

Adaptive response and split-dose effect of radiation on the survival of mice

ASHU BHAN TIKU and R K KALE*

*Free Radical Biology Laboratory, School of Life Sciences, Jawaharlal Nehru University,
New Delhi 110 067, India*

**Corresponding author (Fax, 91-11-26187338; Email, rkkale@hotmail.com)*

Although the importance of radiation-induced adaptive response has been recognized in human health, risk assessment and clinical application, the phenomenon has not been understood well in terms of survival of animals. To examine this aspect Swiss albino mice were irradiated with different doses (2–10 Gy) at 0.015 Gy/s dose rate and observed on a regular basis for 30 days. Since almost 50% lethality was seen with 8 Gy, it was selected as the challenging dose for further studies. Irradiation of mice with conditioning doses (0.25 or 0.5 Gy) and subsequent exposure to 8 Gy caused significant increase in the survival of mice compared to irradiated control. The splitting of challenging dose did not influence the efficiency of conditioning doses (0.25 Gy and 0.5 Gy) to induce an adaptive response. However conditioning doses given in fractions (0.25 Gy + 0.25 Gy) or (0.5 Gy + 0.5 Gy) were able to modulate the response of challenging dose of 8 Gy. These results clearly showed the occurrence of adaptive response in terms of survival of animals. The conditioning dose given in small fractions seemed to be more effective. The findings have been discussed from a mechanistic point of view. The possible biological implications, potential medical benefits, uncertainties and controversies related to adaptive response have also been addressed.

[Tiku A B and Kale R K 2004 Adaptive response and split-dose effect of radiation on the survival of mice; *J. Biosci.* **29** 111–117]

1. Introduction

Ever since Olivieri *et al* (1984) have shown a reduction in the number of chromosome aberrations in lymphocytes given a small conditioning dose prior to exposure to higher challenging dose of ionizing radiation, there is growing interest in the radiation-induced adaptive response. Different systems have been tested for adaptive response induced by small doses of radiations using various biological end points such as sister chromatid exchanges (Morimoto *et al* 1986), mutation frequency (Sanderson and Morley 1986; Rigaud and Moustacchi 1996) and chromosome repair in human lymphocytes (Shadely and Wolff 1987); survival in normal, cancer-prone and neoplastic cells (Boothman *et al* 1996); clone-forming ability in human keratinocyte cells (Kleczkowska and Althaus 1996); clonogenicity in HT 29 cells (Wouters and Skarsgard 1997) and neoplastic transformations in human cell lines (Redpath and Antoniono 1998); cytogenetic effects in periph-

eral blood lymphocytes of rabbits (Cai and Liu 1990); chromosome aberrations and bone marrow micronuclei in mice (Farooqi and Kesavan 1993); and proliferation and survival of spleen cells obtained from irradiated mice (Wang and Cai 2000). Recently adaptive response at biochemical levels has also been demonstrated in tissues of irradiated mice (Yamaoka *et al* 1991; Zhang *et al* 1998; Tiku and Kale 2001). The significance of radiation-induced adaptive response has been well recognized. Since the data from epidemiological studies are still insufficient to define its implications for human health, risk assessment and therapeutic measures (Wolff 1998; Skov 1999a; Dasu and Denekamp 2000), the results from animal experiments particularly survival studies are suggested to be extremely important (Wang *et al* 1999; Yonezawa 2000; Kadhim *et al* 2001).

In the present work, we report radioadaptive response in terms of survival of Swiss albino mice and also its modulation by fractionation of conditioning as well as challenging dose.

Keywords. Adaptive response; low dose; radiation; survival

2. Material and methods

2.1 Animals

Male, Swiss albino mice (7–8 weeks old) were used for the present study. They were housed (6 animals per cage) in polypropylene cages and maintained in the air-conditioned University animal facility providing standard food (Hindustan Lever Ltd.) and water *ad libitum*. The studies were conducted according to the ethical guidelines of the Committee for Control and Supervision of Experiments on Animals, Government of India, on the use of animals for scientific research.

