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ADAPTIVE RESPONSE STUDIES MAY HELP CHOOSE ASTRONAUTS FOR LONG-TERM SPACE TRAVEL

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ABSTRACT

Long-term manned exploratory missions are planned for the future. Exposure to high-energy neutrons, protons and high charge and energy particles during a deep space mission, needs protection against the detrimental effects of space radiation. It has been suggested that exposure to unpredictable extremely large solar particle events would kill the astronauts without massive shielding. To reduce this risk to astronauts and to minimize the need for shielding, astronauts with highest significant adaptive responses should be chosen. It has been demonstrated that some humans living in very high natural radiation areas have acquired high adaptive responses to external radiation. Therefore, we suggest that for a deep space mission the adaptive response of all potential crew members be measured and only those with high adaptive response be chosen. We also proclaim that chronic exposure to elevated levels of radiation can considerably decrease radiation susceptibility and better protect astronauts against the unpredictable exposure to sudden and dramatic increase in flux due to solar flares and coronal mass ejections.

INTRODUCTION

In recent decades, relatively long term space missions have been experienced by some space crews. No doubt, in the near future deep space journeys, up to a few years long, will be planned. Despite current advances, there are still some major problems that limit the duration of such long-term space missions. Microgravity and radiation risk from high level cosmic rays exposure are important concerns that need to be addressed prior to a long-term space mission. It has been reported that microgravity increases the radiation susceptibility of living organisms by a synergistic effect (Reitz *et al.*, 1989). If this is true, the radiation risk would be considerably increased in long term space travel. Trapped protons and electrons from the South Atlantic Anomaly, galactic cosmic radiation (GCR), and solar energetic particles are the three major sources of the space radiation environment in low Earth orbit (Badhwar, 2000). In the astronauts, carcinogenesis is the major risk at the doses and dose rates encountered in space (Edwards, 2001). Adaptive response, that is an increased radioresistance in cells or organisms exposed to a high challenging dose after exposure to a low adapting dose, can considerably reduce the radiation susceptibility of humans (Olivieri *et al.*, 1984). It has recently been shown that neutrons can induce adaptive response in Chinese hamster V79 cells (Marples and Skov, 1996) or human lymphocytes (Gajendiran *et al.*, 2001). These findings, if confirmed by similar adaptive response experiments with high-energy protons and heavy ions, can reduce the radiation susceptibility during long-term stay in space.

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CHRONIC SPACE RADIATION VS. TRANSIENT ACUTE EXPOSURES

Although GCR is believed to be isotropic throughout interstellar space, solar flares and coronal mass ejections can produce a sudden and dramatic increase in flux of particles (Benton and Benton, 2001) and expose the space crews to transient high levels of ionizing radiation as depicted in Fig. 1. If we define a solar particle event as a period in which the flux of protons E>10 MeV exceeds 10 particles /s cm-2 sr (NOAA Space Environment Center Definition), there was a solar particle event on 5% of the days (18 days/year) during most of the active years of each solar cycle (Feynman and Ruzmaikin, 1999). However in 1989, solar particle events were observed on 51 days. Furthermore, astronauts receive extra doses in the course of their extravehicular activities (EVAs). Although spacecraft shielding is generally greater than 1 g/cm2 (1-5 g/cm2 for STS or 8-15 g/cm2 for MIR), EVA suits are considerably thinner and astronauts during EVAs might be exposed to much higher radiation doses than inside the spacecraft (Thomson, 1999). The dose equivalent in a spacecraft with aluminum walls (2 g cm-2) at solar minimum during a 406-day Mars mission is estimated to be 0.73 Sv (Badhwar et al., 1992). Also during a deep space mission an anomalously large solar energetic particle event may occur that expose astronauts to radiation skin doses up to approximately 25 Gy and dose equivalent to the blood-forming organs (BFO dose) will be up to 2 Sv with no shielding (Letaw et al., 1989). Solar particle events can occur any time with a slight preference of extremely large events to happen during descent from a maximum of solar activity. It has been estimated that exposure to extremely large solar particle events such as the one that occurred in August 1972 or the even larger one, in February 1956 would kill the astronauts in interplanetary space without massive shielding (Obe et al., 1999).

