ONCOLOGY

THE ELECTROPHYSIOLOGICAL ANALYSIS OF DISTURBANCES IN THE TROPHIC ACTION OF THE NERVOUS SYSTEM DURING THE DEVELOPMENT OF A MALIGNANT TUMOR

(BASED ON THE RESULTS OF ANIMAL EXPERIMENTS)

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(Received December 26, 1958. Presented by Active Member Amn SSSR V. N. Chernigovskii)

It has been shown by clinico-physiological observations on patients suffering from carcinoma, polyposis or ulcer of the stomach that the development of malignant tumors is associated with disturbance of the neuro-humoral regulation, as a result of a lowering of the tone of the sympathetico-adrenal system [1-4].

By way of studying in greater detail the character of the changes taking place in the various divisions of the nervous system during tumor development, and of ascertaining the importance of the tone of the sympathetic nervous system to the rapidity of development of the tumor in the body, we carried out certain investigations, the results of which are described in this article.

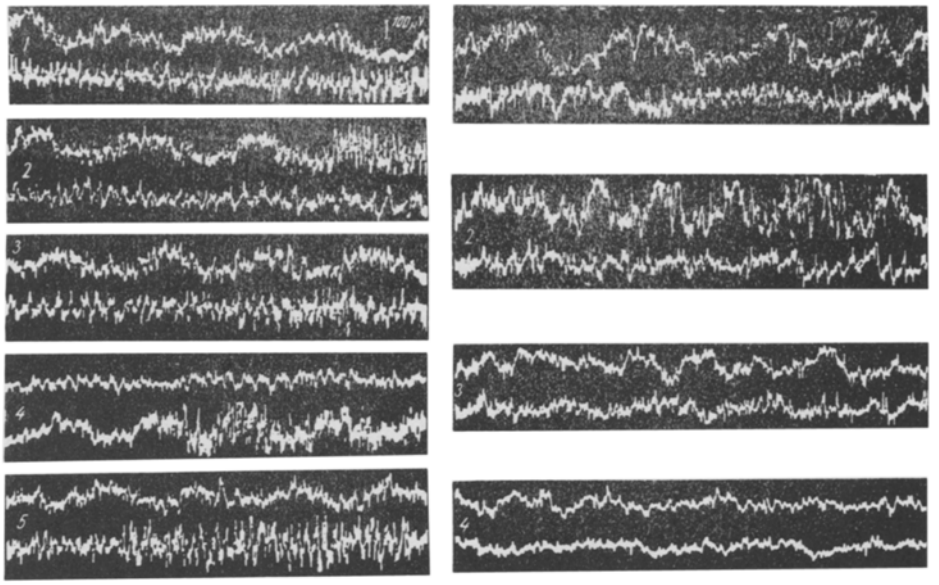
EXPERIMENTAL METHOD

Electrophysiological experiments were carried out on rabbits in which a Brown-Pearce tumor had been transplanted. Before transplanting of the tumor, unipolar and bipolar electrodes were introduced into different divisions of the central nervous system. In chronic and acute experiments stimultaneous recordings were made of the so-called spontaneous bioelectrical activity of the cerebral cortex, the hypothalamus and the cerebellum during the period of development of the tumor and until the animal's death, using a multi-channel oscillograph. In acute experiments we also recorded the bioelectrical activity of the superior cervical sympathetic ganglia.

EXPERIMENTAL RESULTS

In the chronic experiments, during which the bioelectrical activity of the various divisions of the nervous system was continuously recorded in 14 rabbits, it was found that on the 7th-11th day after transplantation of the tumor there was a sharp increase in the bioelectrical activity of the cerebral cortex. This took the form of an increase in the amplitude and frequency of the slow and rapid waves of the electroencephalogram. The bioelectrical activity of the cerebral cortex and hypothalamus is simultaneously recorded on the separate strips in Fig. 1 a and b, which are in sequence corresponding with the growth of the tumor. The increase in the bioelectrical activity of the cerebral cortex, as we were able to observe subsequently, was found to have a reflex effect a short time afterwards on the centers of the hypothalamus (see Fig. 1, a, 1 and 3) and also of the cerebellum (Fig. 2, a, 1 and 2) and the sympathetic ganglia (see Fig. 2, b, 1 and 2).

