THE STUDY OF TOLERANCE AND OF THE POTENTIATION PHENOMENON IN RELATION TO THE BROWN-PEARCE CARCINOMA OF RABBITS

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Research workers in many countries have devoted increasing attention in recent times to the phenomenon of potentiation. Although the study of this problem began in the 1930s, it was not until very recently that the nature of this paradoxical immunological phenomenon became understood. It was on this account that the term "XYZ phenomenon" was used for a long time to denote the phenomenon of potentiation, stressing its enigmatic nature. As a result of numerous investigations during the last few years certain properties of the "stimulating" factor have been explained, and this has enabled an approach to be made to the study of its mode of action [6-11, 13, 14]. The fundamental question connected with the study of the potentiation phenomenon at the present time is that of the identity of, or the difference between the antigens responsible for immunity and the stimulation of tumor growth, and also for the phenomena of tolerance and "potentiation." Although there are reports in the literature [12] that the two last phenomena are closely related, no special study of this problem has yet been made.

We thought it interesting to compare these two phenomena in relation to the Brown-Pearce rabbit carcinoma. This tumor is regarded as one of the classical models for studying the potentiation phenomenon; the preliminary inoculation of rabbits with an extract of frozen tissue from a Brown-Pearce carcinoma causes stimulation of tumor growth if these animals are subsequently inoculated with fresh tissue from the same tumor [2-5]. Meanwhile the preliminary inoculation of rat embryos or newborn rats with an extract of mixed organs of a healthy rabbit makes them tolerant of a subsequent inoculation with Brown-Pearce carcinoma [1].

In the present research we attempted to discover if the potentiation phenomenon can be produced in rats in the same way as it is observed in rabbits. The experiments were based on the technique used in the study of the potentiation phenomenon.

EXPERIMENTAL METHOD

Young rats, aged 2-6 weeks, were inoculated intraperitoneally or subcutaneously with an extract of frozen Brown-Pearce carcinoma tissue or of normal organs of a healthy rabbit. The extract was made up in physiological saline in a dilution of 1:4 in relation to the weight of tissue taken, and was injected subcutaneously or intraperitoneally into the rats in a dose of 1.0-1.5 ml. In the different experiments the extract was injected once or 4 or 6 times; the intervals between the injections were 3-4 days.

At intervals of 3, 7, 14, and 21 days after the completion of preparation of the experimental and corresponding control (unprepared) rats, the animals were inoculated intraperitoneally with a suspension of Brown-Pearce carcinoma in a dose of 0.5 ml. To check the activity of the tumor suspension used for inoculation, on each occasion it was injected at the same time into rabbits and tolerant 5-7-day old rats. Under these circumstances active growth of the tumor was observed in the rabbits and tolerant rats.

The experimental and control rats remained under observation for a period of 1 month after inoculation: the rats were inspected regularly, and those dying from any cause whatever were autopsied. At the end of the month all the animals were sacrificed and autopsied.

EXPERIMENTAL RESULTS

Of the 60 rats receiving a preliminary injection of extract of frozen tumor or normal rabbit tissue, after inoculation with Brown-Pearce carcinoma only 3 rats developed tumors, and moreover, all these tumors were absorbed. All 3 tumors were found in rats receiving 4 preliminary intraperitoneal injections of frozen normal tissue and inoculated with the tumor suspension 14 and 21 days after completion of the preparation. None of the 40 control rats developed tumors.

The absence of any significant difference between the rate of successful tumor transplantation in the experimental and control animals demonstrated that the natural species resistance of rats to the tumor heterotransplant could not in practice be overcome by means of a preliminary inoculation with frozen tumor and normal tissue extracts.

At the same time as adult rats were inoculated with extracts of frozen Brown-Pearce carcinoma tissue or of normal rabbits' organs, these same extracts were injected 4 times into newborn rats. At the age of 5-6 days, the young rats were inoculated with the tumor suspension. The animals remained under observation for 1 month. The results obtained, shown in Table 1, indicate that although these extracts were ineffective in stimulating tumor growth in the fully grown rats, they were effective in producing tolerance of the heterotransplant in the newborn rats: tumors developed in all the inoculated young rats, and in most of them the rate of growth was very rapid, terminating in death of the rats on the 12-16th day after inoculation.

TABLE 1. Inoculation of Newborn Rats with Brown-Pearce Carcinoma

Preliminary treatment of rats	No. of rats	No. of positive inoculations	No. of rats dying from tumors	No. of rats in which tumors were absorbed
With extract of Brown-Pearce carcinoma	40	40 (100%)	26 (65%)	14 (35%)
With extract of normal rabbits' organs	25	25 (100%)	17 (68%)	8 (32%)
Control animals (no preparation)	30	6 (20%)	1 (3.3%)	5 (16.6%)

Comparison between the negligible percentage of positive inoculations in the fully grown rats and the 100% of successful inoculations of the tumor in the newborn rats shows that tolerance to this tumor can be produced in newborn rats by means of extracts of Brown-Pearce carcinoma and of normal rabbits' organs, and that growth of the tumor in fully grown rats cannot be stimulated.

The results may be interpreted differently: it appears highly probable that the phenomenon of tolerance and the phenomenon of potentiation are caused by the same agents which, however, may show their activity only during the first days of the postnatal life of experimental animals; in later stages of development these antigens are ineffective. On the other hand the results do not exclude the possibility that tolerance and potentiation of tumor growth may be due to different antigens.

Whatever our interpretation of the results, the following conclusion holds: notwithstanding the similarity between these immunological phenomena, they are based on different processes, associated with differences either in the antigens or in the conditions necessary for the action of the same antigen to be brought into play.

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