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

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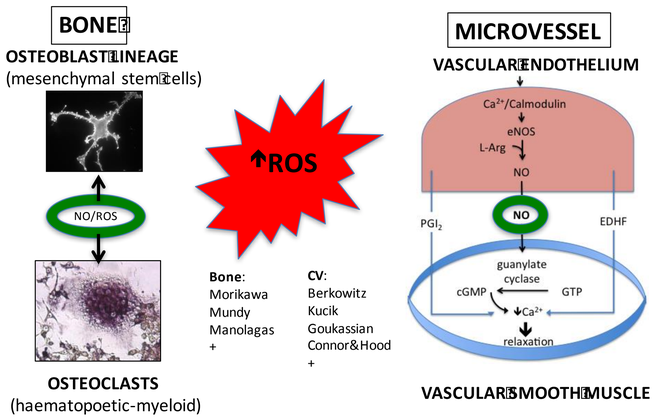
INTRODUCTION

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 group describe experimental findings with mice testing various aspects of our hypothesis[1-3], and 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 help develop effective ways to prevent that bone loss.

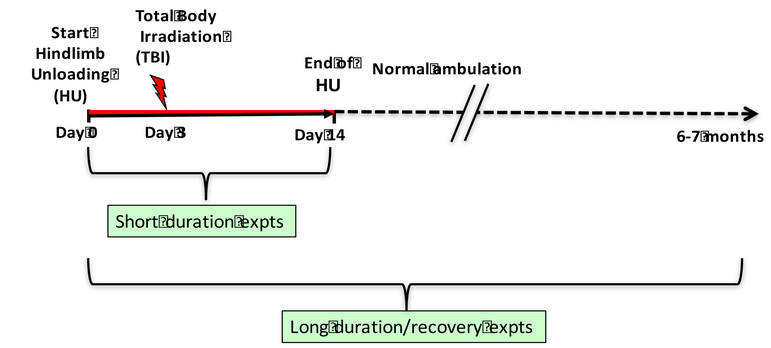
HYPOTHESES

Weightlessness and radiation together 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



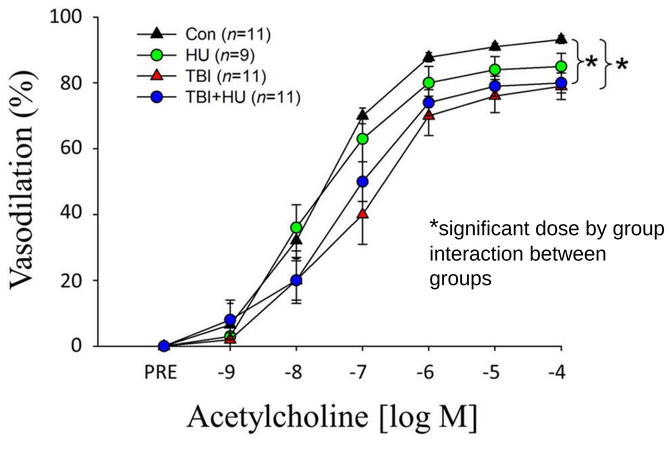
Experimental Groups: 2X2
Normally loaded (NL)
Hindlimb Unloaded (HU)
Irradiated (TBI)
Hindlimb Unloaded + Irradiated

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

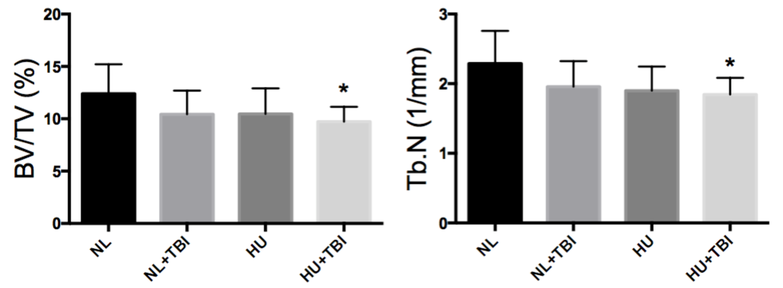
Late effects of HZE, but not transient HU, on vasodilation (via NO signaling mechanism) at 6 to 7 months post-treatment

Hindlimb microvessel: (gastrocnemius feed artery)



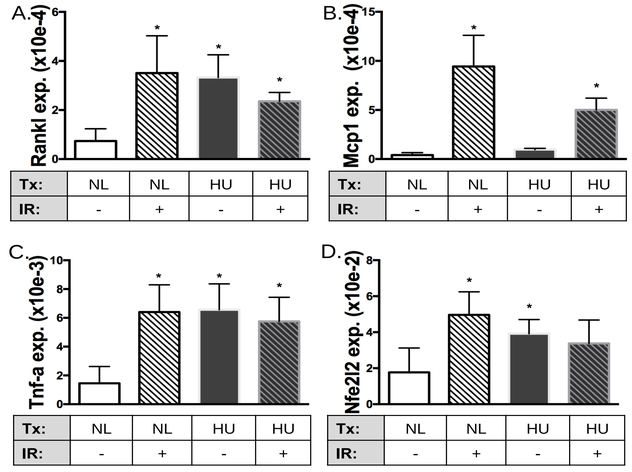
Delp MD et al. Apollo Lunar Astronauts Show Higher Cardiovascular Disease Mortality: Possible Deep Space Radiation Effects on the Vascular Endothelium. Sci Rep. 2016 Jul 28;6:29901.

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.



Mice were irradiated with ^{137}Cs (2Gy). At one day post-IR, mice were euthanized and bone marrow cells were collected for analysis of gene expression by qPCR. Y-axis values indicate relative expression levels of gene of interest normalized to *Gapdh* using the ΔCt method. Data shown are mean ± S.D. (n=5-6/group) and analyzed by 1-factor ANOVA. *p<0.05 compared to NL by Dunnett's post hoc test.

CONCLUSION

Radiation exposure and simulated weightlessness cause persistent antioxidant responses in marrow, decrements in bone microarchitecture and altered vasodilation properties of associated vasculature.

ACKNOWLEDGEMENTS

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