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The Effect of Gravity on the Nervous System

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Abstract

Gravity affects the nervous system of living organisms. This book chapter reviews historical and recent findings on how changes in gravity affect cellular and subcellular parameters of human and animal cells as well as the timing and shaping of complex sensorimotor responses. With an emphasize on weightlessness, partial, and hypergravity conditions, the gravity dependencies of living organisms have been manifested on different levels of organization, ranging from changes in biophysical properties of single cells to the intact nervous system. An effort has been made to integrate the various findings into a consistent model for a better understanding of how the components of the nervous system interact as a response to acute and long-term gravitational variation. Especially with planned long-term manned missions to Mars and beyond, knowledge about the impact of increased and decreased gravity on the nervous system is essential for the physical and cognitive preparation to assure the success of space missions and human survival in space.

Keywords: gravity, microgravity, hypergravity, adaptation, reflex, sensorimotor function, biophysical properties, electrophysiology

1. Introduction

The gravitational force on Earth has remained constant in direction and magnitude since the formation of the planet [1]. Therefore, living species including plants, animals, and humans have evolved to cope with and rely upon gravity equal to 1 g. Throughout the history of the Earth, all living organisms adapted their cellular and behavioral function to this particular physical environment characteristic for our home planet. Gravity—as a permanent and constant vector-calibrated stimulus—led to various gravity-perceiving systems in organisms

that control growth or influence movement and behavior. But what happens if this constant stimulus is changed?

Future challenges in terms of long-term interplanetary manned space missions moved the adaptability of living organisms and their vital systems to heterogravitational habitats into scientific focus [2]. With emphasis on our astronomical neighbors Mars and Moon with a reduced gravitational force of approximately a third and a fifth of the Earth's gravitation, it became apparent that orbital or interplanetary space explorations require knowledge about gravity-perceiving systems, which determine movement, cognition, and survival [3]. In the past decades, space research manifested a significant gravity dependency for various biological processes and vital systems. A special focus lies on the animal and human nervous system (NS) as it is crucial for integration of sensory input, for example, from the vestibular system, movement control, and terrestrial locomotion on Earth. The NS governs muscle contraction enabling the body to counteract the gravitational force and controlling locomotor patterns and reflexes during the evolutionary shift from aqueous to terrestrial life. For interplanetary and orbital missions in future human space flight, knowledge about the gravity sensitivity of the NS is crucial to anticipate major challenges, train the astronauts, and prepare adequate countermeasures to conserve elementary sensorimotor skills during long-term partial-gravity exposure.

The NS is a network of neurons and fibers which transmits nerve impulses between parts of the body. It is composed of interconnected nerve and supporting glial cells. The mechanism of neuronal communication is based on electrochemical coupling, the modulation of intra- and extracellular ions to modify the electrical properties of a cell (intracellular signaling), and the controlled release of transmitters (intercellular communication). Resulting action potentials (APs) are the basic communication unit, and their conduction frequency serves as the coding for the stimulus' intensity.

One of the fundamental circuits within the central nervous system (CNS) to control muscle contraction is the monosynaptic reflex arch [4]. These reflexes are neuromuscular reactions in response to an external stimulus, which lead to fast muscle contractions. The magnitude of muscle contraction depends on the magnitude of sensory input. Allowing mobility of terrestrial life, sensory input from the vestibular and visual systems and proprioception is processed by the NS, and by means of muscle innervation, appropriate forces are generated to control simple posture or movement [5–10]. These sensorimotor competencies are crucial for life. Since the first manned spaceflight of Yuri Gagarin in 1961, the effect of microgravity on the human body has been intensively investigated. In the decades since his first spaceflight, many experiments have been performed which made gravity-induced changes on astronauts and cosmonauts apparent. With an emphasis on weightlessness and our astronomical neighbors Mars and Moon [2, 5], the authors found directly related health effects, among others a persistent modulation in the sensory [7, 11] and motor system [12] and the resulting structural loss of muscle [13] and bone mass [14]. In addition, there are modulations in the neuromuscular system underlying those health-related changes that open up many questions on how the variation of gravity influences the NS. These questions led to numerous experiments to investigate the effect of varying gravity conditions on the different levels of organization, from

the molecular and cellular level, up to the whole NS and its interconnection with movement control and mobility. The functional properties of these levels were thoroughly investigated, however, with barely any interconnection.

