30 Pharmacological Countermeasures to Spaceflight-Induced Alterations of the Immune System

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30.1 Introduction

Opportunities for microbes to establish infections are enhanced under spaceflight conditions because space travel stimulates their growth (Chap. 15) and has a negative impact on immune functions. Indeed, it has been shown that spaceflight affects lymphoid organs (Gridley et al. 2003; Baqai et al. 2009) and induces variations in peripheral blood leukocyte subsets (Chap. 9). Neutrophil, monocyte, and NK cell functions are affected by spaceflight (Chaps. 10–12). The activation of T lymphocytes is also severely depressed under low gravity conditions (Cogoli et al. 1984) because interleukin-2 (IL-2) and IL-2receptor gene expression are modified, the delivery of the costimulatory signal to activate the B7/CD28 pathway and the protein kinase A (PKA) signaling pathway, which is a key early regulator in T cell activation, are hindered. Furthermore, a TH2 cytokine shift is associated with spaceflight. If this TH2 shift persists during long missions, it could represent a significant clinical risk for TH2-related autoimmune diseases, allergies, hypersensitivities, and disease susceptibility related to diminished cell-mediated immunity. Studies on plasma antibody levels did not reveal significant changes after short spaceflights (Rykova et al. 2008), but contradictory results were reported after long missions. Indeed, several studies (Konstantinova et al. 1993; Bascove et al. 2008, 2009; Guéguinou et al. 2009, 2010) reported increased levels of immunoglobulin while Rykova et al. (2008) reported normal amounts of antibodies after prolonged space missions. Lastly, a differential sensitivity of cellular and humoral immunity to spaceflight conditions seems to exist because it was shown that the cellular, but not the humoral, systems are affected by short periods of flight.

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A. Choukèr (ed.), *Stress Challenges and Immunity in Space*,
DOI 10.1007/978-3-642-22272-6_30, © Springer-Verlag Berlin Heidelberg 2012

Taken together, these data demonstrate that spaceflight-induced modifications of the immune system could have an immediate impact on mission objectives. The development of efficient countermeasures to combat the deleterious effects of spaceflight on the immune system is therefore an area that should be considered more thoroughly before we undertake prolonged space voyages. Furthermore, the observations presented above are also found in the elderly (Cancro et al. 2009) and people subjected to chronic or acute stress (see Chap. 4). Indeed, the age-associated decline in immune function, which is known as immunosenescence, is characterized by a large dysfunction in innate and adaptive immune system responses (for review see Weiskopf et al. 2009). Chronic stress reduces B and T lymphocyte responses and lowers antibody production (Glaser et al. 2000). Acute stress induces the reactivation of latent viruses, decreases NK cell activity, increases interleukin-6 (IL-6) secretion, and increases neutrophil numbers in peripheral blood (Glaser and Kiecolt-Glaser 2005). Finding countermeasures to spaceflight-associated immune alterations are therefore also of interest to counter immunosenescence and the effects of stress-inducing situations on Earth.

30.2 Effect of Combined Antioxidant Treatment

Increased oxidative stress, which is harmful for cells and can induce many disorders, has been observed after radiation exposure and is associated with spaceflight (Stein and Leskiw 2000; Wan et al. 2005). Indeed, lipopolysaccharide (LPS)-activated splenocytes from mice that flew on the space shuttle mission STS-118 produced more IL-6 and interleukin-10 (IL-10) and less tumor necrosis factor (TNF)-α than control mice (Baqai et al. 2009). The same study showed that many of the genes responsible for scavenging reactive oxygen species (ROS) were upregulated after the flight, suggesting that cells attempted to scavenge ROS produced during spaceflight. An increase in the superoxide response by murine polymorphonuclear neutrophils was also reported even after short periods of microgravity (Fleming et al. 1991). Furthermore, it was shown that the urinary concentration of 8-hydroxy-2′-deoxyguanosine, a marker of oxidative damage to DNA, was higher and that red blood cell superoxide dismutase, an antioxidant enzyme that functions as a superoxide radical scavenger, was lower in astronauts after long-duration spaceflight (Smith and Zwart 2008). Consequently, research was undertaken to determine if antioxidants could protect organisms from radiation-induced oxidative stress. Two studies showed that a mixture of L-selenomethionine (SeM), vitamin C, vitamin E succinate, alpha-lipoic acid, and *N*-acetyl cysteine improved the survival of mice after exposure to protons or to a potentially lethal dose of X-rays (Wambi et al. 2008, 2009) (Table 30.1). Pretreatment of mice with this mixture of antioxidants resulted in significantly higher total white blood cell and neutrophil counts in the peripheral blood and increased bone marrow cell counts after irradiation. Moreover, antioxidants increased Bcl-2 (B cell lymphoma-2, proteins regulating anti-apoptotic mechanisms) and decreased Bax (Bcl-associated X protein promoting apoptosis), caspase 9, and TGF (transforming growth factor)-β1 mRNA expression in the bone marrow after X-ray irradiation (Wambi et al. 2008). In mice or rats exposed to high-energy