Therefore, long-term deep space missions expose astronauts to both chronic space radiation and acute high levels of energetic radiations during solar particle events or EVAs. It is generally believed that the biological effects of small dose rates of ionizing radiation may produce no detectable effects. However, the biological effects of a high dose preceded by a low dose radiation may be significantly different than a high dose alone. Potential interactions from low dose A and high dose B can either be a simple additivity (AB= A + B), adaptive responses (AB < A + B) or synergistic effects (AB > A + B) as shown in Fig. 1. Long-term follow-up studies show that the type of interaction is determined by intrinsic factors such as genetic constitution of each individual (Ikushima and Mortazavi, 2000). Even though responses for low-LET radiations (mainly photons and beta particles) are documented to some extent, there are no data on possible interactions of high-energy protons or high-LET heavy ions. However significant adaptive response has been observed in some humans after exposure to high levels of low and high LET natural radiation (Mortazavi and Karam 2002, Ghiassi-nejad et al., 2002). It should be noted that exaggerated sensitivity to radiation after exposure to a low dose has also been observed (Bosi and Olivieri, 1989, Aghamohammadi and Savage, 1991). A 3-year follow up study has shown that the exaggerated sensitivity to radiation is not a transient response and possibly depends on genetic factors (Mortazavi and Ikushima, unpublished data). The data are consistent with the results of the experiments, which have been performed on monozygotic and dizygotic twins (Kalina and Nemethova, 1997). Although the frequency of damage in cells exposed to low dose alone or challenge dose alone, was not different than those of control study participants, an extraordinary increased damage in the cells exposed to a high dose after a small dose has been observed (Ikushima and Mortazavi, 2000). Based on these results, G2 assays due to possible interactions of different levels of radiation doses cannot predict the radiosensitivity of potential astronauts during a long-term space mission. Thus we suggest that ground based adaptive response studies are essential in determining the interactions between different dose rates of low-LET as well as high-LET radiations in lymphocyte samples of potential crew for deep space missions.

ADAPTIVE RESPONSE AND INTERINDIVIDUAL VARIABILITIES

When living organisms are exposed to a variety of DNA damaging stresses such as UV, alkylating or oxidizing agents and heat, adaptive responses are induced which cause resistance to the agent (Samson and Cairns, 1977). The early investigations of Wolff and his colleagues showed that cultured human lymphocytes, which were exposed to a low dose of ionizing radiation had fewer chromatid aberrations induced by a subsequent high dose as compared to the lymphocytes that have not been exposed to a low dose (Olivieri et al., 1984). Since 1984, many investigators have demonstrated radioadaptive response in plant cells (Cortes et al., 1990), insects (Fritz-Niggli and Schaeppi-Buechi, 1991), Chinese hamster V79 cells (Ikushima, 1987), cultured human lymphocytes (Wiencke et al., 1986), human embryonic and HeLa cells (Ishii and Watanabe, 1996), occupationally exposed persons (Barquinero et al., 1995), cultured animal lymphocytes (Flores et al., 1996), and in vivo studies on laboratory

animals (Wojcik and Tuschl, 1990). It has been shown that the pre-exposure of the cultured cells to low doses of radiation is not instantaneous but takes 4-6 hours to become fully active (Shadley et al., 1987). Furthermore, the same experiments showed that the induced adaptive response in pre-irradiated cells persists for at least three cell cycles.

