

EFFECT OF ADRENALECTOMY ON CHANGES IN CONTACT
HYDROLYSIS OF CARBOHYDRATES IN ANIMALS WITH
SARCOMA 45 AND DURING TREATMENT WITH THIOPHOSPHAMIDE
AND 5-FLUOROURACIL

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UDC 616-006.3.04-092.9-085.277.3-059:616.45-
089.87]-07:616-008.934.54-074

Disturbances of contact hydrolysis of carbohydrates and of enzyme production by the intestinal epithelium observed in animals with sarcoma 45 and also in intact animals and animals with tumors treated with thiophosphamide and 5-fluorouracil did not arise in adrenalectomized animals receiving 1% NaCl instead of water. If these animals were given hydrocortisone, the usual changes were observed.

An earlier investigation [2] showed that administration of certain chemotherapeutic antitumor drugs to intact animals causes marked changes in contact hydrolysis of carbohydrates and in enzyme formation in the intestinal epithelial cells. A decrease in the intensity of these processes also is observed in animals with implanted tumors. Single injections of the same compounds lead to temporary restoration of the normal values of these indices of intestinal epithelium function [3]. On the other hand, adrenocortical hormones have been found to regulate contact digestion [1].

The object of this investigation was to study how changes in contact hydrolysis of carbohydrates in animals with sarcoma 45 and also in intact animals and animals with tumors treated with thiophosphamide and 5-fluorouracil, depend on the state of adrenocortical function.

EXPERIMENTAL METHOD

Experiments were carried out on 190 noninbred albino rats of both sexes weighing 160-180 g. All the adrenalectomized animals were divided into eight groups. The rats of groups 1 and 2 were injected with chemotherapeutic antitumor compounds and given ordinary water (group 1) or 1% NaCl instead (group 2) to drink. The animals of groups 3 and 4 were given salt; in group 3 the chemotherapeutic substances and hydrocortisone were given simultaneously, while in group 4 hydrocortisone was injected for three days before the experiment. Healthy rats and rats with intact adrenals treated with the chemotherapeutic substances acted as controls for these four groups.

The rats of groups 5 and 6, which received salt, were inoculated with sarcoma 45, but in group 6, by contrast with group 5, for the three days before the experiment the animals received hydrocortisone. In groups 7 and 8 the rats with sarcoma 45 and receiving salt were injected with chemotherapeutic antitumor compounds, and the animals of group 8 in addition received hydrocortisone for the three days before the experiment. Healthy rats and rats with tumors acted as the control for groups 5-8.

The adrenals were removed by the same method as in [1]. The substances were injected intraperitoneally once a day: thiophosphamide in a dose of 0.16 mg/kg, 5-fluorouracil (20 mg/kg), and hydrocortisone (0.015 mg/kg). The tests were carried out when the tumor was two weeks old and three days after injection of the antitumor compound.

Chemotherapeutic Department, Moldavian Research Institute of Oncology, Kishinev. (Presented by Academician of the Academy of Medical Sciences of the USSR A. I. Chernukh.) Translated from *Byulleten' Éksperimental'noi Biologii i Meditsiny*, Vol. 75, No. 5, pp. 33-37, May, 1973. Original article submitted July 28, 1972.

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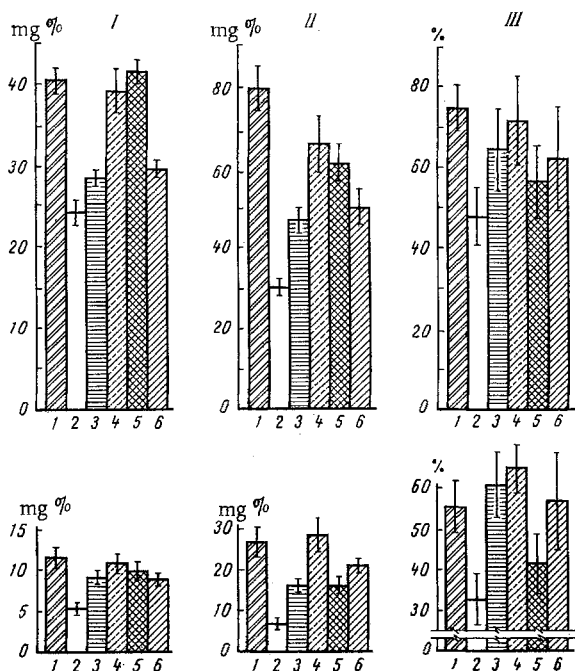