particles radiation, D- or L-SeM or a combination of selected antioxidant agents, which included SeM, could also prevent the decrease in total antioxidants by regulating the expression of genes involved in the repair of radiation-induced DNA damage (Kennedy et al. 2004, 2007). These data indicate that antioxidants, alone or in combination, are promising countermeasures for protection against adverse biological effects from space radiation.

30.3 Nucleotides

Nucleotides are beneficial for health because they positively influence lipid metabolism, immunity, and tissue growth, development, and repair (Gil 2002). Rapidly proliferating tissues, such as those of the immune system, are not able to fulfill the

Table 30.1 Effect of countermeasures on immune parameters

Countermeasure	Experiment performed	Results	References
Antioxidants	Irradiated mice + antioxidants	– Antioxidants prevented the decrease of the antioxidant status of animals exposed to protons or high-energy particles	Kennedy et al. 2007
	Irradiated mice (X-rays) + antioxidants	– ↑ survival – ↑ white blood cells and neutrophils in blood – ↑ bone marrow cell counts – ↑ Bcl-2 mRNA in bone marrow – ↓ Bax, caspase 9 & TGF-β1 mRNA in bone marrow	Wambi et al. 2008
Nucleotides	*In vitro* Mouse splenocytes cultured under simulated microgravity conditions and stimulated with PHA + nucleotides	– Nucleoside-nucleotide mixture and uridine restored splenocyte proliferation – ↑ IL-1β, IL-2 & IFN-γ with the nucleoside-nucleotide mixture	Hales et al. 2002
	In vivo Hindlimb-unloaded mice + nucleotides	– RNA and uracil restored popliteal lymph node proliferation, PHA-induced proliferation of splenocytes, IL-2 & IFN-γ production	Kulkarni et al. 2002, 2005
	In vitro Mouse splenocytes cultured under simulated microgravity conditions and stimulated with PHA + nucleotides	– PHA-induced proliferation of splenocytes restored by uridine and nucleoside-nucleotide mixture	Kulkarni et al. 2002, 2005
	In vivo Hindlimb-unloaded mice + nucleotides	– ↑ proliferation – ↑ IL-2 & IFN-γ – ↓ corticosterone plasma level	Yamauchi et al. 2002

(continued)

Table 30.1 (continued)

Countermeasure	Experiment performed	Results	References
AHCC	Hindlimb-unloaded mice infected with *K. pneumoniae* + AHCC	– ↓ mortality – ↑ time to death and ability to clear bacteria – ↑ anti-*K. pneumoniae* IgG levels	Aviles et al. 2003
	Normally housed mice + AHCC	– ↑ spleen cell proliferation induced by Con-A or LPS – ↑ IL-2 & IFN-γ after Con-A stimulation – ↑ IL-4, IL-6 & IL-10 after LPS stimulation – ↑ nitric oxide production in peritoneal cells	Aviles et al. 2004
	Hindlimb-unloaded mice + AHCC	– No effect on splenocyte proliferation induced by Con-A or LPS – ↑ IL-2 & IFN-γ after Con-A stimulation – ↑ nitric oxide production in peritoneal cells – Restored peritoneal cell function	Aviles et al. 2004
DHEA	*In vitro* KLH-primed mouse splenocytes stimulated with KLH + DHEA	*TH2 favored* – ↑ IL-4 – ↓ IFN-γ	Du et al. 2001
	In vitro Mouse splenocytes stimulated with Con-A and LPS + DHEA	– ↓ IL-1, IL-2 & IFN-γ – ↑ IL-10 – IL-4, IL-6 & TNF-α not affected	Powel and Sonnenfeld 2006
	In vivo Retrovirus infected mice + DHEA	*TH1 favored* – ↑ IL-2 & IFN-γ – ↓ IL-6 & TNF-α	Araghi-Niknam et al. 1997
	In vivo Old female mice + DHEA	– ↑ IL-2 & IFN-γ – ↓ IL-6 & IL-10	Inserra et al. 1998

