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PROTECTION AGAINST RADIATION INDUCED CHROMOSOME INJURY BY SULFHYDRYL COMPOUNDS

R. GUPTA and P. UMA DEVI

Abstract

The radiation induced changes in a critically radiation-sensitive tissue, bone marrow of Swiss albino mice and its modification by two sulfhydryl compounds, MPG and WR-2721, were studied cytogenetically after whole body exposure to 0.5, 1.5, 3.0, 4.5 and 6.0 Gy of ^{60}Co gamma radiation. The changes in the structural arrangements of chromosomes in the bone marrow were studied at various post-irradiation times from 1 to 28 days. Both the control (irradiated) and experimental (drug + irradiation) animals showed qualitatively similar types of aberrations; the severity of lesions increased with the radiation dose. The maximum damage in all the groups was seen on day 1, post-irradiation. Both the drugs afforded better protection at lower doses of exposure, their effectiveness decreasing with an increasing radiation dose. Of the two drugs, WR-2721 was more effective than MPG against initial aberration yield but the former, at the present drug dose, showed some toxic effect at the later post-irradiation intervals (2 weeks onward) as manifested by an increase in the chromatid breaks and polyploidy.

In recent years, there has been a considerable interest in the possible application of radioprotectors in radiation therapy. Since the first demonstration by PATT et coll. (18), of the protective ability of cysteine, a large number of chemicals have been tested for their protective properties against radiation. The initial interest was followed by disappointment because of the severe toxicity of these drugs in animals. During the search for more effective but less toxic protectors, WR-2721, a phosphoro-thioate derivative of cysteamine was found to be less toxic and much more effective than the parent compound (28). Similarly MPG, a synthetic thiol compound, has been reported to protect against radiation induced damage at a non-toxic optimal dose of 20 mg/kg body weight with a DRF of 1.4 (23). The damage induced by ionizing radiation, which leads to the loss of proliferative capacity in mammalian cells, is known to be located mainly in the nucleus (19). In this context, chromosome aberrations are important since they are the final manifestations of the DNA strand breaks. In the present investigation the influence of MPG and WR-2721 on radiation induced chromosomal aberrations in the bone marrow of mice was compared.

Material and Methods

Adult male Swiss albino mice about 6 to 8 weeks old, weighing 22 to 25 g, maintained on standard mice feed (obtained from Hindustan Lever Ltd., Delhi) and water ad libitum, were used in the experiment. The animals were divided into 3 groups. The first group which was given distilled water (volume equal to volume in drug treated groups) before exposure served as control. The animals of the other two groups were injected intraperitoneally with either MPG (donated by Santen Pharmaceuticals, Osaka, Japan) at a dose of 20 mg/kg body weight 15

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Table 1

Frequency of chromosomal aberrations in the non-drug treated and drug treated mice exposed to 0.5 Gy gamma radiation

Time after irradiation	Treatment	Percentage of aberrant cells ± SE	Difference between			Types of aberrations		Per cent aberrations
			C–EM	C–EW	EM–EW	Stable	Unstable	
	C	6.00±0.86				25	14	6.5
1 d	EM	2.33±0.21	p<0.002	p<0.001	NS	13	1	2.3
	EW	1.33±0.42				12	2	2.3
	C	4.83±0.31				24	5	4.8
2 d	EM	2.00±0.37	p<0.001	p<0.001	NS	10	2	2.0
	EW	1.17±0.31				5	2	1.16
	C	3.66±0.42				19	3	3.6
4 d	EM	1.83±0.54	p<0.02	p<0.001	NS	23	2	4.16
	EW	1.00±0.45				3	3	1.0
	C	3.11±0.31				18	1	3.16
7 d	EM	1.16±0.48	p<0.01	p<0.001	NS	6	1	1.16
	EW	0.83±0.31				3	2	0.83
	C	1.66±0.33				6	4	1.6
10 d	EM	0.67±0.33	NS	p<0.02	NS	3	1	0.66
	EW	0.50±0.22				2	1	0.5
	C	0.83±0.31				5	0	0.83
14 d	EM	0.83±0.17	NS	NS	NS	4	1	0.83
	EW	0.33±0.21				2	0	0.33
	C	0.67±0.33				4	0	0.66
28 d	EM	0.33±0.21	NS	NS	NS	2	0	0.33
	EW	0.33±0.21				2	0	0.33

