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The Blood-Brain Barrier in Space: Implications for Space Travelers and for Human Health on Earth

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Astronauts have flown to space for decades, but the effects of spaceflight on human health have not been fully clarified yet. Several pathologies have only been detected after it has become customary for astronauts to spend months rather than days in space and with the advance of inflight monitoring. Examples include the neuro-ocular spaceflight associated syndrome, changes to the brain's white matter, and, more recently, altered cerebral blood flow and related hypercoagulability. This review outlines spaceflight-induced brain disorders in astronauts and putative contributing factors. It next presents ongoing and upcoming studies of the BBB onboard space platforms. Finally, it describes how the space environment can be harnessed for improving drug-delivery across the BBB for humans both in space and on Earth.

Keywords: blood-brain barrier, spaceflight, space exploration, astronaut, weightlessness, microgravity, aviation, drug delivery

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1 INTRODUCTION

Space is considered to be the last frontier of human health and a contributor to medical innovation (Alwood et al., 2017; Cinelli and Russomano, 2021). Important environmental factors endured by space travelers include microgravity, exposure to space radiation, hostile or close environments, isolation, confinement, and distance from Earth (Patel et al., 2020). These conditions affect virtually every system in the human body, including the brain and the vasculature. Risk depends on the type and the duration of flight, and is expected to be considerably higher during missions beyond Low Earth Orbit (LEO) (Eyal and Derendorf, 2019; Stepanek et al., 2019). Two key features of the spaceflight-associated physiological changes are particularly relevant for medical research and development: accelerated aging and disease processes, and their reversibility (or lack thereof) upon return to Earth. At the molecular and cellular level, the microgravity of space can alter the physico-chemical properties of protein crystals, membranes and cells. Such alterations may be harnessed for better understanding of the structure of BBB receptors and therapeutic proteins, engineering of 3D constructs of the neurovascular unit, and designing new drug formulations (Amselem, 2019; Ryder et al., 2020).

Blood-brain interfaces (the BBB and the blood-cerebrospinal fluid barrier, BCSFB) maintain brain homeostasis by controlling the influx and efflux of compounds and cells from the brain. Within the neurovascular unit, microvascular endothelial cells form the major barrier between the circulation and the brain. The microvascular endothelial cells of the brain are non-fenestrated and are sealed together with tight-junction proteins. Uptake transporters and membrane receptors enable the cerebral uptake of essential compounds and medications whereas efflux transporters protect the brain against potentially noxious compounds. Enveloping pericytes and astrocytic endfeet aid in

maintaining the BBB integrity and function. Neuronal input and demand further interact with those cells and regulate the cerebral capillary network (Eyal et al., 2009; Han et al., 2017; Lochhead et al., 2020).

Due to the unique features of the BBB, drug delivery for the treatment of neurological diseases and brain disorders remains a major challenge. The BBB prevents the brain uptake of most drugs, with the exception of small hydrophilic compounds with a mass lower than 150 Da and highly hydrophobic compounds with a mass lower than 400–600 Da that can cross the BBB by passive diffusion (Santaguida et al., 2006; Cecchelli et al., 2007; Morofuji and Nakagawa, 2020). Hence, drug treatment of neurological diseases such as Parkinson's and Alzheimer's diseases, or their delivery to cerebral sanctuaries of tumor cells and viruses, is challenging. Accordingly, finding new approaches for drug delivery across the BBB is crucial, particularly for macromolecules such as monoclonal antibodies (mAb) (Santaguida et al., 2006; Banks, 2016; McInerney et al., 2017; Han, 2021; Omidi et al., 2021; Parakh et al., 2021; Terstappen et al., 2021; Pan and Nicolazzo, 2022). Current approaches are aimed at increasing paracellular and transcellular BBB permeability, e.g., by opening of tight junctions, enhancing transcytosis, and inhibition of active efflux (Han, 2021). In this context, the spaceflight environment can be disruptive, offering yet unexplored opportunities to improve drug delivery to the brain.

