

Vertebrates in Space

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Outline

- Fundamental questions
- Microgravity: changing the gravity vector
 - Early consequences
 - Dependencies of physiological responses
- Complexities:
 - Spaceflight environment
 - Microgravity experiment
 - Variables, species, controls
- Toward an integrated, molecular physiology
- Ground-based analog
- ISS: Concluding comments
 - (*useful references)

Fundamental questions*

- What are the organism's responses to microgravity at the tissue level?
- What are the molecular, cellular & physiological mechanisms that account for the observed responses?
- What is the gravity (G) threshold or G dose-dependence needed for normal tissue function?
- How does microgravity modify the organism's responses to other spaceflight stimuli?
- What are the implications of microgravity responses for human health and countermeasures, both in space and on earth?

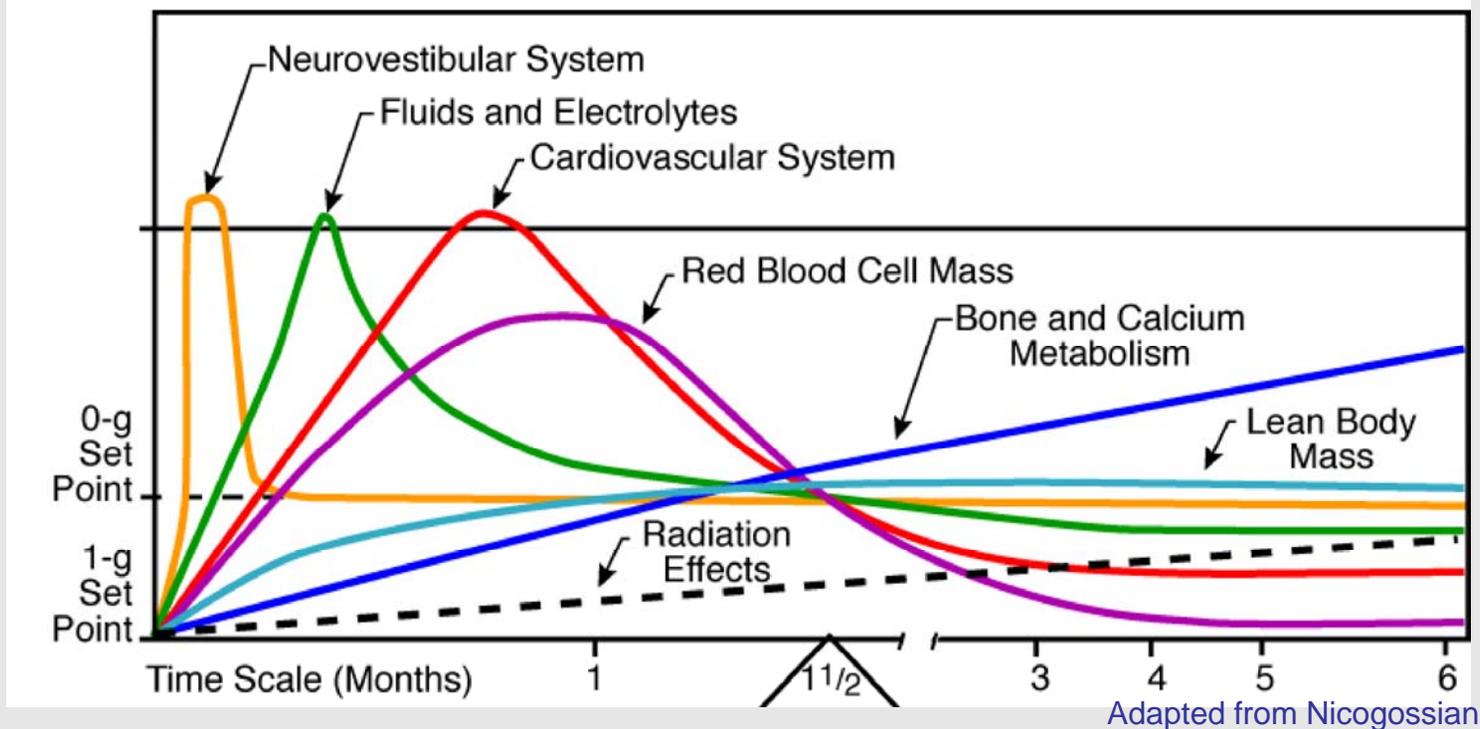
Changing the magnitude and direction of gravity vector: Early consequences

