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EFFECT OF CHEMICAL CARCINOGENESIS ON SYMPATHETIC NERVOUS SYSTEM FUNCTION IN ANIMALS

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In the modern view the process of chemical carcinogenesis embraces mainly two stages: first — circulation of the carcinogen in the body after introduction and the chain of its metabolic conversions, second — binding of metabolites of the carcinogen with the biological substrate of target cells. On entering the cell, these metabolites can bind with all its components: with the cell membrane, cytoplasmic organelles, and nucleus. Numerous investigations have helped to reveal the character of interaction between metabolites of the carcinogen and the substrate leading to malignant transformation of the cells [5, 6]. Another point to note is that when the action of a carcinogen is examined at the cellular level, the possibility that it may also affect other systems of the body, including nervous, vascular, and endocrine systems, must be taken into account. In this connection the question arises: What effect may carcinogens have on overall neurohumoral regulation of trophic processes as a whole, and in particular during the latent period before appearance of a tumor.

Considering that the sympathetic nervous system participates directly in neurohumoral regulation of trophic processes in the tissues, in the investigation described below an attempt was made to study to what degree a chemical carcinogen, introduced into animals, affects its functional state. For this purpose bioelectrical activity of structures of the sympathetic nervous system was investigated in healthy normal rats and in rats treated with the hepatocarcinogen 4-dimethylaminoazobenzene (DAB). This was all the more interesting because previously, in experiments on animals with a transplanted Brown-Pearce tumor, recording bioelectrical activity in different parts of the nervous system showed that tumor development depends on depression of the state of hypothalamic function and a disturbance of transmission of excitation in sympathetic ganglia [7]. Clinical physiological observations also have shown that in patients with malignant tumors, tone of the sympathicoadrenal system is low [8, 9]. Biochemical studies of tissues of malignant tumors of man and animals (mice and rabbits) have revealed a low concentration of noradrenalin, mediator of the sympathetic nervous system, in the tumors themselves and also in the affected organs [2-4].

EXPERIMENTAL METHOD

Experiments were carried out on noninbred rats weighing 150-200 g under pentobarbital anesthesia (50 mg/kg, intraperitoneally). In experiments on 25 healthy rats synaptic transmission of excitation through the inferior mesenteric ganglion (IMG) under normal conditions were studied in situ. In response to stimulation of the preganglionic trunk (intermesenteric tract) action potentials (AP) arising both in the tract itself and in postganglionic nerves (intestinal nerve, innervating the colon, and the ipsilateral hypogastric nerve, innervating the urinary bladder) and other pelvic organs, were recorded. A scheme of IMG of the rat, with

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the arrangement of bipolar silver stimulating (S) and recording (R) electrodes on the nerves, is given in Fig. 1.

The preganglionic nerve was stimulated from an electronic stimulator with radiofrequency attachment, by pulses 0.5-1.0 msec in duration, with a frequency of 5 to 150 Hz and strength of 0.5 to 10 V. After preamplification, AP were recorded on a cathode-ray oscilloscope. Under the same conditions, the effect of the hepatocarcinogen DAB, injected intraperitoneally in an oil—benzene mixture in a single dose of 250 mg/kg, on synaptic transmission of excitation through IMG was investigated in 15 rats. Recording of AP in the nerves of these rats began 24 h after injection of the carcinogen, and continued daily for the next 12 days. The dosage and mode of injection of the carcinogen, and also the times of observation on the character of transmission of excitation in IMG were chosen with regard to morphological, immunological, and biochemical features observed in the animal ("early responses") after injection of a single dose of carcinogen, and corresponded to features in tumors induced by them [10].

Only the oil—benzene mixture without carcinogen was injected into animals of the control group (seven rats).

EXPERIMENTAL RESULTS

Comparative analysis of the state of synaptic transmission of excitation through the sympathetic ganglion on recording AP in pre- and postganglionic nerves of IMG in normal rats and rats receiving DAB included consideration of the following parameters: latent period of development of AP, their amplitude, the duration of the potentials, and optimal discharge frequency reproducible without disturbance in pre- and postganglionic nerves. Thresholds of stimulation of the preganglionic nerve for AP development also were considered.

AP of pre- and postganglionic nerves of the rat IMG in response to stimulation of the preganglionic nerve under normal conditions are shown in Fig. 1. It can be seen that AP arise in the preganglionic nerve after a shorter latent period, their amplitude is higher, and their duration shorter than AP in postganglionic nerves — in the hypogastric and intestinal nerves, in which the presence of synaptic delay during transmission of excitation in IMG is reflected. The mean latent period of AP in the preganglionic nerves was 7.6 ± 1.1 msec, their amplitude 106 ± 7.3 μV, and their duration 17 ± 0.6 msec; the optimal frequency of spike conduction was 50-60/sec. In the hypogastric nerve the mean latent period was 20 ± 1.0 msec, amplitude of

