γ-TOCOTRIENOL MITIGATES CARDIOVASCULAR EFFECTS OF SIMULATED SPACE RADIATION IN MALE C57BL/6 MICE

Ashley Nemec-Bakk[1], Vijayalakshmi Sridharan[1], Reid D Landes[1], Preeti Singh, Maohua Cao[2], John W Seawright[3], Xingui Liu[4], Guangrong Zheng[4], Paari Dominic[5], Rupak Pathak[1], Marjan Boerma[1]

1 University of Arkansas for Medical Sciences, 2 Texas A&M University, Dallas, 3 McLennan Community College, 4 University of Florida, 5 Louisiana State University Health Sciences Center

Presenting Author Contact Information: ANemecbakk@uams.edu

Abstract

Organizations and countries across the world are planning human missions into deep space. During those missions, astronauts will be exposed to low doses of ionizing radiation in the form of protons and heavy ions. While there is concern about long-term adverse tissue effects of exposure to space radiation, there are currently no pharmacological countermeasures against these adverse effects. γ-Tocotrienol (GT3) is a natural form of vitamin E that has antioxidant properties, can modify cholesterol metabolism, and has anti-inflammatory and endothelial cell protective properties. The purpose of this study was to test whether GT3 could mitigate cardiovascular effects of oxygen ion (^{16}O) irradiation in a mouse model. Male C57BL/6J mice were exposed to whole-body ^{16}O (600 MeV/n) irradiation at doses of 0 or 0.25Gy at 6 months of age and were followed up to 9 months after irradiation. Animals were administered GT3 (50 mg/kg/day SQ) or vehicle, on Monday – Friday starting on day 3 after irradiation for a total of 16 administrations. Ultrasonography was used to measure *in vivo* cardiac function and blood flow parameters. Cardiac tissue remodeling and inflammatory cell infiltration were assessed with histology and immunoblot analysis at 2 weeks, 3 and 9 months after radiation. ^{16}O significantly increased cardiac ejection fraction and fractional shortening 9 months after exposure. Irradiated mice had indications of collagen type 3 remodeling in the heart, in addition to significantly high levels of left ventricular CD2, CD68 protein content at 2 weeks and 3 months' time points, mass cell tryptase protein at 3 and 9 months' time points, and visible mitochondrial damage. GT3 mitigated the effects of ^{16}O radiation on cardiac function, the expression of the collagen type 3 peptide, and markers of mast cells, T-cells and monocytes/macrophages in the left ventricle. These results suggest GT3 may be a potential countermeasure against late degenerative tissue effects of ionizing radiation in the heart.

Introduction

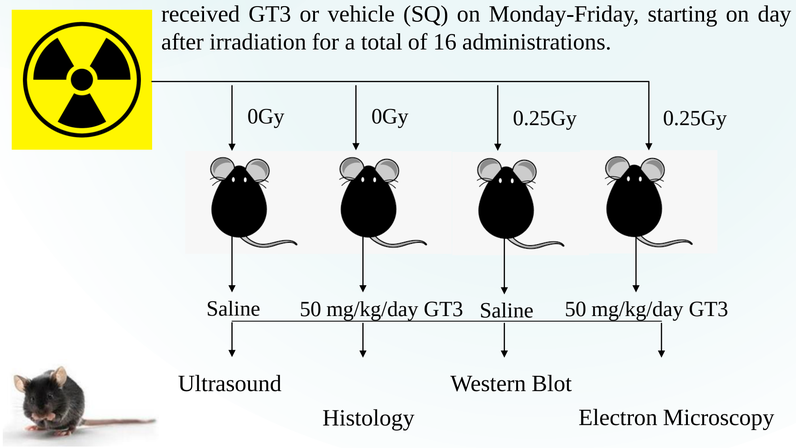
- Astronauts on missions into deep space will be exposed to low dose ionizing radiation in the form of high energy charged particles.
- Ionizing radiation is known to have adverse cardiovascular effects that typically manifest months to years after exposure.
- There are currently no countermeasures to reduce the effects of space radiation.
- γ-Tocotrienol (GT3) is a natural form of vitamin E that has radioprotective properties and several benefits in the cardiovascular system.

Objective

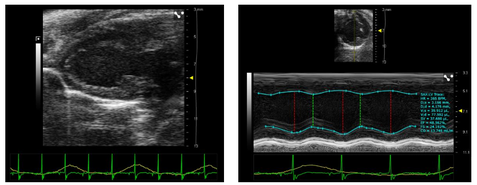
To determine whether GT3 administration throughout the first few weeks after irradiation could mitigate the long term adverse effects of ^{16}O in the heart.

Methods

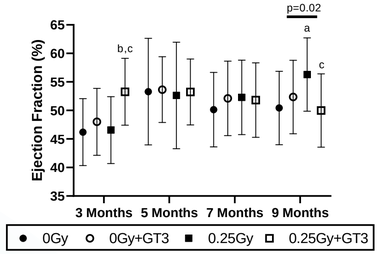
Male C57Bl/6 mice were exposed to whole body ^{16}O irradiation and received GT3 or vehicle (SQ) on Monday-Friday, starting on day 3 after irradiation for a total of 16 administrations.