2 EFFECTS OF SPACEFLIGHT ON THE BRAIN

Spaceflights, beginning with the short-duration Apollo era missions, were associated with decrements in operational capabilities, including altered driving performance. Changes were recorded across neurological domains, including cognition, sensation, movement, and coordination (Roy-O'Reilly et al., 2021). More recently, the NASA Twins Study demonstrated significantly reduced cognitive performance after 340 days of spaceflight as compared to preflight values (Garrett-Bakelman et al., 2019). The reports on reduced performance after long space missions have been supported by findings from neuroimaging studies, which provided evidence for alterations in the structure and positioning of the brain and in its ventricles (Roy-O'Reilly et al., 2021). Changes were observed in the CSF volume, along with ventricular expansion and upward shifts of the brain (Roberts et al., 2017; Van Ombergen et al., 2019; Jillings et al., 2020). For instance, one magnetic resonance imaging (MRI) study in 11 cosmonauts whose average mission duration was 169 days identified mean increases of 13.3 and 10.4% in the volumes of the lateral and the third ventricles, respectively (Van Ombergen et al., 2019). Cerebral fluid accumulation might be involved in the etiology of cerebral disorders in space. For example, locally elevated CSF sheath pressures in the orbital subarachnoid space have been linked to the ocular changes that occur during prolonged spaceflight, known as spaceflight-associated neuro-ocular syndrome (SANS) (Lee et al., 2017). Other findings include decreases in frontal and temporal gray matter volumes and changes in white matter volume (Koppelmans et al., 2016; Roberts et al., 2017; Van Ombergen et al., 2018; Van Ombergen et al., 2019; Jillings et al., 2020). Periventricular white matter hyperintensities (WMH), observed in astronauts after prolonged spaceflight (Alperin et al., 2017), have been associated with declines in cognitive and motor performance in healthy aging (Vernooij et al., 2009; Seidler et al., 2010). The rate of spaceflight-associated white matter changes was estimated at 1.5–2.5% per year, approximately 2-fold faster than that in a large subject sample with a mean age of 50 years (Lee et al., 2019). However, in astronauts these changes were limited to regions near the ventricles and partially reversed by 1 month after landing (Alperin et al., 2017). The urgent need in better understanding of the physiology of the brain barriers in space is arguably best demonstrated by recent event of blood clot in the internal jugular vein of an astronaut in space (Auñón-Chancellor et al., 2020) along with jugular venous blood flow stasis in additional astronauts (Marshall-Goebel et al., 2019). The next sections will describe the effects of individual factors encountered in spaceflight on the BBB, followed by presenting the current knowledge obtained from real spaceflights.

3 RADIATION AND THE BLOOD-BRAIN BARRIER

The vasculature is particularly susceptible to radiation (Chancellor et al., 2014), and irradiation of the brain has long been shown to cause damage to the neurovascular unit. For instance, in patients with supratentorial glioblastoma radiation enhanced the accumulation of a gadolinium (Gd)-based contrast agent in the brain parenchyma, likely by damaging the BBB (Lim et al., 2018). In mice, irradiation with doses of 5–200 Gy decreased the endothelial cell number by up to 15% compared with the pre-treatment values (Ljubimova et al., 1991). In rats, gamma radiation (60 Gy) caused leakage of horse-radish peroxidase, with severe loss of the capillary network (Rubin et al., 1994). A lower dose (4.5 Gy) increased the extravasation of [^{3}H]alpha-aminoisobutyric acid and [^{14}C]sucrose (Diserbo et al., 2002). Treating mice with an anti-tumor necrosis factor (TNF) monoclonal antibody was associated with attenuated radiation-induced BBB dysfunction, astrocyte activation, and leukocyte adhesion suggesting a role for TNF in these processes (Wilson et al., 2009). The exposure in those studies overestimate the radiation dose of most space missions. For instance, Mercury and Gemini crews were exposed over their missions to a total dose in the range of 0.05–2.31 mGy (except for Gemini X where the total dose was 6.18–7.79 mGy), Apollo XIV astronauts received ~11 mGy, and Mir 01–23 cosmonauts were exposed to up to 93 mGy (Maalouf et al., 2011). The predicted average galactic cosmic rays (GCR) absorbed dose rate during a mission to Mars is 0.45 mGy/day (Simonsen and Zeitlin, 2017). A similar phenomenon on missions outside of LEO might yield dose rates of up to 100 mGy/h and 500 mGy/h inside a space vehicle and during an extravehicular activity, respectively (Chancellor et al., 2014).