Fig. 1

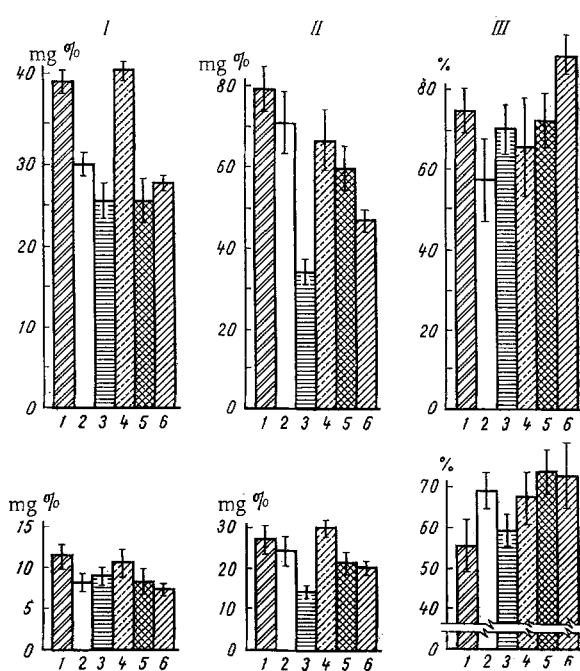


Fig. 2

Fig. 1. Relationship between changes in contact hydrolysis of sucrose (I) and starch (III) and invertase activity of homogenized pieces (II) of the proximal (top columns) and distal (bottom columns) portions of the small intestine after injection of thiophosphamide into intact animals and the state of their adrenocortical function: 1) healthy animals; 2) intact animals after injection of chemotherapeutic compound; 3) adrenalectomized animals receiving ordinary water to drink; 4) the same animals receiving 1% NaCl instead of water; 5) combined administration of chemotherapeutic compound and hydrocortisone to adrenalectomized animals receiving salt; 6) the same animals but three injections of hydrocortisone given.

Fig. 2. Relationship between changes in contact hydrolysis of sucrose (I) and starch (III) and invertase activity of homogenized pieces (II) of the proximal (top columns) and distal (bottom columns) portions of small intestine after injection of 5-fluorouracil into intact animals and state of their adrenocortical function. Remainder of legend as in Fig. 1.

Invertase and amylase activity on the surface of the mucous membrane and the invertase activity of homogenized pieces of intestine were investigated by Ugolev's method [4] in segments from the proximal and distal portions of the small intestine. In this way it is possible to assess the intensity of contact hydrolysis of sucrose and starch respectively and the enzyme-forming function of the intestinal epithelium.

EXPERIMENTAL RESULTS

In the experiments of series I, the results of which are shown in Figs. 1 and 2, the indices of intestinal epithelial function chosen for study were investigated during administration of the chemotherapeutic antitumor compound to animals without tumors. Contact hydrolysis of sucrose in the proximal portion of the small intestine after administration of both compounds to the adrenalectomized animals receiving ordinary water to drink did not differ significantly from that in the treated animals with intact adrenals. Approximately the same decrease in the intensity of contact hydrolysis of sucrose was observed, incidentally, in adrenalectomized animals without additional treatment [1]. Administration of the compound to adrenalectomized animals receiving 1% NaCl instead of water prevented the changes in their intestinal epithelial function [1], and no disturbance of contact hydrolysis of sucrose was observed. A disturbance did arise if the compounds were injected together with hydrocortisone; a single dose of hydrocortisone was sufficient to reveal the harmful action of 5-fluorouracil, but when thiophosphamide was given, the hydrocortisone had to be injected for two further days between the time of giving the thiophosphamide and the time of the experiment. The invertase activity of the homogenized pieces of intestine from adrenalectomized animals

TABLE 1. Relationship between Changes in Contact Hydrolysis of Carbohydrates and Enzyme Formation in Intestinal Epithelium of Animals with Sarcoma 45 and Animals Receiving Thiophosphamide and 5-Fluorouracil and the State of their Adrenocortical Function (M ± m).

