COUNTERMEASURE FOR SPACE FLIGHT EFFECTS ON IMMUNE SYSTEM: NUTRITIONAL NUCLEOTIDES

A. D. Kulkarni1, K. Yamauchi1, A. Sundaresan1,2, G.T. Ramesh3, N. R. Pellis4
1Department of Surgery, Medical School and GSBS, Univ. of Texas Health Science Center, 2USRA/NASA, 3Texas Southern University, 4JSC/NASA, Houston

Microgravity and its environment have adverse effects on the immune system. Abnormal immune responses observed in microgravity may pose serious consequences, especially for the recent directions of NASA for long-term space missions to Moon, Mars and deep Space exploration. The study of space flight immunology is limited due to relative inaccessibility, difficulty of performing experiments in space, and inadequate provisions in this area in the United States and Russian space programs (Taylor 1993). Microgravity and stress experienced during space flights result in immune system aberration (Taylor 1993). In ground-based mouse models for some of the microgravity effects on the human body, hindlimb unloading (HU) has been reported to cause abnormal cell proliferation and cytokine production (Armstrong et al., 1993, Chapes et al. 1993). In this report, we document that a nutritional nucleotide supplementation as studied in ground-based microgravity analogs, has potential to serve as a countermeasure for the immune dysfunction observed in space travel.

We employed two ground-based analogs, HU as an in vivo model and a clinostat bioreactor (BIO) as an in vitro cell culture model. We examined the effects of supplemental nutritional nucleotides on immune function in these analogs. BALB/c female mice (8-10 week old) were divided into the following two groups: control non-HU, and HU for 7 days. Mice were fed either control chow or chow supplemented with RNA or Uracil (referred as NT). Immune function was assessed by in vivo popliteal lymph node proliferation (PLN), and in vitro phytohemagglutinin (PHA)-stimulated proliferation of splenocytes and their cytokine production, (Kulkarni et al, 2002). PLN response was calculated as weight gain in allogeneic challenged lymph node versus weight gain in syngeneic challenged contralateral lymph node. Splenocytes were cultured in vitro in BIO with/without PHA and nucleoside/nucleotide mixture (referred as NS/NT). Cell proliferation was assessed by titrated thymidine uptake assay by thymidine uptake in stimulated cultures versus unstimulated cultures. Cytokines released by cultured and stimulated cells were quantified by ELIZA method (Cayman Co.). PLN response was significantly suppressed in HU mice (P<0.05) and was restored by NT supplemented diets (Figure 1). Splenocytes from HU mice had decreased PHA stimulated proliferation and decreased IL-2 and IFN-γ cytokine levels (P<0.05) as well (Figure 1-A,B,C). These responses were restored by NT diets. In BIO cultures, PHA response was suppressed significantly, and NS/NT restored the proliferation response (Figure 2). Results in these figures are expressed as percent changes in groups. In both models, we documented that dietary and supplemental nucleotides (NT or NS/NT) restored several
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immunological functions in mice including cytokine production, and decreased corticosteroid levels. Many of the parameters of cellular functions are shown in Figure 3. Similar effects are seen by NT supplementation in 1 G (Kulkarni et al., 1990) and in µG analogs. These observations clearly document the advantages and benefits of exogenous source of nucleotides in the form of nutritional NT supplementation. Observed decrease in corticosteroid levels in HU mice by NT supplementation may be one of the potential mechanisms for immune restoration observed in these mice.

Understanding of the mechanisms of immune restoration in microgravity analogs, including CNS mediated effects and their implications, is important in addressing the NASA’s CRP and CRL maps. Nucleotide metabolism is very important for cell cycle. Perturbations in nucleotide metabolism that lead to a variety of diseases are primarily in the de novo pathways. Supplemented nucleotides participate and contribute primarily in the salvage pathway and they are utilized by rapidly proliferating target cells (Kulkarni et al 1990). As compared with the amounts of available nucleotides from the de novo synthesis and the endogenous salvage pathway, the levels of supplemental nucleotides in the experimental (Kulkarni et al., 1990, 2002) and clinical studies are much smaller (Bower et al. 1995, and Carver and Walker, 1995) and without any adverse or untoward effects. The amount of NT added was minimal in all the groups; however, the beneficial effect was seen only in the microgravity analogs of HU or BIO and not in any control groups where there was no demand or stress involved. Thus, in conclusion our studies presented in this report document the critical need of NT supplementation in physiological stress situations; such as space travel, where nutritional supplemental nucleotides have up-regulating and immunoprotective effects with potential as a countermeasure to the observed immune dysfunction in true microgravity.

Key words: nucleotide; nutrition; immunity; space travel

REFERENCES:


