THE EFFECT OF HYPOTHALAMIC STIMULATION ON THE GROWTH TRANSPLANTED SARCOMAS

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The influence of the damage to the cerebral cortex on tumor growth has been repeatedly demonstrated [3, 7, 8 and others]. However, there are only isolated reports dealing with the effect of disturbance of function of the subcortical regions. L. F. Latmanizova [5] demonstrated changes in the electrical activity of the subcortical regions in patients with malignant tumors, and V. S. Sheveleva [13] was able to induce the absorption of a Brown-Pearce tumor by a drugs influencing the hypothalamic autonomic centers. Coujard and Chevreau [14] obtained an osteosarcoma in the guinea pig after local electrolytic damage to the hypothalamic region.

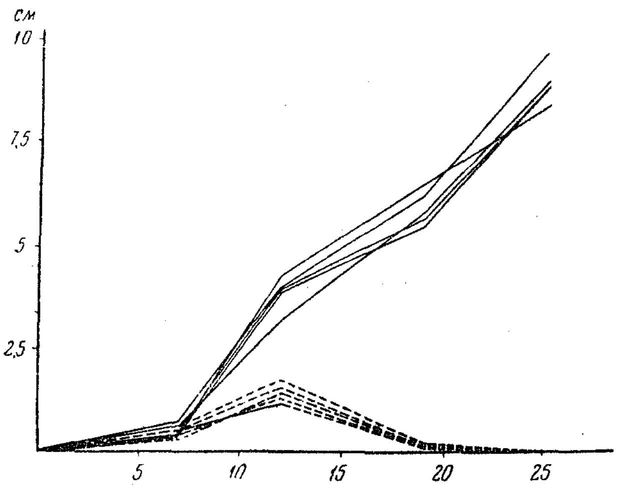

Fig. 1. Change in growth of M-1 sarcoma in control animals (—) and in animals receiving prolonged hypothalamic stimulation begun before the graft was made (——).

It seems to us that the role of the hypothalamus in the development of tumors deserves special study, because this subcortical region regulates metabolic processes through control of the autonomic system, as has been demonstrated in our laboratory [2, 12]. By prolonged hypothalamic stimulation it has been possible to cause an increase in the growth and absorption of experimental ovarian tumors, and also to influence the development of grafted sarcomas [1, 9, 10, 11].

The present work is a further study of the part played by the hypothalamus in the development of transplanted tumors.

METHOD

The experiments were carried out on 130 male and female rats weighing 90-100 g. The tumor was introduced by the injection into the paw of 0.5 ml of a tumor homogenate in Ringer. During the development of the tumors we measured their size, and determined the mean diameter by Schrek's method [17]. The hypothalamus was stimulated either electrically through chronically implanted electrodes, or the introduction of a glass ball 1-1.5 mm diameter. For comparison, the electrodes and spheres were also applied to the cerebral cortex. The electrodes were implanted by the method described previously [12]. As electrical stimulation we used a threshold alternating current sufficient to cause a visible somatic or autonomic response. On one day the stimulus would be applied three times for 40 seconds at 5-7 minute intervals, and in some experiments the procedure would be repeated daily, and in others on alternate days. The position of the ends of the stimulating electrodes was determined histologically by Campos silver impregnation. To identify the stimulated structures we used the map of the hypothalamus made by Krieg [16], and the stereotactic atlas of Fifkova and Maršal [15].

RESULTS

We carried out five sets of experiments, three with a transplanted M-1 sarcoma and two with a grafted sarcoma 45.

In the first set of experiments, electrodes were implanted into the hypothalamus of male rats, and electrical stimulation was applied through them every other day for $1\frac{1}{2}$ months. Then the five experimental and five control animals received a transplanted M-1 sarcoma. After it had been grafted, the electrical stimulation was continued for one month, bringing the total time to $2\frac{1}{2}$ months. At first the tumor increased in size in both the experimental and control animals, but later in the former it began to shrink and was finally completely absorbed, whereas in the controls it continued to grow as usual (Fig. 1).

TABLE 1. Weight of Tumors in the Control Animals and in others in which Electrical Stimulation was Applied to the Hypothalamus, Starting after the Transplantation

Statistical quantity	Control animals	Experimental animals
n (number of experiments)	15	15
M (arithmetic mean)	62	105
σ (mean square deviation)	8.0	15.6
m (mean error of the series)	2.1	3.8
P	—	0.001
1 − P (from Sh. D. Moshkovskii's formula)	—	1

TABLE 2. Weight of the Tumors in the Control Animals and in Animals Exposed to Hypothalamic and Cortical Stimulation before the Graft was Made.