Control = C; MPG treated experimental = EM; WR-2721 treated experimental = EW.
Percentage of aberrant cells in normal population=0.33±0.17.

to 25 min before exposure (experimental, EM) or WR-2721 (courtesy Yamanouchi Pharmaceutical Co. Ltd., Tokyo, Japan) at a dose of 400 mg/kg 30 to 45 min before exposure (experimental, EW). Before injection, the pH of MPG was adjusted to 6.4 with 0.1 N NaOH as the aqueous solution of the drug is highly acidic. Both drugs were prepared immediately before use. The animals of the three groups were then exposed to 0.5, 1.5, 3.0, 4.5 or 6.0 Gy of gamma radiation from a ^{60}Co beam therapy source at a dose rate of 0.72 Gy/min. Six animals from each group were autopsied at various post-irradiation times, i.e. 1, 2, 4, 7, 10, 14 and 28 days. Two hours prior to autopsy, the animals were given 1% colchicine subcutaneously at a dose of 0.25 ml/100 g body weight. Metaphase plates from femoral bone marrow were prepared by the air drying technique of EVANS (7) with a slight modification and slides were blindly scored for chromosomal aberrations. At least 600 cells were counted from each group at each autopsy.

Results

The major types of changes which could be identified were chromatid break, chromosome break, ring, dicentric, exchange figure, pulverization and polyploidy. In the distilled water injected sham-irradiated animals, the spontaneous frequency of cells carrying chromosome aberrations was found to be 0.33±0.17 per 100 metaphases.

In the MPG-treated sham-irradiated group, the aberration frequency was in the same range as in the sham-irradiated controls. However, WR-2721 when given as a single i.p. injection of 400 mg/kg produced some breaks mainly of the chromatid type and also induced polyploidy at later intervals (details to be published elsewhere).

In the irradiated control animals examined on day 1 after irradiation the percentage of aberrant cells and the number of aberrations/100 cells (per cent aberrations) showed a dose-dependent increase. At low exposure doses (Tables 1, 2) the stable aberra-

Table 2

Frequency of chromosomal aberrations in the non-drug treated and drug treated mice exposed to 15 Gy gamma radiation

Time after irradiation	Treatment	Percentage of damaged cells ± SE	Difference between			Types of aberrations		Per cent aberrations
			C–EM	C–EW	EM–EW	Stable	Unstable	
	C	18.67±2.13				74	67	23.5
1 d	EM	7.00±0.86	p<0.001	p<0.001	p<0.02	40	56	17.0
	EW	4.00±0.69				29	7	6.0
	C	5.33±0.42				22	22	7.3
2 d	EM	2.67±0.21	p<0.001	p<0.001	NS	13	6	3.16
	EW	2.17±0.31				11	4	2.5
	C	4.50±0.43				28	3	5.16
4 d	EM	2.33±0.33	p<0.002	p<0.001	p<0.05	11	3	2.3
	EW	1.17±0.40				8	0	1.3
	C	3.17±0.48				12	7	3.1
7 d	EM	1.83±0.31	p<0.05	p<0.01	NS	8	3	1.83
	EW	0.83±0.40				3	2	0.83
	C	1.17±0.31				6	1	1.16
10 d	EM	1.00±0.26	NS	NS	NS	5	1	1.0
	EW	0.83±0.31				3	2	0.83
	C	0.67±0.33				2	2	0.66
14 d	EM	0.33±0.21	NS	NS	NS	2	0	0.33
	EW	1.00±0.26				2	4	1.0
	C	0.67±0.22				3	1	0.66
28 d	EM	0.33±0.21	NS	NS	NS	2	0	0.33
	EW	1.17±0.40				3	4	1.16

tions were more frequent than unstable aberrations. With increasing exposure doses, the unstable aberrations increased and exceeded that of the stable ones (Tables 3–5). In the 4.5 and 6.0 Gy groups extreme fragmentation and pulverization of chromosomes were common. In all groups the proportion of aberrant cells was highest on day 1. It then progressively declined with time and was drastically reduced already on day 2.

