EFFECT OF TESTOSTERONE PROPIONATE ON INDUCTION OF RENAL CAPSULE ANGIOSARCOMAS BY 1,2-DIMETHYLHYDRAZINE IN CASTRATED MICE

V. S. Turusov and G. Yu. Chemeris

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KEY WORDS: angiosarcomas; 1,2-dimethylhydrazine; testosterone propionate.

Male CBA mice in a high percentage of cases develop tumors, called pararenal angiosarcomas, under the influence of 1,2-dimethylhydrazine (DMH) [3]. It has been shown [5] that these tumors develop from the renal capsule and that preliminary castration of male mice almost completely prevents their induction.

In the investigation described below restoration of the frequency of tumors in castrated male mice during administration of DMH together with testosterone propionate (TP) was studied and, in addition, an attempt was made to identify the stage of carcinogenesis (initiation or promotion) on which TP acts; for this purpose the hormone was injected either simultaneously with DMH or after the end of DMH administration. A third aim of the investigation was to discover whether pararenal angiosarcomas can be induced in castrated females by combined administration of DMH and TP (in previous experiments injection of DMH into intact or castrated females did not induce the formation of these tumors [2]).

EXPERIMENTAL METHOD

Male and female CBA mice, aged 2-3 months, were obtained from the "Stolbovaya" Nursery, Academy of Medical Sciences of the USSR. DMH·2HCl was injected subcutaneously in distilled water in a dose of 8 mg/kg body weight (calculated as base) once a week for 15 weeks. The mice were killed 40 weeks after the beginning of DMH administration. TP was injected subcutaneously once a week in olive oil in a sessional dose of 0.5 mg per mouse. Depending on the experimental conditions the male mice were divided into the following groups: 1) injection of DMH; 2) castration + DMH (castration was carried out 3 weeks before the beginning of DMH administration); 3) castration + DMH + TP (administration of TP began 2 weeks before the first injection of DMH and ended simultaneously with DMH — total 17 injections; TP was injected each time the day before the corresponding DMH injection); 4) castration + DMH + TP (injection of TP was started after administration of DMH had ended and continued until the end of the experiment); 5) castration + DMH + TP (TP was injected first, as in the animals of group 3, but the injections were continued until the end of the experiment — 40 weeks). In group 6, female mice started to receive DMH together with TP 3 weeks after castration (total 15 injections of DMH and 32 injections of TP).

Dying and sacrificed animals were autopsied; organs with visible changes were fixed in 10% formalin, embedded in paraffin wax, and stained with hematoxylin and eosin.

EXPERIMENTAL RESULTS

The scheme of the experiment and frequency of renal capsule angiosarcomas 40 weeks after the beginning of DMH administration are shown in Fig. 1. Renal capsule angiosarcomas were dark red tumors measuring from 2-3 mm (in which case they were easily separated from the kidney together with its capsule) to 2-2.5 cm in diameter. Large tumors sometimes invaded the kidney tissue but sometimes they were easily separated from the kidney. Histologically

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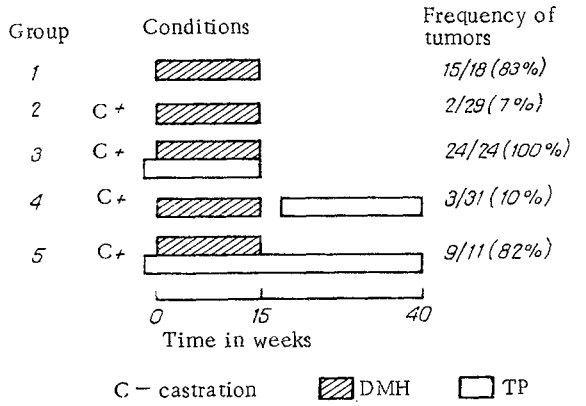

Fig. 1. Frequency of renal capsule angiosarcomas in different experimental groups. C) Castration, shaded rectangles — DMH, unshaded rectangles — TP. Percentage of animals with tumors shown in parentheses. Abscissa, time (in weeks).

the large tumors were different versions of angiosarcomas; in the initial stages development of the tumor could be traced from the kidney capsule.

DMH induced tumor development in 83% of male mice (group 1) but preliminary castration sharply inhibited induction (7%, group 2). The effect of TP depended entirely on the time its administration began.