Test object	Group of animals	Invertase activity (mg %)		Amylolytic activity on surface of mucous membrane
		surface of mucous membrane	homogenate	
Proximal portion	I	47,1±2,1	69,1±3,5	69,8±9,7
	II	27,8±1,7	51,4±3,2	78,1±8,2
	III	45,5±3,0	71,4±2,9	68,0±12,2
	IV	37,3±1,6	50,4±4,2	79,3±4,3
	V	51,2±4,2	74,7±2,3	36,1±6,2
	VI	41,2±3,2	48,4±2,9	58,9±8,5
	VII	52,7±4,7	60,9±5,2	41,8±10,4
	VIII	51,1±4,8	63,5±8,6	40,1±10,9
Distal portion	I	16,9±2,4	30,1±3,7	63,2±8,4
	II	7,6±1,6	13,9±3,4	66,8±5,8
	III	13,9±1,6	30,0±3,9	70,7±10,7
	IV	18,1±1,8	37,0±2,0	49,2±10,8
	V	13,4±1,5	22,0±1,8	60,7±8,3
	VI	11,5±1,1	22,1±2,6	69,7±5,8
	VII	16,9±1,5	25,4±1,9	32,4±9,7
	VIII	13,8±1,7	25,9±2,8	30,6±7,4

receiving water to drink fell more after administration of 5-fluorouracil but less after administration of thiophosphamide than that of animals with intact adrenals. However, these differences were more likely to be due to the adrenalectomy itself than to injection of the antitumor compounds. This conclusion is confirmed by the fact that in the animals receiving 1% NaCl instead of water there was no statistically significant decrease in the invertase activity of the homogenized intestine compared with the healthy animals receiving both 5-fluorouracil and thiophosphamide. A statistically significant difference was observed only when the compounds were given together with hydrocortisone; in that case the decrease was more marked when hydrocortisone was given for the three days before the experiment.

No statistically significant difference in amylolytic activity on the surface of the mucous membrane was observed between the adrenalectomized animals receiving the compounds and the control.

In the distal portions of the small intestine the changes were similar in character to those in the proximal, but they were less marked.

The results of investigation of the relationship between changes in contact hydrolysis of carbohydrates in animals with sarcoma 45 and receiving chemotherapy and the state of their adrenocortical function are given in Table 1. Growth of sarcoma 45 in adrenalectomized animals receiving salt was not accompanied by the usual disturbances of the final stages of contact hydrolysis of carbohydrates and enzyme formation in the intestinal epithelium observed in animals with intact adrenals. These disturbances did occur in rats receiving hydrocortisone for the three days before the experiments.

After a single injection of thiophosphamide into the adrenalectomized animals with tumors, these processes showed more appreciable change by comparison with the same animals not receiving the compound. However, the contact hydrolysis of starch was appreciably disturbed. Injection of 5-fluorouracil led to a significant decrease in the invertase activity of the homogenized pieces of intestine. Combined administration of the antitumor compounds and hydrocortisone, unlike administration of hydrocortisone alone, did not cause a disturbance of the initial stages of contact hydrolysis of carbohydrates, by comparison with the results for adrenalectomized animals with sarcoma 45 not receiving chemotherapy.

Contact hydrolysis of starch after combined administration of the chemotherapeutic compounds and hydrocortisone was considerably reduced in intensity, although in the proximal portion of the small intestine, because of the great individual variations, the differences between the mean values of amylolytic activity in the treated and untreated adrenalectomized animals with sarcoma 45 were not statistically significant ($P > 0.05$).

The changes in the state of intestinal epithelial function in animals with experimental tumors and in these and intact animals treated with certain antitumor chemotherapeutic compounds were thus shown to be dependent on adrenocortical hormones. No disturbances occurred in adrenalectomized animals receiving 1% NaCl instead of water to drink, but they did arise if the animals were given hydrocortisone.

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