Campaign: Impact of Long-Term Space Flight on Host Physiology and Health

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Extended Abstract

The impact of short-term (one-year or less) space flight on human physiological functions have been documented fairly well. Shuttle flight and International Space Station missions have allowed us to determine impact on physiological systems ranging from hematopoiesis, bone metabolism, muscle atrophy and eye function. However, we do not have a good understanding of the impact of long-time space flight on physiological systems when it constitutes a significant portion of the animal's life. Most experiments with rodents have been limited to periods of 40 days or less; with the longer flights coming most recently on the International Space Station. This manuscript proposes multiple campaigns to allow us to determine the impact of long-term space flight on host biology and physiology. Included in this investigation is significant experimentation on the developmental stages of host biology. These campaigns will be amenable to both low Earth orbit platforms, Gateway and even lunar missions.

Background

The quest to understand the impact of space on host biological function has received considerable attention over the last few decades. Both Russian (http://mgtairbekov.com/experimentsprograms/) and American (https://doi.org/10.1038/npjmgrav.2016.39; https://doi.org/10.1093/pcmedi/pbz022) space flights have focused on making sure we can survive in space. Indeed, humans can survive in space for long periods. The Russian cosmonaut Valery Polyakov was in space for 438 consecutive days aboard the Mir space station in the mid 1990s (https://www.space.com/11337-human-spaceflight-records-50th-anniversary.html). Concurrent with coping with long-term consequences of space habitation, we have had to develop counter measures to counteract bone and muscle degradation (https://doi.org/10.1038/s41526-017-0013-0). Unfortunately, there are some systems, like the eye, that are still poorly understood and still require the development of countermeasures (https://doi.org/10.1038/s41526-020-0097-9). Moreover, the development of *Drosophila* in space results in potentially problematic heart problems that can't be ignored for long-term space habitation and colonization (https://doi.org/10.1016/j.celrep.2020.108445) and neurological issues associated with balance may also be problematic (https://lsda.jsc.nasa.gov/refs/neurolab/sp-2003-535.pdf). Scientists have attempted to look at development of rats in space during the Neurolab campaign on STS-90 and the gross, late development of rats did not appear to be impacted (https://doi.org/10.1016/S0273-1177(03)90385-1). Nevertheless, many questions about the impact of long-term space flight remain unanswered.

To understand how protracted space flight affects mammalian physiology and function, animals will need to be housed for long durations in space. Although it appears that we (humans) can survive over a year in space, we know there are impacts. Moreover, we have little understanding of what long periods of space does to our biology. In particular, even one-year of space flight for a human with a life expectancy of 80 years is probably not a sufficient test of what can happen to physiological and biological systems. However, one year in space for an animal with a life expectancy of 2-3 years (*i.e.* a mouse) is a significant challenge. There are two critical questions that must be answered before we endeavor long-term space missions.

1. What happens when a mammal spends a significant (>50%) of their lifespan in space?

2. How is animal physiology and heath affected if extended times during critical developmental stages occur during space flight?

To address these questions we propose that rodents of various genetic make-ups (*e.g.* C57Bl/6 *vs*. Balb/c *vs*. C3H) (https://doi.org/10.1007/s00109-020-01953-4) must be housed in space for extended lengths of time to gain a better understanding of the issues of long-term space travel on physiological systems and biological function. Multiple mouse systems must be used because of their unique genetic make ups and susceptibilities to disease (https://www.jax.org/why-the-mouse/genetics).

We propose a multi-disciplinary campaign using a systems-wide approach to understand how long-duration space travel affects mammalian biology. This is campaign-level science because physiological system interactions necessitate that multiple systems be examined simultaneously. Systems such as central and peripheral nervous systems, digestive system, endocrine system, immune system, skeletomuscular system, cardiopulmonary system and behavior must be studied in parallel. These are campaign-level initiatives because teams will need to be assembled and the work must be coordinated to maximize the science output. Biomedical science objectives will have to have systems-wide perspective, and only a campaign-level initiative can begin to assemble the teams, equipment and funding to make a worthwhile impact. The cost-to-reward benefits by taking on this campaign-level initiative will help define the impact of space on individual systems but has the potential to determine space's impact on relationships between physiological systems. This will provide significant insight to protecting astronaut health and will have Earth-bound health insights, as well.

