CHEMICAL PROTECTION OF MEG AGAINST IONIZING RADIATION

Report III Relationship between time interval from administration of MEG to irradiation and protective effect

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放射線に対する MEG の化学的保護に関する研究

第III報 MEG 投与から照射までの時間と保護効果の関係

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ＭＥＧ投与から照射までの時間間隔を５分から90分に亘つて変え，マウスに対するＭＥＧの保護効果の投与時間による変化を調べた．照射は短時間（約１分間）に 800r および1000r の全身照射を行い，ＭＥＧは 250mg/kg の腹腔内投与に一定した．

照射マウスにおけるＭＥＧの効果は照射前５分から30分の範囲内の投与ではほゞ等しかつた．照射前60分投与になると効果はかなり減少し，90分の投与ではもはや生存率に対する効果はみられず，平均生存時間は非保護マウスに比べてむしろ短縮される傾向がみられた．

体重減少および平均生存時間も生存率とほゞ同様に，投与から照射までの時間が60分，90分になるとＭＥＧの効果は著明に減少する．

Introduction

It was well known that sulfhydryl-containing compounds such as MEG (β-mercaptoethylguanidine)[1] and MEA (mercaptoethylamine)[2] have a marked protective activity against radiation injuries. However, the mechanism of protection still remains unknown. In order to elucidate this mechanism, it is necessary to obtain accurately the most effective dose of protective agents (optimum dose) and the most effective time interval between the administration of protective agents and irradiation (optimum time). Described in previous paper[3], optimum dose increases with increase in irradiation dose.

It has been reported by previous investigators that the optimum time is from 10 minutes to 30 minutes,[4][5][6] but the accurate determination of the optimum time was difficult because of additional factor of irradiation time. Therefore, some investigators have presented the concept of the so-called "curves of effective concentration of protective agents in the

living body ''[6].

Present paper describes the relationship between protective effect and administration time in mice briefly irradiated to lethal and supralethal dose.

Material and method

Irradiation was conducted on the following condition; Toshiba KXC-18-2 with tube voltage, 180 kVp; filament current, 25 mA; additional filters, 1.0 mmAl; HVL, 0.8 mmCu; target to center-of-mice distance, 30 cm and dose rate, 800 r/min. Mice were exposed to 800 r and 1000 r of total body irradiation in which irradiation time was one minute and 1.25 minutes, respectively. Dose measurement was made by a Victoreen Radocon 575 (probe 602) placed in the center of one of irradiation boxes.

Female mice (ddN uniform strain), 8 weeks old and weighing 23±2 g, were used in this experiment.

MEG (prepared by neutralizing AETBr with dilute NaOH) was administered intraperitoneally 250 mg (as AET) per kilogram of body weight.

The administration time was 5, 10, 20, 30, 60 and 90 minutes before irrradiation.

Estimation of protective effect of MEG was made mainly by the 30-day mortality. In some cases, the 60-day mortality, mean survival time and body weight loss were also examined.

Result

The protective effect against radiation mortality is shown in Tables I and II, and Figs. 1 and 2.

In mice irradiated to 800 r, MEG had a marked effect when administered from 5 to 30 minutes before irradiation and most mice survived. Effectiveness of MEG decreased when administered 60 minutes before irradiation and no effect was observed when administered 90 minutes before irradiation.

Although in mice irradiated to 1000 r, the survival rate of protected groups showed considerably low values as compared with those of groups irradiated to 800 r, the effectiveness of MEG was almost equal when administered from 5 to 30 minutes before irradiation. MEG was also non-effective when administered 90 minutes before irradiation. Last column in Table II shows the mean survival time of mice which died within 30 days. Survival time

Table I The 30-day and the 60-day survival in 800r irradiated mice with and without protection

Time interval (min)	No. of animals	The 30-day survival (%)	The 60-day survival (%)
Unprotected	10	20	0
5	20	95	95
10	20	100	90
20	20	100	100
30	20	100	100
60	20	75	70
90	10	0	0

