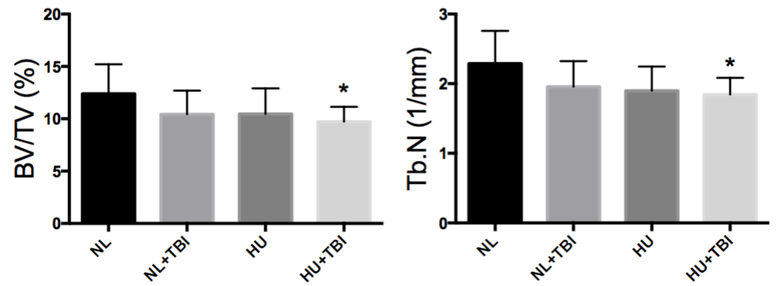
Late effects of HZE, but not transient HU, on vasodilation (via NO signaling mechanism) at 6 to 7 months post-treatment

Hindlimb microvessel: (gastrocnemius feed artery)



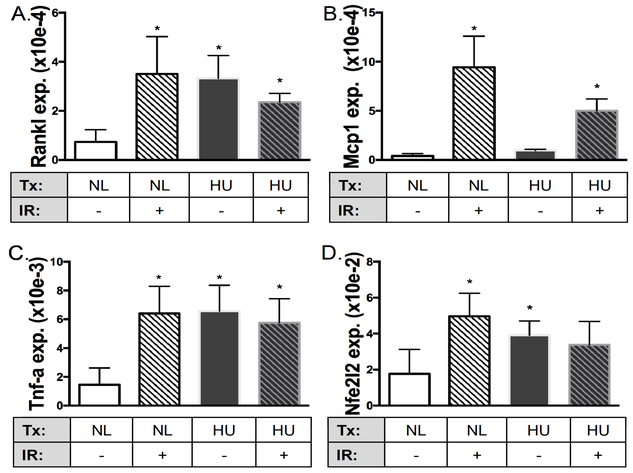
Delp MD et al. Apollo Lunar Astronauts Show Higher Cardiovascular Disease Mortality: Possible Deep Space Radiation Effects on the Vascular Endothelium. Sci Rep. 2016 Jul 28;6:29901.

Combined exposure to HZE radiation and HU results in persistent decrements in cancellous bone microarchitecture at 6-7 months post-treatment



Microcomputed tomography (microCT) analyses of tibiae. BV/TV (%): % bone volume; Tb.N.: trabecular number; *p<0.05 compared to NL by one-way ANOVA using Dunnett's post-hoc test

Radiation and HU as single factors invoke similar pro-osteoclastogenic and antioxidant responses in bone marrow. HU and IR combined do not result in additive effects under these experimental conditions.



CONCLUSION

SUMMARY
• In short term: irradiation and simulated weightlessness
•activate transient antioxidant responses in bone and marrow (Alwood)
•alter antioxidant enzymes expression differently and in combination, cause greater deficits in vasodilation (Ghosh 2016)
•treatments with a dietary supplement (dried plum) but not various antioxidants, prevents short term bone loss casued by radiation (Schreurs)

• In long term: irradiation (but not simulated weightlessness)
•causes persistent deficits in microvessel vasodilation and elevated pro-oxidant enzyme expression (xanthine oxidase) (Delp)
•causes deficits in cancellous bone microarchitecture and bone marrow-derived osteoblast progenitor and stem cell growth.

CONCLUSION:
• Cumulative evidence from our studies on this project support our main hypothesis that simulated weightlessness and irradiation cause oxidative stress and tissue dysfunction; this occurs via various mechanisms that are likely to be both shared and unique to each treatment and tissue
• Our findings show that antioxidant supplements alone are insufficient to prevent bone loss (Schreurs), although may be more effective in combination with interventions that target key mechanisms of bone loss and vascular dysfunction.

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