INDUCED CARCINOGENESIS UNDER VARIOUS INFLUENCES ON THE HYPOTHALAMUS

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Investigations of recent years have shown that the hypothalamic area of the brain is the center in which the influences of the environment are effected and the endocrine functions of the organism are coordinated.[1,9,14] It is also a well-known fact that disturbance of the endocrine regulation plays an important part in the development of hormone-dependent tumors.[4,5,7] It is quite evident that to understand the mechanisms of the effect of the nervous system on carcinogenesis, it is necessary to ascertain the role of the hypothalamus in this process.

The question of the role of the hypothalamus in carcinogenesis was advanced and discussed at the eighth anticancer congress in Moscow in 1963. In his report, A. Lacassagne said that the time had come when we must establish the endocrine disturbances accelerating or inhibiting the development of tumor that may be linked with the disturbance of hypothalamic function.[8]

There are very few indications in the literature of the role of the hypothalamus in tumor development.

Some psychopharmacological substances possessing properties affecting the hypothalamic centers may be used to analyze the role of the hypothalamus.[8] When these drugs are administered, substantial changes occur in endocrine balance, which cannot but affect the emergence and development of hormone-dependent tumors.

In earlier researches we studied the effect on carcinogenesis of various influences on the hypothalamus. We applied reserpine[12] in DMBA-induced carcinogenesis of the mammary glands in rats. Administration of reserpine together with DMBA led to a decrease in the number of diseased animals and a prolongation of the latent period. However, in the case when reserpine was administered after termination of DMBA administration, it was found to have a stimulating effect on tumor development. One of us (I.K. Khayetsky[13]) showed that electrolytic lesions of various zones of the hypothalamus and prolonged illumination of the animals alter the latent period and frequency of DMBA-induced tumors of the mammary glands in rats.

The present experimental study is devoted to induced carcinogenesis of the mammaries in rats upon administration of ipraside and to induced thyroid gland tumors following electrolytic influences on the hypothalamus.

Effect of Ipraside on the Development of DMBA-Induced Tumors of The Mammary Glands

When conducting these researches, we proceeded on the assumption that there is a two-phase character to induced carcinogenesis of the mammaries.[2,3]

Ipraside was administered during introduction of the carcinogen, when interaction of the carcinogen occurs with the mammary gland cells, or some time after introduction of DMBA, i.e., when development of the tumor takes place.

Mature female albino rats weighing 110–120 g were used in the experiment. The carcinogen was injected i.v. in quantities of 2 mg per animal, five times at intervals of one week. The total dose was 10 mg. The latent period of development of the tumor was defined as the time elapsing between the last carcinogen injection and the appearance of a palpable tumor. The tumors were removed for histological examination. During the administration of pharmacological substances, vaginal washings were examined for estimation of the endocrine state of the organism. Ipraside was injected s.c. daily in the course of 30 days. The initial dose was 100 mg/kg during the first five days, then 6 mg/kg until the end of the course. The control animals received s.c. injections of physiological solution. The results of the investigation are presented in TABLE 1.

A study of the effect of ipraside on carcinogenesis is of great interest, since reserpine and ipraside are known to produce opposite effects in the central divisions of the nervous system and in the periphery.[6]

It has been shown that ipraside retards sexual maturity in rats as a consequence of suppression of the gonadotropic function of the pituitary.[10] No data on the effect of ipraside on carcinogenesis of the mammary gland were found in the literature, but in experiments with dithiocarbamoyl–a substance similar to ipraside in its mechanism of action–inhibition of methyl cholanthrene mammary gland carcinogenesis was revealed.[11]

Our data (TABLE 1) also indicate that ipraside, when administered together with the carcinogen, suppresses tumor formation and prolongs the latent period of the tumor's appearance. On the other hand, ipraside did not substantially affect the development of tumors.

Effect of Lesions of the Anterior Hypothalamus on the Development of Tumors of the Thyroid Gland Induced by 8-Methylthiouracil

Experiments were conducted on male golden hamsters weighing 90–115 g. A stereotaxic device was used to produce bilateral electrocoagulations of symmetrical areas of the anterior hypothalamus in intact hamsters and in hamsters with tumors of the thyroid gland developing after prolonged ingestion of 6-methylthiouracil (MTU). The nature of the development of these tumors was evaluated by comparing their histological structure at the time of lesion of the hypothalamus (or sham operation) and at the end of the experiment.

The investigations showed that lesions of the hypothalamus involving the paraventricular (PV) and ventromedial (VM) nuclei and the walls of the third ventricle led to a decrease in J-131 accumulation by the thyroid gland in most of the animals attended by a certain decrease in the protein-bound iodine of the serum.

TABLE 1
EFFECT OF IPRASIDE ON THE APPEARANCE AND GROWTH OF DMBA-INDUCED TUMORS OF THE MAMMARIES

	Number of Animals at End of Experiment	Number of Animals with Tumors of the Mammaries	Average Number of Tumors of the Mammaries per Rat	Latent Period of Appearance of Tumors (in Days)
DMBA	26	11 (42%)	2.7	76.0
DMBA + ipraside simultaneously with carcinogen	24	7 (29%)	1.3	103.0
DMBA + ipraside after carcinogen	13	6 (46%)	1.3	72.0

A histological study of the thyroid gland showed signs of its hypofunctional state in many of these animals.

Lesion of the above-mentioned hypothalamus structures in animals receiving 6-MTU for a long time (6–15 months) led to an acute decrease (by 47–50%) in the capacity of the thyroid gland to absorb J-131 and to a decrease in thyroid weight by 32–50%, as compared to the sham-operated animals that received strumogen.

A slight destruction of the marginal region of the PV hypothalamus nuclei (preserving their anterior divisions) with simultaneous lesion of the VM nuclei did not arrest the symptoms of hyperstimulation of the thyroid gland with pituitary thyroid-stimulating hormone (TSH) under the effect of 6-MTU.

In the case of total adenomatosis of the thyroid gland, three months after lesion of the PV and partial destruction of the dorsomedial nuclei a reduction is found in the signs of thyroid stimulation by pituitary TSH. Morphological investigations indicated various stages of the regression of adenomatosis and, in some areas, signs of "normalization" of the gland structure.

In the case of glandular and cystopapillary forms of thyroid gland cancer, proliferation of connective tissue may be observed in the thyroid gland three months after lesion of the above-mentioned nuclei of the anterior hypothalamus. This proliferation leads in rare cases to fibrosis of the gland, reduction of the number of follicles, and a fall in their activity.

The investigations indicate that destruction of the above-mentioned nuclei of the anterior hypothalamus in golden hamsters leads in most cases to a fall in the functional activity of the thyroid gland, to depression of the thyrogenic reaction, and with tumorous processes in the gland, to proliferation of connective tissue.

On the basis of the facts obtained it may be inferred that lesion of the anterior hypothalamus leads to a decrease in thyroid gland stimulation by TSH and to attenuation of the signs of malignancy of tumors of the gland induced by 6-MTU.

Thus our investigations offer evidence of the fact that by acting on the hypothalamus it is possible to alter the course of hormone-dependent carcinogenesis. There are grounds for inferring that the influence of the hypothalamus on carcinogenesis is through the endocrine function of the organism.

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