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Review

The Role of Oxidative Stress and Antioxidants in Space Flight

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Abstract: The environment in space is different with that on earth. It has been found that long-term habitation in space could induce several physiological alterations, one of which is the induction of oxidative stress. Two predominant factors, namely space radiation and microgravity, have crucial impacts on oxidative stress in living organisms, including the overproduction of free radicals and the decreased function of antioxidant defense systems. Hence, we discuss the effects of space radiation, microgravity, and a combination of these two factors on oxidative stress and the related underlying mechanisms in the present paper. Moreover, since the intake of dietary antioxidant supplement may have a beneficial role in the astronauts to reduce the oxidative stress induced by space environment, we summarized the antioxidants that have been tested to be effective in reducing oxidative stress.

Keywords: space flight; oxidative stress; antioxidant; radiation; microgravity.

1. Introduction

Human have continued to achieve breakthroughs in space exploration in the last few decades. However, to complete the mission often requires a long-term exposure of astronauts to the special space environment, which is totally different with that on earth surface. The uniqueness of space environment primarily lies in radiation, microgravity, high vacuum, sub-magnetic field, ultra-clean

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environment, and micro-environmental factors inside spacecraft. Accumulating evidences have demonstrated that prolonged exposure to either of these environmental factors, alone or in combination, are known to produce a number of obvious alterations, including neurological disturbances in the central nervous system (DeFelipe et al., 2002; Manda et al., 2008), bone loss (Stein, 2013; Grimm et al., 2016), muscle atrophy (Narici and de Boer, 2011; Stein, 2013), and cardiovascular deconditioning (Coupe et al., 2009; Zhu et al., 2015; Takahashi et al., 2017), which could pose a threat to the health of the astronauts and the success of the mission. Therefore, these health risks associated with long-term manned space missions have attracted great research attention.

It has been found that space flight is associated with an increase in oxidative stress as evidenced by some experiments (Stein, 2002; Versari et al., 2013). Oxidative stress has been reported to be involved in many chronic and degenerative diseases, such as atherosclerosis, coronary heart diseases, diabetes mellitus, neurodegenerative diseases (such as Alzheimer and Parkinson diseases), ageing and cancer (Azizova, 2002; Valko et al., 2007; Santilli et al., 2015). In recent years, some scientists have connected the development of pro-oxidative conditions to some physiological changes during space stay. For instance, a study found that space flight affected endothelial cell function of mice by triggering oxidative stress. In details, space flight induced an increase in lipid peroxidation products in mouse erythrocytes. Besides, space flight also induced antioxidant defenses in the flight erythrocytes with a significant increase in glutathione content compared with both vivarium and ground control erythrocytes, although this induction was not sufficient to prevent damages caused by oxidative stress (Versari et al., 2013). Moreover, a review pointed out that decreasing the imbalance between the production of endogenous oxidant defenses and oxidant production by increasing the supply of dietary antioxidants may lessen the severity of the increase in oxidative stress (Stein, 2002). Many natural products have been found to contain high contents of antioxidants, such as fruits, vegetables and some edible flowers (Guo et al., 2012; Li et al., 2013; Deng et al., 2013; Li et al., 2014), which have the potential to be developed into appropriate dietary antioxidant supplement for astronauts during space exploration missions. Therefore, the present review aims to summarize the information on oxidative stress induced by special space environment and the antioxidants that have been tested to be effective in reducing the oxidative stress induced by simulated space conditions, such as radiation and microgravity. This review is helpful to the researchers in the space exploration fields to develop dietary supplement to improve the health condition of astronauts.

2. Oxidative Stress Induced by Radiation

The sources of hazardous radiation in space include galactic cosmic rays and solar particle events such as solar flares (Sihver et al., 2015). Exposure to these hazardous radiations could induce

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severe oxidative damage in living organs. For instance, a study investigated whether low dose charged particle irradiation could induce oxidative stress in cultured neural stem cells and the rodent brain. The results showed that low doses (< 1 Gy) of charged particles caused an acute and persistent oxidative stress, since the levels of reactive oxygen and nitrogen species were increased early after (< 1 week) irradiation and were generally dose responsive. Low dose irradiation also significantly impaired novel object recognition in mice 2 and 12 weeks following irradiation (Tseng et al., 2014). In addition, a study investigated the synergistic effect of high charge and energy (HZE) particle radiation and chronological age on the embryos of *Oryzias latipes* (Japanese medaka fish), which were exposed to HZE particle radiation at doses overlapping the range of anticipated human exposure. The results showed that HZE particle radiation dose and aging synergistically induced chronic oxidative stress. Besides, mitochondria had an elongated and enlarged ultrastructure, and livers also had distinctive cystic lesions (Zheng et al., 2014). Besides, astronauts are exposed to increased body iron stores and radiation. A study showed that dietary iron and radiation, alone and combined, contributed to oxidative stress that was related to immune system alterations in circulation and the colon (Morgan et al., 2014). Another study found that exposure to ^{16}O particle radiation caused aging-like decrements in rats through inducing oxidative stress, inflammation and inhibiting autophagy function (Poulose et al., 2011). Besides, the evidence indicated that exposure of cell populations to ionizing radiation could affect both the irradiated and nonirradiated bystander cells in the population, the so-called bystander effect (Azzam et al., 2004). A study showed that the progeny of bystander cells that were co-cultured with cells irradiated with iron or silicon ions, but not protons, exhibited reduced cloning efficiency and higher levels of chromosomal damage, protein oxidation and lipid peroxidation compared with controls (Buonanno et al., 2011). In addition, it's reported that the bystander effect was transmitted by means of extracellular DNA (ecDNA) fragments to nonirradiated cells, and oxidative stress played a significant role in development of an adaptive response in irradiated and nonirradiated human lymphocytes after inducing the bystander effect by low-dose X-radiation.