This chapter systematically reviews results on how changes in gravity affect neurons of human and animal as well as temporal and spatial characteristics of complex sensorimotor responses. For that purpose, the subject of this chapter is divided in three subthemes: the gravity dependence of subcellular and cellular parameters associated with neuronal activation is followed by an outline of the sensitivity of the human NS to gravitational variation in the context of movement. To interconnect these transdisciplinary findings, a working model is introduced on how the effects observed on the molecular and biophysical level may impact the sensorimotor control of the NS. The chapter ends with a conclusive statement that refers to movement in terms of long-term interplanetary manned space missions.

2. Gravity and the nervous system

2.1. The gravity dependence of subcellular and cellular parameters

A variety of life science experiments executed in gravity conditions different from Earth gravitation, 1 g, have been executed in cellular model systems. With an emphasize on subcellular and cellular parameters and the associated biophysical attributes, most of the *in vitro* experiments have been conducted on short-term gravity-research platforms as drop towers and parabolic flights. Findings from the late twentieth century and recent findings manifest a significant gravity dependency of the basic cell function associated with changes in membrane and channel properties as well as the underlying biophysical characteristics. Results are outlined in the following subchapter.

2.1.1. Membrane parameters

From experiments with unicellular organisms [15] and various cell types as immune cells [16] and neuronal cells [17], it is well established that single cells react to changes in gravity even though they do not have dedicated gravity-sensing structures. One of the major components that all these cell types and organisms have in common is the cell membrane. These complex structures are mainly composed of proteins and lipids [18].

To communicate, cells of the nervous system are able to modify their membrane potential. This ability is based on the activity of integrated membrane proteins as ion channels and ion pumps. But it is well known that the physicochemical state of the lipid membrane can directly modify the function of membrane proteins [19, 20]. In non-space-related experiments, it was shown that the closed-state probability of nicotinic acetylcholine receptors (nAChRs) increased with a decreased membrane fluidity [21]. These nAChRs are a major player in the sensorimotor system as they are located in the motor end plates that form the interface between the neuronal system and the muscles.

Due to these findings, experiments have been performed to monitor the changes of membrane viscosity in micro- and hypergravity with several models (artificial asolectin vesicles and human neuronal SH-SY5Y cells). In all models, the membrane fluidity significantly increases in microgravity and decreases in hypergravity, but in a different distinctness [22]. The difference in distinctness might be explained with the absence of a cytoskeleton in artificial membranes or a different lipid composition.

Nevertheless, this finding, that the membrane fluidity is gravity-dependent, will have a huge impact on biological and medical gravity research, as this is a basic physical mechanism that affects every cell in an organism [23].

2.1.2. Ion channel parameters

Ion channels are crucial for neuronal communication. They form controllable pores through the cell membrane. Charged ions can diffuse through these pores, following electrical and chemical gradients, changing the electrical properties of the cell. Ion channel parameters as open- and closed-state probability have been investigated by using pore-forming peptides which can be used as ion channel analogs. Until now, no native ion channel proteins have been used for gravity research.

The open-state probability of porin channels from *Escherichia coli* is significantly decreased in microgravity, whereas in hypergravity, it is increased. No effect on conductance was found [24].

Similar findings have been made with alamethicin, a pore-forming peptide from *Trichoderma viride*. In microgravity, the activity of alamethicin is decreased, whereas in hypergravity, it is increased [25, 26].

The effect on ion channels is—similar to changes in membrane fluidity—fully reversible and fast. With the onset of a different gravity condition, the open-state probability is changed, returning to normal as soon as the experiment returns to normal 1 g gravity.

2.1.3. Electrophysiological properties of single cells

By having a stable-resting potential, a cell is able to communicate. By changing the activity of relevant ion channels, the membrane potential can be modulated. During parabolic flight, the resting potential of human neuronal cells is significantly depolarized in microgravity and it is hyperpolarized in hypergravity. During microgravity, the depolarization is about 3 mV [27]. This gravity dependence of resting potential is not limited to excitable cells as neuronal cells; it was also found during a drop-tower mission in SF21 cells, an ovary cell line from the insect *Spodoptera frugiperda* [17].

Again in parabolic flight, in microgravity, the transmembrane currents in oocytes from *Xenopus laevis* show a significant decrease at a holding potential of −100 mV, whereas in hypergravity, there is a tendency of increased currents [28].