Statistical quantity	Control animals	Experimental animals, stimulated: With electrodes	With spheres	With electrodes	With spheres
n	28	7	5	7	7
M	41	15	15	32	41
σ	9.3	5.0	6.6	15.0	30.0
m	2.5	1.9	3.0	5.7	12.0
P	—	0.001	0.001	0.1	0.1
1−P	—	1	1	> 0.1	> 0.1

In the second set of experiments, electrodes were implanted into the hypothalamus of 15 male rats, and one week later a M-1 sarcoma was transplanted into 15 experimental and 15 control animals. Electrical stimulation was not begun until after the graft had been made, and was then continued every other day for a total time of less than one month until the animals were killed. Now the reverse result was obtained, and there was a much more active growth of the tumor in the experimental groups than in the controls (Table 1).

TABLE 3. Weight of Tumor in the Control Animals and in Animals Exposed to Hypothalamic Stimulation Started Before the Tumor was Grafted

Statistical quantity	Control animals	Experimental animals, stimulated With electrodes	With spheres
		In hypothalamus	
n	7	7	2
M	21	8.2	7.2
σ	5.0	4.1	3.6
m	1.9	1.5	1.6
P	—	0.001	0.001
1 − P	—	1	1

It was shown statistically that the results were significant. Besides the usual statistical treatment by the formula of Student and Fisher, we also calculated the quantity 1 − p from Sh. D. Moshkovskii's formula [6], which has been designed for a comparison of tumor size taking into account their variability.

In the third set of experiments, electrodes were implanted into 14 male rats, in 7 in the hypothalamus, in 7 in the cortex; 14 rats received spheres: in 7 rats they were placed in the hypothalamus (2 succumbed), and in 7 rats they were placed in the cortex. The animals were stimulated daily for three weeks, and then 26 experimental and 28 control animals received a graft of a M-1 sarcoma. Stimulation was continued after the graft had been made for a total time of two months and one week.

Cortical stimulation caused various tumor growth changes. In most cases the tumors in the animals of this group were smaller than in the controls, but in some cases they were much larger.

Electrical stimulation of the hypothalamus through the implanted electrodes, and the presence of the small spheres in the hypothalamus caused a reduction in the rate of growth of the tumors (Table 2).

In the fourth and fifth groups of experiments with sarcoma 45, we studied only the suppressive influence of prolonged stimulation of the hypothalamus begun before transplantation of the tumors.

In the first set of experiments, in seven of the rats electrodes were implanted in the hypothalamus, and in seven others small spheres were introduced into the same region. Electrical stimulation was applied through the implanted electrodes daily for one month. Then the 14 experimental and seven control animals received sarcoma 45, and stimulation was continued. The animals were killed two weeks after the graft had been made, in order to determine the weight of the tumor during its most active period of growth. The results showed that the prolonged electrical hypothalamic stimulation, or the presence of the spheres in the hypothalamus strongly suppressed the growth of sarcoma 45 (Table 3).

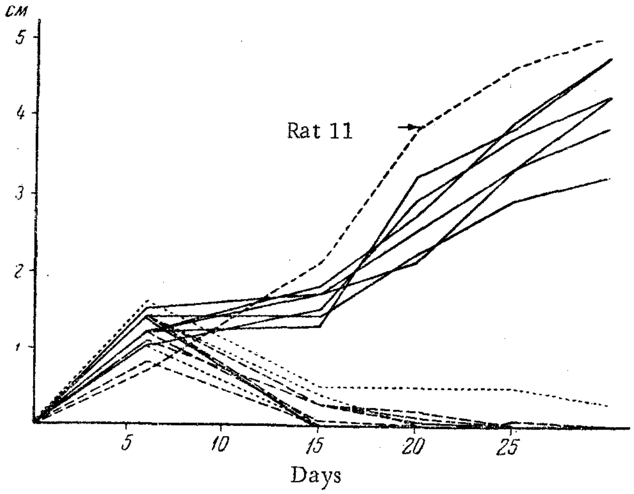

Fig. 2. Growth changes of sarcoma 45 in control animals, and in others in which prolonged hypothalamic stimulation was applied from the day of grafting onwards. ——— mean diameter of tumor in control animals; .... ditto in animals with electrodes implanted in the hypothalamus; – – – – ditto in animals with small spheres implanted in the hypothalamus.