2.2 Irradiation

Animals were irradiated in air at room temperature in a gamma chamber (240 TBq, ^{60}Co , Model 4000A); obtained from Bhaba Atomic Research Centre (BARC), Mumbai. The dose rate was estimated by the Fricke dosimetry, and was 0.015 Gy/s.

2.3 Survival studies

Survival was monitored daily and was reported as percentage of animals surviving 30 days after last irradiation. During the entire course of study the individual body weight of the mice was recorded everyday. From this average change in body weight per mouse per treatment group was calculated. After running a pilot experiment for dose response studies, animals were divided into eight categories comprising of 18–31 mice per treatment group.

Mice were divided into following groups:

Group 1: unirradiated mice, served as control.

Group 2: mice irradiated with 8 Gy, served as irradiated control.

Group 3: mice pre-treated with conditioning dose of 0.25 Gy and subsequently irradiated with a challenging dose of 8 Gy at an interval of 6 or 24 h.

Group 4: mice pre-treated with conditioning dose of 0.5 Gy and subsequently irradiated with a challenging dose of 8 Gy at an interval of 6 or 24 h.

Group 5: mice pre-treated with conditioning dose of 0.25 Gy and subsequently irradiated with a challenging dose of 8 Gy split into two equal doses of 4 Gy spaced at an interval of 24 h.

Group 6: mice pre-treated with conditioning dose of 0.5 Gy and subsequently irradiated with a challenging dose of 8 Gy split into two equal doses of 4 Gy spaced at an interval of 24 h.

Group 7: mice pre-treated with conditioning dose of 0.25 Gy followed by another dose of 0.25 Gy after 6 h. The chal-

lenging dose of 8 Gy was delivered 24 h after exposure to the second fraction of conditioning dose.

Group 8: mice pre-treated with conditioning dose of 0.5 Gy followed by another dose of 0.5 Gy after 6 h of first irradiation and subsequently irradiated with a challenging dose of 8 Gy spaced at an interval of 24 h to the second fraction of conditioning dose.

2.4 Statistical analysis

The statistical analysis was performed using χ^2 test with Yates correction to show significance of difference between different treatment groups.

3. Results and discussion

Animals were irradiated with different doses of gamma rays (2–10 Gy) and then returned to their cages. They were observed on regular basis for thirty days. The radiation-induced death profile is shown in table 1. No deaths were observed with radiation doses between 0–4 Gy. However, 6 Gy and beyond caused mortality which increased with dose. Mice died within the first ten days after exposure to 6 Gy and no further deaths were reported thereafter. Mortality was observed till the end of the second week in mice exposed to 8 Gy. For mice irradiated with 10 Gy deaths were seen even beyond 20 days. Thirty-day survival response of mice irradiated with different doses (6, 8 and 10 Gy) is shown in figure 1A. These findings were consistent with earlier reports (Prasad 1982). LD 50/30 for mice was found to be 7.86 Gy. It may be mentioned that the body weight was adversely affected at higher doses particularly with 8 and 10 Gy. There was no significant change in average body weight of mice irradiated with 2 and 4 Gy.

Since, more than 50% animals died with 8 Gy within thirty days, this dose was used as challenging dose to study the adaptive response in terms of survival. Mice pre-exposed to conditioning dose of 0.25 or 0.5 Gy were irra-

Table 1. Effect of different doses of gamma rays on the death profile of Swiss albino mice.

Dose (Gy)	Total No. of animals	No. of animals survived (till 30 days)	Death rate (%)
0	24	24	0
2	24	24	0
4	24	24	0
6	24	21	12.5
8	24	10	58.33
10	24	2	91.67

diated after 6 h or 24 h with 8 Gy and regularly observed for thirty days (table 2). Pre-irradiation of mice with conditioning doses resulted in significant increase in the survival compared to the group of animals irradiated with 8 Gy only (figure 1B).

