CHANGES IN MECHANISMS OF INFLUENCE OF THE HYPOTHALAMUS ON TUMOR DEVELOPMENT

Yu. N. Bordyshkov

UDC 616-006-092:616.831.41

Electrical stimulation of the hypothalamus if commenced after transplanation of tumors stimulates their growth. This stimulation by the hypothalamus is effected through the adrenal cortex. The biochemical link in the tumor cell itself through which the corticoids act is ribosomal protein synthesis.

* * *

It has previously been shown that high-frequency electrical stimulation of the hypothalamus of threshold intensity, carried out a long time before transplantation inhibits growth of sarcomas 45 and M-1, while on the contrary, stimulation of the hypothalamus after transplantation stimulates their growth [9].

In the present investigation the object was to determine the pathways through which this effect on the hypothalamus on tumor tissue is brought about.

EXPERIMENTAL METHOD

Electrical stimulation of the hypothalamus (4/sec, 0.5 msec) was applied three times daily for periods of 45 sec through permanently implanted electrodes, producing a well-defined somatic response. However, this stimulation did not produce stress because it was used only in threshold intensity.

The method of implanting the electrodes was described previously [2, 8].

The experiments of series I were performed on two groups of animals. In group 1 (21 animals) electrodes were implanted into 11 animals and 10 acted as controls. Three days later a hepatoma RS-1 was transplanted into all the animals, and stimulation began next day. All the animals were sacrificed 17 days after the beginning of stimulation and their tumors were weighed. The animals (38) of group 2 were inoculated with sarcoma 45 one week before the beginning of electrical stimulation of the hypothalamus. Five days after transplantation, bilateral adrenalectomy was performed on 12 animals which were then kept in warm cages, receiving milk with 0.8% sodium chloride instead of water. Stimulation of the hypothalamus was carried out in 7 adrenalectomized animals. Electrical stimulation of the animals of group 2 (except the controls, and only the adrenalectomized animals) started the day after adrenalectomy and continued for 9 days, after which the tumors in all the animals were measured and their volume calculated from Schreck's formula. Fourteen animals with a sarcoma 45 acted as controls.

The experiments of series II were performed on three groups of animals with a hepatoma RS-1. In the animals of group 1 (31) the effect of hypothalamic stimulation was studied against a background of administration of amphenon, a drug selectively inhibiting adrenal cortical function [5]. Hypothalamic stimulation was started 10 days after transplantation of hepatoma RS-1. Amphenon was given via gastric tube in a dose of 10 mg in the form of a suspension in physiological saline before stimulation of the hypothalamus. In the course of the experiment each animal received 100 mg of the preparation. In the 40 animals of group 2 the effect of hypothalamic stimulation was studied against the background of administration of ribonuclease (RNase), desoxyribonuclease (DNase), and methylthiouracil (MTU). RNase (Hungarian manufacture) and DNase (Soviet manufacture) were injected intravenously in doses of 70 mg before the period of stimulation (5 times altogether). MTU was given through a gastric tube as a suspension in milk (10 mg daily for 10 days).

Experimental Division, Rostov-on-Don Oncological Institute, Ministry of Health of the RSFSR (Presented by Active Member of the Academy of Medical Sciences of the USSR N. N. Zhukov-Verezhnikov). Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 65, No. 6, pp. 68-71, June, 1968. Original article submitted December 3, 1968.

TABLE 1. Effect of Hypothalamic Stimulation on Growth of Sarcomas in Adrenalectomized Animals

Group No.	Character of procedure	Size of tumor (in cm^3)	P
1	Control	13.6±3.4	<0.05 (1-2)
2	Stimulation of hypothalamus	26.4±4.6	>0.05 (1-3)
3	Adrenalectomy	9.05±3.5	
4	Adrenalectomy+ stimulation	10.0±4.5	<0.02 (2-4)

TABLE 2. Effect of Hypothalamic Stimulation on Growth of Hepatoma RS-1 with Inhibition of Adrenal Cortex by Amphenon

Group No.	Character of procedure	Size of tumor (in cm^3)	P
1	Control (n = 9)	19.2±0.84	<0.02 (1 and 2)
2	Stimulation of hypothalamus (n = 7)	28.9±4.00	<0.02 (2 and 3)
3	Stimulation + amphenon (n = 8)	15.8±3.1	>0.05
4	Amphenon (n = 7)	15.2 ± 2.34	

TABLE 3. Changes in Weight of Tumors in Animals with Hypothalamic Stimulation Against the Background of Action of RNase, DNase, and MTU

Group No.	Character of procedure	Weight of tumor (in g)	P
1	Control (n=8)	8.0±0.39	
2	Hypothalamic stimulation (n=8)	10.0 ± 0.56	<0.01
3	RNase (n=5)	5.7±0.50	<0.001
4	Stimulation + RNase (n=5)	5.2±0.51	<0.001
5	DNase (n=5)	9.0 ± 1.36	> 0.05
6	Stimulation + DNase (n=5)	12.2±1.75	<0.02
7	MTU (n=7)	9.5±0.89	> 0.05
8	Sarcolysin + stimulation (n=7)	11.3±1.10	<0.01

