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The effects of microgravity on cellular elements of the central nervous system - astrocytes, microglia, neurons, oligodendrocytes, and oligodendrocyte precursor cells

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Abstract

The microgravity of space has a number of detrimental effects on the central nervous system of astronauts and cosmonauts. This includes the development of increased intracranial pressure and cerebrospinal fluid volume, thickening of the meninges, attrition of gray matter and the number of neuronal synapses, aberrant astrocyte structure and function, changes in the morphology, distribution and proinflammatory activity of microglia, and detrimental effects on the ontogeny and functioning of oligodendrocytes and their precursor cells.

In this article, I review what is known about the ontogeny, physiology and anatomy of astrocytes, microglia, neurons, oligodendrocytes, and oligodendrocyte precursor cells and detail the effects of microgravity and/or simulated microgravity on these key cellular elements of the central nervous system.

Keywords: Microgravity; Central Nervous System; Astronauts; Cosmonauts; Spaceflight

1. Introduction

All terrestrial forms of life have had millions of years to adapt to Earth's gravity (9.8 m/sec^2). Central nervous systems (CNS) constructed of astrocytes, microglia, neurons, oligodendrocytes and oligodendrocyte precursor cells are fully adapted to this gravity field. But man's recent venture into space, where the force of gravity is one millionth of that on Earth, has thrown nature a curve ball, in effect rejecting these adaptations and replacing them with a new set of rules.

The microgravity of space has a number of detrimental effects on the CNS of astronauts and cosmonauts. This includes the development of increased intracranial pressure and cerebrospinal fluid volume, thickening of the meninges (particularly the dura matter), attrition of gray and white matter and the number of neuronal synapses, and aberrant functioning of astrocytes, microglia, neurons, and oligodendrocytes [1-6].

In this review, I discuss the effects of microgravity and simulated microgravity on the main cellular constituents of the central nervous system - astrocytes, microglia, neurons, oligodendrocytes and oligodendrocyte precursor cells.

2. Materials and Methods

This narrative review is on the effect of microgravity on the central nervous system. The research strategy included the following: 1. defining the key topics; 2. identifying key words or synonyms that represent each of the key topics; 3. an online PubMed and Google Search of key topics and key words; and 4. a refinement of the search based on initial findings.

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Data restrictions included articles with identical samples and identical outcomes, identical samples with different outcomes, increased samples and identical outcomes, and decreased samples with identical outcomes. Key topics included astrocytes, astrocytes and microgravity, brain, brain and microgravity, glial cells, glial and microgravity, microglial cells, microglial cells and microgravity, neurons, neurons and microgravity, oligodendrocytes, oligodendrocytes and microgravity, and oligodendrocyte precursor cells, and oligodendrocyte precursor cells and microgravity. Keywords include microgravity; central nervous system; astrocytes; microglia; neurons; oligodendrocytes; oligodendrocyte precursor cells; astronauts; cosmonauts; spaceflight.

3. Results

3.1. Astrocytes

Astrocytes comprise the majority of cells in the mammalian brain. They are involved in a wide range of functions, including the regulation of blood flow, ion balance, synaptic maturation, and the formation and maintenance of the blood-brain barrier. Additionally, they play an important role in the response to injury and inflammation [7]

During embryonic development astrocytes are derived from ventricular zone radial glial cells in a complex and tightly regulated process that involves the interplay of multiple transcription factors and signaling pathways. This includes transcription factors sex determining region Y box 9 (Sox 9), oligodendrocyte 2 (Olig2), and NK2 homobox 2.2 (Nkx2.2), which are required for the generation of astrocytes in the spinal cord, as well as transcription factors Forkhead box protein J1 (FoxJ1) and glutamine asparate transporter (Glast) which are involved in the differentiation of astrocytes in the brain. Additionally, the signaling pathways of neurogenic locus notch homolog protein 1 (Notch1) and brain morphogenic proteins (BMPs) have been shown to play crucial roles in regulating astrocyte specification and differentiation. Transcription factors inhibitor of DNA binding 4 (Id4) and platelet-derived growth factor receptor alpha (Pdgfra) are selectively expressed in subpopulations of astrocytes in the brain and spinal cord, suggesting that these cells may have specialized roles in the CNS [7-9].

