CHANGES IN THE HYPOTHALAMUS, RETICULAR FORMATION, AND PITUITARY OF RATS DURING DEVELOPMENT OF INDUCED SUBCUTANEOUS TUMORS

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The dynamics of structural changes in the hypothalamus, reticular formation, and pituitary of rats at different phases of development of tumors induced in the animals by 9,10-dimethyl-1,2-benzanthracene was studied. In the phase of appearance of subcutaneous tumors structural and functional changes were found in the hypothalamus, reticular formation, and pituitary.

KEY WORDS: *induced subcutaneous tumors; hypothalamus; reticular formation; pituitary gland.*

Tumor development is determined by complex interaction between the host and the tumor, in which the nervous and endocrine systems of the host play the leading role [2-4, 10-17]. However, relatively few studies have been made of the dynamics of structural changes in the hypothalamus, reticular formation, and pituitary to take into account the phases of development of induced tumors. They have been devoted to changes in the anterior hypothalamus, or the reticular formation, or the pituitary [5-7].

The object of this investigation was to study the dynamics of structural changes in the hypothalamus, reticular formation, and pituitary of rats in different phases of development of induced subcutaneous tumors.

EXPERIMENTAL METHOD

Experiments were carried out on 158 noninbred male albino rats and female Wistar rats aged 4-5 months and weighing 80-120 g. Carcinogenesis was induced in 108 animals by subcutaneous injection of 9,10-dimethyl-1,2-benzanthracene in the region of the right thigh in a dose of 2 mg in 0.5 ml of peach oil per rat. The remaining animals served as the control (only peach oil was injected in the same dose) and intact groups. The experimental animals were decapitated 5, 10, 15, 30, 45, 60, 90, 120, 150, 180, and 210 days after injection of the DMBA, and the control and intact rats at the same times as the experimental animals (until 120 days). On average 7-13 experimental and 4-6 control and intact animals were killed

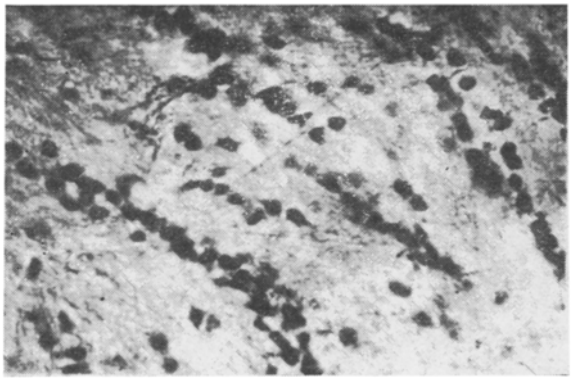

Fig. 1. Supraoptic nucleus: destruction and death of many neurons. Here and in Fig. 2, staining by McManus–Hotchkiss method, 280×.

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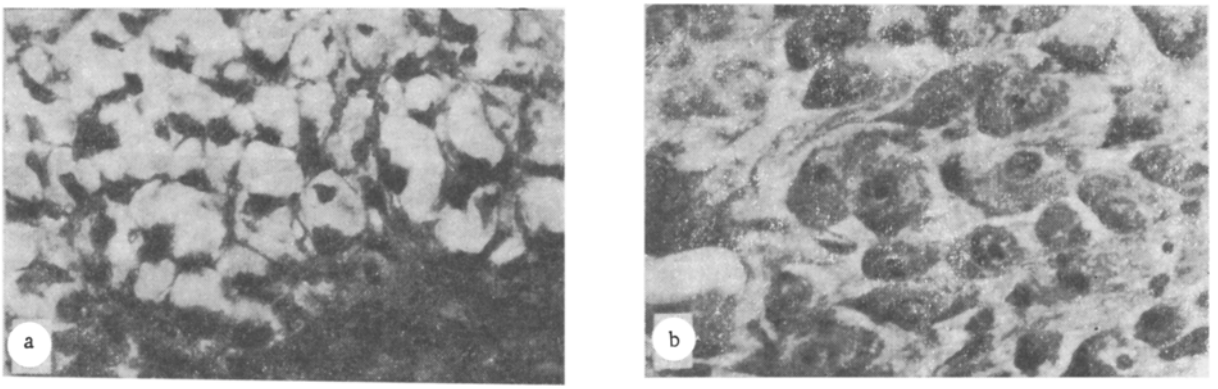

Fig. 2. Supraoptic nucleus: a) rapid progression of tumor: destruction and death of secretory neurons; b) slow growth of subcutaneous tumor: hypertrophy of neurons which contain finely granular neurosecretion in their perikaryon.

at each time. The specified parts of the brain and the pituitary gland of the animals of all groups were fixed in a saturated aqueous solution of mercuric chloride with 10% neutral formalin (9:1), in Gendre and Bouin's mixtures, and in 10% neutral formalin and were then embedded in paraffin wax, after which serial sections were cut to a thickness of 3-5.μ. Sections of the brain and pituitary were stained by the McManus–Hotchkiss method, for nucleic acids with Einarson's gallocyanin with or without counterstaining with a 1% alcoholic solution of phloxin, with methylene blue by Nissl's method, for RNA by Brachet's method, with azan by Heidenhain's method, and for neurosecretion by the method of Maiorova and Milenkov. Frozen brain sections were impregnated by Nauta's method, by Nauta's method in the modification of Chausov et al. [15], by the Bielschowsky–Gros method, and for neuroglia by the Rio Hortega method.