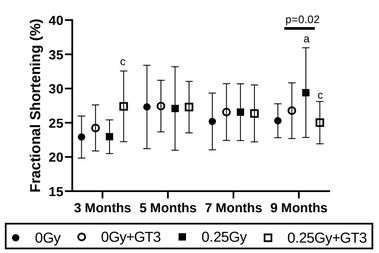


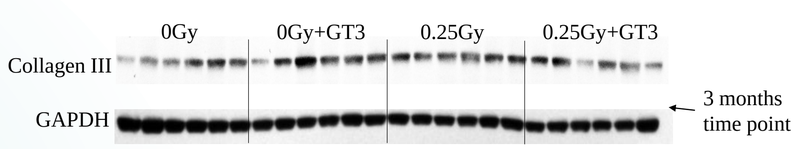
Results

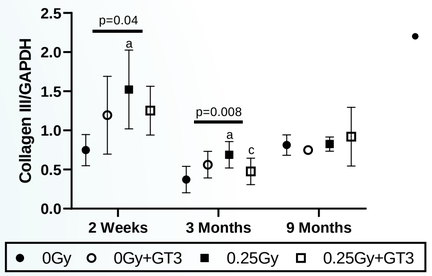


- ^{16}O exposure caused minor changes in cardiac function.
- GT3 mitigated the increase in ejection fraction and fractional shortening measured at 9 months after irradiation.

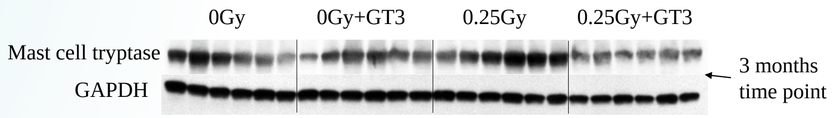


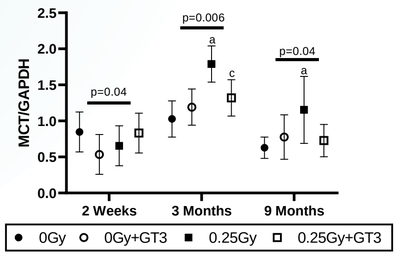




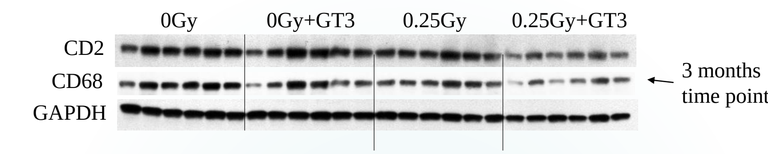


- ^{16}O exposure did not result in cardiac fibrosis. However, left ventricular content of a 75 kDa collagen III peptide was increased, indicating cardiac extracellular matrix remodeling could be occurring.

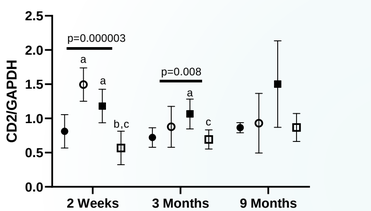


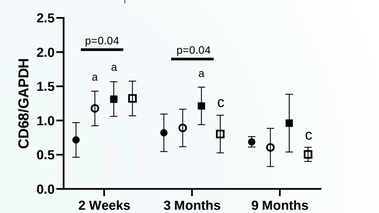


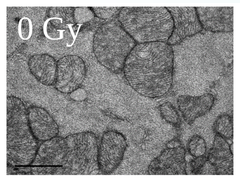
- Our previous radiation studies have demonstrated a correlation between fibrosis and mast cells.
- Mast cell tryptase was increased after ^{16}O exposure, suggestive of cardiac remodeling.

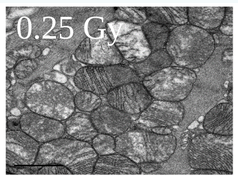


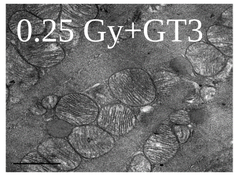
- Left ventricular markers of T-lymphocytes (CD2) and macrophages/monocytes (CD68) increased after exposure and these increases were mitigated by GT3.











- Cardiac mitochondria showed damaged cristae after ^{16}O exposure.
- GT3 is known to have protective effects on mitochondria, which was also seen in this study.

Conclusions

- Simulated space radiation induced mild changes in cardiac function, some indications of tissue remodeling, and markers of immune cells.
- GT3 was able to mitigate the effects of space radiation on cardiac function, collagen type III peptide content and immune cell markers when administered after exposure.
- GT3 could be considered as a safe radiation countermeasure for astronauts during or after their space missions.

Acknowledgements

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