Although, in adaptive response the conditioning dose is known to protect against the radiation damage induced by subsequent high doses, its mechanism is not very well understood (UNSCEAR 1994; Wolff 1998). Initial exposure to small doses of radiations is known to condition the cells to enhance DNA repair ability, produce protective proteins to minimize the indirect damaging effect of subsequent high doses of radiations (Yamaoka *et al* 1994, 1998; Cai *et al* 1999), stimulate proliferation as well as

immune response (UNSCEAR 1994) and induce delay in the passage of cells through the cell cycle (Filippovich *et al* 1998). Selective elimination of irreparably damaged cells by apoptosis is considered another mechanism of cell defense contributing to adaptive response (Cregan *et al* 1994; Potten *et al* 1994). The increased radioresistance after the conditioning doses has also been associated with increased antioxidant potential of cells. Elevated levels of antioxidant enzymes, increase in endogenous glutathione (GSH) and removal of free radicals are suggested to be responsible for adaptive response (Yamaoka *et al* 1991; Zhang *et al* 1998; Yukawa *et al* 1999). Induction of the protective mechanisms by low doses of radiation has been demonstrated at the molecular level using ultra sensitive

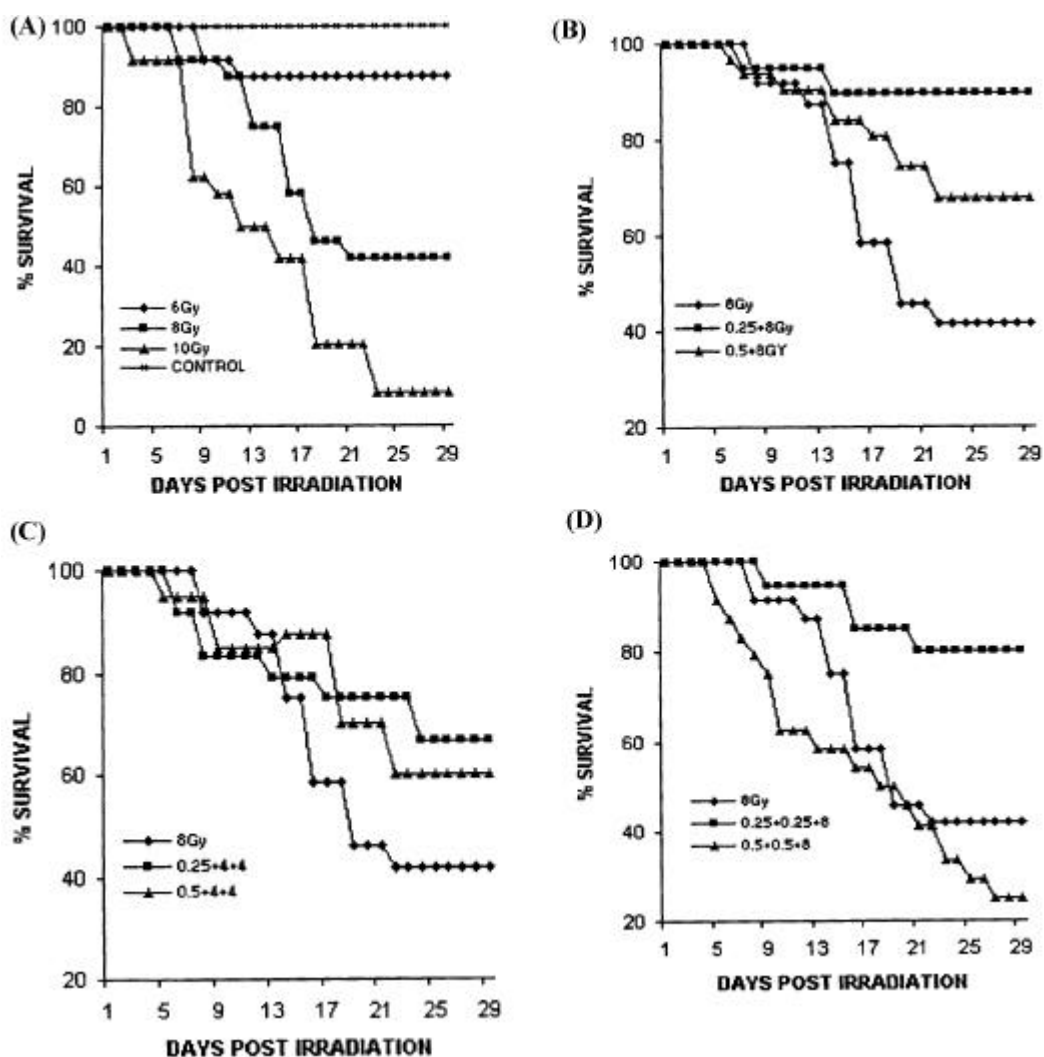


Figure 1. 30-day survival (%) of mice as function of time. (A) Effect of exposure to different doses of radiation (6–10 Gy) on survival of mice. (B) Effect of pre irradiation with 0.25 and 0.5 Gy followed by exposure to 8 Gy challenge dose. (C) Effect of exposure to fractions (4 Gy + 4 Gy) of challenging dose on low dose radiation induced response to survival. (D) Effect of conditioning dose delivered in fraction on adaptive survival of Swiss albino mice.

Table 2. Effect of conditioning doses of gamma rays on the 30 day survival of mice challenged by lethal dose of 8 Gy.

Conditioning dose I (Gy)	Inter treatment time (h)	Challenging/conditioning dose II (Gy)	Inter treatment time (h)	Challenging dose (Gy)	No. of mice	No. of mice that survived till day 30th	Survival (%)