2.1.4. Propagation of action potentials

Action potentials (APs) are the basic communication unit in the nervous system. The intensity of a stimulus is frequency-coded: while the amplitude of APs remains constant, their

frequency differs dependent on the stimulus strength. In microgravity obtained by drop tower, the rate of action potentials triggered by spontaneous active leech neurons is significantly increased [29]. This means on the level of single cells, more action potentials are generated in weightlessness.

Simultaneously, the conduction velocity of APs on the axonal level is decreased in microgravity and increased in hypergravity. This was demonstrated in parabolic flight missions *in vitro* in isolated earthworm axons and isolated rat axons and *in vivo* in intact earthworms. [29]. Again, the changes are fast and fully reversible.

2.2. The gravity dependence of the human nervous system

In addition to the abovementioned molecular and cellular experiments, a variety of studies have been conducted to investigate the effect of gravity on the nervous system in humans [4, 10, 30–34]. In the context of movement control, it becomes apparent that the biophysical attributes underlying cell communication and the nervous capacity to inhibit and facilitate neural pathways are of fundamental importance to activate and control the skeletal muscle, allowing the living organisms to displace themselves. On the complex sensorimotor level, the gravitational force determines human movement control, and its impact is considered to be of major relevance for the astronaut's safety management in scenarios that require spontaneous or chronic adaptation to an astronomical environment different from the Earth. Not only are short-term platforms as parabolic flights and centrifuges used for this research, the experiments are also conducted during long-term space missions or exploration class missions (up to 1.5 years).

A frequently used technique is the peripheral nerve stimulation (PNS) as it is a noninvasive and reliable approach, providing information about nerve communication including temporal and spatial characteristics of direct motor (M-wave) and reflector responses (Hoffmann(H)-reflex) of the skeletal muscle [35, 36]. By external electrical stimulation, neurons, axons, or cell bodies are depolarized, and the bipolar potential difference of the muscle is measured and interpreted [4]. The nerve *tibialis posterior* and the muscle *soleus* have been established as a model for describing the adaptation processes of the neuromuscular system with emphasize on the temporal and spatial characteristics of the electromyographic signal.

2.2.1. Spatial attributes

The shaping of the potential difference includes peak-to-peak amplitudes normalized to the input stimulus and is associated with the magnitude of the muscle output [37]. Furthermore, the stimulation threshold corresponds to the threshold for axonal excitation with a minimal current evoking a muscle contraction [4].

2.2.2. Stimulation threshold of the H-reflex

The needed electrical stimulation to depolarize an axon to generate a constant muscle response can be interpreted as the responsiveness of a nerve to external stimuli. In reduced gravity conditions, similar to Moon (0.16 g) and Mars (0.36 g), generated in parabolic flights, higher

stimulation currents for PNS were needed to depolarize the neurons. In hypergravity (1.8 g), the needed currents were smaller [4]. Although the respective partial-gravity level lasts only 24–33 s [10] and effects are reversible within seconds, it can be concluded that the stimulation threshold is acutely increased in reduced gravity and decreased in hypergravity.

2.2.3. Amplitude of the H-reflex

The H-reflex amplitude describes the neuronal output signal of the reflectory reaction of muscles and is proportional to the muscle contraction after peripheral electrical stimulation of sensory fibers in their innervating nerves. Gravity dependency has been reported in cross-sectional study designs with neuroplastic changes for amplitudes of H-reflexes and stretch reflexes [10, 30–34]. The peak-to-peak amplitudes increased during hypergravity, independently from the method of stimulation [10, 33].

In micro- and reduced gravity, the results are more inhomogeneous. Experiments in Mars and Moon gravity showed a gravity dependence in the decrease of peak-to-peak amplitudes of Hmax. Less gravity resulted in a higher decrease in Hmax amplitude [4]. Nevertheless, in microgravity, the H-reflex was either not changed [10, 34] or it was increased [30–33]. A long-term experiment on the International Space Station (ISS) revealed a decrease of H-reflexes in space [38]. This decrease was found for 5 months in space, but it was recovered shortly after the return to Earth.

The inhomogeneous findings might be explained by (1) active adaptation processes during long-term missions and (2) mainly due to differences in methodology [4].

The amplitudes of the different sections of the H-reflex depend on the stimulation threshold. As the threshold is gravity-dependent, this has to be taken into account when a constant stimulus intensity is used during the experiments [30–33]. H/M-wave recruitment curves are independent of stimulation threshold [10, 34]. As a consequence, gravity-induced changes in H-reflex amplitudes elicited with a constant and submaximal stimulus are rather attributed to threshold shifts than changes in gravity [30–33].

