STUDIES ON THE RESTORATION FROM RADIATION DAMAGE WITH CHEMICAL TREATMENTS : A PRELIMINARY REPORT

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薬剤による放射線障害回復の研究 予報

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肝末およびRNAヌクレオチド混合物(ヌクレトン)について,γ線分割照射に対する効果を,ハツカネズミを材料として,平均体重,生存日数,平均耐容積算線量を指標として調べた.この二者ことに後者は著効があり,これは放射線障害からの回復が,これらの薬剤によつて促進される為であろうと考えた.

これによつて,薬剤による回復の促進の可能性が示されたので,今後大いにこの方面の研究を推進する必要がある.

1. Introduction

It has been generally assumed that the recovery from radiation damage is actually a process of replacement of damaged cells, rather than a simple reversibility. Thus in the studies on chemical protection great emphasis has been placed on the studies of agents which are capable of preventing radiation damage (1).

However there are probably none that would be feasible for protection on man. Recently the recovery from the partial damage has been observed in cells cultured *in vitro* (2). In such a situation the possibility to enhance the recovery with chemical agents should be studied more intensively than before. The treatment of radiation injury after exposure, if it is effective, would offer greater possibilities for prevention of death and for improvement of radiation therapy.

Maisin et al. (3) showed the improvement of survival in rats with yeast RNA. Members of Institute of Nuclear Sciences, Belgrad, Yugoslavia published papers concerning curative effects of DNA or RNA in mammals and mammalian cells (4,5,6).

In the present investigation the effects of desiccated liver and nucleic acid derivatives (a RNA mononucleotide mixture) on survival of mice exposed to single X- or repeated

γ-irradiations have been studied.

Enhancement of recovery was observed in some cases of repeated γ-irradiations. In other cases the effect should be studied further before any conclusion will be reached.

2. Experimental methods and results

2-1. Experiment 1 : Desiccated liver

Mice of the CBA strain bred in the Department were used at about three months of age, average body weight 30g. Irradiations were given with γ-ray from ^{60}Co of a therapeutic apparatus delivered at 65 r/min in air at 50 cm from the source. Whole body irradiations of 395 r were given to every mouse once a week until death of the animal.

Desiccated liver A is the vacuum-dried, defatted powder prepared from mammalian liver and desiccated liver F a similar one from fish liver. Of these the former corresponds to desiccated liver in the National Formulary of the United States. They were produced by Riken Vitamine Oil Co. Ltd. and supplied for study by its courtesy. The powder was mixed with usual laboratory chow (Funabashi Farms) at 10 per cent in weight. The mice were fed the test food from one week before the series of irradiation, and given tap water *ad libitum*.

Changes in body weight and survival curves were compared among three groups of animals (5 for each group): these fed with desiccated liver A and F and without liver (control food).

Changes in mean body weight of surviving animals during the experiment are shown in Fig. 1. Body weights were decreased gradually by repeated exposure in the control group, but remained rather constant until the fourth week in the liver-fed groups. Thus, the difference in body weight is remarkable at the third and fourth week. The differences are statistically significant, though the survivals were similar to each other at this time.

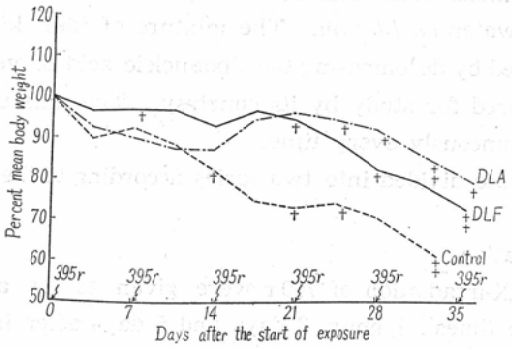

Fig. 1. Effect of desiccated liver on mean body weight during repeated exposures
+ denotes death of an animal

Mean survival time and mean accumulated dose until death are shown in Table 1. Increase in both of these values were observed in liver-fed animals especially liver A, but not statistically significant.

Talbe 1 Effect of desiccated liver (First experiment, 395 r per week)

Treatment	Mean survival time (days)	Mean accumulated dose (r)	Body weight at 20th day (gr.)
D. L. A	30± 7	1501±711.0	38±0.33
D. L. F	26± 6	1501± 593.1	37±0.34
Control	25± 4	1106± 632.0	28±0.38

An additional experiment was performed using C57BL/6 mice with a little lower dose, 365 r per week. The result (Table 2) shows a similar but a little greater difference in survival than in the former experiment but not statistically significant.

Table 2 Effect of desiccated liver (Second experiment, 365 r per week)

Treatment	No. of animals	Mean survival time** (days)	No. of surviving animals at 58days *
Male			
D. L. A	5	43.2± 4.4	0
D. L. F	5	42.0± 7.7	0
Control	5	34.2±10.0	0
Female			
D. L. A	5	49.0±12.5	2
D. L. F	5	51.6± 3.9	3
Control	5	34.4± 6.6	1

* Experiment was finished at 58 days after the first exposure.
** Survival time for living animals at the end of experiment was taken as 58 days.