Two stages can be distinguished in tumor development. During the first stage (initiation) the carcinogenic metabolite formed as a result of activation of the procarcinogen (in this case DMH) reacts with DNA, causing, it is considered, irreversible changes in its structure and leading to transformation of the normal cell into a tumor cell. Agents acting on this stage (cocarcinogens) can affect either metabolism of the procarcinogen or binding of the metabolite with DNA. In the second stage of carcinogenesis (promotion) tumor cells multiply, leading to the appearance of a tumor. Agents stimulating this stage (promotors) affect intercellular interaction and differentiation and proliferation of tumor cells.

TP, if injected simultaneously with DMH (group 3) completely restored the frequency of tumors (100%) depressed as a result of castration. Under these conditions TP could act on DMH metabolism in the target organ or on binding of the carcinogenic metabolite with DNA, i.e., on the stage of initiation of carcinogenesis. A promoter effect also could take place, i.e., stimulation of the transformed cells.

In group 4, in which TP was given after the end of DMH administration, and it thus could not affect the initiation stage and could only have a promotor effect, the frequency of tumors (10%) was just as low as in group 2, in which DMH administration followed castration. Consequently TP in this system did not exhibit a promotor effect; however, it must be recalled that the action of TP in group 4 began 19 weeks later than in group 3.

In group 5, in which TP was given throughout the period of observation (during and after the end of DMH administration), tumors appeared in nine of 11 mice. The promotor effect could be manifested as the earlier death of animals with tumors or tumors of a larger size than in the animals of group 3, but this was not the case. In similar experiments in which sarcomas of the uterus were induced by DMH in mice of the same line, an estrogen injected after the end of DMH administration significantly shortened the time of appearance of the tumors [4] or, in other words, exhibited a distinct promotor effect. Injection of DMH together with TP into castrated females (group 6) led to the appearance of angiosarcomas in 22 of 24 mice (92%), i.e., it had the same action as when DMH was injected into intact males or when DMH and TP were given simultaneously to castrated males. DMH did not induce the development of renal capsule angiosarcomas inintact females when administered for 10 or 30 weeks [2, 4]. Tumors of this kind likewise did not arise when DMH was given to castrated females [2]. These findings indicate that the absence of induction of these tumors in females is connected not with the inhibitory action of the estrogens, but withthe low androgen level.

The results of the present experiments show that the stimulating action of TP on induction of renal capsule angiosarcomas by DMH is due to the effect of the hormone on the tumor initiation phase, in the complete absence (at least under these experimental conditions) of any promotor effect. Bakshi et al. [6] showed in an Ames' system with dimethylnitrosamine that the microsomal fraction from male kidneys gave a much greater mutagenic effect than that from female kidneys, and that this effect was potentiated even more by administration of an androgen. Another theoretically possible mechanism of the stimulating action of TP is through β-glucuronidase. It is considered [1] that conjugates of DMH metabolites with glucuronic acid, formed in the liver, are broken down in the target organ by the action of β-glucuronidase, whose activity in the kidneys is induced by androgens [8].

Sarcomas of the kidney capsule, including those of vascular genesis, are also known in man; they are found equally infrequently in men and women, and like the experimental tumors, they can infiltrate kidney tissue or leave it intact [7].

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BIOCHEMICAL DIFFERENCES IN TUMOR CELLS OF EHRLICH'S ASCITES CARCINOMA STRAINS SENSITIVE AND RESISTANT TO 5-FLUOROURACIL

M. P. Shlemkevich

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In the search for biochemical criteria of sensitivity and resistance of tumor cells to 5-fluorouracil (5FU) the principles governing accumulation of 5FU in the acid-soluble fraction (ASF) and its incorporation into RNA were studied in experiments *in vitro* and *in vivo* and the state of the adenylate cyclase system was compared in strains of Ehrlich's ascites carcinoma sensitive and resistant to 5FU.

EXPERIMENTAL METHOD

Experiments were carried out on noninbred albino mice weighing 20-25 g into which an Ehrlich's ascites carcinoma naturally sensitive to 5FU was transplanted. A strain of the tumor with induced resistance to 5FU was obtained in mice into which, after transplantation of the tumor, 5FU was injected intraperitoneally daily in a dose of 15 mg/kg body weight. The strain of tumor resistant to 5FU was obtained at the 20th subculture of the tumor.

Department of Biochemistry, L'vov Medical Institute. [Presented by Academician of the Academy of Medical Sciences of the USSR A. M. Chernukh (deceased).]

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