Radiation leads to cellular damage by both direct and indirect pathways. Direct pathways involve ionization of DNA, RNA, proteins and lipids. Indirect damage results from generation of reactive oxygen species (Fauquette et al., 2012; Chancellor et al., 2021). Radiation damage can lead to necrosis, apoptosis, autophagy, or senescence (Allen and Limoli, 2022). Specifically in brain capillary endothelial cells, radiation resulted in reduced expression of the tight junctional protein zonula occludens (ZO)-1 (Fauquette et al., 2012), formation of actin stress fibers (Fauquette et al., 2012), and increased lipid peroxidation, in association with glutathione depletion (Mertsch et al., 2001). In addition, a post-mortem analysis of normal tissue from patients treated with radiation therapy for glioblastoma demonstrated depletion of pericytes in necrotic tissue even in the normal brain, despite the absence of morphological changes to the vasculature (Lee et al., 2018). In mice, heavy-ion irradiation of the brain activated microglia and induced inflammation in the hippocampus (Encinas et al., 2008) and the dentate subgranular zone (Rola et al., 2005), although the involvement of the BBB in the inflammatory processes has not been reported.

4 HYPERCAPNIA AND THE BLOOD-BRAIN BARRIER

The mean levels of carbon dioxide on the International Space Station (ISS) can be approximately ten-fold than those in Earth's atmosphere (3.4 mmHg vs 0.3 mm Hg at standard pressure). Hypercapnia elevates cerebral blood flow and intracranial pressure, with increased risk of headache for every 1 mmHg increase in carbon dioxide levels (Law et al., 2014). More than 60 years ago, exposure of rabbits to 10% carbon dioxide in oxygen has been shown to cause vascular damage and increased the cerebral permeability of trypan blue (Clemedson et al., 1956). Later studies demonstrated hypercapnia-induced increases in the permeability of the BBB to other molecules, including lactate (Knudsen et al., 1991) and albumin (Cutler and Barlow, 1966; Hochwald et al., 1973). More recently, studies in rodents demonstrated that hypercapnia exacerbates hypoxemia-induced increases in BBB permeability (Liu et al., 2020) and reduces the expression of the tight junctional proteins zonula occludens (ZO)-1, occludin, and claudin-5 (Ding et al., 2020).

5 MICROGRAVITY AND THE BLOOD-BRAIN BARRIER

While there is a vast literature on spaceflight-induced alterations in endothelial cells of non-cerebral origin, much less in know about endothelial cells that consist the BBB. Many *in vitro* studies applied simulated microgravity to model the physiological changes that occur in space, although there is a gap between the levels of gravity obtained during simulation and the microgravity of space (10^{-2}–10^{-3} g for ground simulators and parabolic flights, versus 10^{-5}–10^{-6} onboard the ISS). Accordingly, these studies usually mimic many, but not all the physiological changes that occur in space (Amselem, 2019). Briefly, true and simulated weightlessness conditions caused dysregulation of motility and adhesion to substrates of endothelial cells which were isolated from peripheral blood vessels, e.g., the aorta and umbilical veins (Infanger et al., 2006; Grimm et al., 2009). Other changes involved the cytoskeleton, extracellular matrix, mitochondrial distribution, angiogenic response, apoptosis, cell growth, and cell cycle regulation (da Silveira et al., 2020; Dittrich et al., 2018; Maier et al., 2015; Morbidelli et al., 2005; Barravecchia et al., 2021; Crawford-Young, 2006; Grenon et al., 2013; Janmaleki et al., 2016; Kapitonova et al., 2013; Kapitonova et al., 2012; Wehland et al., 2013). In human umbilical vein endothelial cells (HUVEC), microgravity increased the permeability to fluorescein isothiocyanate (FITC)-tagged dextran (Shi et al., 2022) and promoted activation of inflammatory reactions with a shift towards senescence (Versari et al., 2013).