Arrows indicate up and down modulations

needs of cell nucleotides exclusively by de novo synthesis and consequently use the salvage pathway that recovers nucleotides from the blood and diet. Nucleotides modulate the immune system (Nagafuchi et al. 1997; Holen et al. 2006). They influence lymphocyte maturation, activation, and proliferation. Likewise, they affect lymphocyte subset populations in the blood and are involved in enhancing macrophage phagocytosis and delayed hypersensitivity as well as allograft and tumor responses. In addition, they contribute to the immunoglobulin response (Navarro et al. 1996; Nagafuchi et al. 1997; Maldonado et al. 2001), which has a positive effect on clearing infection. The molecular mechanisms by which

nucleotides modulate the immune system are largely unknown. Nucleotides may influence protein biosynthesis as well as signal membrane transduction mediated by the interaction of exogenous nucleosides and their receptors. They may also contribute to modulating the expression of a number of genes, including those involved in the immune system.

Because nutrient absorption and metabolism appear to be altered under spaceflight conditions (see Chap. 29), several studies have analyzed the effects of an exogenous source of nucleotides on immune function using ground-based models of microgravity. Hales et al. (2002) and Kulkarni et al. (2002, 2005) have shown that the decreased splenocyte proliferation in response to phytohemagglutinin (PHA) under simulated microgravity can be restored by a nucleoside-nucleotide mixture and uridine but not by inosine. This observation indicates that pyrimidines are more effective for immunoprotection of the hosts (Table 30.1). In vitro studies also revealed that cultured splenocytes secreted more IL-1β, IL-2, and interferon (INF)-γ in the presence of a nucleoside-nucleotide mixture. In addition, Kulkarni et al. (2002, 2005) performed in vivo studies that demonstrated that popliteal lymph node proliferation, PHA-induced splenocyte proliferation, and IL-2 and IFN-γ production, which are significantly suppressed in hindlimb-unloaded mice (a ground-based model of choice for simulating spaceflight conditions on Earth (Morey-Holton and Globus 2002)), are restored by RNA and uracil. Similarly, Yamauchi et al. (2002) showed that in hindlimb-unloaded mice, nucleotides significantly increased in vivo lymph node proliferation and ex vivo lymphoproliferation response to alloantigen and mitogens, respectively, and IL-2 and IFN-γ production. Moreover, a lower plasma corticosterone level was observed in hindlimb-unloaded mice with RNA and uracil-supplemented diet. Thus, nucleotides and especially uracil/uridine possess immunoprotective effects. These molecules are therefore potential countermeasures for the observed immune dysfunction associated with space travel.

30.4 AHCC

Another interesting compound is the active hexose-correlated compound (AHCC). AHCC is an extract prepared from cocultured mycelia of several species of *Basidiomycete* mushrooms that contains 40% of polysaccharides (β-glucan and acetylated α-glucan which are known to have immune-stimulating effects), amino acids, and minerals. Despite the fact that it is not yet an approved drug, AHCC is the second most popular complementary and alternative medicine used by cancer patients in Japan. It is available to the general public without a prescription. Its legal status is that of a functional food. AHCC may help in the treatment of cancer. Indeed, a cohort study showed a significantly longer no recurrence period and an increased overall survival rate in 113 postoperative liver cancer patients taking AHCC (Matsui et al. 2002). Another study showed that AHCC significantly enhanced cisplatin-induced antitumor effect (Hirose et al. 2007). Several studies have shown that this product has also a positive effect on human and rodent immune systems, including the enhancement of host resistance to influenza and West Nile viruses, the prevention of