In both drug treated groups similar qualitative types of lesions were found as in the controls. Quantitatively, however, the damage was less pronounced in the drug treated groups. On day 1 the frequency of aberrant cells was significantly reduced in both experimental groups; the per cent aberrations was also lower in these groups than in the controls. Of the two drugs, WR-2721 was the more effective. In the animals pretreated with either drug and exposed to low doses (0.5, 1.5 Gy) the initial yield of stable aberrations was reduced and that of unstable ones (e.g. rings and dicentrics) inhibited. At higher doses, MPG treated animals showed similar types of stable and unstable aberrations as seen in the corresponding controls but their frequencies were significantly reduced. In the WR-2721 treated animals exposed to higher radiation doses the formation of stable aberrations, acentric fragments, rings and exchange figures was greatly reduced and the frequency of severely damaged cells negligible in comparison with controls and MPG treated animals. Further, in the WR-2721 group pulverization was not found on the first day after irradiation even after the highest radiation exposure, i.e. 6 Gy.

Even though the normal values were not reached on day 28 in any of the control groups a significant difference from normal was observed only in the 6.0 Gy group. In the MPG pretreated animals, the aberrant cell percentage reached normal levels at 4 weeks in the 0.5, 1.5 and 3 Gy groups; in the 4.5 and 6 Gy groups, the values were still elevated but the difference from normal was not significant. In the WR-2721 pretreated animals the reduction of the proportion of aberrant cells at day 1 was highly significant after all the exposures ($p<0.001$). Nevertheless, recovery was not complete at 4 weeks ex-

Table 3

Frequency of chromosomal aberrations in the non-drug treated and drug treated mice exposed to 3 Gy gamma radiation

Time after irradiation	Treatment	Percentage of aberrant cells ± SE	Difference between			Types of aberrations		Per cent aberrations
			C–EM	C–EW	EM–EW	Stable	Unstable	
1 d	C	49.67±1.53	p<0.001	p<0.001	p<0.001	195	544	123.16
	EM	18.33±0.96				99	152	41.13
	EW	6.50±0.50				21	32	8.83
2 d	C	5.83±0.71	NS	p<0.02	NS	32	6	6.33
	EM	4.17±0.79				10	20	5.0
	EW	3.33±0.56				20	6	4.3
4 d	C	5.00±0.82	NS	p<0.001	p<0.001	24	10	5.6
	EM	4.50±0.56				14	15	4.8
	EW	1.09±0.37				5	1	1.0
7 d	C	3.33±0.62	NS	p<0.01	p<0.01	14	9	3.8
	EM	3.17±0.60				14	6	3.3
	EW	1.09±0.37				5	3	1.3
10 d	C	0.83±0.31	NS	NS	NS	4	1	0.83
	EM	1.17±0.31				6	1	1.16
	EW	0.83±0.34				4	3	1.16
14 d	C	0.33±0.21	NS	p<0.002	p<0.002	2	0	0.33
	EM	0.33±0.21				2	0	0.33
	EW	1.50±0.22				6	5	1.83
28 d	C	0.67±0.21	NS	p<0.002	p<0.002	2	2	0.66
	EM	0.33±0.21				2	0	0.33
	EW	1.50±0.22				2	7	1.5

cept in the 0.5 Gy group. In the other exposure groups, the aberrant cell proportion at the later intervals was much higher than normal and it was even higher than in the controls irradiated with 1.5, 3.0 and 4.5 Gy (Tables 2–4). This increase was mainly due to chromatid breaks and polyploids

Discussion

An increase in the frequency of percentage aberrant cells as well as the percent aberrations, with increasing irradiation dose, is discussed in detail elsewhere (10). A linear dose dependent increase in the proportion of aberrant cells has also been reported by earlier workers (2, 8, 14, 15).