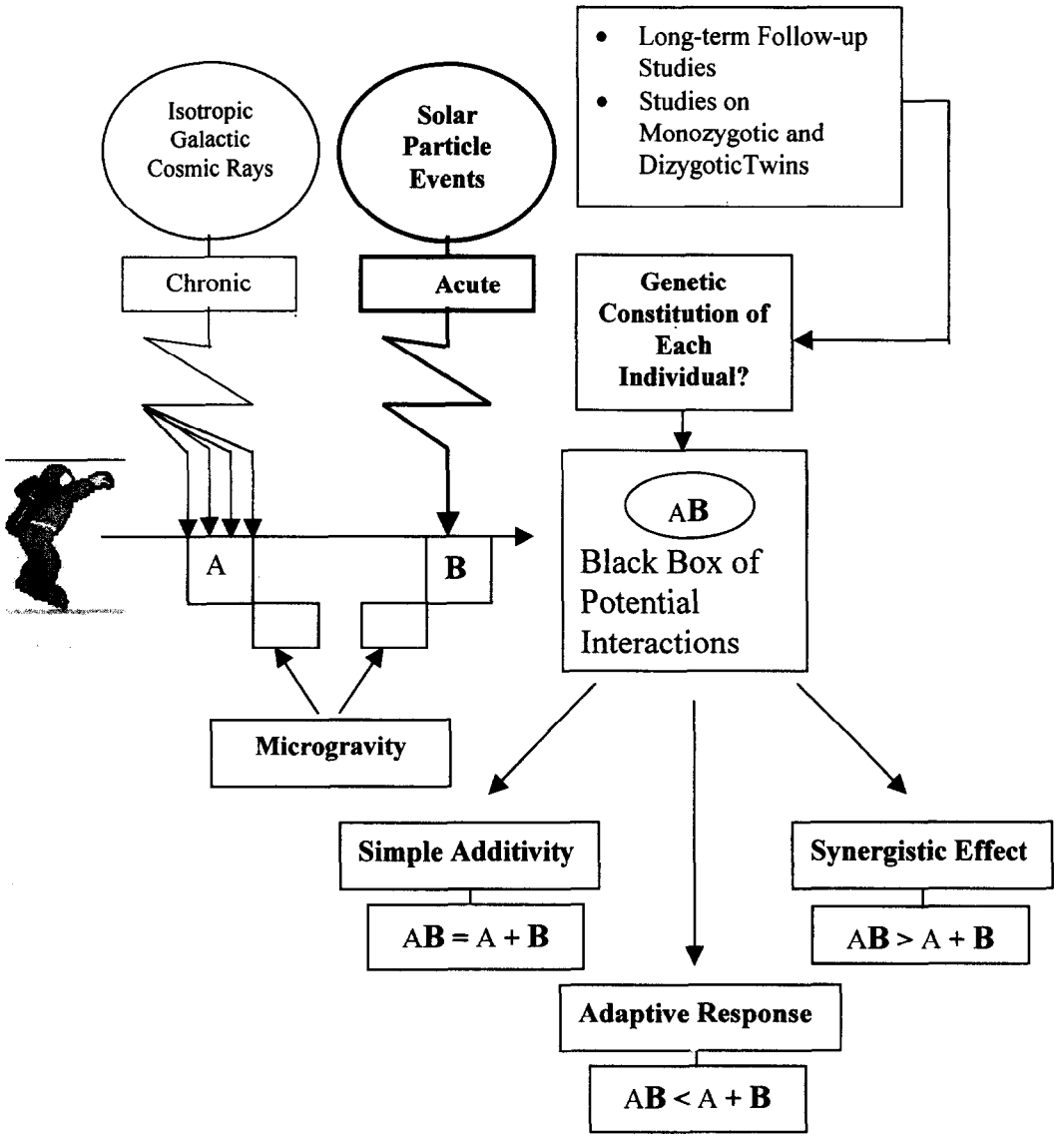

Fig. 1. Possible interactions between low level galactic cosmic radiation and acute high doses due to sudden increase in particle flux in unpredictable events such as a solar particle event.