The initial increase in the bioelectrical activity of the nerve centers in the rabbits was connected with the effect of impulses reaching the central nervous system from the interoceptors in the course of development of the tumor and multiple metastases. We showed that procaine when injected in the region of the tumor and



a b

Fig. 1. Changes in the bioelectrical activity of the cerebral cortex (upper tracing on the strips) and hypothalamus of a rabbit (lower tracing on the strips) during the development of a Brown-Pearce tumor (a) in a rabbit with increased reactivity of the hypothalamus and (b) in a rabbit with diminished reactivity. In the case of (a): 1) bioelectrical activity of the cortex and hypothalamus before transplanting of the tumor; 2) on the 11th day after transplantation of the tumor; 3) on the 15th day after transplantation of the tumor; 4) on the 23rd day after transplantation of the tumor; 5) on the 26th day after transplantation of the tumor. Time marker – 1/20 second (shown above one strip for all the electroencephalograms). In the case of (b): 1) bioelectrical activity of the cerebral cortex and hypothalamus before transplantation of the tumor; 2) on the 15th day after transplantation of the tumor; 3) on the 21st day after transplantation of the tumor; 4) on the 23rd day after transplantation of the tumor. Time marker as in Fig. 1, a.

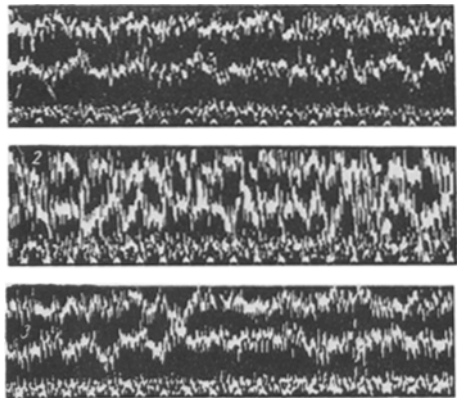


Fig. 2a. Action potentials of the cerebral cortex, hypothalamus and cerebellum. 1) before transplantation of a Brown-Pearce tumor; 2) on the 14th day after transplantation of the tumor; 3) after the action of procaine (on the 14th day after transplantation of the tumor).

retroperitoneally (10 ml of a 0.25% solution) caused a sharp fall in the bioelectrical activity of the centers (Fig. 2, a, 3). After the effect of the procaine had worn off (in 30-40 minutes) the excitation of the centers was usually restored.

During the subsequent development of the tumor, on the 20th-25th day from the moment of transplantation, the bioelectrical activity of the cerebral cortex began to fall gradually until the time of death of the animals, but not in all of them. As we were able to show, all the changes in the functional state of the cerebral cortex taking place after the initial rise in its excitation were closely connected with the character of the changes developing reflexly in the functional state of the autonomic centers, and in particular in the hypothalamus and the sympathetic ganglia. In those cases when the state of excitation developing reflexly in the hypothalamus was considerable in degree and stable by comparsion with the initial background – there were 3 such animals among the 14 in this series (see Fig. 1, a, 3-5) –, the level of excitation of the nerve cells of the cere-

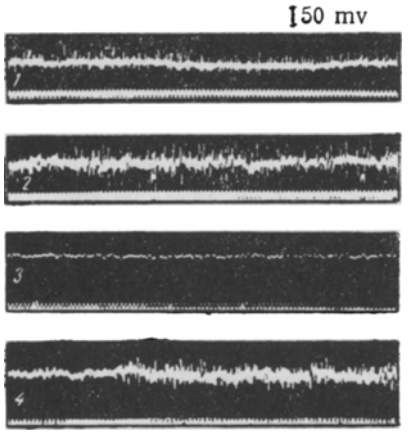


Fig. 2b. Character of bioelectrical activity of the superior cervical sympathetic ganglion of the rabbit. 1) before transplantation of a Brown-Pearce tumor; 2) bioelectrical activitity of the ganglion 10 days after transplantation of the tumor; 3) bioelectrical activity of the ganglion in the presence of a developing tumor with multiple metastases in the abdominal region; 4) recovery of the bioelectrical activity of the ganglion as the result of the action of combined drugs. Time marker – 1 second (below – 1/60 sec).