0	0	0	0	0	24	24	100
0	0	0	0	8	24	10	41.66
0.25	6	0	0	8	19	17	89.47*
0.5	6	0	0	8	31	21	67.74
0.25	24	0	0	8	18	14	77.77**
0.5	24	0	0	8	19	12	63.15
0.25	6	4	24	4	24	16	66.66
0.5	6	4	24	4	20	12	60
0.25	6	0.25	24	8	20	16	80*
0.5	6	0.5	24	8	24	6	25

*Significantly different from irradiated control $P < 0.01$.

**Significantly different from irradiated control $P < 0.05$.

assay for DNA damage (Le *et al* 1998). The adaptive response was suggested to be linked to metabolically produced reactive oxygen species (ROS) (Feinendegen *et al* 1987). In normal cells, the fluctuations in ROS production triggers biochemical feedback controls affecting the DNA damage control system. Similarly, radiolytically generated ROS at conditioning doses might also induce the corresponding feedback controls leading to adaptive response. Apart from this, ROS might directly influence the regulatory proteins or act as signal for certain gene expression which in turn conditions adaptive response (Jayashree *et al* 2001). An adaptive response in terms of glyoxalase system in the liver and spleen of mice suggested the involvement of vital biochemical processes in the protective action of conditioning dose (Tiku and Kale 2001). In the present study also it was quite possible that the pre-exposure of animals to the conditioning doses (0.25 and 0.5 Gy) might have induced/activated the protective mechanisms and rendered more resistance to the subsequent challenging dose (8 Gy).

It was found that the conditioning dose of 0.25 Gy was more effective than 0.5 Gy. 89% and 68% survival was seen in animals pre-irradiated with 0.25 Gy and 0.5 Gy respectively and then irradiated with 8 Gy after 6 h. These levels of survival were quite high compared to the 41% survival of mice those received only challenging dose (8 Gy). Influence of time between the conditioning and challenging dose on the adaptive response was also examined. It could be mentioned that the extent of adaptive response declined as the time between the conditioning dose and challenging dose increased from 6 to 24 h.