A modeling analysis which was published in 2007 predicted that higher steady-state intracranial pressure, together with reduced blood colloid osmotic pressure, would reduce BBB integrity (Lakin et al., 2007). Studies which tested this hypothesis were published only a decade later. Bellone et al. evaluated cerebral effects of simulated gravity (by tail suspension), chronic exposure to low-dose gamma radiation (a total dose of 0.04 Gy), or a combination of both (Bellone et al., 2016). After 3 weeks of simulated microgravity, but not gamma radiation, mice displayed increased exploratory and risk-taking behavior as compared to controls without differences in the outcomes of cognitive tests. The combination of simulated microgravity and radiation, but not each factor alone, was associated with a significant change in aquaporin-4 (AQP4), a water channel protein concentrated at perivascular astrocyte membranes. AQP4 levels, which are elevated when the BBB is compromised, are critically involved in the formation and dissolution of cerebral edema (Amiry-Moghaddam et al., 2003; Frydenlund et al., 2006), suggesting a role for BBB dysfunction in the observed behavioral changes. In another rat study, 21 days of tail suspension resulted in inflammatory cellular infiltration and nuclear pyknosis in the cortex (Yan et al., 2021). Transmission electron microscopy demonstrated a widened intercellular space of endothelial cells, swollen pericytes, and unclear mitochondria cristae. Expression of the tight junction proteins claudin-5, VE-cadherin, and β-catenin decreased by half or more, without a change in occludin and ZO-1 expression. A proteomic analysis discovered 554 differentially expressed proteins, which were mainly enriched in those regulating the cell-cell junction and cell-extracellular matrix biological pathways. Simulated microgravity additionally induced apoptosis and oxidative stress injury, as well as changes in actin cytoskeleton, which is important for cell adhesion. Compared to the control group, the content of Evans blue and Texas red-dextran in the brain was significantly increased, by 31% and 37.2%, respectively, indicating higher BBB permeability. The study also demonstrated that the Ras-related C3 botulinum toxin substrate 1 (Rac1)/Wiskott-Aldrich syndrome protein family verprolin-homologous protein 2 (Wave2)/actin-related protein 3 (Arp3) signaling pathway could be an important contributor to the observed BBB disruption under simulated microgravity.

Taken together, these studies support disorders of cerebral small vessels as one mechanism that could explain the above-mentioned WMH observed in astronauts. On Earth, dynamic contrast-enhanced (DCE) MRI study in 201 patients found that BBB leakage and interstitial fluid volume were higher in WMH than normal-appearing white matter, and that BBB leakage in WMH predicted declining cognition at 1 year (Wardlaw et al., 2017). In another DCE–MRI study, the leakage volume of the WMH was significantly larger in patients with cerebral small vessel disease compared with controls. The authors suggested that in those patients, subtle BBB leakage and extravasation of blood components may cause brain tissue damage and exacerbate local vascular changes (Zhang et al., 2017). More recently, BBB leakage at baseline in patients with cerebral small vessel disease was associated with a change in parenchymal diffusivity (a quantitative marker of microstructural tissue condition) in proximity of the WMH. That is, BBB impairment might play an early role in subsequent white matter degeneration (Kerkhofs et al., 2021).