Some antioxidants showed protective effects against the oxidative stress induced by radiation. In a study, γ-radiation induced oxidative stress in the heart and kidney of rats as evidenced by elevated levels of lipid peroxidation and decreased activities of endogenous antioxidants (SOD, CAT, GPx, and GSH). Post-treatment with hesperidin (50 and 100 mg/kg bw/day, orally) for 7 days following exposure to γ-radiation significantly attenuated these changes, and histopathological examination of the heart tissue of rats treated with hesperidin also showed minimal damage when compared to those exposed to γ-radiation alone (Park et al., 2009). In another study, carbon ion irradiation induced a significant increase in the teratogenesis of the zebrafish embryos, and oxidative stress was also induced as shown by increased malondialdehyde (MDA) content, decreased glutathione (GSH) content and alterations in antioxidant enzyme activities, such as catalase (CAT) and superoxide dismutase (SOD).

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Pretreatment with ferulic acid alleviated the irradiation-induced oxidative damage marked by changes in mortality, morphology, antioxidant enzyme activities and the MDA and GSH contents (Si et al., 2013). Moreover, a group focused their efforts on studying the protective effects of dietary antioxidant supplementation against radiation. Firstly, they found that the Bowman-Birk Inhibitor Concentrate (BBIC) and a combination of several antioxidants (N-acetylcysteine, ascorbic acid, sodium ascorbate, co-enzyme Q10, α-lipoic acid, L-selenomethionine, and vitamin E succinate) were effective in protecting against radiation-induced oxidative stress and complete or nearly complete protection was achieved by treating the MCF10 human breast epithelial cells or mice with these supplements (Guan et al., 2004 & 2006; Wan et al., 2006; Kennedy et al., 2007). Furthermore, they investigated the effects of two antioxidant dietary supplements on the harderian glands of mice, one was called the AOX supplement (a mixture of L-selenomethionine (SeM), N-acetyl cysteine (NAC), ascorbic acid, co-enzyme Q10, α-lipoic acid and vitamin E succinate), and the other was known as Bowman-Birk Inhibitor Concentrate (BBIC). The results suggested that the two dietary antioxidant formulations had major suppressive effects in the later stages of radiation-induced carcinogenesis (Kennedy et al., 2011). Moreover, the same team found that these two different dietary countermeasures also reduced the risk of developing malignant lymphoma in animals exposed to space radiation compared to the irradiated animals maintained on the control diet, and also reduced the yields of a variety of different rare tumor types observed in the animals exposed to space radiation (Kennedy et al., 2008).

Collectively, radiation can induce oxidative stress in organisms, and some antioxidants, such as hesperidin, ferulic acid and combination of several antioxidants, have been reported to prevent or decrease the oxidative stress induced by radiation. Moreover, some antioxidants may also be able to suppress radiation-induced carcinogenesis, which is also related with reducing the oxidative stress induced by radiation.

3. Oxidative Stress Induced by Microgravity

Microgravity is a great concern for human activities in space environments because it can cause the redistribution of fluids in the body during space travel (Stein, 2002). Accumulating studies have demonstrated that microgravity could induce oxidative stress in organisms. For instance, a study found that simulated microgravity (achieved by a rotary cell culture system) increased the production of ROS in rat neuronal PC12 cells, and decreased the activity of intracellular antioxidant enzymes, such as SOD, GSH-Px and CAT at 96 h after the microgravity onset. Besides, simulated microgravity also induced partial G_1 phase arrest, elevated senescence-associated P-galactosidase activity, and activated both p53 and p16 protein pathways linked to cell senescence, indicating that simulated microgravity induced cellular senescence in PC12 cells through inducing oxidant stress (Wang et al., 2009). A study

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recruited 20 male volunteers reported that after 60 days of simulated microgravity (-6° head-down-tilt bed rest), the serum and salivary vitamin C and E concentrations of the volunteers were significantly decreased, whereas MDA and 8-OHdG levels were significantly increased (Rai et al., 2011). Besides, a study found that simulated microgravity induced several adverse effects in *Caenorhabditis elegan*, including the induction of oxidative stress, and the administration of ascorbate inhibited these adverse effects (Zhao et al., 2017). In addition, simulated microgravity induced a decrease in the SOD levels in the hippocampus of rats, and an increase in the ROS generation (Wang et al., 2016).