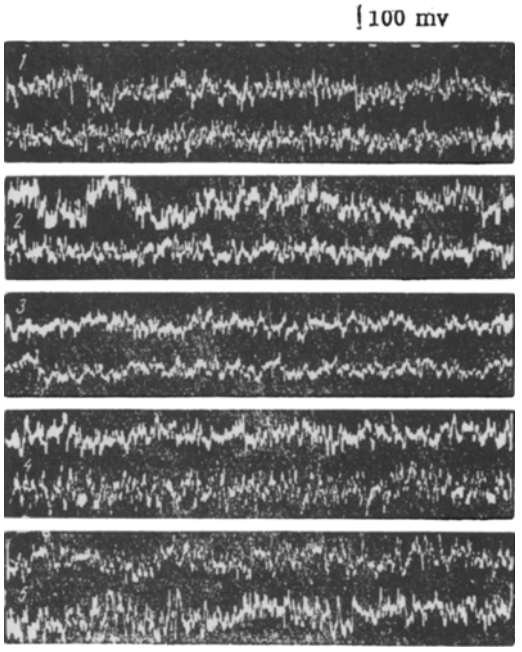


Fig. 3. The stimulating effect of a drug combination on the bioelectrical activity of the cerebral cortex (upper tracing on the strips) and of the hypothalamus (lower tracing on the strips) of a rabbit, diminished by the presence of a Brown-Pearce tumor. 1) bioelectrical activity of the cerebral cortex and hypothalamus before transplantation of the tumor; 2) on the 11th day after transplantation of the tumor; 3) on the 15th day after transplantation of the tumor; 4) on the 23rd day after transplantation of the tumor; 5) on the 30th day after transplantation of the tumor. Time marker – 1/20 second (shown above one strip for all the electroencephalograms).

bral cortex increased correspondingly (see Fig. 1, a, 5), for before this they were gradually falling under the influence of prolonged afferent impulses from the periphery and, after their initial excitation, were in a state of lowest activity (see Fig. 1, a, 4).

Tests of the bioelectrical activity of the superior cervical sympathetic ganglia of the rabbit in acute experiments (on the 27th day after transplantation of the tumor) showed that the synaptic transmission of impulses in the ganglia continued to be preserved; occasionally an increase in the impulsation could even be observed, analogous to that shown in Fig. 2, b, 2.

The increased activity of the hypothalamus in a number of rabbits was connected with high lability and reactivity of the nerve cells of the hypothalamus. This could be judged by the periodic sharp bursts of "spontaneous" bioelectrical activity observed under normal conditions, before transplantation of the tumor (see Fig. 1, a, 1, at the end).

In rabbits with a lesser degree of lability of the nerve cells of the hypothalamus, in response to the sharp increase in the bioelectrical activity of the cerebral cortex after transplantation of the tumor, a depression of hypothalamic activity took place in consequence of the reflexly induced brief burst of excitation; this may be judged by the reduction in the amplitude of the potentials (see Fig. 1, b, 4). Aganist this background, the initial excitation of the cerebral cortex of the rabbits was later (on the 15th-28th day from the moment of transplantation of the tumor) replaced by a fall in the level of the bioelectrical activity, which took the form of a sharp

reduction in the amplitude of both the slow and fast waves of the electroencephalogram. Tests of the bioelectrical activity of the superior cervical sympathetic ganglia in an acute experiment on the same rabbit (on the 23rd day after transplantation of the tumor) showed that the synaptic transmission of the impulses in the ganglia was practically absent. As a result, inhibition had then developed in the peripheral division of the sympathetic nervous system (see Fig. 2b, 3). We also studied the functional state of the sympathetic ganglia in rabbits during growth of the tumor in another series of acute experiments in which the bioelectrical activity of the ganglia was recorded on different days after transplantation of the tumor (10 rabbits); a disturbance of the transmission in the ganglia of the sympathetic nervous system, in which inhibition had developed, always preceded deterioration in the state of the rabbits.

The electrophysiological data obtained gave evidence of a direct interconnection between the functional state of the various divisions of the nervous system. The character of the reactivity of the hypothalamic centers, and also the functional state of the cells of the sympathetic ganglia(through which the central nervous system is known to send impulses for mobilization of the energy resources of the body) are directly concerned in the maintenace of the functional state of the cells of the cerebral cortex at a definite level, thereby ensuring the general regulation of the trophism of the tissues of the central nervous system.

As the experiments showed, the character of the relationship between the processes of excitation and inhibition on the cerebral cortex, the hypothalamus and the sympathetic ganglia determined the direction of development of the pathological process taking place in the animal. With increased excitation of the centers of the autonomic nervous system (and, in particular, of the hypothalamus and the sympathetic ganglia, through which a continous flow of impulses passes to the periphery), the neuro-humoral regulation of the tissues was maintained at a corresponding level, and the body took active measures to fight against the malignant tumor. After the initial growth of the tumor, in some cases it was observed to undergo absorption. At autopsy on one of the animals of this group on the 27th day an almost complete absence of metastases was observed. In two rabbits, after 2 months, the tumor and metastases which initially had been palpable in the abdominal region had completely disappeared.

Conversely, in rabbits in which the initial lability of the nerve cells of the hypothalamus and the sympathetic ganglia was not sufficiently high, the increased excitation of the cerebral cortex during growth of the tumor induced reflexly a state of lowest activity in these cells, leading to the development of inhibition in these structures. Since it developed in the first place in the sympathetic ganglia, it rendered impossible the regulation of the trophic processes in the tissues of the central nervous system. With cessation of the flow of impulses in the peripheral part of the sympathetic nervous system, it is evident that the necessary increase in excitation of the cells of the nerve centers themselves, and in particular of the cerebral cortex, was absent, whereas their increased activity was essential to balance the trophic disturbances in the tissues arising under the influence of the developing tumor and mestastases.