In contrast to microgravity, the hypergravity experienced by space travelers is transient (during launch and, to a greater extent, during return to Earth). In mice, centrifugation at 2 g for 1 or 50 days, but not short exposure to hypergravity (5 g, as during landing) resulted in immunoglobulin G extravasation into the hippocampal parenchyma. These findings imply that the duration of hypergravity might be more important than its intensity. The authors suggested that centrifugation may serve as means for opening the BBB, although this is less likely to occur in the clinical setting (Dubayle et al., 2020).

A ground-based spaceflight model is parabolic flight, which yields alternating brief periods of microgravity as described above and hypergravity (1.8 g). In volunteers who participated in such a flight, blood flow in the vertebral artery increased during gravitational transitions from micro-to hypergravity, along with reduction in nitric oxide (indicating elevated free radicals) and increased glio-vascular glial fibrillary acidic protein (GFAP) and S100B. The latter is a 10 kDa protein expressed in glia and Schwann cells whose plasma levels may be elevated after trauma without brain injury (Hier et al., 2021). No change was observed in biomarkers of neuronal-axonal damage (neuron-specific enolase, neurofilament light-chain -NFL, ubiquitin carboxy-terminal hydrolase L1 and tau). These findings provided a first indication for the presence of cerebral markers in systemic circulation as an outcome of gravitational transitions, indicating minor BBB damage. The suggested etiology was hyperperfusion, together with oxidative stress (Bailey et al., 2020).

Silvani et al. (2021) developed an innovative hybrid *in vitro* vascularized glioblastoma-on-a-chip model. Under simulated microgravity conditions, the system demonstrated a significant cell morphological and mechanotransduction response, representing a tool for investigating cancer mechanobiology and the blood-tumor barrier.

6 EFFECTS OF SPACEFLIGHT ON THE BLOOD-BRAIN BARRIER

Only one published study evaluated spaceflight-associated BBB changes in a preclinical model in real microgravity (Mao et al., 2020). In that study, 35 days of spaceflight increased the expression of hippocampal AQP4 in the mouse brain, supporting the above-mentioned combined effect of microgravity and radiation in mice (Bellone et al., 2016). Other changes included increased expression of platelet endothelial cell adhesion molecule-1 (PECAM-1) and decreased ZO-1 expression, indicating a disturbance of BBB integrity. The proposed contributors to these changes were chronic mild inflammation and oxidative damage.

A pilot study tracked the concentrations in plasma of brain-specific proteins before and after spaceflight. The study was conducted in 5 male cosmonauts (mean age, 49.2 years) who spent almost a year in space. Blood samples were collected 20 days before launch and post-flight (1 day, 1 week, and 21–25 days after landing). The samples were analyzed by a single-molecule array immunoassay for five biomarkers of brain damage: NFL, GFAP, total tau, and two amyloid-beta proteins. Plasma levels of three of the biomarkers—NFL, GFAP and the amyloid beta protein Aß40—were significantly higher after the cosmonauts returned from the ISS, partially overlapping with the results obtained following a parabolic flight (Bailey et al., 2020). The timing of peak values varied across individuals, but the trends of elevated biomarkers were consistent across the five participants. High levels of these biomarkers have been associated with potential axonal disintegration process (NFL) and astrocytic activation (GFAP), suggesting that different components of the brain parenchyma are affected by microgravity (zu Eulenburg et al., 2021). However, the changes in brain function could not be distinguished from BBB disruption during spaceflight or landing. It is hoped the future investigations will clarify the cause for the elevated brain markers in plasma.

The last mission to the ISS investigating the behavior of human BBB in space so far was launched in April 2022 (AXIOM-1), as a part of Rakia mission (Ramon Foundation and Israel Space Agency). Among the experiments performed by Israel's second space traveler, Eytan Stibbe, was a study led by Dr. Itzik Cooper which analyzes the effects of microgravity on vascular function in the brain (**Table 1**).