Table II The 30-day survival and the mean survival time in 1300r irradiated mice with and without protection

Time interval (min)	No. of animals	The 30-day survival (%)	Mean survival time (day)
Unprotected	10	0	7.6
5	20	65	20.6
10	20	55	21.2
20	20	70	15.3
30	20	50	15.1
60	20	15	13.0
90	10	0	6.2

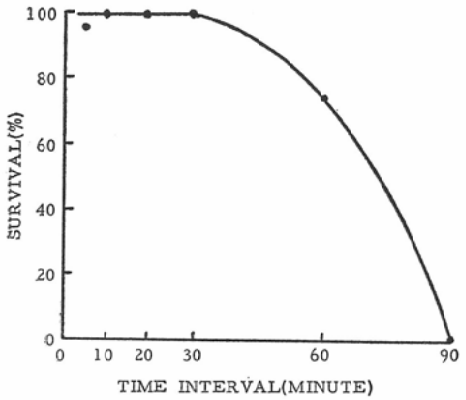

Fig. 1 The survival rate in 800 r irradiated mice plotted against the time intervals between the administration of MEG and irradiation

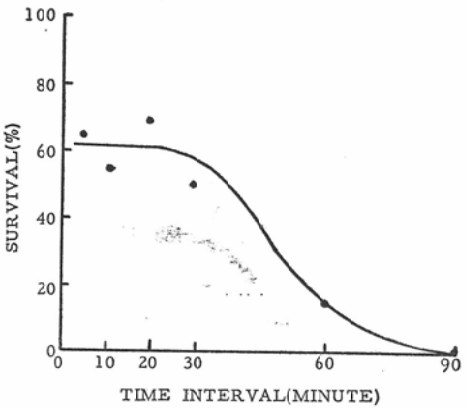

Fig. 2 The survival rate in 1000 r irradiated mice plotted against the time intervals between the administration of MEG and irradiation

was gradually shortened with elongation of time interval between irradiation and administration of MEG. From the data of mean survival time it was found that MEG administered 20 minutes and before that before irradiation was slightly less effective than that administered from 5 to 10 minutes before irradiation.

The changes in body weight of mice which survived more than 30 days after irradiation are shown in Figs. 3 and 4.

Chapman[7] and Sawada[8] observed that change of body weight in mice to sublethal and lethal X-irradiation showed a biphasic response. That is, there is a small loss of body weight about the fifth day after irradiation followed by a large loss about the second week after irradiation. The former is related to intestinal injuries and the latter to hematopoietic injuries.

MEG markedly altered the second weight loss pattern as seen in Figs. 3 and 4. The protective effect of MEG on hematopoietic injuries has been reported by Urso et al[9] and by Antoku et al[10][11], but this can be also demonstrated from its protection against body weight loss.

Estimation of effectiveness of MEG cannot be quantitatively made from the data of body weight loss because mice which died were excluded. However, it can be said that the mo-

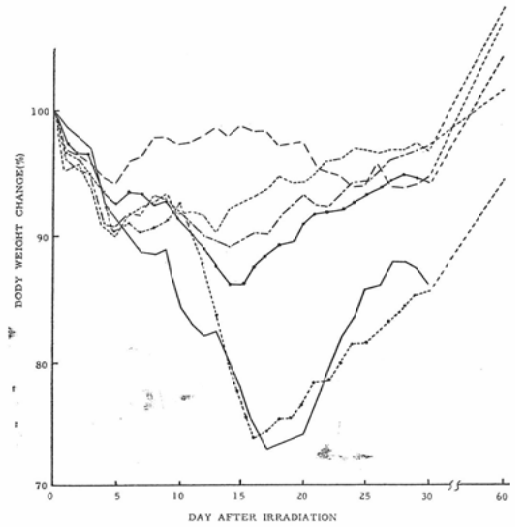

Fig. 3 Body weight change in 800 r irradiated mice with protection at various injection times and without protection
—— Unprotected, ····· 5 minutes before irradiation, --- 10 minutes, — — — 20 minutes, —•— 30 minutes, ···•··· 60 minutes

