VIEWPOINT

Microgravity and Cosmic Radiations During Space Exploration as a Window Into Neurodegeneration on Earth

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Astronauts involved in long-duration spaceflight missions are exposed to specific risk factors known to induce profound changes of brain structure and function whose potential long-lasting effects are still under investigation.[1] These changes range from sleep alterations, modifications of brain morphometry, vision impairment, mood shifts, and loss of appetite as well as cognitive deficits, including decrements in attention and executive functions.[2] Among the substantial list of stressors, the effects of microgravity and galactic cosmic radiations constitute the most relevant ones and are at the core of current and future NASA efforts to identify effective countermeasures. Interestingly, while reduced gravity force seems responsible for cephalad fluid shift that potentially affects protein clearance mechanisms, cosmic radiations seem to promote the accumulation of amyloid-β in mouse models, induce neuroinflammation, and further alter hippocampal-related cognition.[2] Considering available evidence, a pattern of spaceflight-induced accelerated brain aging seems to emerge in addition to established aging-like effects on cardiovascular and musculoskeletal systems (ie, carotid intima-media thickness increments, inflammatory response, bone loss, muscle atrophy, and DNA telomere modifications, as documented in the recent 1-year long NASA Twin Study[1]). While this raises important issues about astronauts' health, it can also constitute a window into the neurophysiopathology of neurodegenerative processes in humans, which could potentially benefit life on Earth.

The Effect of Microgravity

Microgravity determines a conspicuous fluid shift from the lower to upper body (approximately 2 L, mostly on the venous compartment) because of the loss of hydrostatic gradient pressure, normally attracting fluid toward lower limbs.[3] On the other hand, the effect of slightly elevated levels of carbon dioxide in the International Space Station is currently under investigation regarding the theoretical potential for arteriolar vasodilatation induction, similarly to what is typically observed after acute high-level carbon dioxide exposure on Earth.[3] The loss of hydrostatic gradient seems to cause an imbalance of intracranial pressure (ICP) diurnal variation, now considered the most likely mechanism behind spaceflight-associated neuro-ocular syndrome (SANS[3]). In particular, nonpathological partial elevation in ICP during long-term missions (comparable with the nocturnal increase of ICP on Earth) could be transmitted to the subarachnoid space enveloping the optic nerve, consequently causing a pattern characterized by, for example, optic disc edema, hyperopic shifts, globe flattening, cotton-wool spots, and choroidal folds that is experienced by 40% of astronauts after long-term spaceflight.[1] Data collected in the recently released NASA Twins study support this pathophysiological model, showing distension and increased pressure in the internal jugular veins as well as SANS signs,[1] even though many potential additional factors should be considered, such as the role of reduced central venous pressure.[3]

Interestingly, venous congestion could also impair cerebrospinal fluid (CSF) outflow, which under normal conditions drains into the dural sinuses via the arachnoid granulations. If the CSF outflow is altered, it is reasonable to postulate that protein clearance might be negatively affected, leading to an accumulation of waste products in the brain, such as amyloid-β and tau protein.[4] Moreover, the modification of brain structures experienced after a long-term space mission could also compress venous as well as lymphatic vessels responsible for CSF drainage. In this regard, Roberts and colleagues[5] have showed how the subarachnoid space at the vertex of the head and in posterior brain regions is reduced in healthy nonastronaut participants undergoing a spaceflight analog-based experiment (ie, head-down tilt), a phenomenon also partially observed in astronauts after long-duration missions. Such "brain shift" could reduce CSF drainage at the level of arachnoid granulation (ie, vertex) into the meningeal lymphatic vessels. This also aligns with a proposed theory stating that the alteration of the CSF circulatory system may represent a potential substrate of Alzheimer disease (AD) and normal-pressure hydrocephalus (NPH) depending on the prevalent impaired mechanism being CSF production or reabsorption, respectively.[4] Accordingly, the coexistence of AD and NPH has been repeatedly demonstrated, suggesting an association between the 2 disorders, even though the evidence is still limited. Interestingly, brain morphology alterations reported in astronauts closely resemble those of NPH (eg, ventriculomegaly, a narrowing of the vertex sulci, and a dilatation of the Sylvian fissures); however, they lack the classic clinical presentation (eg, gait apraxia and urinary incontinence). As recently suggested by Roberts and Petersen,[6] hydrocephalus associated with long-term spaceflight (HALS) is likely to represent a peculiar syndrome caused by microgravity in which brain maladaptive mechanisms are to some extent similar to those observed on Earth. Presumably there is no single agent factor responsible for HALS, but rather a multifactorial pathogenesis with structural and functional changes leading up to a synergistic effect. Investigating HALS and SANS syndromes can help elucidate the complex association between exposure to space-related stressors, CSF dynamics, fluid shift,

AD, and NPH, with possible insights for space exploration and clinical research on neurodegeneration.