TABLE 4. Effect of Hypothalamic Stimulation on Growth of Hepatoma RS-1 Against the Background of Sarcolysin

Group No.	Character of procedure	Weight of tumor (in g)	P
1	Control (n = 9)	8.0±1.87	<0.001 (1 and 2)
2	Sarcolysin (n = 5)	2.2±0.99	<0.001 (2 and 3)
3	Sarcolysin + stimulation (n = 7)	6.1±1.50	<0.02 (1 and 3)

The hepatoma RS-1 was transplanted 5 days before the beginning of hypothalamic stimulation. In the 20 animals of group 3 the effect of hypothalamic stimulation was studied against the background of action of sarcolysin.

Sarcolysin was injected intraperitoneally in a dose of 2 mg before each period of hypothalamic stimulation for 10 days. Stimulation began 12 days after transplantation of the hepatoma.

The localization of the ends of the stimulating electrodes was determined in the animals of all series at the end of the experiment in brain sections cut on a freezing microtome and impregnated with silver by Kampos's method. Stereotaxic coordinates given in the atlas of Fifkova and Marsala [13] were used.

EXPERIMENTAL RESULTS

In the animals of series I subjected to hypothalamic stimulation, the tumors grew more intensively than in the controls. The mean weight of the tumors in the stimulated animals was 14.2 g and in the controls 8.1 g ($P < 0.001$). Similar results were obtained in the animals of group 2 (Table 1).

Series I also showed that adrenalectomy abolishes the stimulant action of the hypothalamus on tumor growth, although in itself it had no statistically significant effect on tumor growth.

The results of series II (Table 2) showed that inhibition of adrenal cortical function prevents the stimulant action of the hypothalamus on tumor growth. Amphenon itself had only a tendency to inhibit tumor growth.

Table 3 shows that inhibition of thyroid function does not prevent the stimulant effect of the hypothalamus on tumor growth.

The study of the concrete pathways of the hypothalamic effect showed that it is evidently associated with activation of ribosomal protein synthesis in the tumor cells and had no direct relationship to changes in DNA function (see the action of RNase and DNase in Table 3).

The animals receiving sarcolysin stimulation intensified tumor growth when inhibited by sarcolysin (Table 4).

It has recently been found that the primary effect of sarcolysin is inhibition of oxidative phosphorylation, connected with injury to the structure of the mitochondria [1, 7]. Initially, sarcolysin stimulates both oxidative phosphorylation and DNA biosynthesis, and only later does it inhibit incorporation of various precursors into RNA and DNA [1, 3, 4, 6]. However, it is very important to note that RNA synthesis de novo not only was not inhibited, but was actually intensified by comparison with that in tumor cells not damaged by sarcolysin [11]. Accordingly, sarcolysin when administered to an animal before stimulation of the hypothalamus did not prevent RNA synthesis, thus permitting hormonal influences arising from the hypothalamus and acting through the adrenal cortex to stimulate metabolism in the tumor tissue. During the action of RNase, however, when this pathway was blocked, the hypothalamus no longer had any influence on the tumor tissue.

The study of localization of the tip of the stimulating electrodes in the brain of all the experimental animals showed that they were situated in various nuclei of the middle and posterior hypothalamus (nucleus of the mamillary body, tuber cinereum, dorso-medial hypothalamic nucleus, lateral hypothalamic zone). No definite relationship could be found between the hypothalamic effect and localization of the electrode in a particular nucleus.

LITERATURE CITED

1. A. K. Belousova, Biochemical Approaches to the Chemotherapy of Tumors [in Russian], Leningrad (1965).
2. Yu. N. Bordyushkov, Effect of Electrical Hypothalamic Stimulation on the Development of Intrasplenic Ovarian Transplants and Development of Tumors in Them [in Russian], Author's abstract of candidate dissertation, Rostov-on-Don (1962).
3. S. Ya. Davydova, In: Problems in the Chemotherapy of Malignant Tumors [in Russian], Moscow (1960), p. 326.
4. V. A. Kirsanova and Yu. S. Gurevich-Usykina, Cited by A. K. Belousova.
5. E. A. Minenkova and E. M. Vermel', Vopr. Onkol., No. 10, 106 (1965).
6. M. A. Novikova, Vopr. Med. Khimii, No. 6, 414 (1958).
7. V. G. Proshchenko, Tsitologiya, No. 1, 38 (1965).
8. M. A. Ukolova and Yu. N. Bordyushkov, Byull. Éksperim. Biol. i Med., No. 8, 126 (1958).
9. M. A. Ukolova, Yu. N. Bordyushkov, and L. Kh. Garkavi, Byull. Éksperim. i Med., No. 5, 326 (1962).
10. E. Fifková and J. Mařsala, Stereotaxie Podkorových Struktur Mozku Krysy, Králíka a Kočku, Praha 111 (1962).
11. E. G. Trams, M. V. Nadkarni, and P. K. Smith, Cancer Res., 21, 897 (1961).