The adaptive response is known to remain for a few hours and diminish thereafter in cellular systems (UNSCEAR 1994). Our results have shown that *in vivo* also there is a decrease in the adaptive response as the time between conditioning and challenging dose increased from 6 to

24 h. In biochemical studies mice pre-treated with conditioning doses of 0.5 Gy and challenged with a dose of 4 Gy at an interval of 3, 6 or 12 h also showed a continuous decrease in the glyoxalase I activity with increase in time between conditioning and challenging dose (Tiku and Kale 2001). However, the enhanced survival rate was reported in mice pre-irradiated with 0.05 Gy of X-rays 2 months before a second exposure to a mid-lethal dose (Nose *et al* 2001). Further, a priming dose of 0.3 Gy on gestation day 11 significantly increased the number of living fetuses and reduced the incidence of congenital malformation caused by exposure to 5 Gy of X-rays on gestation day 12 in mice (Wang *et al* 1998). The postnatal physiological and neurological development of prenatally irradiated animal studies showed high postnatal mortality in prenatal adapted mice and survivors suffered from various detrimental effects such as growth retardation and behaviour alterations (Wang *et al* 1999). Thus, the time interval between priming and challenging dose of radiations is perhaps one of the important factors which influences the adaptive response.

Various conditioning doses (1 cGy to 1 Gy) have been tested for their ability to induce adaptive response using different biological end points in different systems. Our studies showed that the lower conditioning dose of 0.25 Gy was more effective than 0.5 Gy in inducing the adaptive response (table 2). Decrease in the efficiency of conditioning dose to induce the adaptive response with increase in its magnitude is still not completely understood. In many animal studies, the conditioning dose were well above the doses that produce an adaptive response in cellular systems (Cronkite *et al* 1950; Dacuisto and Major 1959; Yonezawa *et al* 1996; Wolff 1998; Nose *et al* 2001) their differential response has been attributed to number of factors including quality of radiations, biological endpoints and test systems (Cai and Liu 1990).

In the present study, mice receiving an adaptive response dose of gamma-rays showed the resistance to subsequent high dose of radiation resulting in the increased animal survival. This finding is likely to have the potential implication for preventing normal tissue from detrimental effect following cancer radiotherapy. However, Boothman *et al* (1998) have shown that an adaptive survival response was the result of misregulated cell cycle checkpoint response occurring in the G1 phase and argued that the increased survival was not necessarily beneficial. It was further suggested that the rescued cells might pass abnormal genome into following generation of cells resulting in carcinogenesis. Importantly these findings were not supported by other studies where adaptive doses reduced the spontaneous neoplastic transformation *in vitro* (Azzam *et al* 1996; Redpath and Antoniono 1998). Moreover, exposure of mice to low doses of radiation was shown to lower the incidence of tumours as compared to control mice and also reduced subsequent radiation induced tumours (Bhattacharjee 1996; Ishii *et al* 1996). Thus, adaptive survival response may have some important implications in human health.

In the present study, modulation of survival of mice by splitting the challenging dose and fractionation of conditioning dose was also undertaken. The split dose response was examined using total challenging radiation dose of 8 Gy delivered into two equal fraction (4 Gy + 4 Gy). Animals were irradiated first with the conditioning dose of either 0.25 or 0.5 Gy followed by split dose (4 Gy + 4 Gy) separated by an interval of 24 h. Results are shown in figure 1C. The extent of adaptive response was quite similar between both the groups of animals, which received 8 Gy as single or split dose (table 2). However, the general health of the animals belonging to the group irradiated with split dose was better as it was quite evident from the increased body weight (data not shown). The repair of sub-lethal damage is expected to occur during the time interval between the split (4 Gy + 4 Gy) doses and the same might have contributed to the improved health.