Upon entry into space/orbit:

- Re-distribution of body fluids *
 - Fluid shifts (headward in humans) lead to rapid, compensatory changes in circulatory system
- Weightlessness: reduced gravitational loading*
 - musculoskeletal system
 - all other tissues
- Vestibular disorientation*

Changing the gravity vector:

Later physiological responses are:
time-dependent
inter-related
structural



Complexities: Spaceflight environment

In space, some variables tend to be poorly controlled:

- Each with potential to exert profound physiological effects
- May complicate within and between experiment comparisons

- reduced gravity
- gravity transitions
- unique aspects of housing*
(e.g., 3D vs 2D cage space)
- other stressors
(e.g., noise)
- radiation*
(possible interactions)

Complexities: Microgravity experiments

1 - variables

- Differences potentially can arise due to:

- launch (transient acceleration, vibration)

- landing (transient acceleration, vibration)

 - e.g., muscle damage due to landing *

- timing of onset/treatment

- timing of sample recovery

 - gravity transition effects

- Many of these factors can be tested in control experiments;

 - necessitates robust, supportive ground-based research

Complexities: Microgravity experiments

2 - Species selection

- NASA has flown a variety of vertebrates; embryonic, juvenile and/or adults, e.g.
 - Fish
 - Frogs
 - Newts
 - Mice
 - Rats
 - Quail
 - Non-human primates
- **Rodents most frequent**
 - well known (dis)advantages of rats vs. mice
 - some factors less appreciated in past: influence of stress, age

Complexities: Microgravity experiments

3 - Controls

Careful consideration of potential controls

- Possible animal control groups:
 - Housing (flight hardware, standard)
 - Onboard centrifuge--1G *
- Time delayed recovery of controls
 - To mimic conditions flight recovery
- Other spaceflight experiments
 - e.g., control for stress: adverse effect of spaceflight on bone occurred despite adrenalectomy *
- Other ground control experiments
 - e.g., vibration/acceleration

Toward an integrated, molecular physiology

1- Spaceflight experiments

- Accomplished by:
 - Employing molecular and cell biology tools, together with physiology
 - e.g., via analysis of cell behavior and gene expression post-flight *
 - Tissue sharing
 - Design of past (and future) space flight experiments facilitates better understanding of integrated physiology.

Toward integrated, space physiology: Rodent spaceflight experiment: example #1

Multidisciplinary

Muscle

Riley DA, et al. *In-flight and postflight changes in skeletal muscles of SLS-1 and SLS-2 spaceflown rats.* J Appl Physiol 1996. 81(1):133-44.

Neuro

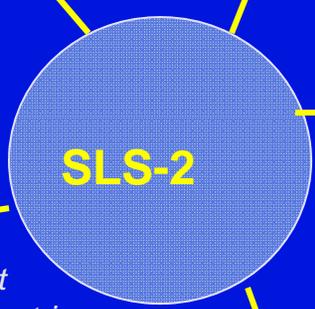
Fagette S, et al., *Central and peripheral noradrenergic responses to 14 days of spaceflight (SLS-2) or hindlimb suspension in rats.* Aviat Space Environ Med. 1996;67(5):458-62.

Bone

Evans, Glenda L, et al. *Spaceflight has compartment and gene-specific effects on mRNA levels for bone matrix proteins in rat femur.* J. Appl. Physiol. 84(6): 2132–2137, 1998

Durnova G, et al. *Histomorphometric study of tibia of rats exposed aboard American Spacelab Life Sciences 2 Shuttle Mission.* J Gravit Physiol. 1996;3(2):80-1.

SLS-2



Immune

Lesnyak A, et al. *Effect of SLS-2 spaceflight on immunologic parameters of rats.* J Appl Physiol. 1996 ;81(1):178-82.