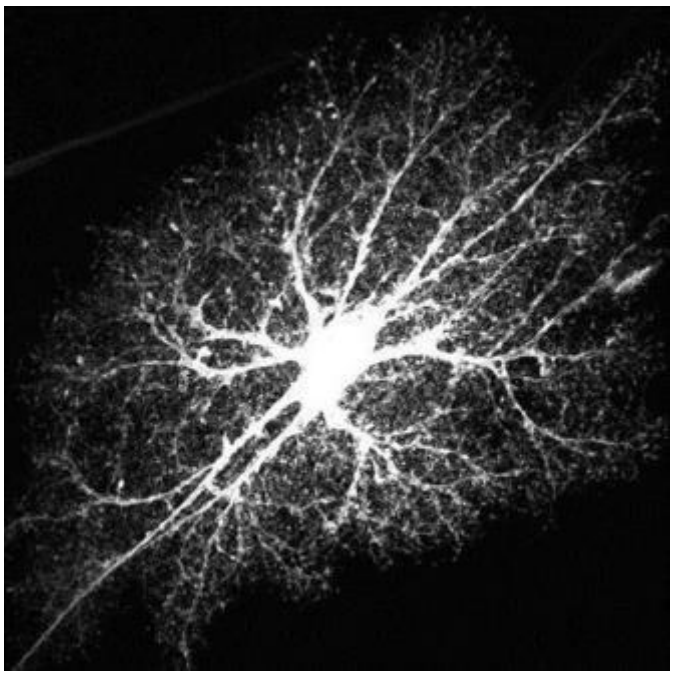

Figure 1 A microscopic view of a rodent astrocyte. A single rodent astrocyte can cover a spatial domain that ranges between 20,000 and 80,000 μm^3, wrap multiple neuronal somata, associate with 300-600 neuronal dendrites, and contact ~100,000 individual synapses. Image attributed to Eric A. Bushong, Maryann E. Martone, Mark H. Ellisman. PMID 15036382. Link CCDB 1063.

Astrocytes generate a dense network of delicate processes that terminate on neuronal synapses. A single rodent astrocyte can cover a spatial domain that ranges between 20,000 and 80,000 μm^3, wrap multiple neuronal somata, associate with 300-600 neuronal dendrites, and contact ~100,000 individual synapses. In humans, a single astrocyte can occupy a volume that is 30 times the volume seen in rodents while associating with ~ 2,000,000 synapses. They

display an array of neurotransmitter receptors and transporters by which they sense neuronal activity and direct morphological change [7-9] (Fig. 1).

3.2. Astrocytes and Microgravity

Microgravity has been shown to have a number of adverse effects on astrocytes. This includes alterations in their cytoskeletal organization and in their expression of genes involved in differentiation and in the regulation of ion channels, neurotransmitter transporters, and extracellular matrix proteins. Additionally, simulated microgravity has been shown to alter astrocyte-neuron communication, which has implications for synaptic plasticity and cognitive functioning [10-12].

3.3. Microglia

Microglia are the resident immune cells of the CNS. They play a critical role in immune surveillance as well as in the maintenance of tissue homeostasis and neuronal function [13]. They originate from myeloid progenitor cells in the yolk sac and migrate to the CNS during the early stages of brain development where they undergo maturation and differentiation into regionally specific phenotypes [14]. They exist in different activation states ranging from a homeostatic (or "resting") state to various forms of activation, including proinflammatory (or "classical") activation and anti-inflammatory (or "alternative") activation [15].

