INDUCTION OF CEREBRAL TUMORS WITH METHYLNITROSOUREA

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Induction of brain tumors in rats by methylnitrosourea is described. The effect of disturbances of the hormonal balance on the onset of tumors is demonstrated and their morphology investigated.

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Investigations involving experimental simulation of brain tumors are particularly important to the development of the theoretical foundations of modern neurooncology. Until recently such tumors were reproduced as a rule by direct injection of carcinogenic hydrocarbons into the brain [3, 4, 8, 9, 17-19]. By induction of tumors and creation of transplantable strains, research workers have obtained much information on subjects such as precancer of the brain, the cytology of the gliomas, and the classification of these tumors. The importance of a number of factors facilitating carcinogenesis in the central nervous system, especially disturbances of hormonal homeostasis [1-4], has been established. However, the technical aspects of these investigations have had one serious drawback – the carcinogen was injected directly into the brain substance. For this reason considerable interest has been shown in results indicating that brain tumors can be obtained by extracerebral (intravenous or oral) administration of compounds of the nitrosamine group [10, 11, 13-15], the carcinogenic action of which has been studied by several authors [5, 7, 16].

The object of the present investigation was to study the carcinogenic action of methylnitrosourea on tissue cells of the central nervous system and to examine the effect of disturbances of hormonal homeostasis on this process.

EXPERIMENTAL METHOD

Methylnitrosourea was synthesized in the Laboratory of the Department of Organic Chemistry (Head, Professor I. P. Tsukervanik), Tashkent University, by the method described by Guben [12]. It was identified by its physicochemical properties, and especially its melting point (121-124°). The carcinogen was kept at 0°. A 1% solution for injection into animals was prepared in distilled water immediately before the experiment (temperature of solution 15-20°).

Experiments were performed on nonimbred female albino rats aged 2-3 months and weighing 80-100 g. Methylnitrosourea (1% solution) was injected intravenously (into the caudal vein) into all the animals once every week in a dose of 5 mg/kg body weight until death.

Three series of experiments were carried out: in the rats of series I (10 animals) hormonal disturbances were produced on the 25th day of the experiments by single x-ray irradiation of the ovaries (dose 600 R) by E. A. Ird's method [6]; a disturbance of hormonal homeostasis was produced in the animals of series II (20) on the 50th day of the experiment by feeding them for 15 days with 6-methylthiouracil (dose 10 mg/kg body weight); the rats of series III (12) were controls and received only methylnitrosourea.

EXPERIMENTAL RESULTS

The results showed that methylnitrosourea, when injected intravenously, is a fairly powerful carcinogen with definite affinity for the tissue structures of the central nervous system. Neoplasms of the brain were found in 10 of the 34 rats surviving until the appearance of tumors, and 1 rat developed a mammary gland tumor. The high incidence of brain tumors in animals with artificially produced disturbances of

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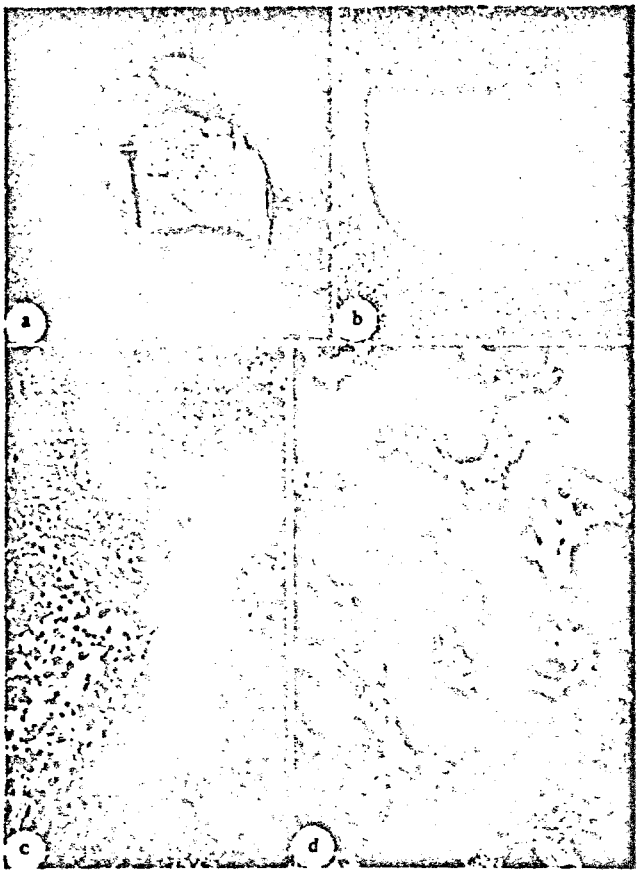

Fig. 1. General appearance and histological structure of brain tumor in a rat induced with methylnitrosourea. a) External appearance of brain with tumor; b) frontal section through brain at level of tumor; c) part of tumor in zone of infiltration (hematoxylin–eosin, 100×); d) structure of oliogodendroglioma (Van Gieson, 200×).

hormonal balance (in 3 of 7 rats in series I, in 6 of 10 in series II) compared with the controls (in 1 of 6 rats) should be noted. Disturbance of the hormonal balance also affected the times of appearance of the first tumors. In series I, for instance, the minimal latent period was 173 days, in series II 334, and in series III 363 days. The total dose of carcinogen administered (in mg/kg body weight) was 130, 185, and 220 mg, respectively, i.e., it was least in series I.

The tumors were located mainly in the right cerebral hemisphere (8 of 10 rats), usually in its depth, and often invading the lateral ventricle or base of the brain. No tumors of the spinal cord were found.

A description of one observation will be given as an illustration.

The results of morphological examination of a tumor induced in an experiment of series II (Fig. 1a and b) showed that this tumor had a comparatively uniform structure and consisted of loosely arranged, mainly monomorphic, small round cells with a compact round nucleus. The tumor showed moderate power of infiltration, and small foci of hemorrhage were seen. By its structural features the neoplasm could be identified as a malignant glioma – an oliogodendroglioma (Fig. 1c and d). Electron-microscopic examination showed that most of the tumor consisted of small cells with round and ovoid nuclei. The nuclei were clearly outlined and usually contained one nucleolus. Chromatin was concentrated near the nuclear membrane. The cytoplasm was comparatively poor in organelles. The mitochondria (small) were often in groups. The granular endoplasmic reticulum was moderately well-defined, as also was the Golgi apparatus. Other cells were seen with a slightly larger nucleus, oval or elongated in shape, often with two nuclei. Chromatin was often located near the nuclear membrane in the form of coarsely dispersed aggregates.

Besides these cell organelles, the cytoplasm contained lipid granules, vacuoles, and structures resembling pseudomyelin figures. All the cells had clearly defined cell and plasma membranes; intercellular spaces were not conspicuous.

The results thus show that administration of nitrosamines presents wide opportunities in experimental neurooncology for analysis of its fundamental theoretical aspects. They also show that besides the direct action of a carcinogen on the tissues of the central nervous system, an important role in the genesis of cerebral tumors induced by means of methylnitrosourea is played by certain other factors, primarily the neuroendocrine system regulating homeostasis.

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