Krishnamurthy and colleagues suggested that altered activity of transporters at the BCSFB with subsequent increase in osmotic load of the cerebrospinal fluid may contribute to the spaceflight-associated hydrocephalus (Krishnamurthy et al., 2021). However, given the absence of information on transporter activity at blood-brain barriers in space, this has yet to be investigated. Data on these transporters are urgently required, because transport across brain barriers not only modifies osmotic load, but also controls the distribution of essential compounds, drugs and other xenobiotics between blood, brain, and the CSF. For instance, downregulation of BBB uptake carriers for glucose and amino acids may deprive the brain of these compounds. On the other hand, reduced functionality of the efflux transporters P-glycoprotein (P-gp) and the breast cancer resistance protein (BCRP) at the BBB can enhance the cerebral distribution of substrate drugs, thus increasing their therapeutic effects, CNS toxicity, or both (Lee et al., 2001; Eyal et al., 2009; Nicolazzo and Katneni, 2009; Han et al., 2017). Examples of P-gp substrate medications which are available onboard the ISS include non-sedating antihistamines, which might become sedative in the

TABLE 1 | Blood-brain barrier-associated experiments conducted onboard the International Space Station.

Experiment	PI	Launch/Start date	Landing/End date	References
Rodent Research-9 (RR-9), including three Space Biology investigations, among which effects of long-duration spaceflight on cerebral vascular function and structure. SpaceX's 12th commercial resupply services (CRS-12) mission.	Delp, Michael; Mao, Xiao Wen; Willey, Jeffrey S. (United States)	14 August 2017	17 September 2017	Mao et al. (2020)
Organs-on-Chips as a Platform for Studying Effects of Microgravity on Human Physiology: Blood-Brain Barrier-Chip in Health and Disease (SpaceX CRS-17 mission)	Hinojosa, Christopher Emulate, Inc. (United States)	May 4, 2019	June 3, 2019	(Keeter, (2018); Giulianotti and Low, (2019); Low and Giulianotti, (2019); NASA, (2022))
The effects of microgravity on the blood-brain barrier (SpaceX CRS-24 mission)	Hinojosa, Christopher Emulate, Inc. (United States)	December 21, 2021	January 24, 2022	ISS National Laboratory, (2021) Mission completed. Results not published yet
Human BBB in space	Cooper, Itzik	April 8, 2022	April 25, 2022	Eng.rakiamission, (2021)
The effect of space flight and exposure to microgravity on BBB as a potential platform for treating Alzheimer's Disease. Axiom Space's Ax-1 mission first private astronaut mission to the space station	Sheba Medical Center, Tel Aviv			Mission completed. Results not published yet

absence of effective P-gp-mediated efflux, and calcium channel blockers (Eyal and Derendorf, 2019; Eyal, 2020).

7 SPACEFLIGHT AND DRUG DELIVERY ACROSS THE BLOOD-BRAIN BARRIER

Because spaceflight accelerates aging and tissue degeneration, treatments for preventing microgravity-induced pathophysiological changes have been adapted to diminish age-dependent diseases. One example is the development of the drug denosumab, aimed to prevent loss of bone mass, whose development gained from findings in rodents flown onboard the ISS (Amselem, 2019). Similarly, the space conditions may potentially unveil novel BBB pathways which may be targeted by drug delivery platforms. A study by the pharmaceutical company Emulate conducted on the ISS using an Organ-on-Chip approach (PI: Dr. Chris Hinojosa) analyzed the effect of space-related stressors on the BBB. The brain-chip consisted of neurons and vascular endothelial cells in a micro-engineered environment (Keeter, 2018) (**Table 1**). The results are hoped to provide insight into the relationship between inflammation and brain function, as well as the effectiveness of anti-inflammatory drugs in maintaining BBB integrity, for a better understanding of neurodegenerative diseases. Emulate also participated in a more recent SpaceX CRS-24 mission to examine the effects of microgravity on the BBB (**Table 1**).