As mentioned earlier, the adaptive response is induced by a single exposure to low dose. However, it is not known whether adaptive response is modulated with repeated or protracted irradiation. For studies on fractionation of conditioning dose, animals were irradiated with two conditioning doses (0.25 Gy + 0.25 Gy) or (0.5 Gy + 0.5 Gy) separated by 6 h and then exposed to single challenge dose of 8 Gy after 24 h (figure 1D). The dose 0.25 Gy given twice enhanced the survival quite significantly. The level of survival was found to be 80%. This was quite higher than the survival (67%) of animals which were exposed to single conditioning dose of 0.5 Gy prior to challenging dose of 8 Gy. On the other hand survival reduced to 25% in the group of animals which were irradiated to 0.5 Gy + 0.5 Gy dose prior to 8 Gy (table 2).

These results suggested that the conditioning dose given in small fractions are probably more effective in inducing the adaptive response. Two fractions of conditioning dose (0.5 Gy + 0.5 Gy) almost abolished the adaptive response and increased the lethality. These results probably supported the idea that cell is required to receive a certain amount of signal within a given interval of time for adaptive response to be expressed (Shadely and Wiencke 1989).

The results of present study have clearly shown the existence of adaptive survival response in mice. It may have relevance to various areas of radiation research. Further, these results supported the possibility that workers exposed to low doses of radiation may have less risk of cancer and diagnostic radiation could decrease cancer risk. In addition, the results also supported the idea that adaptive response could be manipulated for medical and other benefits. However, there have been doubts about the potential benefits of adaptive response as there is no firm evidence that adaptive response reduces health risks. Further, adaptive processes appeared to be highly transient and last no more than a few hours following conditioning doses (UNSCEAR 1994). Perhaps due to this, there is split opinion among researchers on the implications of adaptive response in the present risk assessment methods for carcinogenesis. For example, Cai (1999) and Ikushima (1999) argued that the case for adaptive response effect is quite compelling that the linear no-threshold (LNT) dose response model should be reconsidered immediately. On the other hand Mossman and Ledesma (1999), Olivieri (1999) and Skove (1999b) felt strongly that change in the policy should not be made until reasonable progress has been made in unraveling mechanisms underlying adaptive response. Since the relevance of adaptive response to radiogenic cancer risk in humans remains uncertain and enough is not known about this phenomenon, it has been suggested not to modify the entire set of existing guidelines (Skov 1999b). Most fundamentally, the LNT model ignores the role of repair processes, immune reactions and apoptosis leading to radiation harmesis as well as induced resistance. Therefore, there is urgent need to bridge the gap between LNT hypothesis and adaptive response.

It could be concluded that pre-irradiation of mice with conditioning doses (0.25 and 0.5 Gy) provided a significant protection in terms of survival against the subsequent challenging dose of 8 Gy. These findings showed the existence of adaptive survival response in mammalian system. The conditioning dose of 0.25 Gy was more effective than 0.5 Gy. Importantly, the extent of adaptive response was found to decline as the time of exposure between conditioning and challenging dose increased from 6 to 24 h. It supports the fact that adaptive effect is transient and lasts for few hours. Thus, the findings of the present work clearly showed the occurrence of adaptive response in terms of survival of mice. It is significant that the con-

ditioning dose given in small fractions (e.g. 0.25 Gy + 0.25 Gy) was more effective in inducing the adaptive response. However, two fractions (0.5 Gy + 0.5 Gy) of conditioning dose failed to induce the adaptive response. Hence, there appeared to be a window of range of radiation dose which could protect animals against subsequent higher doses. It was possible that cells need to receive a certain amount of signal within a given time interval for adaptive response to be expressed. The findings of present work may have significance in risk assessment and radiation protection. It could possibly be manipulated for medical and other benefits. However to harvest the benefits there is urgent need to address some of the uncertainties and controversies related to adaptive response.

Acknowledgments

ABT is grateful to the Department of Science and Technology, New Delhi for financial support under the Young Scientist Scheme.

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MS received 30 August 2003; accepted 29 December 2003

Corresponding editor: VIDYANAND NANJUNDIAH