PHARMACOLOGY

THE EFFECT OF CRUDE DEXTRAN AND OF THE PYROGENIC POLYSACCHARIDE OF B. PROTEUS VULGARIS ON THE SURVIVAL OF WHITE MICE AFTER TOTAL IRRADIATION

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When studying the effect of crude dextran on the development of edema in burned tissues and on the hemoconcentration in thermal burns, we became interested in the other properties of this preparation.

In connection with the study of the properdin system, several reports have appeared in the literature during recent years showing an increase in the resistance of animals to infection (especially to infection by Gram-negative bacteria) after the parenteral injection of various soluble high-polymer polysaccharides (crude dextran and levan, mucin, the lipopolysaccharides of Gram-negative bacteria and so on) and insoluble polysaccharides (zymosan, obtained from yeasts and from the walls of bacterial cells [2, 3, 6, 8, 10]). Indications have also appeared that preparations of this type may increase the chances of survival of animals exposed to the action of ionizing radiation. Pillemer [7] reported the increased survival of irradiated mice after they had been given a preliminary injection of zymosan. Ross [9] observed the favorable effect of zymosan, levan and crude dextran. Mefford, Henkel and Loefer [6], in a minor experiment, observed that a positive effect on the survival rate of irradiated mice was produced by giving the pyrogenic polysaccharide preparation pyromen with the drinking water. Smith, Alderman and Gillespie [11] observed an increase in the rate of survival of irradiated mice and hamsters after a preliminary injection of bacterial lipoplysaccharides. It is interesting that in the case of hamsters, these preparations were effective when given immediately after irradiation.

So far as can be judged by the absence of appropriate publications in the literature, this new possible method of influencing the chances of survival of irradiated animals has not yet attracted the attention of Soviet scientists. It may be suggested, however, that a similar mechanism played a part in the increased rate of survival of mice, vaccinated before irradiation, observed by N.N. Klemparskaya and her co-workers [1].

EXPERIMENTAL METHOD AND RESULTS

We tested the effect on the rate of survival of irradiated white mice of native dextran, obtained from the Central Order of Lenin Institute of Hematology and Blood Transfusion, precipitated twice with ethyl alcohol, and of the pyrogenic polysaccharide of B. proteus vulgaris obtained in our own laboratory. Each preparation was injected into the caudal vein of the mice, in the form of a solution made up in pyrogen-free physiological saline in a volume of 0.2 ml. Healthy mice, weighing on the average 22.1-24.7 g, kept for a long time under observation in the vivarium, during the course of which they gained weight, were selected for the experiment. The animals were irradiated from a cobalt source, at a distance of 65 cm, at a dosage rate of 1150 r/hour. The dose of radiation was 800 r. Observations on the animals continued for 30 days after irradiation.

The first experiment was to secure pilot information on the effect of crude dextran, injected intravenously at different periods, on the rate of survival of irradiated mice. For this purpose, dextran was injected into the mice in a dose equivalent, on the average, to 0.1 g/kg body weight. Injections were given to the mice of the different groups 3 hours after irradiation and 3, 12 and 24 hours and 2, 3, 5 and 7 days before irradiation. One group of irradiated mice did not receive dextran (irradiation control); one further group was not irradiated and received no injections of dextran (biological control). Table 1 gives an idea of the results of this experiment.

TABLE 1

Survival of Irradiated Mice after Intravenous Injection of Crude Dextran at Different Times (all animals in the experiment, males)

Group No.	Time of injection of dextran in relation to time of irradiation	No. of mice in group	After 30 days		
			number of dead animals	number of survivors	% of survivors
1	Within 3 hours	50	35	15	30
2	After 3 hours	50	36	14	28
3	After 12 hours	50	20	30	60
4	After 24 hours	50	34	16	32
5	After 2 days	50	33	17	34
6	After 3 days	50	49	1	2
7	After 5 days	50	50	0	0
8	After 7 days	50	50	0	0
9	Irradiation control	50	49	1	2
10	Biological control	50	0	50	100

TABLE 2

Survival of Irradiated Mice after Injection of Crude Dextran in Different Doses (all animals in experiment, males)

Group No.	Dose of dextran, in g/kg	No. of mice in group	After 30 days		
			number of dead animals	number of survivors	% of survivors
	Injection 12 hours before irradiation				
1	0.1	50	34	16	32
2	0.05	50	32	18	36
3	0.02	47	32	15	32
4	Physiological saline	50	48	2	4
	Injection 3 hours after irradiation				
5	0.1	50	40	10	20
6	0.05	50	43	7	14
7	0.02	50	38	12	24
8	Physiological saline	50	50	0	0
9	Irradiation control	50	50	0	0
10	Biological control	50	0	50	100

Injection of dextran 3, 5 and 7 days before irradiation was found to be completely ineffective. In the remaining groups, from 28 to 60% of the irradiated animals survived, as against an almost 100% mortality in the control group. The highest survival rate (60%) was observed when dextran was injected 12 hours before irradiation. It is a particularly interesting fact, however, that injection of dextran 3 hours after irradiation prevented the death of 30% of irradiated mice.