Microglia respond to a variety of environmental signals, including pathogen-associated molecular patterns (PAMPs), damage associated molecular patterns (DAMPs), cytokines, chemokines, neurotransmitters, and neuropeptides [16]. They play a critical role in neuronal function in part because of their ability to monitor and remove synapses (synaptic pruning) [17-19]

Microglial morphology varies depending on their degree of activation. When resting, these cells have a small, compact body and numerous branching processes. When activated, they retract their processes and assume a more ameboid shape (Fig. 2).

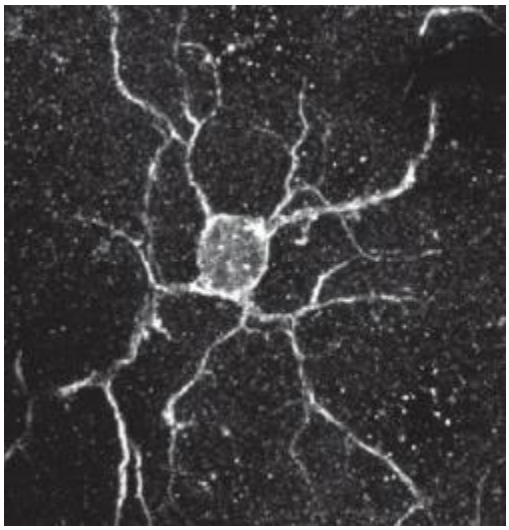

Figure 2 A resting microglial cell. Note the small soma and multiple branching processes. Image attributed to Savage, J.C., St-Pierre, MK., Carrier, M. *et al.* Microglial physiological properties and interactions with synapses are altered at presymptomatic stages in a mouse model of Huntington's disease pathology. J Neuroinflammation 17, 98 (2020). https://doi.org/10.1186/s12974-020-01782-9.

3.4. Microglia and microgravity

Studies have shown that exposure to microgravity can alter the morphology and activation of cortical microglia. They may exhibit a more rounded shape with shorter processes and reduced phagocytic activity. These changes are attributed to altered intracellular signaling and gene expression. Understanding the effects of gravity on microglia can help to improve our understanding of how these cells function and how to protect the CNS during spaceflight [20,21].

3.4.1. Neurons

Neural progenitor cells arise during embryonic development from the neuroepithelium of the neural tube. They migrate from the ventricular zone to form the various regions of the brain and spinal cord, a process that is tightly regulated by a complex series of molecular signals, including growth factors and transcription factors [22-25].

Neurons are responsible for receiving, storing, and transmitting information. They perform these functions by establishing multiple synapses with other neurons and with astrocytes and oligodendrocytes and by producing a variety of neurotransmitters including glutamate, gammaaminobutyric acid, acetylcholine, dopamine, serotonin, histamine, epinephrine, norepinephrine, endorphins, and substance P. They are essential for all nervous system functions, including perception, cognition, and movement [26-28].

Neurons are characterized by their unique shape, which includes a cell body (soma), dendrites, and an axon (Fig. 3).

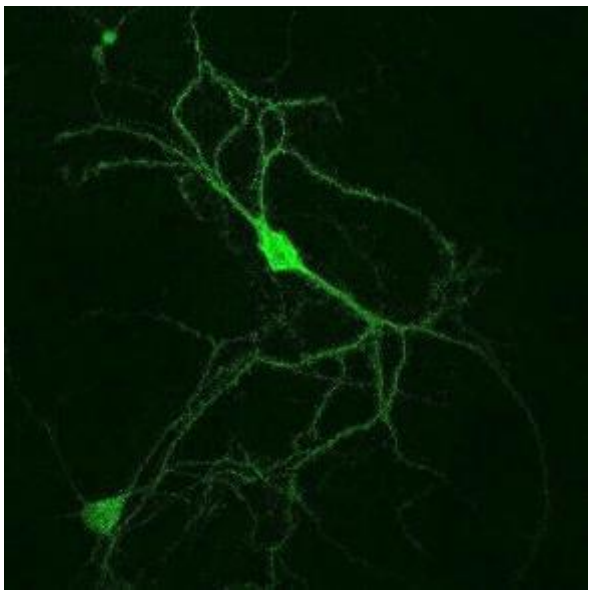

Figure 3 Two neuron somas with their axons and dendrites. Image attributed to Sergb95 - Own work, CC BY-SA 4.0, https://commons.wikimedia.org/w/index.php?curid=72569606