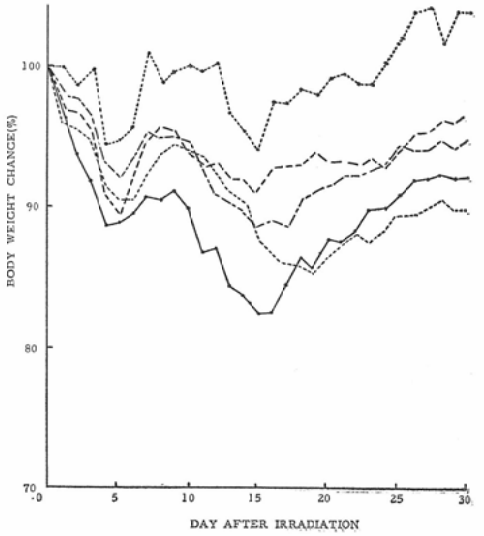

Fig. 4 Body weight change in 1000 r irradiated mice with protection at various injection times and without protection
····· 5 minutes before irradiation, --- 10 minutes, — — —20 minutes, —•— 30 minutes, ···•··· 60minutes

dification of body weight loss was good in mice administered MEG 10 and 20 minutes before irradiation.

Maisin et al[12] and Doherty et al[9] observed a secondary weight loss in lethally irradiated rats injected with MEA and in lethally irradiated mice injected with MEG. In this experiment, secondary weight loss was also observed in 800 r and 1000r irradiated mice with protection, but it was smaller than cases without protection. However, Bacq et al[13] and the author[3] did not observed a secondary weight loss in 700 r irradiated mice with protection, and 600 and 700 r irradiated mice with protection. Therefore, it is felt that the appearance of secondary weight loss depends on irradiation dose.

Discussion

Various values have been obtained regarding optimum time. It was reported to be 30 minutes by Katsuhara[4], 10 minutes by Muta et al[5] and 10 to 20 minutes by Okamura et al[6]. However, as protective agent, Katsuhara used AET_{Br} which was not adjusted to neutral pH, Muta et al used MEG_{Br}, and Okamura et al used MEG_{SO_4}. These data cannot compared because the irradiation time and the chemical form of protective agents are different.

The author observed that the effectiveness of MEG on mortality and body weight loss was equal among mice administered MEG 5 minutes to 30 minutes before irradiation in which irradiation time was so short that its effect could be ignored.

Optimum time has a important meaning in elucidating the mechanism of chemical

chemical protection. This is because factors necessary for protective effect seem to changes quantitatively in a pattern similar to the change in survival rate due to administration time. Although they have not been determined at present stage, total MEG content in irradiation animals, temporarily binding MEG content, free SH content and depression of oxygen tension in tissue can be considered.

Heiffer et al[14)15)] observed that SH content in blood reached the highest value 5 minutes after injection of cysteamine and cystamine. According to the observation made by the author, total S^{35} (MEG) in general decreased gradually with elongation of time after injection. Free S^{35} (MEG) content and binding S^{35} (MEG) content also decreased.

If total MEG, free SH and binding MEG were need for protective activity, MEG should be more effective when administered 5 minutes before irradiation than when administered 10 minutes and before that. None the less, the foregoing result has shown that free SH and total MEG do not play a major role in the protection of SH compounds.

Summary

Mice were irradiated to total body of 800 r and 1000 r briefly (about 1 minutes), varying the time interval between injection of MEG and irradiation. The following result was obtained.

Effectiveness of MEG in irradiated mice was almost equal when administration time ranged from 5 minutes to 30 minutes before irradiation but it decreased 60 minutes. When administered 90 minutes before irradiation, MEG failed to increase survival rate over that of unprotected mice and brought about a slight reduction in average length of survival after irradiation.

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