There are reports indicating lack of radioadaptive response in cultured human lymphocytes (Bosi and Olivieri, 1989, Olivieri and Bosi, 1990). Long-term follow up studies indicate that lack of radioadaptive response is not a temporary effect (Mortazavi et al., 1999) and in contrast with the early reports of Olivieri and Bosi (1999) does not depend on transient physiological factors (Ikushima and Mortazavi, 2000, Mortazavi et al., 2000). On the other hand, it has been shown that in some individuals, exaggerated sensitivity to radiation after exposure to a low dose was observed. A 3-year follow up study showed that the exaggerated sensitivity to radiation is not a transient response and possibly depends on some stable factors such as genetic constitution of each individual (Mortazavi and Ikushima, unpublished data). The data confirm the results of Kalina and Nemethova (Kalina and Nemethova,

1997) who showed that individual differences in radioadaptive response between the monozygotic twins were negligible but in the case of dizygotic twins, these variations were much greater and were comparable to those observed in unrelated individuals.

ADAPTIVE RESPONSE AND NEW HORIZONS IN SPACE RADIATION PROTECTION

During the past two decades worldwide studies on the different aspects of adaptive response and recognition of its positive health effects have lead to a more realistic assessment of the risk of radiation. It was generally believed that the presence of adaptive response does not mean that the low dose radiation is beneficial to living organisms (Sagan, 1989, Wolff, 1989). After publication of the preliminary results on the presence of adaptive response in the residents of high background radiation areas of Ramsar (Mortazavi et al., 2001), some scientist reported that the induced adaptive response may have considerable implications in radiation protection. Pollycove and Feinendegen (2001) reported that Ramsar results suggest that chronic low dose radiation may be protective against accidental high dose radiation.

Early experiments showed that neutrons fail to induce an adaptive response in human lymphocytes (Wiencke et al., 1987, Khandogina et al., 1991). On the other hand it was reported that low doses of X-rays decreased the yield of chromosomal aberrations induced by subsequent exposure to high-LET radiation (Wolff et al., 1991). The frequency of chromatid deletions in human lymphocytes that were treated with radon after pre-exposure to a 2cGy adapting dose of X-rays, was about 50% of those exposed to radon alone. This study showed that chromosomal repair mechanisms induced by low-LET radiations may also effectively reduce the chromosomal aberrations induced by high-LET radiations.

High LET particles induce an increased frequency of chromosome breakage and highly complex chromosome rearrangements (Kawata et al., 2001). It has recently been shown that neutrons can induce adaptive response in Chinese hamster V79 cells (Marples and Skov, 1996) or human lymphocytes (Gajendiran et al., 2001). Interestingly, when Chinese hamster V79 cells were exposed to low adapting doses of X rays (low LET), Bragg-peak negative pi mesons (intermediate/high LET) or neutrons (high LET), the largest increase in plating efficiency and survival were evident after neutron adapting doses (Marples and Skov, 1996). Although the differences were not statistically significant, the trend in the data suggested that cells which survive neutron adapting doses were adapted more effectively to respond to the X ray challenge dose (Marples and Skov, 1996). These findings, if confirmed by large-scale adaptive response experiments with high-energy protons and heavy ions, can reduce the radiation risks during a long-term stay in space.

As noted earlier, a 4-6 hour time interval is needed between the adapting and challenge doses for expression of an adaptive response and that the response persists for at least 3 cell cycles. We believe these factors do not limit the application of the adaptive response for astronauts who are continuously exposed to high levels of radiation during a long-term mission. We proclaim that when solar flares start, the cells are "ready to response" due to their acquired adaptive response.

It has been shown that in high background radiation areas (HBRAs), inhabitants whose cumulative radiation doses were as much as 170 times more than those of a nearby control area (2,550 mSv and 15 mSv respectively) were significantly more radioresistant to chromosomal damage when subjected to 1.5 Gy challenge dose (Ghiassi-nejad et al., 2002, Mortazavi et al., 2002, Mortazavi and Karam 2002). The relationship between the degree of adaptive response (as indicated by the k-value) and cumulative lifetime dose is an important finding. The radioadaptive response of the residents of HBRAs is more pronounced (lower k values) at higher cumulative doses except for 2 residents, whose cumulative doses are much higher than the others. That is, increased dose from natural radiation decreases the radiation sensitivity of the cells.

