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Review article

Risk of defeats in the central nervous system during deep space missions

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ABSTRACT

Space flight factors (SFF) significantly affect the operating activity of astronauts during deep space missions. Gravitational overloads, hypo-magnetic field and ionizing radiation are the main SFF that perturb the normal activity of the central nervous system (CNS). Acute and chronic CNS risks include alterations in cognitive abilities, reduction of motor functions and behavioural changes. Multiple experimental works have been devoted to the SFF effects on integrative functional activity of the brain; however, the model parameters utilized have not always been ideal and consistent. Even less is known regarding the combined effects of these SFF in a real interplanetary mission, for example to Mars. Our review aims to systemize and analyse the last advancements in astrobiology, with a focus on the combined effects of SFF; as well as to discuss on unification of the parameters for ground-based models of deep space missions.

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1. Introduction

Following a number of successful orbital and planetary missions with unmanned spacecraft, the space agencies of the world's leading countries have begun to consider the prospect of human exploration of deep space. Despite several decades of studying the medical and biological problems of spaceflight (Livshits, 1967), these issues are now regaining relevance. In contrast to an orbital flight, leaving the Earth's magnetic field is fraught with the dangers of exposure to ionizing radiation (IR) and more specifically, the high-energy nuclei component of cosmic rays (HZE). Thus, during a 3-year-long mission to Mars, it is estimated that 13% of neurons in the CNS will be permeated at least once by an iron ion and at the same time ~50% of neurons in the *hippocampus* will be permeated by charged particles with an atomic number greater than 15 (Curtis et al., 1998). Other SFF include hypo-magnetic field, hypo- and hyper- gravity, isolation, cabin microclimate and changes to circadian rhythms which not only negatively affect the CNS functions individually, but in combination, significantly modulate the mutual effects. While earlier, the physiological and functional approaches predominated in studies for these SFF, more recent works have been devoted to analysing of structural and functional changes at both the cellular and molecular level. Most of gaps in knowledge are currently related to defeats of CNS integrative functions that severely affect the operating activity of astronauts. There is a significant amount of conflicting data on the impairments of cognitive abilities caused by SFF, and on the mechanisms underlying these disorders. Currently, researchers are focusing the greatest effort on studying the negative effects of IR and are giving significantly less attention to the other factors. To date, the neurochemical and molecular mechanisms underlying the cognitive impairments resulting from effects of SFF (as separately as in combination) are not clearly understood (Laack and Brown, 2004; Shtemberg, 2014).

Furthermore, much of the information about the potential risks to the CNS is contradictory. However, any observable cognitive impairments resulting from exposure to irradiation by HZE has not been shown (Cherry et al., 2012; Haley et al., 2013). It is worth mentioning, there were significant variations in the effective values and time intervals in which SFF were applied in ground-based simulations of interplanetary space travel. More recently, several research groups (Cucinotta et al., 2013; Kim et al., 2014a) have made attempts to standardize the radiation exposure conditions as applied to a ground-based simulation of a flight to Mars. There is a serious need for a comprehensive analysis of these latest achievements in astrobiology, especially regarding the studies focused on the combined effects of SFF on the CNS in both ground-based and orbital experiments.

This review provides a fresh look at the effects of individual SFF and their combined action on the pathophysiology of neuronal injury. The purpose of this information systematization is to provide a better understanding of the potential risks to the CNS from these SFF and to propose potential targets for pharmaceutical intervention.

2. Spaceflight factors

During a spaceflight, when a manned spacecraft is in space, the environmental factors significantly affect well-being of living organisms. Moreover, these effects depend on the dynamics of the spacecraft's movement within its flight trajectory. In particular, these SFF include: hypo- and hyper-gravitation, hypo-magnetic field (HMF), ionizing radiation, microclimate of the living space and personal isolation. In combination, the SFF's may act as synergistically as antagonistically regarding the CNS functions. Study of these effects is timely and therefore of extreme importance in modern astrobiology.

It is logical to assume that the pathophysiological process begins with destruction of a single neuron or of their ensemble, and may proceed differently. In the first case, intrinsic reparation systems and compensatory mechanisms may attenuate the resulting damage, especially if the external SFF's are eliminated. In the second instance, the pathological process may develop locally and progress to involve more and more brain structures. It can go in various directions due to inflammation, apoptosis/necrosis, or autoimmune reactions. Since it might be difficult to choose the correct pharmaceutical agent(s) to halt these processes, the various nootropics, cytoprotectors, and anti-inflammatories may be useful to consider. However, it can go in a single direction, when the damage to neuronal tissue distributes in neuronal network, due to disturbances in neural signal transmission, breaking highly-integrated structures (Greicius and Kimmel, 2012; Masuda-Suzukake et al., 2014; Raj et al., 2012). This mechanism of SFF-initiated damage progression is often accompanied by behavioural alterations, and at the stage of proliferation we can trace the molecular mechanisms of the pathophysiological process as well as identify potential targets for pharmaceutical intervention or for preventive therapy. In summary, new approaches for risk assessment are needed to provide the necessary data and knowledge for development of models for the CNS damages caused by space radiation.

2.1. Ionizing radiation

Ionizing radiation is among the most dangerous factors in space environment. It significantly affects the life of astronauts during an inter-planet flight and a stay on the surface of a planet, when there is no strong magnetic field and/or dense atmosphere. The component of ionizing radiation, highly charged particles (HZE) – represent a significant danger. Their kinetic energy is measured in electronvolts (eV) – a unit of energy equal to approximately 16×10^{-20} J. By definition, it is the amount of energy gained (or lost) by a single electron moving across an electric potential difference of 1 V. In radiation health physics the absorbed dose of radiation is measured in units of Gray (Gy), where 1 Gy = 1 J/kg. However, not all sources of radiation have the same biological effectiveness, and the dose equivalent measured in units of Sieverts (Sv) takes this into account. The dose equivalent (in Sv) is equal to the dose in Gy multiplied by the quality factor (Q), where Q is a function of the linear energy transfer (LET) – the rate of energy loss of a particle, measured in keV/μm of water (Measurements, 2000).

The primary sources of ionizing cosmic radiation are the Earth's radiation belts, galactic cosmic rays (GCR) and a so-called solar wind – plasma emissions from the solar corona and photosphere (Fig. 1). Secondary radiation, mainly represented by neutrons, electrons, mesons and γ-rays, is generated when the primary radiation interacts with different objects and directly with the living tissue (Song et al., 2001).

GCR consist of ~83% high-energy protons (10–10,000 MeV), 13% – alpha particles, 3% – electrons and about 1% HZE with an atomic number greater than 2 (0.1–1000 GeV) and an average energy of about 1000 MeV/nucleon (Meyer et al., 1974; Parker et al., 1979). There are also particles with ultrahigh energy of up to 3×10^{20} MeV (Taubes, 1993). The main elements that compose HZE part of GCR are shown in Table 1. GCR represent the main danger during space missions. The intensity of cosmic rays is modulated by the changes in the interplanetary magnetic field and the heliosphere, caused by the cycles of solar activity and the solar flare. The content of the solar wind is quite similar to the one of GCR (Fig. 1); however, an energy of the IR, the main component, lays between 0.7–15 keV and rarely exceeds 100 MeV. Such high energy is typical for HZE,