The increase in complex aberrations with exposure dose may be attributed to the number of initial breaks and to the repairability of the breaks. At lower doses, fewer breaks are produced and the probability of restitution is higher. With an increasing radiation dose, the number of breaks increases, which enhances the chances of interaction between broken segments, leading to an increase of complex aberrations. This conclusion is in line with the reports of PUROTT (20) who demonstrated that at low doses the effects are mainly due to one hit events. An increase of two hit aberrations with increasing radiation dose has been reported by SAX (22) in Tradescantia.

An increase in the frequency of unstable aberrations with increasing radiation doses has been reported by DOLPHIN & LLOYD (6) and LITTLEFIELD & JOINER (14). BENOVA & BAEV (1) also observed that at high exposures there is a higher proportion of irreversible damage and a reduced repair capacity. The steep decline in the number of aberrant cells on day 2 may be attributed to the rapid cell turnover and selection against abnormal cells, the damaged cells either losing their capacity for proliferation (interphase death) or competing unfavourably with the cytologically undamaged cells, as has been suggested by MCKAY et coll. (16). The more gradual decrease in the 0.5 and 1.5 Gy groups may be due to the fewer unstable aberrations as compared with the stable ones. According to LITTLEFIELD & JOINER

Table 4

Frequency of chromosomal aberrations in the non-drug treated and drug treated mice exposed to 4.5 Gy gamma radiation

Time after irradiation	Treatment	Percentage of aberrant cells ± SE	Difference between			Types of aberrations		Per cent aberrations
			C−EM	C−EW	EM−EW	Stable	Unstable	
	C	55.67±3.04				272	532	134.0
1 d	EM	42.17±2.21	p<0.01	p<0.001	p<0.001	223	238	76.83
	EW	19.17±0.95				108	122	38.3
	C	7.67±0.61				26	40	11.0
2 d	EM	5.83±0.83	NS	p<0.01	NS	40	4	7.3
	EW	3.50±0.88				24	6	5.0
	C	5.33±0.67				34	8	7.0
4 d	EM	6.50±0.88	NS	p<0.001	p<0.001	36	8	7.3
	EW	2,00±0				8	4	2.0
	C	2.00±0.26				4	3	1.16
7 d	EM	3.67±0.95	NS	NS	NS	19	3	3.6
	EW	1.33±0.61				5	3	1.33
	C	1.50±0.23				6	3	1.5
10 d	EM	3.33±0.99	NS	NS	p<0.05	16	4	3.33
	EW	1.00±0				4	2	1.0
	C	0.83±0.31				4	1	0.83
14 d	EM	1.50±0.56	NS	NS	NS	7	2	1.5
	EW	2.33±0.76				8	6	2.3
	C	1.16±0.31				6	1	1.16
28 d	EM	1.00±0	NS	NS	NS	5	1	1.0
	EW	1.67±0.61				6	4	1.66

(14) the latter are less deleterious and can propagate in vitro.

The present findings, that MPG and WR-2721 protect chromosomes of bone marrow against radiation, are in agreement with those of earlier investigators using other chemicals (3, 5, 9, 27). Protection of human peripheral lymphocyte chromosomes by MPG has been demonstrated by TANAKA & SUGAHARA (25) and TANAKA (24). Protection of bone marrow stem cells by MPG as reported earlier (21) may be attributed to the chromosomal protection observed in the present investigation.

Although there are no earlier reports on the protection of chromosomes by WR-2721, a large number of publications exist on its protective action against radiation death and tissue injury. These have been reviewed by YUHAS et coll. (29). The protection against hemopoietic death reported by YUHAS & STORER (28) may reflect the reduction of radiation induced chromosome abnormalities in the bone marrow cells demonstrated in the present experiment.