Some dietary strategies, including some antioxidants, have been reported to alleviate the oxidative stress induced by microgravity. A study investigated the protective effects of several flavonoids against the oxidative damage induced by microgravity in neuroblastoma SH-SY5Y cells. Among the 20 selected flavonoids, isorhamnetin and luteolin treatment showed protective effects by preventing microgravity-induced increases in ROS, nitric oxide (NO) and 3-nitrotyrosine (3-NT) levels, and a decrease in antioxidant power. Isorhamnetin and luteolin treatment also downregulated the expression of inducible nitric oxide synthase (iNOS), and oxidative stress was significantly inhibited by an iNOS inhibitor in SH-SY5Y cells exposed to simulated microgravity, which indicated that isorhamnetin and luteolin protected against microgravity-induced oxidative stress through inhibiting the ROS-NO pathway (Qu et al., 2010). Besides, a study investigated the effects of dietary soy protein, aminoguanidine (AG) and L-carnitine (LC) as antioxidants in rats under simulated microgravity. The results showed that the MDA levels in tissues (including brain, heart, lung, liver, stomach, pancreas, small intestine, kidney and testes) were elevated by hind-limb suspension ($p < 0.05$). Treatment of LC, AG, and the soybean diet decreased the peroxide formation as evidenced by the lower MDA levels ($p < 0.05$) in the animals, indicating that LC, AG, and a soybean diet might have a protective role in the reduction of lipid peroxidation damage produced by stress (Chowdhury et al., 2008).

However, some inverse results were reported in the literature. For instance, a study reported that peroxidase (POD) and SOD activities in tomato leaf samples processed by spaceflight and simulated microgravity increase notably (Chen et al., 2015). Besides, a study investigated the effect of gravity deprivation on endogenous antioxidant enzymes in *Xenopus laevis* embryos developed for 6 days. The results showed that glutathione content and the activity of antioxidant enzymes increased in the embryos (Rizzo et al., 2009). Moreover, another study found that after 7 days treatment of simulated microgravity, the Anabaena PCC 7120 cells showed increased ROS production, and higher activities of intracellular antioxidant enzymes, such as SOD and CAT compared with the controlled samples. On the contrary, the contents of gluathione decreased in the treated cells (Li et al., 2004). This may be because that the generation and scavenging of free radicals in organisms is in a state of dynamic balance under normal conditions. Large amount of reactive oxygen free radicals can be produced under adverse stress, such as microgravity. In order to resist the damage caused by ROS, organisms often

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increase their activities of protective enzymes such as POD and SOD to remove excess reactive oxygen free radicals as a kind of protective mechanism. In this way organisms could adapt themselves to the environmental stress of microgravity (Chen et al., 2015).

4. Oxidative Stress Induced by Combination of Radiation and Microgravity

It was found that the combined treatment of low-dose irradiation and simulated microgravity (achieved by hindlimb unloading) significantly altered oxidative stress biomarkers (including elevated level of 4-hydroxynonenal protein and decreased activity of SOD) in the brain cortex of mice, which indicated that combined treatment of low-dose irradiation and simulated microgravity might increase the likelihood of brain injury and reduce antioxidant defense (Mao et al., 2016). Another study investigated the effect of treatment of hydrogen molecule on the oxidative stress and bone loss induced by modeled microgravity both *in vivo* and *in vitro*. The SD rats were exposed to hindlimb suspension (HLS) and simultaneously treated with administrated with hydrogen water (HW), and the results showed that the treatment with HW alleviated the augmentation of malondialdehyde content in femur and lumbar vertebra induced by HLS. Besides, in cultured MC3T3-E1 and RAW264.7 cells, incubation with HRM inhibited modeled microgravity-induced ROS formation (Sun et al., 2013).

5. Conclusions

The space environment is predominantly characterized by space radiation and microgravity. The phenomenon of increased oxidative stress during the space flight has been demonstrated in multiple kinds of organs and cells, such as erythrocytes, endothelial cells, brain, neuronal cells and skeletal muscles. The evidence included the overproduction of lipid peroxidation products (MDA), and the reduced function of antioxidant defense systems (such as the antioxidant enzymes) induced by radiation and simulated microgravity in laboratory. These results have indicated the necessity of efforts to reduce the oxidative damage induced by space special environment. Some natural antioxidant such as hesperidin, ferulic acid, isorhamnetin, luteolin, N-acetylcysteine, ascorbic acid, alone or combined, have been found effective in alleviating the oxidative stress induced by simulated space conditions. However, these simulated space conditions often mimic only a single aspect of the space due to the difficulty of simulating the complicated space environment. Therefore, future studies should focus on investigating the effects of more dietary antioxidants on the oxidative stress under the conditions that is as closely to the real space environment as possible.

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