Ichiki AT, et al. *Effects of spaceflight on rat peripheral blood leukocytes and bone marrow progenitor cells.* J Leukoc Biol. 1996 ;60(1):37-43.

Blood

Allebban Z, et al. *Effects of spaceflight on rat erythroid parameters.* J Appl Physiol. 1996 Jul;81(1):117-22.

Toward integrated, space physiology: Rodent spaceflight experiment: example #2

Focused
(in-flight dissection)

Protein Expression

d'Ascanio, P. *Fos and FRA Protein Expression in Rat Nucleus Paragigantocellularis Lateralis During Different Space Flight Conditions*, Brain Research Bulletin, vol. 59(1), Oct 2002, pp. 65-74.

Anatomy

J. Knierim, et al. *Three-dimensional spatial selectivity of hippocampal neurons during space flight*. Nature Neuroscience: Vol.3 No.3, March 2000.

Yamasaki, M. *Effects of Space Flight on the Histological Characteristics of the Aortic Depressor Nerve in the Adult Rat: Electron Microscopic Analysis*. Biol Sci Space, vol. 16(2).

Holstein GR, et al. *Anatomical observations of the rat cerebellar nodulus after 24 hr of spaceflight*. J Gravit Physiol. 1999 Jul;6(1):P47-50.

Gene Expression

Pompeiano, O. *Gene Expression in Rat Vestibular and Reticular Structures during and after Space Flight*. Neuroscience, vol. 114(1), 2002, pp. 135-155.

Neuromuscular

Deschenes MR, et al. *Recovery of neuromuscular junction morphology following 16 days of spaceflight*. Synapse. 2001 Dec 1;42(3):177-84.

Neurolab

Toward an integrated, molecular physiology- Ground based analogs e.g., rodent hindlimb unloading*



- Causes:
 - Cephalid fluid-shift
 - Selective unloading of hindquarters
- Enables extensive analyses of recovery, transitions, and countermeasures
- Model for bedrest, disuse, inactivity

In rats:

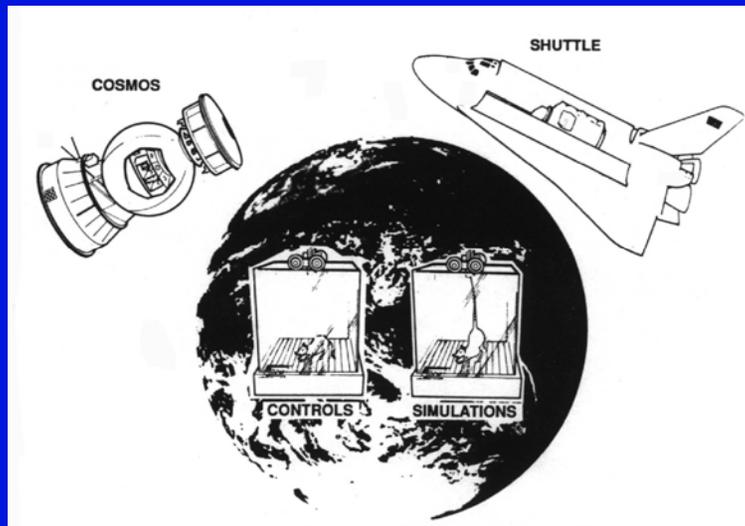
- Adverse musculoskeletal effects occur in unloaded hindquarters.
- Changes in cardiovascular, immune system, other.
- Endocrine changes: e.g., 1,25(OH)₂vitaminD₃, growth hormone/IGF
consistent with findings from spaceflight

In mice:

- Endocrine, organ and immune responses indicate influence of unloading and stress*
consistent with findings from spaceflight

ISS: Concluding comments

- Animal experiments are needed for understanding the mechanisms of responses to microgravity.
- Animal experiments already revealed effects & mechanisms of short term spaceflight with insight into possible countermeasures.
- It is still not known when, or even if, some adverse changes eventually plateau.
- ISS: unique opportunity to advance space biology and translational research to explore the long-term consequences of spaceflight.



***Select useful references**

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