In order to verify the importance of the higher functional activity of the autonomic nerve centers to the arresting of growth of a malignant tumor in the body, we carried out the following series of experiments. Chronic experiments were conducted on 10 rabbits into the cerebral cortex and hypothalamus of which electrodes had been introduced. Starting on the 15th-20th day after transplantation of the tumor (when the development of inhibition in the central nervous system under the influence of afferent impulses could be judged by the character of the bioelectrical activity of the cerebral cortex and hypothalamus; Fig. 3, 3) we gave intravenous injections twice a day for 40-45 days (1ml/ kg body weight) of a drug combination of our own composition. This combination included drugs stimulating oxidation-reduction processes in the tissues and improving the synaptic transmission of impulses (riboflavin, thiamin, ascorbic acid, nicotinic acid, calcium chloride).

It was shown by daily observations of the bioelectrical activity of the nerve centers that, in those cases when the action of the drug combination brought about an improvement in the synaptic transmission of nerve impulses and in the functional state of the nerve cells, the inhibition developing in the synapses of the nervous system was abolished. This was observed in 6 of the 10 experimental rabbits.

After the action of the drug combination had begun, high bioelectrical activity was most rapidly restored in the sympathetic ganglia (which we checked by an acute experiment) and in the hypothalamus, not being directly under the action of afferent impulses (see Fig. 2b, 3, 4; Fig. 3, 4). Immediately after the increase in the activity of the autonomic nervous system, a persistent increase in the bioelectrical activity of the cerebral cortex also was observed, as shown by an increased amplitude of the slow and quick waves of the electroencephalogram (see Fig. 3, 4, 5).

In addition to this, from one to two weeks after the injections of the drug combination had started, cessation of growth and gradual reduction in the size of the tumor was observed, and 60 days after its transplantation into experimental animals, the tumor completely disappeared. In the last 8-10 days, absorption of the tumor took place despite the fact that injections of the drug were discontinued.

This was undoubtedly connected with the fact that the level of activity of the nerve centers continued to be raised. As the experimental results showed, against the background of the increased functional activity of the nerve centers and of the improvement in neuro-humoral regulation as a result of the action of the drugs composing the drug combination, an essential reorganization of the cells and tissues took place.

The results obtained from animal experiments in which the bioelectrical activity of different divisions of the nervous system was recorded against a background of the development of a transplanted Brown-Pearce tumor showed that the intensity of development of the tumor in the animal body was directly dependent on the functional state of the autonomic nervous system, and in particular, of the sympathetic nervous system. The sooner after the excitation(induced reflexly in the sympathetic nervous system by the flow of impulses to the center from the site of development of the tumor) that inhibition developed in the ganglia of the sympathetic nervous system, the more intensively did the tumor develop and produce extensive metastases, leading to the death of the animal. Conversely, the more resistant the centers of the hypothalamic region and the ganglia of the sympathetic nervous system (as a result of high lability of their cells) to the action of the stimuli reaching them reflexly from the periphery, the slower the tumor developed.

By maintaining the functional activity of the centers of the sympathetic nervous system with drugs stimulating oxidation-reduction processes, it was possible to create favorable conditions for the restorations of the disturbed synaptic transmission of nervous impulses through the ganglia.

This, in its turn, by enabling the regulation of the trophism of the tissues of the central nervous system, brought about a cytological reorganization of the tissues, leading to absorption of the malignant cells of the transplanted Brown-Pearce tumor.

SUMMARY

The bioelectrical activity of the cerebral cortex, hypothalamus, cerebellum and the superior cervical sympathetic ganglia was simultaneously recorded in rabbits against the background of a gradual development of a transplanted Brown-Pearce tumor.

The data obtained demonstrated that the intensity of tumor development depended on the functional condition of the autonomic nervous system, primarily of the sympathetic division.

The more rapid the development of inhibition reflex in the ganglia of the sympathetic nervous system and hypothalamus (following reflex excitation under the effect of impulses passing from the site of tumor development to the central nervous system) – the more accelerated the tumor growth with spread of metastases, this finally resulting in the animals' death. Conversely, the more stable (from high lability of the cells) the ganglia of the sympathetic nervous system to the action of reflex impulses from the periphery – the slower the development of the tumor. By raising the functional condition of the sympathetic nervous system with the aid of a number of substances stimulating oxidation-reduction processes, it became possible to maintain the excitation in the central nervous system for a prolonged period of time. In these conditions resolution of the transplanted Brown-Pearce tumor took place.

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