The Link Between Spaceflight Anemia and Early-onset Neurodegeneration

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ABSTRACT

When astronauts first enter spaceflight, the changes in gravity and pressure at high altitudes results in neocytolysis and spaceflight anemia, releasing an abundance of iron into the bloodstream. Little is known about what the long-term effects of this phenomenon entail, and there is large concern within the scientific community that it may negatively impact cognitive function.

Iron is an important nutrient that can cross the blood-brain barrier into the cerebrospinal fluid, where it may be sequestered by developing microglia. Previous research on Earth found that iron overaccumulation in the brain is not only linked to Alzheimer's, but could also disrupt microglial function, leading to an overproduction of cytokines and reactive species that damage healthy neurons and induce progressively worsening neurodegeneration and cognitive decline. This is particularly concerning for astronauts in space, as spaceflight anemia combined with their iron-fortified diets could cause microglial overactivation, and lead to the development of early-onset Alzheimer's disease.

We are interested in investigating the link between abnormally high iron levels and the implications it has on CNS function and cognitive decline. Specifically, we are interested in discovering if the increased levels of iron in the bloodstream are significant enough to have an impact on cognitive function.

HYPOTHESIS

Research done on Earth using artificial cosmic radiation has suggested that microglial activation can be induced by radiation exposure levels similar to those aboard the ISS. In addition, another study found that increased iron levels in the brain were associated with increased levels of microglial activity.

Prolonged, high doses of cosmic radiation and the accumulation of iron in the brain could both be important factors in inducing early-onset neurodegeneration, as iron over-sequestration increases the rate at which microglia produce cytotoxins. From these findings, we hypothesize that the excess iron in the brain resulting from spaceflight anemia is directly associated with neurodegenerative disease and cognitive decline.

In our experiment, we expect to see increased levels of iron, cytotoxins, and ferritin, as well as ferritin and cytotoxic gene expression within the cerebrospinal fluid and microglia. If the increased levels of iron do cause excess iron to pass the blood-brain barrier, then there would be increased levels of ferritin to facilitate iron transport and microglial sequestration. We theorize that this increased uptake of iron by microglia causes an increase in cytotoxic gene expression, producing higher levels of cytotoxins.

MATERIALS

In this experiment, we use the miniPCR and the fluorescence viewer. These tools will allow us to generate and analyze data with the RT-qPCR method, which generates evidence of correlation between the iron abundance, microglial iron uptake, and increased cytotoxin production. The miniPCR will also allow researchers to instantly amplify and analyze DNA aboard the ISS, preventing accidental damage and reducing unnecessary costs in transporting data back to a laboratory on Earth for analysis. In addition, the miniPCR is less expensive and easier to use than a regular PCR machine, while maintaining similar levels of function and accuracy. This makes it ideal for our study which requires the analysis of a large variety of mRNA fragments.

Our experiment also incorporates the fluorescence viewer, which will function alongside a spectrophotometer to quantitatively assess the abundance of certain fragments of DNA. Because the fluorescence viewer and spectrophotometer are relatively small and simple to use, it eliminates the need for a complicated data analysis procedure. Most importantly, using the RT-qPCR method to directly analyze genetic activity allows us to directly answer our research question and support the results of the study with concrete and conclusive evidence.

PROCEDURE

Our experimental plan uses standard lab mice as human models. We propose using three groups of mice, one to be studied on Earth with no treatment as the control, one to be sent to the ISS with no treatment as the experimental-1 group, and one to be sent to the ISS with an iron-overloaded diet as the experimental-2 group. The control group and experimental-1 group will receive standard mouse feed (35mg iron daily intake), and the experimental-2 group will receive a supplemental diet of 2% carbonyl iron daily to test if the iron released by spaceflight anemia has a significant impact on microglial activation.

At zero, one, six, and twelve months, we will harvest cerebrospinal fluid from each of our subjects with RT-qPCR to analyze the levels of FTL and IL-2 gene expression (genes associated with ferritin and cytokine production respectively). To obtain quantifiable results, we tag FTL and IL-2 with fluorescent primers and fluoresce them under a spectrophotometer to view the levels of gene expression. Possible experimental outcomes include different levels of gene expression that vary directly with iron sequestration and cytokine production levels, which vary directly with microglial activity.

REQUIRED ENVIRONMENT

The unique conditions aboard the ISS, which include microgravity and increased levels of cosmic radiation, are crucial to our study because of their difficulty to replicate on Earth. Since astronauts experience pressure and gravity changes from liftoff and spaceflight, their bodies undergo homeostatic regulation to adapt to their new environments. In the case of our experiment, astronauts develop spaceflight anemia, which decreases their red blood cell count and increases their iron availability, which is the main focus of our study. The homeostatic processes of the human body in space cannot easily be simulated on Earth, which is why our experiment must be performed on the ISS.

This study will help improve our understanding of the link between iron, microglia, and neurodegenerative diseases, both in space and on Earth. The results of this study can be significant in developing treatments for Alzheimer's and Parkinson's disease, and in identifying specific, dietary-related, risk factors to prevent astronauts from developing early-onset neurodegeneration. The latter will be especially important in long-duration space missions; for example, one of the major limiting factors restricting our exploration of Mars is that we do not know how long-term exposure to microgravity and cosmic radiation impacts the human body.

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