3.4.2. Neurons and microgravity

Neurons undergo changes in their excitability, synaptic transmission, and plasticity in the microgravity of spaceflight. This includes a reduction in their firing rates as well as alterations in their membrane properties and synaptic protein expression. Studies using simulated microgravity models, such as rotating wall vessels or clinostats, have demonstrated similar effects on neuronal function and structure. These findings suggest that exposure to microgravity or simulated microgravity can induce modifications in the neuronal network, potentially impacting cognitive functions and overall brain health. [29-32].

3.4.3. Oligodendrocytes

Oligodendrocytes evolve from oligodendrocyte precursor cells (OPCs) in temporally distinct waves from the ganglionic eminences, the cortical ventricular zone and the outer subventricular zone of the developing brain [33]. In addition, Huang and associated have identified an EGFR expressing pre-oligodendrocytes that originates from outer radial glial cells thus providing an additional source of human cortical oligodendrocytes. The expression of the protoadhesion 15 gene (PCDH15) by oligodendrocyte precursors serves to limit their expansion thereby contributing to oligodendrocyte homeostasis [34] .

Oligodendrocytes are responsible for producing and maintaining the myelin sheath, the insulator of neuronal axons in the CNS. They are subdivided into interfascicular and perineuronal types. Interfascicular oligodendrocytes are aligned in rows between the nerve fibres of white matter whereas perineuronal oligodendrocytes are found in close proximity to the somata of neurons in grey matter. In addition to myelinating axons, oligodendrocytes are involved in the regulation of ion homeostasis, the formation of synapses, the maintenance of the blood-brain barrier, and learning and

memory. The myelin sheaths they produce are comprised of cholesterol and sphingolipids interspersed with myelin basic protein and proteolipid protein.

3.4.4. Schwann cells perform similar functions in the peripheral nervous system [35, 36].

Oligodendrocytes respond to a variety of environmental signals that promote their proliferation, differentiation, migration, myelination and/or survival. These include platelet derived growth factors [37], the proinflammatory cytokines tumor necrosis factor-alpha and interleukin-6 [38] and extracellular matrix proteins including laminins (positive regulators) and fibronectin, tenascin-C, hyaluronan, and chondroitin sulfate proteoglycans (negative regulators) [39] . Neuronal synaptic activity has also been shown to influence oligodendrocyte proliferation and myelination [40].

The size of oligodendrocytes may vary depending on their location. Generally, they have a cell body diameter ranging from 4 to 10 micrometers with processes that can extend for several millimeters. They have dense nuclei and cytoplasms and display a variable number of myelin forming processes (myelin internodes). They lack cytoplasmic glucose and fibrils but have large numbers of microtubules in their internode channels. These channels allow for the exchange of nutrients and signaling molecules between the soma and its internodes (Fig. 4).