The protective efficiency of the two drugs decreased with an increasing radiation dose. This may be explained by the findings of BENOVA & BAEV (1), that at high exposure there is more irreversible damage and less repair activity and hence smaller chances for the drug to intervene. It has also been demonstrated by MODIG et coll. (17) in vitro that MPG reduces the initial yield of single strand breaks in irradiated Chinese hamster cells.

The incidence of polyploidy showed no definite relation to the exposure dose even though the frequency of polyploids on day 1 post-irradiation rose with an increasing dose in the control and experimental groups. An increased frequency persisted longer after higher exposures but had disappeared at the last autopsy in the control and the MPG treated animals. In the WR-2721 treated animals, though the polyploid cells decreased markedly after day 1, an increase in their number was observed at later intervals after all the doses except 0.5 Gy. It seems likely that in the latter case the polyploid cells were few and sparsely distributed and therefore escaped de-

Table 5

Frequency of chromosomal aberrations in the non-drug treated and drug treated mice exposed to 6 Gy gamma radiation

Time after irradiation	Treatment	Percentage of aberrant cells ± SE	Difference between			Types of aberrations		Per cent aberrations
			C–EM	C–EW	EM–EW	Stable	Unstable	
1 d	C	62.67±7.07	NS	p<0.001	p<0.002	274	553	137.83
	EM	47.17±3.29				243	324	94.5
	EW	24.17±4.54				139	146	47.5
2 d	C	10.67±0.67	p<0.001	p<0.001	NS	69	83	25.3
	EM	5.50±0.96				29	19	8.0
	EW	4.17±1.14				13	20	5.5
4 d	C	5.33±0.76	p<0.002	p<0.01	NS	26	12	6.3
	EM	1.50±0.42				9	7	2.6
	EW	2.33±0.33				11	5	2.6
7 d	C	2.83±0.60	NS	NS	NS	11	7	3.0
	EM	1.50±0.22				8	2	1.6
	EW	1.33±0.33				5	3	1.3
10 d	C	2.67±0.42	p<0.05	p<0.02	NS	7	9	2.6
	EM	1.33±0.33				6	2	1.3
	EW	1.17±0.31				6	3	1.5
14 d	C	2.67±0.56	p<0.05	NS	NS	6	10	2.6
	EM	1.17±0.31				6	1	1.16
	EW	2.00±0.45				4	8	2.0
28 d	C	3.00±0.69	p<0.01	NS	NS	14	4	3.0
	EM	0.67±0.33				2	2	0.66
	EW	1.67±0.81				4	6	1.6

tection. The drug appears to have a toxic effect at later intervals even if it efficiently protects the cells against early chromosomal aberrations. Induction of polyploidy by other related SH compounds like cysteamine has been previously reported (11–13).

An increase in the percentage of aberrant cells at 2 weeks in WR-2721 treated animals is partly due to an increase in the frequency of polyploids. The persistence of higher numbers of aberrations, i.e. chromatid breaks and acentric fragments at 4 weeks may be due to the possibility that: 1) the cells carrying such aberrations may lie dormant and then enter division, 2) some latent breaks may show up and/or, 3) such an aberration may not be lethal for the cell carrying it and therefore retained through cell cycles.

Similar phenomena have been observed by earlier workers such as LITTLEFIELD & JOINER (14), who reported that in some instances the cells bearing stable radiation induced lesions may propagate in vivo, and COOPER & HSU (4), who observed that cells carrying deletion of heterochromatic segments of sex chromosomes could survive for 30 days. Persistence of anaphase bridges in the intestinal crypt of mice has been reported after high dose exposure (26).

Thus, comparing the two drugs employed in the present investigation, it appears that WR-2721 is a better protector against early induction of chromosomal aberration by radiation but manifests certain toxic effects at later intervals which seem to add to the radiation damage and exaggerate the adverse effects. A comprehensive mechanism of the action of the two drugs, i.e. whether they protect DNA as a target or the enzymes of repair or both, still remains an open question.

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