This campaign will necessitate the following needs be met:

1. The need for the development of rodent facilities for rodents and their long-term housing.

Place priority on developing equipment/facilities to better house rodents to assess their response to space. The development of user friendly facilities is necessary for husbandry but for potential animal manipulation. These facilities must accommodate neonates born in space or introduced into space at a relatively young age so that developing biological and physiolgical sytems can be studied in the context of space flight.

2. Real-time measures of rodent (other hosts) health and behavior

Real-time monitoring of rodents will be necessary to survey animal health and determine if their condition is worse because of space flight. Ideally, this monitoring would be done remotely. The continued development of this technology is necessary and expected, as outlined in the 2020 NASA Technology Taxonomy roadmap and NASA Space Biology Plan for Vertebrate Animal Biology. Ronca *et al*. (https://doi.org/10.1038/s41598-019-40789-y), noted novel behavioral changes in mice flown in Rodent Research 1 (RR1). Those rodents had behavioral changes and the RR1 mission demonstrated the benefits of monitoring animals *in situ* to observe changes in health and behavior.

3. Assessment of genetic mouse models in space

Many genetic rodent models, such as humanized, transgenic, and knockout (including CRISPR/CAS9) have been created. It is possible that some of these mice don't show a significant phenotype on Earth. However, the space environment may be a trigger to the stressed mice to express a phenotype. Such scenarios should motivate studies to reveal host biological systems needed for continued good health in space environments. In addition, the use of genetic over expression should complement this work to identify possible countermeasures.

4. Determine possible differential impact of space flight on sexes

Men and women display differences for many diseases (https://doi.org/10.1089/jwh.2014.4914; https://doi.org/10.1016/S0140-6736(20)31561-0). Women, for instance, show greater susceptibility to autoimmune disorders, which are leading causes of women's disabilities in western countries (https://doi.org/10.4415/ann_16_02_12). Animal models will be useful for these studies. For example, the apolipoprotein E-deficient (apo$E^{-/-}$) mouse, showing sex differences in atherosclerosis expression (https://doi.org/10.1186/1476-511X-10-211). Currently sex differences and the impact of space flight is poorly understood. Crew makeup of flights flown from the 1960's to 2013 found that female astronauts only made up 11% of the population (https://doi.org/10.1089/jwh.2014.4914). The prospect of future long-term space flight must address sex differences to optimize crew performance.

A typical campaign will include biologists that focus on central and peripheral nervous systems, digestive system, endocrine system, immune system, skeletomuscular system, cardiopulmonary system and behavior. Other scientists and experts can be added to the teams as needed (*e.g.* geneticists and hematologists). Central themes for each campaign will be identified before the assembly of the teams to optimize the expertise needed. Coordinated documentation of meta data and archiving must be a high priority. Veterinary support is also a necessity. The team will also need to agree on which platform(s) will optimize the experiment (*e.g.* low Earth orbit for microgravity *vs.* lunar for partial gravity). The precedent for space team science was set with experiments such as SLS-1 (https://doi.org/10.1016/0094-5765(88)90032-X), and SLS-2 (https://doi.org/10.1016/0094-5765(95)00129-8, https://doi.org/10.4271/881027), and Neurolab (https://books.google.com/books?id=xAc_AQAAMAAJ&dq=Neurolab+results&lr=&source=gbs_navlinks_s)

as well as Russian Bion collaborations (https://doi.org/10.1371/journal.pone.0104830). The scientific revelations of those previous campaigns suggest that the campaign approach is justified and will increase our understanding of the effects of long-term space flight on host physiology and health.

Summary

The impact of long-term space travel where the time frame is either at sensitive stages of development or reflects a significant percentage of the animal's life span is poorly understood. The next ten years of space biological and physiological research must address these issues. This science must be done with a systems integrated approach and must be done in a well coordinated fashion among biologists of various disciplines. The continued improvement in the archiving of protocols, metadata and system interactions will also have to be part of this campaign. The equipment and facilities needed, the expertise of the research teams and the cost justify this as campaign-level science.