In the second experiment, we studied, in greater detail and with a more complete control, the survival rate of irradiated mice after the intravenous injection of different doses of crude dextran at the times which gave

TABLE 3

Survival of Irradiated Mice after Injection of Pyrogenic Polysaccharide of B. proteus vulgaris 12 Hours before Irradiation (all animals in the experiment, females)

Groupe No.	Dose of polysaccharide, in γ/ kg	No. of mice in group	After 30 days			After 50 days		
			No. of dead animals	No. of survivors	% of survivors	No. of dead animals	No. of survivors	% of survivors
1	1	50	32	18	36	36	14	28
2	10	50	20	30	60	23	27	54
3	Physiological saline	50	42	8	16	43	7	14
4	Irradiation control	50	44	6	12	44	6	12
5	Biological control	50	0	50	100	0	50	100

the most interesting results in the first experiment, i.e., 12 hours before and 3 hours after irradiation. In this experiment, besides the general control of irradiation and the general biological control for each of these times, we separated a control group of mice which was injected with 0.2 ml of sterile, pyrogen-free physiological saline before or after irradiation respectively.

The results of this experiment are shown in Table 2. On this occasion, we were unable to obtain such a high rate of survival among the mice injected with crude dextran – this did not exceed 36% in the most succesful case (2nd group). However, the previous relationship was clearly revealed: a higher rate of survival when dextran was given 12 hours before irradiation, a lower rate when it was given 3 hours after irradiation, and almost 100% mortality among the animals of the control groups. No essential differences were found in the survival rate depending on the dose of crude dextran given (0.1; 0.05 or 0.02 g/ kg).

In addition to the higher rate of survival of the mice injected with dextran, the radiation sickness in these animals had a milder course. The animals were more mobile, their neat appearance was restored sooner, and they gained weight more rapidly. For instance, 25 days after irradiation, the mean weight of the animals in the group receiving dextran was 95-105% of the initial weight, but that of the control groups was 67-78% of the initial weight. In the mice which were injected with dextran before irradiation, the loss of weight at the climax of the radiation sickness was observed to be less, also; 12 days after irradiation, it reached 84-87%, as compared with 79-81% in the control animals.

Besides crude dextran, we tested the pyrogenic polysaccharide from B. proteus vulgaris. This was injected intravenously into mice 12 hours before irradiation, in doses of 1γ and 10γ/ kg body weight, made up to 0.2 ml in volume with pyrogen-free physiological saline. The mice were irradiated under the same conditions as in the previous experiment. The results of this experiment are shown in Table 3. On this occasion, the rate of survival of the mice of the control groups to the end of the month was higher than in the two previous experiments, which might have been due to, among other things, difficulty in reproducing the conditions and the greater resistance of females to the action of radiation. However, in both groups of animals which received injections of pyrogenic polysaccharide, the survival rate was higher than in the control groups (30-60% respectively, compared with 12-16% in the control animals).

In contrast to crude dextran, however, injection of pyrogenic polysaccharide did not perceptibly improve the general condition of the irradiated mice. Even at the end of a month, many of them appeared ill; the weight of the animals had not been restored at this period. The control mice at this time appeared healthy – neat and tidy in appearance and more mobile. It was decided to prolong the period of observation to 50 days.

During this period, more animals of the various groups died, but the essential difference in the rate of survival of the control mice and those receiving polysaccharide in a dose of 10γ/ kg body weight remained (see Table 3). The last mouse of this group to die did so on the 35th day after irradiation. At the end of the 50 days all the mice appeared healthy; they were neat and tidy and mobile. The animals continued to gain weight.

The first two experiments showed that crude dextran possesses a well-marked ability to lower the mortality of irradiated mice. It should be emphasized that some slight (between limits of 14-28%), but regularly repeated, reduction in mortality was also observed when crude dextran was injected 3 hours after irradiation. Pyrogenic polysaccharide of B. proteus vulgaris also considerably increased the rate of survival of irradiated mice.

For the time being, we will leave aside the question of the mechanism of action of the preparations tested. We shall merely point out that besides their ascribed property of stimulating the properdin system, they evidently also activate other mechanisms of nonspecific resistance.

SUMMARY

Native dextran injected intravenously in doses of 0.1, 0.05 and 0.02 gm per kg of body weight, 12 hours before the irradiation, reduces the mortality rate of mice from radiation sickness, 32 to 60% of mice treated with dextran survived for a month, with an almost 100% death rate in the control group. Considerable increase in the percentage of surviving animals was also noted with the pyrogenic saccharide (obtained from B.proteus vulgaris), administered in the dose of 10 γ kg, 12 hours previous to the irradiation. 14 to 30% of mice which received native dextran after the irradiation survived. The death rate in the control group equalled almost 100%.

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