2.2.4. Temporal attributes

Temporal characteristics of motor and reflectory responses are characterized by latencies relying on the nerve's conduction velocity [39], duration, and inter-peak intervals (IPI) associated with the conduction speed along the muscle fibers at the neuromuscular junction where the nerve interconnects with the muscle [40].

2.2.5. Neuromuscular latency

Neuromuscular latency describes the time between a given stimulus and the measured muscle response. The latency of H-reflex and M-wave in the *Soleus* muscle was investigated in many experiments, short term [4, 32] and long term [40], but the results are again ambiguous, similar to the findings for the amplitudes of H-reflex. In eight subjects, Ritzmann et al. showed an increase in H-reflex latencies with gradually decreasing gravity (from hyper to 1 g

to Mars to Lunar gravity) with a simultaneous tendency of an increase of M-wave latencies [4]. However, Ohira et al. showed that hyper- and microgravity had no immediate effect on the H-reflex and M-wave latencies; unfortunately, they did not give information about the sample size [32].

2.2.6. Inter-peak interval

By interpreting the IPI between the negative and the positive maxima of the biphasic amplitude, information about the conduction velocity from the motor end plate to the muscle fibers can be gained. The motor end plates (or neuromuscular junction) are the interface between the nervous system and the muscles. It could be showed that the IPIs of the peak *M. soleus* M-wave and H-reflex significantly increase with decreasing gravity from hyper- to 1 g to Mars to Moon gravity conditions [4]. This finding can be interpreted that the conduction velocity at the neuromuscular junction is decreasing in reduced gravity and is increasing in hypergravity. This effect occurs immediately and is fully reversible.

2.2.7. Duration

The duration of the H-reflex is established as the interval from the first rise of the electromyographic signal until return to baseline. Ritzmann et al. demonstrated a gradual decrease in H-reflex duration with increasing gravitation from lunar to Martian to earth gravitation to hypergravity [4]. Accordingly, the duration of the M-waves showed a strong tendency to decline with increasing gravitation. As the duration of the motor and reflectory responses cover information about the conduction velocity of signal transmission from the motor end plate to the muscle fibers, results indicate a major impact of gravity on the temporal characteristics of sensorimotor responses.

3. A model for the immediate adaptation of the nervous system to changes in gravity

The following model integrates the results from the various experiments that have been carried out in the past decades from cellular level up to the neuromuscular interface. To avoid long-term adaptation processes, only immediate effects have been taken into account. The model was designed in a bottom-up approach, starting at the very base level of gravity dependence. Therefore, it can be used as a framework for future—more complex data—as long-term adaptation processes and the gravity dependence of for example, the human brain.

3.1. Molecular level

Micro- and hypergravity change the biophysical properties of biological membranes in every cell in the body. This is not due to some biological effect or process, it is a change in thermodynamic properties of biological membranes [20]; therefore, this can be seen as the basic principle of how gravity affects cells as neuronal cells, for example.

On Earth, it is well known that the properties of membrane-integrated proteins as ion channels depend on the physical state of the membrane. Lateral pressure or membrane fluidity is an important component, for example, the open state of alamethicin pores clearly depends on the lateral pressure of the membrane [41], and the pore activity increases with an increased lateral pressure. An increased lateral pressure can be interpreted as decreased membrane fluidity. This was also shown for other ion channels, for example, the closed-state probability of nicotinic acetylcholine receptor channels increases (the open-state probability decreases) toward decreased membrane fluidity [21].

The pore activity of alamethicin and the open-state probability of ion channels is also gravity-dependent [24, 25]. In microgravity, the open-state probability decreases, whereas in hypergravity, it increases.

As membrane fluidity is affected by gravity and due to the fact that ion channels are affected by membrane fluidity, the first part of the model can be described as follows:

In microgravity, the membrane fluidity is increased. This changed membrane fluidity decreases the open-state probability of ion channels. This effect is inversed in hypergravity: membrane fluidity decreases and the open-state probability of ion channels increases (**Figure 1**).

3.2. Single cells

It was shown that cells slightly depolarize in microgravity—the membrane potential gets more positive—and they hyperpolarize in hypergravity. With a light depolarization of the resting potential, the threshold to trigger action potentials is reached more easily. This effect was demonstrated in spontaneous active leech neurons. The rate of APs increased in microgravity.