thymic apoptosis induced by dexamethasone, the increase of natural killer cell activity, and the induction of IL-12 production (Burikhanov et al. 2000; Matsui et al. 2002; Yagita et al. 2002; Nogusa et al. 2009; Wang et al. 2009). Consequently, it was tested on hindlimb-unloaded mice that present decreased resistance to bacterial infections (*Klebsiella pneumoniae* and *Pseudomonas aeruginosa*) (Belay et al. 2002; Aviles et al. 2003). Indeed, hindlimb unloaded mice showed significantly increased mortality and reduced mean time to death, increased levels of corticosterone, reduced ability to clear bacteria from their organs, and delayed production of anti-*P. aeruginosa* IgG antibodies, by comparison with controls. Aviles et al. (2003) showed that the administration of AHCC for one week before suspension and throughout the 10-day suspension period yielded significant beneficial effects for hindlimb-unloaded mice infected with *K. pneumoniae*, including decreased mortality, increased time to death, and increased ability to clear bacteria (Table 30.1). Furthermore, mice receiving AHCC independent of the type of treatment (hindlimb-unloaded or normally caged) had higher anti-*K. pneumoniae* IgG antibody levels. The same team later demonstrated that AHCC significantly enhanced the function of the immune system in normally housed mice but only enhanced the TH1 response in mice under hindlimb-unloading conditions (Aviles et al. 2004) (Table 30.1). Interestingly, TH1 cytokine production has been shown to be depressed after short- and long-duration missions on the International Space Station (Crucian et al. 2008). Indeed, both groups of astronauts had a low IFN-γ to IL-10 secretion ratio on the day of landing after activation of peripheral blood T cells with anti-CD3 and anti-CD28 antibodies. This observation was confirmed by another study performed on PHA-stimulated splenocytes from mice flown on STS-108, which revealed that both IL-2 and IFN-γ were significantly lower after the flight (Gridley et al. 2003) indicating that a shift toward the TH2 subset is associated with spaceflight. AHCC also restored peritoneal cell functions that are suppressed by hindlimb-unloading and increased nitric oxide production in peritoneal cells isolated from hindlimb-unloaded mice. Other studies showed that AHCC enhanced resistance to infection. In a mouse model of surgical wound infection, mice receiving AHCC were better able to clear bacteria from their systems than control animals (Aviles et al. 2006). AHCC also increased immune function that resulted in a lower bacterial load in a murine model of intramuscular infection (Aviles et al. 2008). In conclusion, AHCC appears to be an efficient immunoenhancer that restores innate immunity, which is greatly affected by hindlimb-unloading, and consequently represents another countermeasure with great potential that warrants further investigation.

30.5 DHEA

Dehydroepiandrosterone (DHEA) is one of the major circulating adrenal cortical hormones in humans and many other warm-blooded animals. This hormone is secreted by the adrenal cortex in response to stress (Kroboth et al. 1999). In the plasma, DHEA is predominantly present as DHEA-S that generates DHEA after cleavage of the sulfate group. For many years, the physiological significance of

DHEA remained elusive. However, many studies have now shown that DHEA has significant immune modulatory functions, exhibiting both immune stimulatory and anti-glucocorticoid effects (for review see Hazeldine et al. 2010). DHEA-S increases superoxide generation in primed human neutrophils in a dose-dependent fashion, thereby impacting a key bactericidal mechanism (Radford et al. 2010). In murine models, exogenous DHEA counteracts stress-induced glucocorticoid immunosuppression and increases the resistance of mice to viral and bacterial infections (Ben et al. 1999; Zhang et al. 1999). In murine model systems of aging, DHEA appears to reverse the immunological defects seen as a consequence of aging. In particular, DHEA increases the ability of old mice to resist experimental viral and bacterial disease (Daynes et al. 1993; Kalimi and Regelson 1990; Straub et al. 1998). DHEA administration also restores immune function after thermal and trauma-hemorrhage injury and reduces mortality rates from septic challenge (Knoferl et al. 2003). In addition, DHEA provides protection against several diseases, including diabetes, oncological disorders, autoimmune disease, and chronic inflammatory illness (Kalimi and Regelson 1990). DHEA appears to be a potent regulator of cytokine production supporting the idea that this molecule acts on T cells, which is the lynch pin of the adaptive immune response. However, conflicting results on cytokine production in the presence of DHEA have been reported (see Table 30.1). In vitro studies (Du et al. 2001; Powell and Sonnenfeld 2006) showed that DHEA may be an important factor for increasing TH2 cytokine synthesis, which encourage vigorous antibody production and are commonly associated with antibody responses important for resisting infection, and decreasing TH1 and proinflammatory cytokine production. However, DHEA has shown an opposite effect in vivo in which a TH2 downregulation (or TH1 upregulation) associated with DHEA administration has been found in old or retrovirus-infected mice (Inserra et al. 1998; Zhang et al. 1999; Araghi-Niknam et al. 1997). These discrepancies may reflect differences in assays used to determine DHEA effects on cytokine production or differences in animals used. Additionally, whereas in vitro DHEA is protected from biomodifications, in vivo DHEA administration could lead to rapid clearance from the blood and conversion to other steroids in peripheral tissue, which can affect T cells differently from DHEA. Despite these contradictory data, DHEA seems to be an interesting countermeasure to fight the effects of spaceflight-associated stress on the immune system.

30.6 Conclusion

The combination of antioxidants and the pharmacologic, immune-directed action of nucleotides, AHCC and DHEA show various degrees of efficiency to restore immune system alterations. Some of these molecules are able to restore one part of the immune response such as AHCC, which mainly restores innate immunity, while others, like antioxidants, have a more general action on the organism. Searching for efficient countermeasures is a promising area of research that deserves more investigation to counter or restore alterations of the immune system in Space and on Earth.

Acknowledgments JPF and his team were supported by the French National Space Agency (CNES).

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