Role of Cosmic Radiation

Within the same framework, cosmic radiation might also play a substantial role. Mice studies involving exposition to space-equivalent radiation (^{56}Fe) doses demonstrate an increase of amyloid-β and fibrillary proteins that is paralleled by impaired cognition and behavior.[2] Interestingly, the brain regions most sensitive to cosmic radiation in mice studies are the (1) hippocampus (associated with impairments in episodic and short-term memory as well as recognition and spatial learning) and (2) the prefrontal cortex, which is associated with the alteration of executive functions.[2] Microscopically, these regions exhibit immature spine and a reduction of dendritic complexity/density, which are positively associated with the grade of memory impairments and persist for up to 1 year after irradiation. These cellular modifications are similar to those presented by neurodegenerative diseases within the dementia spectrum, with epigenetic studies showing how modifying DNA methylation status can lead to the impairment of memory and learning. Evidence of DNA methylations was also reported in the aforementioned Nasa Twin study[1]; however, its association with cognitive deficits has not been tested yet. Moreover, alterations of sleep patterns and sleep quality, typically experienced by astronauts during long-duration missions, can increase the accumulation of waste proteins in the brain, considering that perivascular and nonperivascular protein clearance is prominent during sleep. Additionally, anxiety and depression symptoms have been found in irradiated rodents along with a cognitive flexibility deficit, closely resembling symptoms reported by astronauts during sustained exposure to isolated confined environments. However, microgravity seems to indirectly affect the hippocampus as well, inducing oxidative stress mediated by glucocorticoid receptors and decreasing the quantity of β-synuclein responsible for the prevention of α-synuclein aggregation (increased in microgravity studies[2]). Importantly, although microgravity and cosmic radiation are discussed separately in this article, their association with brain physiology is likely due to a complex synergistic effect. For instance, microgravity-induced fluid shift could affect the dynamics of CSF production (eg, at the level of the choroid plexus) as well as reabsorption (eg, from arachnoid granulations), therefore affecting protein clearance in the context of an already increased level of circulating proteins in the parenchyma due to exposure to cosmic radiations. This, as well as many other potential interactions, should be mapped and addressed as part of a comprehensive multidisciplinary model including neuroimaging, electrophysiology, biological, and clinical data.

Conclusions

All this evidence suggests the opportunity to investigate brain adaptation to long-term spaceflight as a model of aging, possibly informing novel diagnostic markers and countermeasures with relevance for space exploration and patients on Earth. At the same time, recent pathophysiological models of AD and other dementias could be leveraged to adapt countermeasures currently being tested in patients. For instance, gamma aminobutyric acid—ergic dysfunction and inhibitory interneurons' pathology are getting attention as a core element of Alzheimer pathophysiology, leading to cascade effects, including the deficit of high-frequency brain oscillatory activity, altered brain plasticity and excitation/inhibition balance, the accumulation of amyloid-β/tau proteins, and cognitive deficits. Novel noninvasive promising therapies are currently under investigation (eg, multisensory and transcranial electrical stimulation[7]) and could constitute a countermeasure to "accelerated aging" during spaceflight as well as on return to Earth.

As scientists and astronauts navigating the field of space-related aging research, we recognize the need for increasing integration between NASA efforts and academic research. Dedicated conferences and other opportunities for a guided exchange of knowledge could be promoted across federal and academic institutions (eg, the National Institute on Aging), possibly leading to access to facilities for high-complexity experiments (eg, irradiation chambers), novel analogs to mimic the association of microgravity with fluid shift and ICP in-vivo, and an overall simplification of data-sharing procedures. A synergistic effort between clinicians, scientists, and aerospace institutions is needed to ensure this unique opportunity for advancing science and benefitting patients and astronauts will not be missed.

ARTICLE INFORMATION

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