2-2. Experiment 2.: Mixture of RNA mononucleotides

Mice of C57BL/6 strain bred in the Department were used at about 60 days of age, the same number of males and females. They were fed laboratory chow (Funabashi Farms) and given tap water *ad libitum*. The mixture of four kinds of mononucleotides (Nucleton) were produced by decomposing the ribonucleic acid of yeasts by Daigo Nutritive Chemicals Ltd. and offered for study by its courtesy. The mixture 0.25 mg in 0.1cc of saline was given subcutaneously every time.

The experiments were divided into two series according to the exposure and administration methods.

A. Acute X-irradiation

Single whole body X-irradiation of 700 r were given to the animals. The mixtures were administered three times : 1 hour, 3 days and 5 days after irradiation. X-irradiations were made with 200 Kv-X-rays with 1.0 mm Cu and 0.5mm Al filters, delivered at 70r/min, monitored every time with a Radcon dosimeter.

Mortality curves after irradiation with and without the administration are shown in Fig. 2. Each group consists of twelve animals.

No significant difference is observed, though the difference at the fourth and fifth day may suggest some effect.

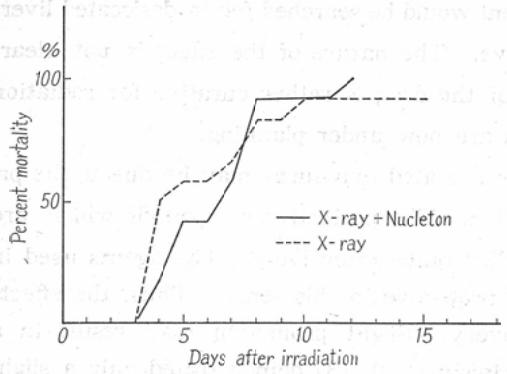

Fig. 2. Mortality curve after 700 r X-irradiation with and without Nucleton

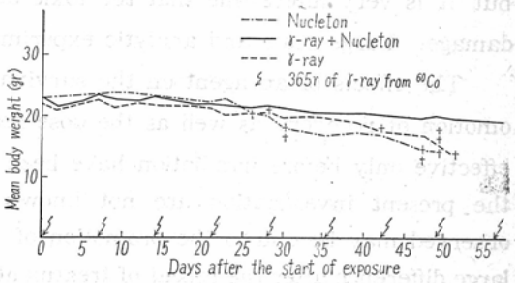

Fig. 3. Changes in mean body weights during repeated irradiation

B. Repeated γ-irradiations

The mice of the same strain and age as in Experiment A were irradiated once a week with 365 r γ-radiation from ^{60}Co until death. Animals were divided into three groups (6 animals for each): The irradiated; subcutaneously injected with the nucleotide mixture three times a week; and injected as well as irradiated.

Mice were fed laboratory chow and given tap water *ad libitum*.

Changes in mean body weight for each group after the start of exposure are shown in Fig. 3. Body weights were gradually decreaced in a similar way for all three groups until death occurred in two of them.

Mean survival time and mean accumulated dose until death are significantly different in the irradiated and injected group as shown in Table 3. Animals of the latter group had been surviving when the experiment was ended sixty days after the start of irradiations. However, the dose of the mixtures used may be quite toxic, as a remarkable reduction of survival time was observed with the administration of the mixture alone.

Table 3 Effect of a nucleotide mixture (Nucleton)

Treatment	Mean surviual time (days)	Mean accumulated dose (r)
γ-irradiation	45.3±3.4	2555
The mixture	38.0±3.9	———
γ-irradiation and the mixture	more than 60	more than 3285

3. Discussion

It has been demonstrated that the desiccated liver adopted in the present study showed a growth promoting effect in rats (7). In order to seperate the effects against radiation from that on growth, mature mice were used in the experiment. Erschoff (8) reported that the survival of rats repeatedly exposed to sublethal doses of radiation was increased when fed standard diet with liver powder. The present result seems to be

in accordance with his results. Effective component would be searched for in desiccated liver.

Effect of RNA nucleotides is very impressive. The nature of the effect is not clear, but it is very interesting that the toxic dose of the drug is rather curative for radiation damage. Large scale and analytic experiments are now under planning.

The effects of an agent on the survival for repeated exposures may be due to the promotion of recovery as well as the dose reduction. The protective compounds which are effective only before irradiation have been studied quite extensively. The agents used in the present investigation are not known as protective in this sense. Thus, the effects observed may be due to the promotion of recovery. Slight promotion may result in a large difference after the repeat of treatment. Maisin et al. (3) demonstrated only a slight increase in LD_{50} with the administration of yeast RNA as mentioned above. But the present results indicate a remarkable effect after repeated exposure.

The possibility of the restoration from radiation damage with chemical agents is clearly suggested in the present study. Further studies on this line should be carried out more intensively than before. The only method available now for the patients who have been accidentally exposed to a large dose of radiations is bone marrow transplantation though a delayed death may occur after the treatment. Curative effects of chemical treatments, if available, may greatly contribute to the treatment of such patients. The methods will be also applicable for the improvement of radiotherapy for cancer patients.

4. Summary

Remarkable increase in survival after repeated γ-irradiations was observed in mice administered with a nucleotide mixture from yeast RNA. And a slight effect on body weight of mice irradiated similarly was demonstrated in mice fed laboratory chow supplemented with desiccated liver. The experiments are not extensive enough to support a new method of chemical treatments after exposure. But the results obtained so far may suggest the possibility to enhance the recovery from radiation damage by chemical treatments.

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