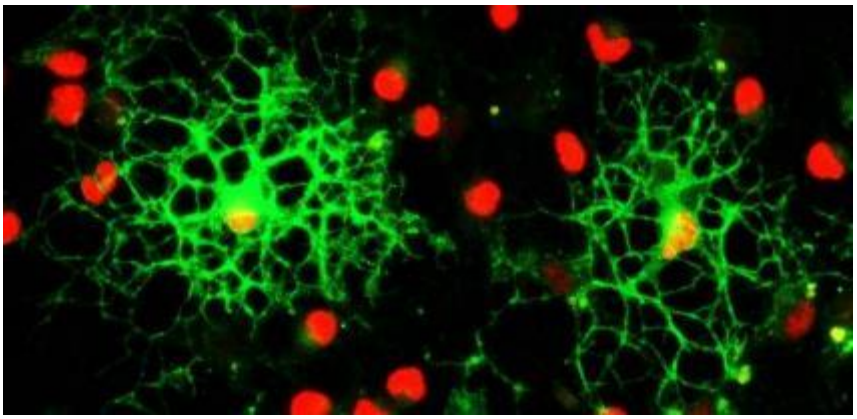

Figure 4 This microscopic image of mouse oligodendrocytes shows the distribution of myelin associated glycoprotein (green) on outspread fine cellular ramifications with multiple intersections. The oligodendroglial lineage marker Olig2 (red) is located in the cell nuclei. Image courtesy of Chih-Yen Wang/Lee, Baylor College of Medicine.

3.4.5. Oligodendrocytes and microgravity

Several studies have investigated the effect of microgravity on oligodendrocyte structure and function. Oligodendrocytes flown on the International Space Station experienced changes in their morphology, in their ability to produce myelin, and in their expression of genes involved in myelination. Similar effects were noted when oligodendrocytes were subjected to conditions of simulated microgravity [41]. In addition, Kim and associates found that microgravity induced proteomic and metabolomic changes in rat brain oligodendrocytes [42]. Notably, Sherman and associates note that microgravity-associated changes in oligodendrocyte homeostasis may contribute to the cognitive and neurological changes observed in astronauts and cosmonauts during spaceflight [43].

3.4.6. Oligodendrocyte precursor cells (OPCs)

The differentiation of oligodendrocyte precursor cells into oligodendrocytes is a complex process that involves multiple stages. Under optimal conditions, OPCs can differentiate into oligodendrocytes within a few days to a week in response to various growth factors, extracellular matrix proteins, neuronal activity, inflammatory signals, neurotransmitters, neuropeptides, and lipids. OPCs play an important role in modulating immune responses in the CNS and promoting neuroprotection and repair following injury. They also play a role in regulating synaptic plasticity, learning and memory [44-46].

OPCs are bipolar cells with a small cell body and two processes: a leading process and a trailing process. The leading process is a long, thin projection that extends from the cell body and moves towards the axon of a neuron. The trailing process is shorter and thicker than the leading process and extends in the opposite direction towards the cell body. OPCs also have numerous filopodia, which are thin, finger-like projections that extend from the leading process and are involved in the process of myelination (Fig. 5).

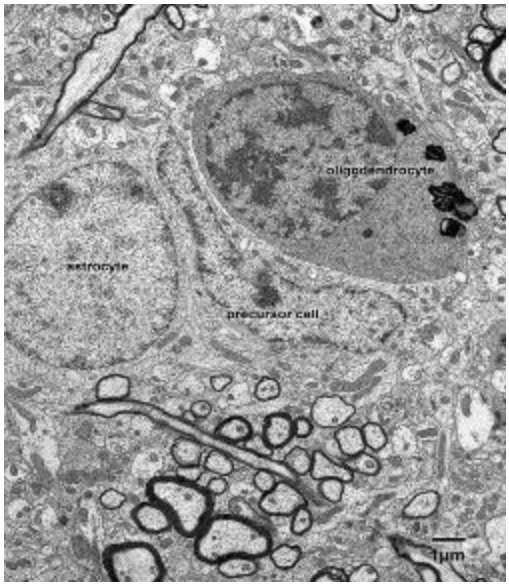

Figure 5 Electron micrograph of a cortical astrocyte, oligodendrocyte, and oligodendrocyte precursor cell. Note the dense nucleus and the myelin fragments in the cytoplasm of the oligodendrocyte. The perikaryal cytoplasm of the oligodendrocyte precursor cell contains a few polyribosomes and mitochondria. Myelinated nerve fibers are scattered throughout the image. Image courtesy of Glenn Kageyama, Boston University, Boston, Massachusetts, USA.