With these findings, the model of gravity dependence on the molecular level can be extended to explain the cellular gravity dependence of single (neuronal) cells (**Figure 2**).
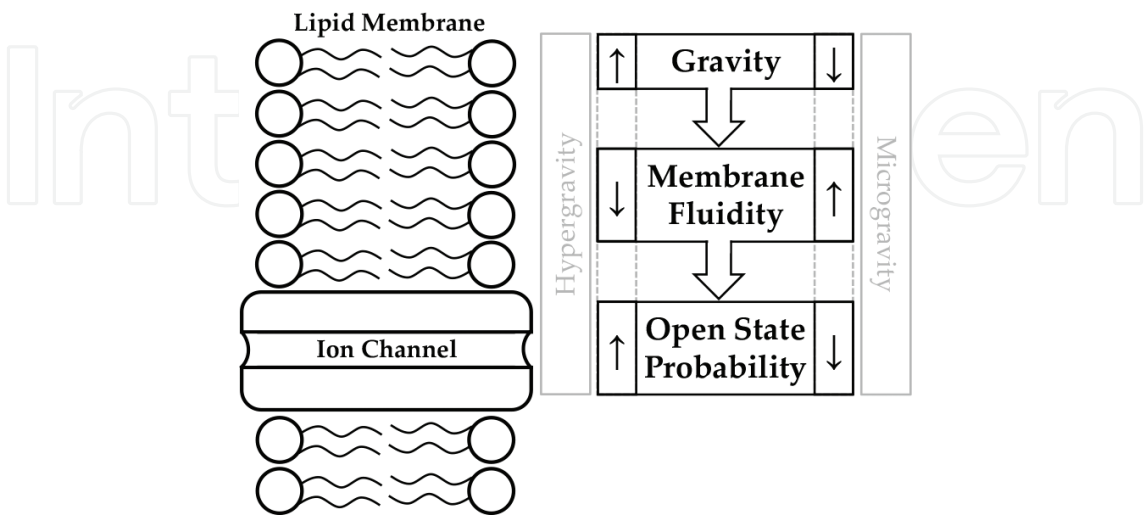

Figure 1. The biophysical gravity dependence of cell membranes and incorporated ion channel proteins. Modified from [42].
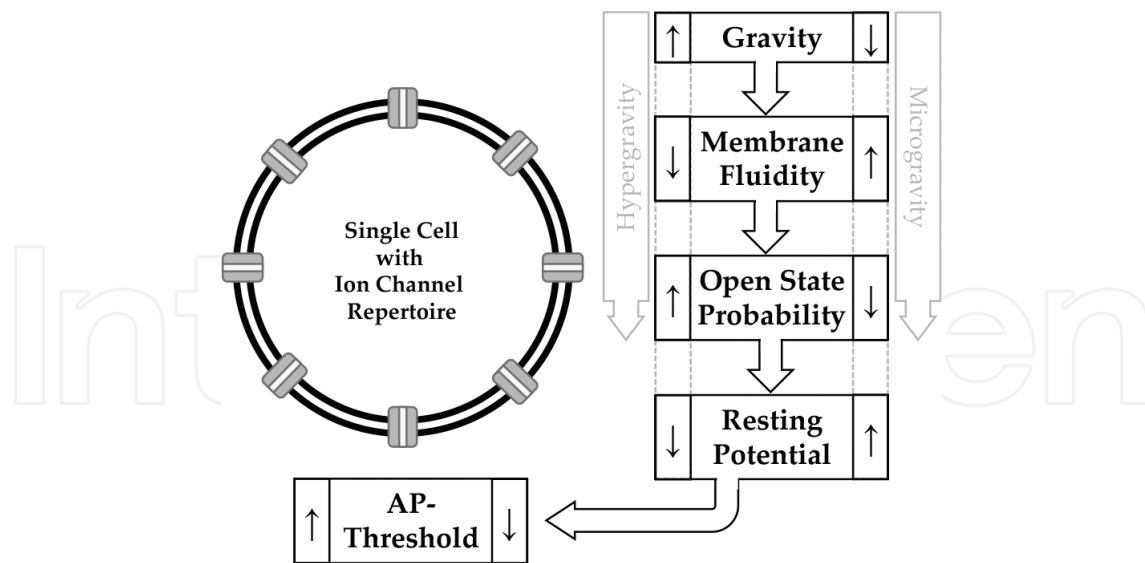
Figure 2. The gravity dependence of a single neuronal cell. Modified from [42].