Three-dimensional cell cultures in microgravity yield improved 3D structures and allow for a more precise appreciation of the role the biophysical constraints play in shaping cell phenotypes and functions (Amselem, 2019). Therefore, understanding microgravity effects can help improve tissue-engineering techniques on Earth. For instance, under simulated weightlessness conditions (but not at 1 g), endothelial EA.hy926 cells formed tube-like structures that resemble vascular intimas, even without scaffolds (Infanger et al., 2006; Grimm et al., 2009). Similarly, the lack of convection and sedimentation in space improved the quality of protein crystals (Giulianotti and Low, 2019), allowing better understanding of the 3D structure of BBB-traversing mAbs (or other proteins) and mAb-receptor interactions (e.g., mAb interactions with the transferrin receptor) (Amselem, 2019; Giulianotti and Low, 2019; Mullard, 2021). This could be utilized to improve drug delivery across the BBB. The use of spaceflight for developing nanofornulations has been recently reviewed and is beyond the scope of this manuscript (Grover et al., 2020).

8 LIMITATIONS OF CURRENT STUDIES AND FUTURE OPPORTUNITIES

A limitation inherent to most spaceflight studies is the small number of patients or samples. On the other hand, ground-based simulations do not capture all aspects of the stressor encountered in space. One example is the above-mentioned tail-suspension test which maintains the pressure of visceral organs on vasculature along with several other dissimilarities to the space environment. A major limitation of many radiation studies is the use of mono-energetic radiation sources, particularly gamma-exposure, which are dissimilar to radiation exposures for astronaut crews. In addition, all the above mentioned spaceflight studies were conducted in LEO. Thus, it is difficult to estimate how and to what extent space radiation would affect human tissues in deep space, beyond the protective shield of the Van Allen radiation belts (Chancellor et al., 2018; Chancellor et al., 2021). For instance, if intense space radiation increases the penetration of blood-borne proteins into the brain, the results may be seizures. Current and future research platforms are being further developed to improve researcher accessibility to space thus

overcoming the limitations associated with ground simulations. These include privately-owned space stations, satellites carrying remote-controlled laboratories (e.g., SpacePharma's DIDO satellites) and reusable uncrewed mini shuttles, such as the European Space Agency's Space RIDER and Sierra Nevada Corporation's Dream Chaser.

9 DISCUSSION

Spaceflight-induced BBB disruption may be associated with the penetration of harmful compounds into the brain and, consequently, potential brain damage. Although the same situation might enhance cerebral drug distribution in space travelers, enhancing both therapeutic and adverse cerebral drug effects, this assumption has yet to be tested. Clearly, any attempt to improve (or avoid) drug delivery across the BBB during spaceflight should consider other physiological changes that may affect systemic pharmacokinetics and pharmacodynamics (Kast et al., 2017; Eyal and Derendorf, 2019; Eyal, 2020; Dello Russo et al., 2022). At the same time, spaceflight offers new opportunities for drug discovery and development. A major benefit of the space environment is finding new biological pathways and drug targets, given that endothelial cells are particularly sensitive to the lack of gravity and radiation.

By definition, treating diseases in astronauts in space implies repurposing, because it cannot be assumed that disease processes are identical on Earth and in space. The need to repurpose drugs for space applications may stimulate research that would yield benefits for patients with brain diseases on Earth. Another advantage is production of 3D tissue constructs of higher quality than under 1 g conditions. Such constructs of endothelial cells could be used for both research and repairment of impaired BBB in patients with cerebrovascular diseases. Moreover, protein crystallization in microgravity can help improve the design of novel antibody-based therapies which target the brain. Hence, the benefits of pharmaceutical research under spaceflight conditions extend well beyond treating astronauts in space; insights gained from such studies can help improve the pharmaceutical care of humans on Earth.

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