3.4.7. OPCs and microgravity

A study published in the journal npj Microgravity in 2019 looked at the effects of microgravity on OPCs. The study used a simulated microgravity system to expose OPCs to conditions similar to those experienced in space. The researchers found that microgravity increased the proliferation of OPCs but reduced their differentiation into mature oligodendrocytes. Similarly, a study using clinostat-simulated microgravity demonstrated that OPCs showed decreased proliferation and increased differentiation into astrocytes. The study also found changes in the expression of genes involved in the process of myelination [47, 48].

4. Discussion

In this review, I have detailed the many adverse effects that microgravity and simulated microgravity can have on the major cellular constituents of the CNS. Under conditions of microgravity, astrocytes, microglia, neurons, oligodendrocytes, and oligodendrocyte precursors undergo changes in structure and in the expression of genes essential for their maintenance of homeostasis. It is likely that these changes contribute to the cognitive, sensory and motor difficulties astronauts and cosmonauts experience while in space, including the negative impact of space travel on attention, memory, and decision-making skills [1-6, 49-53]. Understanding these changes at the cellular level is crucial for developing effective countermeasures to maintain optimal central nervous system performance during space missions.

One major change observed during space flight is a cephalad shift in body fluids. This may lead to an increase in intracranial pressure and ocular changes including globe flattening, choroidal folding, optic disc edema, and optic nerve kinking (the Visual Impairment and Intracranial Pressure (VIIP) syndrome) [54]. On Earth, an increase in intracranial pressure may result in a variety of neurological disturbances, including visual changes and alterations in cognitive and motor functioning similar to those seen in the IIHS syndrome [55]. Frontal lobe biopsies in patients with idiopathic intracranial hypertension have shown evidence of cortical astrogliosis and scattered activation of microglial cells, the latter indicative of an inflammatory response. Also noted are signs of neuronal injury including synaptic stripping, neuro-axonal swellings and axonal torpedos [56]. And Campos-Ordonez and associates documented a reduction in the number of oligodendrocyte precursor cells and oligodendrocytes in the corpus callouses of mice with experimentally induced normal pressure hydrocephalus [57]. Thus cephalad shifts in body fluids during spaceflight have the potential to impair CNS cellular functions beyond the effect of microgravity alone. In this regard, lower body compression systems are now being employed by NASA to prevent cephalad fluid shifts in astronauts during spaceflights [58].

The first animals to develop centralized nervous systems may have been the ctenophores, also known as comb jellies. They are gelatinous marine invertebrates that move through the water by cilia. Ctenophores are considered to be one

of the earliest animals and are the predecessors of the cnidarians, a group that includes jellyfish, sea anemones, and corals. Fossil evidence suggests that ctenophores arose in the Precambrian period ~700-800 million years ago, whereas cnidarians first emerged during the Ediacaran period, approximately 635-542 million years ago [59].

Ctenophores have an elaborate nervous system consisting of a subepithelial nerve net, mesogleal neurons, a sensory aboral organ, tentacle nerves, and a diffuse network of sensory cells. While the evolution of the nervous systems in ctenophores and cnidarians is not fully understood, it is thought to have paved the way for the development of more complex nervous systems in later animal groups, including vertebrates [59].

It is ironic that the first central nervous systems developed in animals that spent their entire life submerged in water or, physiologically speaking, in a world of simulated microgravity. Man is now challenged by the need to adapt to these very same conditions. The urgency to do so is exemplified in his plans to colonize the moon (16.6% of Earth's gravity = 1.622 m/s^2) and, eventually, Mars (38% of Earth's gravity = 3.71 m/s^2).

5. Conclusion

Under conditions of microgravity, astrocytes, microglia, neurons, oligodendrocytes, and oligodendrocyte precursors undergo changes in structure and in the expression of genes essential for their maintenance of homeostasis. It is likely that these changes contribute to the cognitive, sensory and motor difficulties astronauts and cosmonauts experience while in space, including the negative impact of space travel on attention, memory, and decision-making skills. Understanding these changes at the cellular level is crucial for developing effective countermeasures to maintain optimal central nervous system performance during space missions.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

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