3.3. Neuronal system: Sensorimotor system

The influence of different gravity conditions on neuronal tissue is clearly visible. In isolated single axons as well as in living animals and in human test subjects, the propagation velocity of APs is decreased in microgravity and it is increased in hypergravity.

Neuromuscular reflex arcs in humans are influenced by gravity. In microgravity, increased latencies can be measured. An increased latency can be explained with a decreased conduction speed—the APs are slower in microgravity.

In Mars and Moon gravity, a higher stimulus has to be given to get the same Hmax as in 1 g, and the peak-to peak amplitude of the H-reflex is decreased (with heterogeneous data at real microgravity). Unfortunately, as the methods of single-cell electrophysiology and peripheral nerve stimulation are different, their results cannot be compared directly. Nevertheless, a decreased propagation velocity of APs in the axons can also explain the decrease in Hmax in microgravity. Less APs per time arrive at the muscle, which leads to a reduced contraction. Two findings support this explanation: first, the decrease can be compensated with a higher stimulus. Due to the frequency coding of sensory input, a higher stimulus generates more APs per time. With more APs per time arriving at the muscle, the contraction force is increased. Second, the decrease in inter-peak intervals of the H-reflex indicates a decreased signal speed at the neuromuscular junction. In increased gravity, these effects are reversed (**Figure 3**).

In microgravity, the rate of action potentials is increased, while at the same time, the propagation speed of APs is decreased. This might look like an inconsistency, but it is not. It can be explained with a mathematical equation. Matsumoto and Tasaki developed a mathematical model to calculate the conduction speed of APs in unmyelinated axons [43]. This equation can also be used to estimate the conduction velocity of APs in myelinated axons
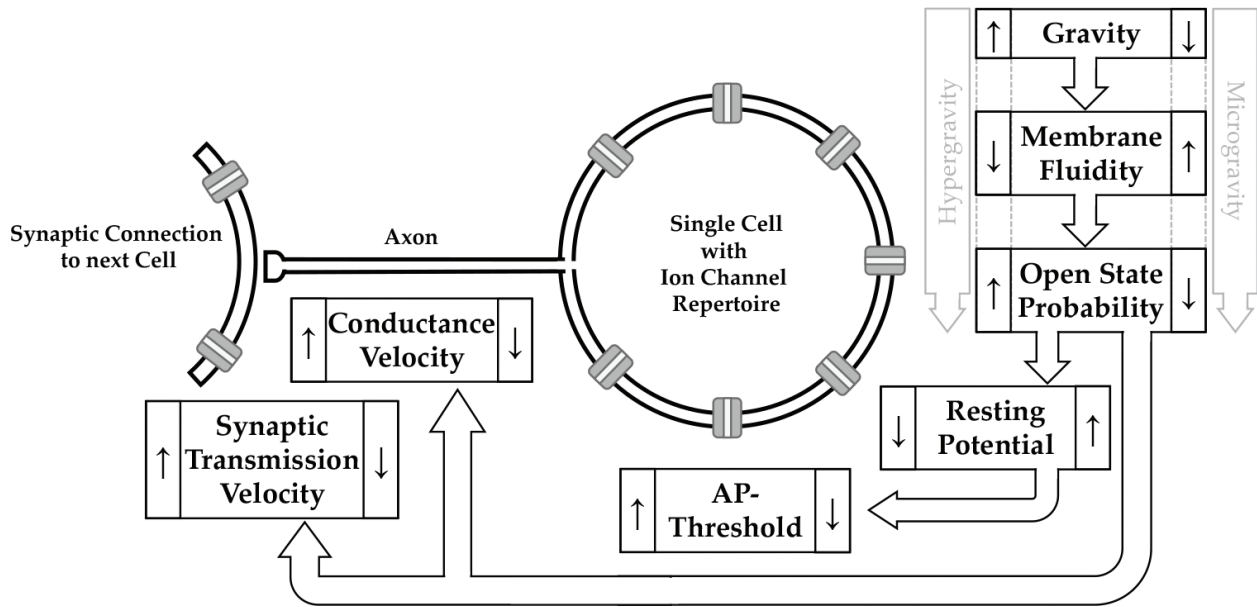
Figure 3. The gravity dependence of a multicellular network, connected via synapses as the sensorimotor system. Modified from [42].

$$v_{axon} \approx \sqrt{\frac{d}{8 \cdot \varrho \, C^2 \cdot R^*}} \tag{1}$$

where v_{axon} = conduction velocity, C = membrane capacity, d = diameter of the nerve, R^* = resistance of the membrane, and ϱ = axoplasmic resistance.