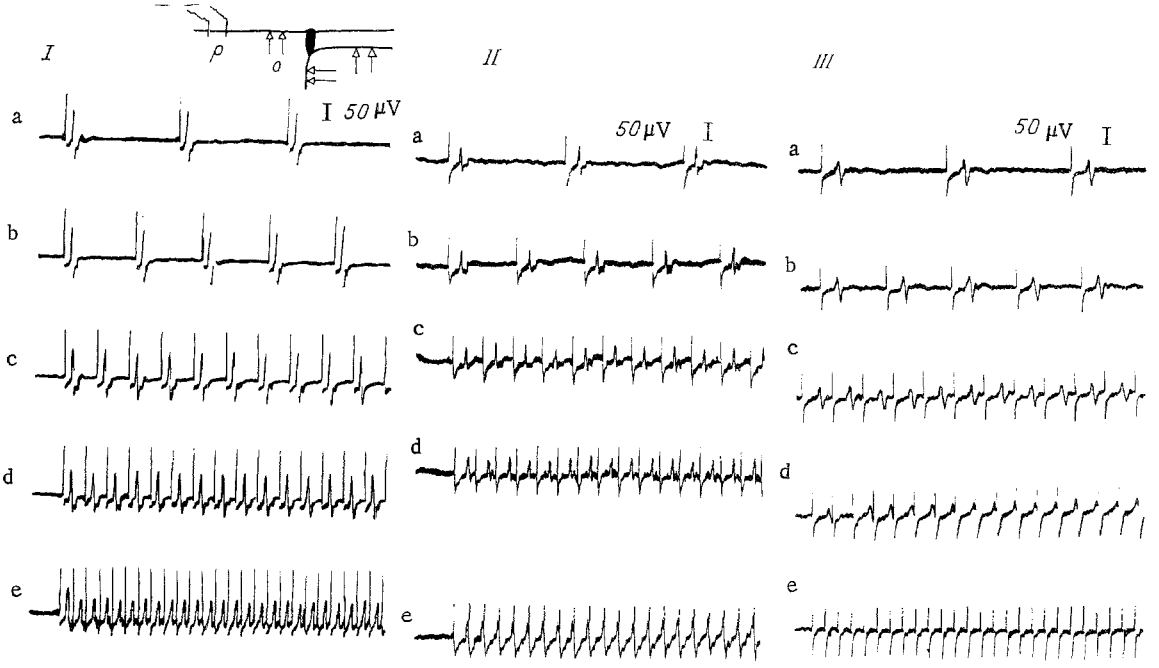

Fig. 1. AP of preganglionic (intermesenteric) nerve (I) and of postganglionic nerves — hypogastric (II) and intestinal (III) — during stimulation with different frequencies under normal conditions. I) (2.0 V, 1.0 msec): a-e) 5, 10, 20, 30, and 50 Hz, respectively; II (2.5 V, 1.0 msec): a-e) 5, 10, 20, 30, and 40 Hz, respectively; III (3.0 V, 1.0 msec): a-e) 5, 10, 20, 30, and 50 Hz, respectively. Here and in Figs. 2 and 3: calibration 50 μV, time marker 50 msec.