In the fifth set of experiments, electrodes were implanted in the hypothalamus of seven male rats, and small spheres were placed in the hypothalamus of another seven (three animals succumbed). For two months stimulation was applied daily to the rats with electrodes, and then all the experimental animals and the seven controls received a graft of sarcoma 45, and stimulation was continued. The tumors became established in all the rats, and in the control animals they continued to grow in the usual way, but in the experimental groups they first became reduced in size, and were gradually completely absorbed (Fig. 2). It is interesting to note that rat No. 11 (which was accidentally transferred into another cage) received no stimulation before the graft was made; electrical stimulation was not begun until after the graft had been introduced (as in the second set of experiments with sarcoma M-1). In this animal, not only was the graft not absorbed, but it was greater than the greatest tumor of the control animal. This fact is in line with the results of the second set of experiments with sarcoma M-1. The rats were observed for three months, and no trace of tumors was observed in them. Because spontaneous absorption of tumors which have attained a diameter of 1 cm is observed in less than 1% of the cases [4], it must be supposed that the absorption of the tumors resulted from the influences we had applied, namely prolonged electrical thalamic stimulation, or the prolonged stimulation due to the implantation of a glass sphere.

The responses observed to electrical hypothalamic stimulation were very varied. We observed the orienting reaction (most commonly), motor and feeding responses, the occurrence of sleep, yawning, washing, increased respiration rate, constriction of the orbital aperture, protrusion of the eye, salivation, and the sexual response.

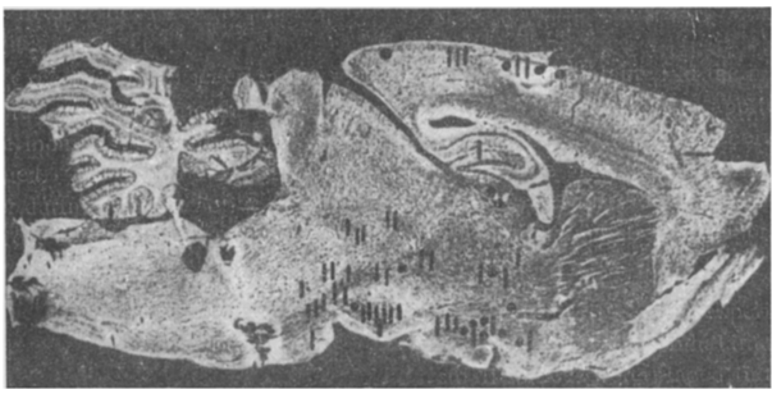

Fig. 3. Diagram of the position of the ends of the stimulating electrodes and of the glass spheres, shown in a saggital section of the rat brain. A short line shows the end of the electrode, a circle indicates a glass sphere.

When we determined the position of the stimulating ends of the electrodes, and of the spheres, we found that they lay in various nerve structures of the posterior, middle, and anterior hypothalamus; in some animals they lay in the part of the thalamus adjacent to the hypothalamus (Fig. 3). In some of the animals in which the cortex was stimulated, the electrodes and spheres lay in the parietal region.

As a result of the work, we have concluded that the hypothalamus may exert two effects: it may increase the growth of a tumor, or inhibit it until complete absorption has occurred. If the stimulation is prolonged and begins long before the grafting of the tumor, it causes suppression of tumor growth of the tumor, or even complete absorption. If however the stimulation is commenced after the graft has been made, it causes activation of tumor growth.

The uniform effect observed during stimulation of various hypothalamic centers may be attributed to the single action of such stimulation on the metabolic processes, as evidenced by researches which we have made on this point [2, 12]. The thought then occurs that here we may be concerned with some nonspecific nervous influence similar to that of the reticular formation, or even with the result of such an influence on metabolic regulation. The possibility of a nonspecific influence of subcortical stimulation on the metabolic processes is in line with the existence of a general adaptation syndrome in response to the action of different stimuli [18].

One way or another we may conclude that the hypothalamus plays an essential part in establishing conditions which either make possible the growth of transplanted tumors, or suppress it.

SUMMARY

Hypothalamic stimulation repeated many times over a long period in albino rats produced one of two different effects on the growth of grafted 45 and M-1 sarcomas. If the stimulation preceded the transplantation, the growth of the tumor was suppressed, and the tumor might even be completely absorbed. If stimulation followed the transplantation, tumor growth was intensified. A number of hypothalamic nervous structures were involved.

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