ADAPTIVE RESPONSE AFTER PROTONS AND HEAVY IONS EXPOSURE

Adaptive response studies in human cells from protons and heavy ions are of great importance. Reproducible experiments showed that very low doses of ionizing electromagnetic radiations or neutrons could induce mechanisms whereby cells became somewhat refractory to the induction of detrimental effects by subsequent exposure to the high doses of low or high LET radiations. Galactic cosmic radiation (GCR), solar cosmic radiation (SCR), and the radiation from the van Allen belts are the three main sources of radiation exposure during space flights (Spurny, 2001). Protons are the main component of galactic cosmic radiation (85.5% of the flux). Also solar cosmic radiation is composed mostly of protons (99% of the flux). Despite their low percentage in the galactic cosmic radiation (1%), heavy ions have significant biological effects due to their high LET (Kawata et. al., 2001).

The majority of radiation dose inside a spacecraft arises from high energy electrons and protons. When the spacecraft shielding is greater than 1 g/cm2, protons dominate the radiation dose (Thomson, 1999). Currently no data are available for induction of adaptive response by high energy protons or heavy ions. Considering the importance of protons and heavy ions in space research, we have planned an integrative project for assessing the radioadaptive response by high-energy protons and heavy ions.

IDENTIFICATION OF AR POSITIVE VS. RADIOSENSITIVE HUMAN SUBPOPULATIONS

In space radiation studies, it has been widely reported that the identification and hence selection of subpopulations that are genetically susceptible to ionizing radiation is of great concern (Hall, 2002). In humans, only the gene for ataxia telangiectasia (AT) has been confirmed to control the radiation susceptibility (Hall, 2002). However, identification of the radiosensitive human subpopulations is not an easy task because (a) only 1-2% of the population is AT heterozygotes (Smilenov et al., 2001), (b) screening for identification of AT is very costly and (c) AT homozygotes can also show adaptive responses (Seong et al., 1995). We believe that adaptive response studies may help identify individuals who are either radioresistant or have high magnitudes of radioadaptive response. Identifying these subpopulations is much easier than radiosensitive subpopulation, and its cost is also much lower.

To use cytongenic adaptive response in selection of astronautes we define the following four quantities:

- CONT - Frequency of spontaneous (background) chromosome aberrations in control or non-irradiated cells: It has been reported that chromosomal radiosensitivity is closely linked to cancer predisposition (Scott et al., 1998, 1999). It has been also shown that the frequency of chromosomal aberrations in peripheral blood lymphocytes is an early biological effect biomarker for cancer risk in humans, reflecting either early biological effects of genotoxic carcinogens or individual cancer susceptibility. Hagmar et al. (1998) reported that based on their results obtained by analysis of data for 3541 subjects examined for chromosomal aberrations (CA), 2703 for sister chromatid exchange, and 1496 for micronuclei (MN), the frequency of CAs in peripheral blood lymphocytes was a relevant biomarker for cancer risk in humans.
- AD and CD – Are the frequency of chromosome aberration for cells exposed to adapting dose and challenge dose, respectively: Frequency of chromosome aberration for cells exposed to a high dose may be associated with an increased risk for cancer (Bondy et al., 2001). Ikushima and Mortazavi (2000) have shown that in human lymphocytes, while AD and CD values are not different than those of other study participants, an increased frequency of chromosomal aberrations in the cells exposed to challenge dose after an adapting dose has been observed. It should be noted that AD and CD alone are not reliable indicators for the prediction of the magnitude of the adaptive response. Frequency of chromatid aberrations in human lymphocytes of 4 healthy individuals given 5 cGy followed by 2 Gy of 150 kVp X-rays is presented in Table 1. More details about chromatid aberrations method and techniques can be found in Ikushima and Mortazavi 2000 publication.

Table 1, shows while 3 individuals demonstrate a radioadaptive response, the first donor demonstrates a significant synergistic effect.

Table 1. Frequency of chromatid aberrations in human lymphocytes treated with 5 cGy followed by 2 Gy of 150 kVp X-rays.