By integrating the data from gravity research and Matsumoto and Tasaki's model, at first view, the inconsistent findings from single-cell electrophysiology and the data from PNS can be brought together quite nicely to a working model on how the sensorimotor system adapts to changes in gravity.

The increased membrane viscosity in microgravity decreases the open-state probability of ion channels, leading to a slightly depolarized membrane potential. With a reduced open-state probability, the resistance of the membrane (R^*) is increased. If axoplasmic resistance (ϱ), membrane capacity (C), and the diameter of the axon (d) are treated as constant in changed gravity, the increased resistance of the membrane leads to a decreased conduction velocity of APs (v_{axon}) while simultaneously APs can be triggered more easily.

To sum up, the described effects are a gravity-dependent decrease in neuronal conduction velocity–or, more general, an increase in electrical and chemical time constants—under reduced gravity and vice versa in hypergravity.

4. Conclusion

In the decades since the first manned space mission, many *in vitro* and *in vivo* experiments have been conducted to investigate the effect of micro- and hypergravity on neuronal processes.

Adaptation processes occur on all levels of organization, from the subcellular level up to the neuromuscular system (and even up to the brain). Unfortunately, till date, the discrete results of these experiments were never brought together to see (1) whether they can be integrated to a working model of neuronal adaptation in varying gravity or (2) to reveal inconsistencies or (3) areas, which have not been investigated yet. This model aims at bringing insight to the short-term adaptation of the neuronal system to varying gravity conditions. Simultaneously—as some points still are based on reasoned assumptions [42]—it has to be seen as a framework, which should be fleshed out more in future experiments to include long-term adaptation processes and the adaptation of the human brain. A more interconnected and interdisciplinary analysis of all the data can serve as a "roadmap," aiming for giving more structure to ongoing and future research.

Findings are of major functional relevance in the application field of manned space flight as well as countermeasure development. As more and more space agencies and private space companies are planning long-term missions into space, for example, to Mars, the effect of gravity—and its absence—on the human organisms has to be understood overreaching all vital body systems to minimize the risks for space-faring humans [2]. Today, scientific outcomes of life science experiments executed in samples of astronauts and cosmonauts encompass a variety of long-term adaptation in regard to their sensory perception, motor execution, and planning as well as complex body motion. They are interrelated to neural adaptation to varying gravity and have been verified as follows (for review, see [44]): a recalibration of sensory perception, vestibular and proprioceptive dysfunction [7, 11], changes in muscle synergies and coordination, a decline of muscle force as well as deficits in posture control [6], locomotion, and functional mobility [8]. Reduced and delayed reflex responses and a decline in intramuscular and intermuscular function occur concomitantly with an increased muscle weakness, fatigue concomitant with a higher fall, and injury prevalence [40, 44]. With a persistency beyond the acute period of space flight, these adaptations are of clinical relevance as manifested by significant adverse effects which entail fragility and bone fractures [14, 44].

To reduce health and life risk throughout long-term exposure to low gravity during manned space explorations, scientists and space agencies developed intelligent exercise technologies and efficient interventions validated in cohorts of space crew members to prevent the human body from deconditioning [2]. Empirical outcomes subject to the NS and its adaptability to changes in gravity are included in the concepts of ancient and future countermeasures as manifested, for instance, for strength or jump exercises, vibration treatment, sensorimotor training, and artificial gravity [44].

Although great efforts have been made to optimize countermeasures, limitation on the cellular level such as changes in membrane fluidity as well as complex adaptations on the spinal level encompassing mechanisms of facilitating and inhibiting is of major relevance and cannot be diminished by countermeasures, only [4, 10, 23].

As astronauts traveling to Mars will live in the absence of gravity for approximately 2 years with transition between weightlessness and planetary gravitational forces at the beginning, middle, and end of the mission, further research and countermeasure development considering the gravity dependency of the NS will be obligate to assure a safe space travel and Earth return in the future [44].

Acknowledgements

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