EFFECT ON CARCINOGENESIS OF CERTAIN PHARMACOLOGICAL SUBSTANCES WITH A MARKED EFFECT ON INFLAMMATION

A. P. Savinskaya

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Previous investigations [7] showed that the induction of tumors by 9,10-dimethyl-1,2-benzanthracene (DMBA) is considerably stimulated by administration of chloropromazine at various stages of the pretumor period. The mechanism of this stimulant action of chloropromazine could be associated with the ability of this drug to depress inflammation [4-6], because there is considerable evidence that inflammation accompanies carcinogenesis and may influence development of the tumor [1-3,8,9,11,etc.].

To investigate this problem, it seemed advisable to study the possible effect of physiological substances having a marked action on inflammation but by different mechanisms on the outcome of tumors induced by a chemical carcinogen. Interest in the trials of these substances was also determined by the fact that they are widely used in clinical practice for the treatment of various diseases.

In the present investigation, the effect of dimedrol (diphenhydramine hydrochloride) diazoline, cortisone, and desoxycorticosterone on the frequency of development of tumors induced by DMBA was studied. The first two have an antiallergic action, but in contrast to dimedrol, diazoline has no marked depressant action on the nervous system [6]. Cortisone and desoxycorticosterone are antagonists in their influence on the inflammatory process [10,11,etc.].

EXPERIMENTAL METHOD AND RESULTS

Experiments were carried out on 382 male albino rats weighing 90-100 g (at the beginning of the experiment). Observations were maintained on the animals for 10 months. Tumors were induced by a single subcutaneous injection of DMBA into the left thigh in a dose of 0.5 mg (in 0.2 ml peach oil). Diazoline was administered by mouth in a dose of 2 mg/kg body weight through a tube, and cortisone, desoxycorticosterone acetate (DOCA) and dimedrol were given intramuscularly, the first two in a dose of 10 mg/kg and dimedrol in a dose of 2 mg/kg.

Administration of the preparations began immediately after injection of DMBA and the animals thereafter received them daily except on Sundays; the duration of one course was from 14 to 30 days.

Diazoline had no significant effect either on the yield of induced tumors or on the time of their appearance, irrespective of the time of administration of the preparation. Only in the second and third group of experiments was a tendency observed towards a slight increase in the percentage yield of tumors, although the difference between the control and experimental groups was not statistically significant ($P > 0.1$).

When the effect of cortisone was studied in similar experimental conditions, no significant difference likewise was found in the incidence of tumors in the experimental and control animals. Only a slight shortening of the pretumor period in the first three groups was observed.

During the study of the effect of cortisone and DOCA (administration for 14-30 days; longer administration of DOCA was impossible because the rat tolerated its effect badly, lost weight, became untidy, less active, and so on) no statistically significant difference was observed between the effect of cortisone and DOCA on the appearance of induced tumors ($P > 0.1$) (Table 1).

By changing the scheme of administration of cortisone, dimedrol, and diazoline (three courses each of 14 days with an interval of 2 months between them), different results were obtained (Table 2). In these conditions diazoline and cortisone considerably reduced the percentage yield of tumors by comparison with the control, whereas dimedrol had only a very slight action.

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TABLE 1. Effect of Cortisone and DOCA on Yield of Tumors Induced by DMBA

Preparation and mode of administration	Number of animals		Time of appearance of primary tumors
	Total	With tumors	
Cortisone, injected for 14 days	21	8	2 months 28 days
DOCA, injected for 14 days	17	6	4 " 22 "
Cortisone, injected for 30 days	20	8	4 " 22 "
DOCA, injected for 30 days	19	9	2 " 22 "
Control	20	6	4 " 22 "

TABLE 2. Effect of Dimedrol, Diazoline, and Cortisone on Yield of Tumors Induced with DMBA

Preparation and mode of administration	Number of animals		Time of appearance of primary tumors
	Total	With tumors	
Dimedrol, three courses, each of 14 days, with interval of 2 months between courses	20	6	5 months 16 days
Diazoline, three courses, each of 14 days, with interval of 2 months between courses	20	1	5 " 16 "
Cortisone, three courses, each of 14 days, with interval of 2 months between courses	20	1	6 " 20 "
Control	20	11	4 " 20 "

Hence, only in this series of experiments when cortisone, diazoline, and dimedrol were used, was a statistically significant effect obtained ($P < 0.01$). Attention is drawn to the fact that, in this series of experiments, cortisone and diazoline gave the same effect. However, taking into account all the results obtained and, in particular, the equal effect of cortisone and DOCA, antagonists in their effect on inflammation, on the yield of tumors and also the results showing the duration of the inflammatory reaction after injection of the carcinogen [2], the results of this series of experiments can hardly be associated with the action of the preparation on the inflammatory process alone. Evidently, the change in the source of the inflammatory process arising immediately after injection of the carcinogen had no significant effect on the yield of tumors. Evidently certain conditions exist in which the process of carcinogenesis becomes sensitive to external influences. However, these conditions are unknown, inconstant, and as yet not deliberately reproducible. This evidently explains the fact that many substances may produce either a positive effect or no effect whatsoever.

If the process of carcinogenesis were necessarily associated with inflammation, antiinflammatory substances would give a more marked and more constant effect. Evidently the inflammatory process merely accompanies carcinogenesis but is not an essential part of it. As an accessory factor, it does not influence carcinogenesis itself, but the development of the rudimentary tumor. Since this effect may differ depending on various conditions, the effect of anti-inflammatory substances likewise is inconstant and varied.

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