	No. of chromatid aberrations (CA) per cell[a]			
Donor	1st	2nd	3rd	4th
Observed frequency of CA	0.60	0.45	0.46	0.62
Expected frequency of CA	0.32	0.60	0.62	0.78
p-value	<0.01	<0.05	<0.05	<0.05
Response	Synergistic	Adaptive	Adaptive	Adaptive
k-value	1.86	0.75	0.74	0.79

[a] 400 cells were scored for each point.

Using micronuclei assay as the end point confirmed the previous results. Table 2 shows the frequency of micronuclei in binucleated cells of the non-responder and 3 new control individuals exposed to 5 cGy followed by 2 Gy of 100 kVp X-rays. Based on the results obtained in this experiment, a common G2 radiosensitivity assay

(Baria et al., 2001) cannot predict cancer risk during a long-term space mission, where the interactions of low chronic cosmic doses and potential high short time doses due to solar activity are inevitable.

Table 2. Frequency of micronuclei in binucleated cells of the non-responder and 3 control donors exposed to 5 cGy followed by 2 Gy of 100 kVp X-rays.

	No. of micronuclei (MN) per binucleated cell[a]			
Donor	1st	2nd	3rd	4th
Observed frequency of MN	0.30	0.24	0.31	0.23
Expected frequency of MN	0.24	0.40	0.31	0.39
p-value	<0.001	<0.001	NS	<0.001
Response	Synergistic	Adaptive	Additivity	Adaptive
k-value	1.25	0.58	1	0.59

[a] 1000 cells were scored for each point.
NS: not significant.

- ADCD - Frequency of chromosome aberration for cells exposed to adapting dose followed by a challenge dose: If the frequency of chromosomal aberrations in cells exposed to both adapting and challenging doses is defined as the "observed" chromosomal aberrations and the "expected" frequency of chromosomal aberrations is defined as AD + CD – CONT, then the induced adaptive response can be determined by comparing the "observed" frequency to "expected" frequency.

- k-value - Coefficient of adaptive response: The coefficient of adaptive response can be calculated as follows: k = Observed CA / Expected CA. If k is significantly less than 1, it indicates induction of an adaptive response. This value varies for different individuals. Individuals with small k value should be considered good candidates for a long-term space mission. Inter-individual variability concerning the capability of each astronaut for adaptation to ionizing radiation has been always ignored. In a recent study, the frequency of chromosomal aberrations in 22 cosmonauts who stayed on average 4-6 months in MIR station was measured (Fedorenko et al., 2001). The results of this study showed that the frequency of cells with dicentrics and centric rings after the mission was approximately 3 times higher than that was scored before the mission. These results are consistent with some earlier reports that showed an increase in the chromosomal aberrations of blood lymphocytes of cosmonauts after a space mission (Testard et al., 1996, Yang et al., 1997). Reviewing the results obtained in the study of Fedorenko shows that among the 22 cosmonauts participated in their study, the after mission percentage of chromosomal aberrations in 6 cosmonauts is less than that of the before mission. Also the after mission frequency of the cells with dicentrics and centric rings in four cosmonauts was less than that of before mission. Interestingly, in one case, the after mission frequency of chromosomal aberrations was about 1/3 of the before mission value. However, as it has been recently reported by Durante et al. (Durante et al., 2001), the use of an appropriate technique for the collection and analysis of chromosomes and the choice of the structural aberrations to be measured are crucial in providing reliable results. Considering statistical uncertainties in these data, further research is needed to clarify whether these findings indicate reproducible adaptive response phenomena.

CONCLUSION

Astronauts are irradiated with high levels of radiation. Solar activity is unpredictable. Space-walking crews and astronauts who participate in long-term space missions may receive high doses of radiation in a short time. Recent findings concerning the induction of adaptive response by neutrons and high cumulative doses of gamma radiation in human cells have opened the possibility of radiation adaptive response in humans. Screening the candidates of long-term space missions by in vitro adaptive response studies will help to identify individuals with low radiation susceptibility and high radioadaptive response. In these selected individuals, chronic exposure to elevated levels of space radiation during a long-term mission can considerably decrease their radiation susceptibility and better protect them against the unpredictable exposure to relatively high radiation levels caused by solar activity.

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