EXPERIMENTAL RESULTS

In the early stages (before the 15th day) of appearance of subcutaneous tumors [1-6] disturbances of the hemodynamics and the flow of cerebrospinal fluid took place in the hypothalamus, reticular formation, and pituitary of the experimental rats. Signs of injury to the neurocytes in the hypothalamus were seen in the neurosecretory, anterior hypothalamic suprachiasmal, dorso- and ventromedial, and infundibular nuclei. Acute swelling of the cells and weakening of neurosecretion were observed in the neurosecretory nuclei, and shrinking of most neurons in the other nuclei. Hypertrophy of the nuclei of the endothelium, oligodendrogliocytes, and, in particular, of the fibrous astrocytes was observed mainly in the hypothalamus and pons.

In the cellular part of the reticular formation neurons of the paragigantocellular, gigantocellular, parvocellular, and red nuclei and of the substantia nigra were more reactive (hypertrophy of the nucleolus, central chromatolysis with a reduction in basophilic substance, coarsening of the neurofibrils) and were selectively severely damaged (total chromatolysis, hyperimpregnation of the nuclei, agglutination and disintegration of the neurofibrils, cell-ghosts, and so on). In the fibrous part of the reticular formation of the medulla, mesencephalon, and diencephalon, signs of irritation were observed in a few fibers (dyschromia, varicosities, pools). In the neurohypophysis, against a background of vascular disturbances, vacuolation of the pituicytes with hyperchromatosis, ectopia and deformation of the nuclei, and a sharp decrease in the content of neurosecretory material were observed; in the adenohypophysis ectasia of the sinusoidal blood capillaries, shrinking of all types of adenocytes, and a sharp decrease in the content of PAS positive and paraldehyde-fuchsinophilic substances in the B- and D-basophilic adenocytes were present.

After 15 to 25 days, against the background of diminution of the disturbances of hemodynamics and cerebrospinal fluid flow and of the degenerative changes in the hypothalamus, reticular formation, and pituitary, compensatory-adaptive reconstruction of the residual structures took place. Signs of normal and increased secretion were observed in the neurons of the neurosecretory nuclei, and in individual secretory neurons and in nerve cells especially of the gigantocellular, parvocellular, and red nuclei of the reticular formation there were already signs of compensatory changes [9]. The residual neurons of the nuclei of the anterior and middle hypothalamus had regained their normal structure. The most marked proliferation of neuroglia was observed in the diencephalon and mesencephalon. In the neuro-

hypophysis the signs of acute swelling of the pituicytes had disappeared and the content of neurosecretory material was increased. Changes in the relative proportions of all types of adenocytes began to appear in the adenohypophysis on account of death of many of the B- and D-basophilic adenocytes and hyperplasia and hypertrophy of the acidophilic adenocytes.

In the late stages (from 75 to 90-120 days) evidence of a breakdown of the compensation mechanisms and of disorganization of the structure reappeared in the hypothalamus, reticular formation, and pituitary. This was expressed morphologically as the development of hemodynamic and degenerative changes [8] (Fig. 1), hypofunction of the secretory nerve cells, cribrose edema in the basal part of the hypothalamus, sclerosis and moderate hyperplasia and hypertrophy of the acidophilic adenocytes in the adenohypophasis with disturbance of the structure of the epithelial layers, and atrophy and death of most of the B- and D-basophilic adenocytes.

Between the 90th and 120th day degenerative-atrophic processes took place in the hypothalamus, reticular formation, and pituitary; they were diffuse in character and extended to all parts of this region of the brain. The intensity of these processes differed in different parts of this region of the brain and pituitary gland and it depended on dynamic relations between the host and the tumor and, in particular, the rate of its growth and necrosis and of its toxic effects, and so on. For instance, in the case of rapidly developing tumors reaching a volume of 270 cm^3 by the 150th-180th day (unlike slowly growing tumors, reaching only 40 cm^3 by that time) the most marked destructive processes combined with vascular disorders were observed in all the hypothalamic nuclei and in the cellular parts of the reticular formation (Fig. 2), whereas in the fibrous parts of the reticular formation and in the lemniscal system reactive processes in the form of numerous fibers with reactive changes were observed. Marked sclerosis, atrophy and death of many pituicytes, and a sharp decrease in the amount of granular neurosecretion and in the number of storage particles were found in the neurohypophysis. Marked hyperplasia and hypertrophy of the acidophilic adenocytes and disturbance of the epithelial interlayers and the formation of continuous sheets of cells were observed in the adenohypophysis. Solitary B- and D-basophilic adenocytes were present. Their degranulated cytoplasm was poor in RNA and in PAS-positive and paraldehyde-fuchsinophilic substances, and their nuclei, unlike those of the acidophilic cells, were poor in DNA. Usually marked hyperplasia and hypertrophy of the acidophilic adenocytes were observed in the case of rapidly progressive subcutaneous tumors; this could indicate that the somatotropic hormone produced by acidophilic adenocytes plays a role not only in the development of the tumor process itself but also in the mechanisms of compensation and decompensation in the nervous and endocrine systems of the host.

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