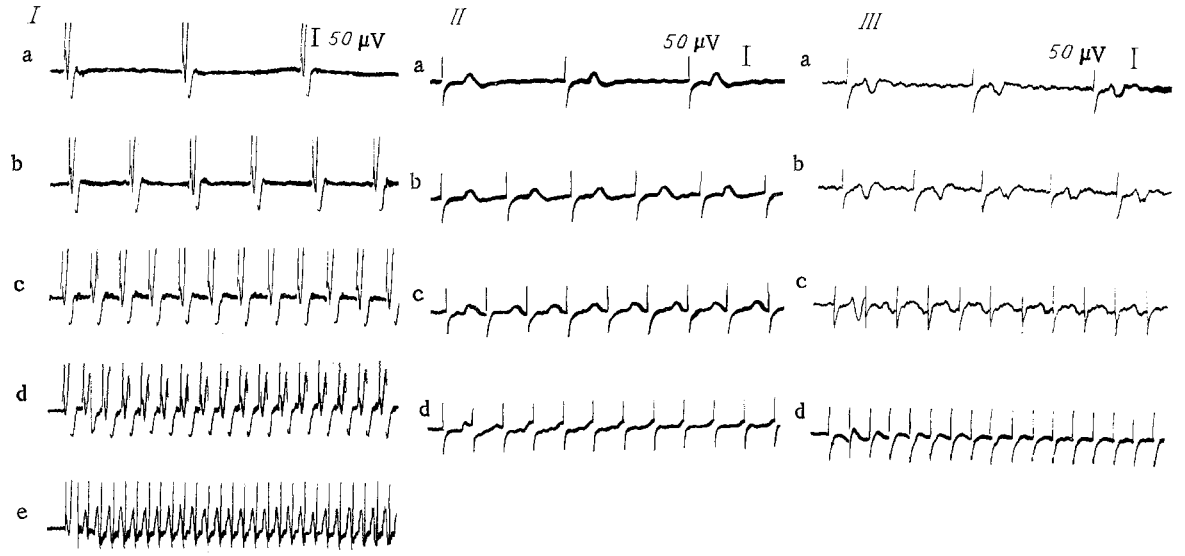

Fig. 2. AP of preganglionic (intermesenteric) nerve (I) and postganglionic nerves — intestinal (II) and hypogastric (III) — in response to stimulation of different frequencies on 2nd day after injection of DAB. I (2.5 V, 1.0 msec): a-e) 5, 10, 20, 30, and 50 Hz, respectively; II (6 V, 1.0 msec): a-d) 5, 10, 15, and 20 Hz, respectively; III (6 V, 1.0 msec): a-e) 5, 10, 20, and 30 Hz, respectively.

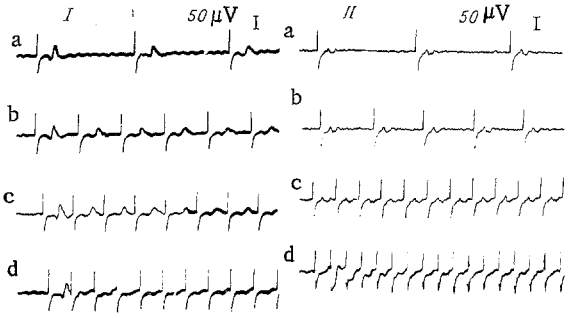

Fig. 3. AP of intestinal (I) nerve on 3rd day and of hypogastric (II) nerve on 9th day after injection of DAB. I (6.5 V, 1.0 msec): a-e) 5, 10, 15, and 20 Hz, respectively; II (6.0 V, 1 msec): a-d) 5, 10, 20, and 30 Hz, respectively.

the potentials 62 ± 8.8 ± V, and their duration 16 ± 0.6 msec. The mean latent period of AP in the intestinal nerve was 22 ± 1.2 msec, their amplitude 70 ± 8.8 μV, and their duration 1.7 ± 1.0 msec. The optimal frequency of spike transmission in both postganglionic nerves averaged 25-30/sec.

Under the influence of DAB the conditions of synaptic transmission of excitation in the sympathetic ganglia showed a marked change on the 2nd day after injection of the carcinogen, even though conduction of impulses in the preganglionic nerves remained the same as normally. It will be clear from Fig. 2 that in both intestinal and hypogastric nerves the latent period of onset of the potentials was lengthened, their amplitude reduced, and their duration increased. On average, compared with normal conditions, during the period of action of DAB from the 2nd to the 12th day after a single injection of the carcinogen the latent period in the hypogastric nerve increased to 29 ± 3.4 msec ($P < 0.02$), the amplitude of the potentials decreased to 32 ± 6.9 μV ($P < 0.01$), and their duration increased to 25 ± 2.3 msec ($P < 0.002$). Changes of the same order were observed in the intestinal nerve. The latent period increased on average to 26 ± 1.5 msec ($P \pm 0.05$), the amplitude of the potentials decreased to 45 ± 8.8 μV ($P < 0.05$), and their duration increased to 26 ± 2.2 msec ($P < 0.01$). Under the influence of DAB thresholds of stimulation to evoke AP in postganglionic nerves rose from 2-3 to 5-6 V. The optimal frequency of impulse conduction through IMG did not exceed 10-15/sec. Despite the low frequency of transmission of impulses through the ganglion, in some of the rats studied the amplitude of the potentials changed immediately (Fig. 3, I). Maximal disturbance of

transmission of excitation in the sympathetic ganglia of the rats, amounting sometimes to a complete block, was observed after a single injection of DAB mainly on the 5th-6th day, and transmission of impulses was fully restored by the 10th-11th day. In some rats, however, marked disturbances of impulse transmission in the ganglia were observed as early as on the first 2-3 days, whereas in others they were observed on the 9th day after injection of the carcinogen (Fig. 3, I, II). This points to individual sensitivity of neurons of the sympathetic ganglia in different animals to this carcinogen, which evidently acts on entry into the body primarily on synaptic transmission of excitation.

In control experiments in which the animals were given an injection of oil—benzene mixture without the carcinogen no abnormalities in conduction of excitation through the ganglion were observed.

On the whole it can be concluded from these results that before appearance of a tumor the effect of the carcinogen, after its introduction into the body, is exhibited on sympathetic nervous system function. By blocking synaptic transmission in sympathetic ganglia the carcinogen causes functional desympathization of organs and tissues. During functional desympathization substantial changes are known to take place in the physicochemical state of cells; in particular, their membrane potential is lowered, permeability of the cell membranes is increased, and polyvalent chemosensitivity develops in the cells [8]. All this creates conditions for penetration of metabolites of the carcinogen into the cells, in which they induce malignant change.

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