MORPHO-PHYSIOLOGICAL CHANGES IN THE ADRENAL CORTEX AND THYMUS DURING GROWTH OF A TRANSPLANTED GLIOBLASTOMA MULTIFORME IN THE RAT BRAIN

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A study of the morpho-physiological changes in the adrenal cortex and thymus growth of a transplanted glioblastoma multiforme in the rat brain revealed marked activation of the glucocorticoid function of the adrenal cortex accompanied by inhibition of thymic function. In animals not developing the disease activation of the thymic reticulo-epithelium was observed whereas the indices of adrenocortical function remained within normal limits.

KEY WORDS: transplanted tumor; adrenal cortex; thymus.

Among the numerous relations between tumor and organism, one of great importance is the character of the connection between the corticosteroid function of the adrenal cortex and the organs of immunologic protection [4]. A fundamental role in the immunologic regulation of tumor growth is played by the thymus [1].

The object of this investigation was to study the coupled changes in the adrenal cortex and thymus during growth of a transplanted tumor in the central nervous system.

EXPERIMENTAL METHOD

Experiments were carried out on noninbred infantile female albino rats (171) weighing 50-70 g, into the brain of which a glioblastoma multiforme (strain 101/12) was grafted. The functional state of the adrenal cortex was determined from their weight and that of the thymus, the corticosterone concentration in the peripheral blood plasma of the animals, and the histomorphological characteristics of the adrenal cortex and thymus. The corticosterone concentration was determined by a fluorimetric method [5] on the IF-1 instrument and expressed in μg/100 ml blood plasma. Blood was collected after decapitation of the animals between 10 and 11 a.m. on the 6th day after transplantation of the tumor in rats with a well-marked clinical picture of the disease. For the morphological investigations the adrenals and thymus were fixed by Gindin's method and embedded in paraffin wax–celloidin and stained with hematoxylin–eosin, Brachet's reaction, the PAS reaction, and for lipids with Sudan III. Intact animals and animals with brain trauma, killed simultaneously with the tumor-bearing rats, acted as the control group. The animals without tumors were killed on the 21st day after the operation.

EXPERIMENTAL RESULTS

Functional tests on the adrenal cortex showed no significant changes in their weight or in the corticosterone concentration in the peripheral blood of the rat on the 6th day after transplantation of strain

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TABLE 1. Weight of Adrenals and Thymus and Corticosterone Concentration in the Peripheral Blood of Intact Rats, Rats with Brain Trauma, and Rats with Transplanted Tumors of the Cerebellum (M ± confidence interval)

Group of animals	No. of animals in experiment	Body weight (in g)	Weight of gland (in mg/100 g body weight)		Corticosterone concentration (in μg/100 ml plasma)
			adrenals	thymus	
Intact, sexually immature	55	85,13±4,06	33,97±1,73	347,6±24,90	12,62±2,57
Rat with brain trauma (15.7 ±1.06 days after operation)	32	82,34±5,72	34,91±2,89	245,95±43,86	14,15±3,37
Rat with transplanted tumor: on 6th day after transplantation	15	89,60±6,57	34,18±2,32	243,42±50,96	16,17±2,85
On 15.7 ±1.06 day after transplantation	39	82,41±6,36	49,43±4,85	169,08±36,34	28,57±4,51

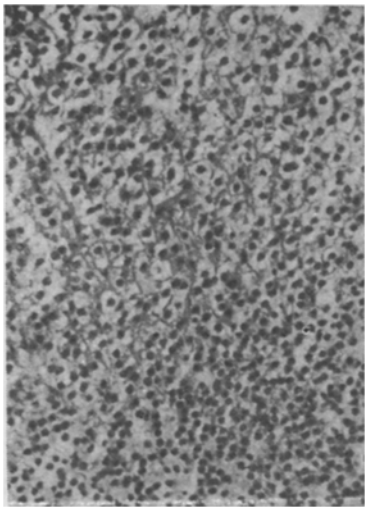

Fig. 1. Foci of vacuolated cells in the zona glomerulosa of the adrenal of a rat with a developing brain tumor. Hematoxylin–eosin, 250×.

101/12 and in rats with brain trauma (time of sacrifice 15.7 ± 1.06 days) compared with the analogous indices in the intact animals. However, a decrease in weight of the thymus was observed ($P < 0.05$), indirect evidence of some increase in the glucocorticoid function of the adrenal cortex in the experimental rats and in the rats with brain trauma (Table 1).

A significant increase in the glucocorticoid function of the adrenal cortex, with respect to all indices, was found at the time of clinical manifestation of the brain tumor; in particular, the corticosterone level in the peripheral blood was twice as high as normal ($P < 0.001$). The dynamics of this process is indicated by the equal decrease in weight of the thymus in the rats with the tumor, killed on the 6th day, and the rats with brain trauma killed on the 15.7 ± 1.06th day, i.e., virtually 10 days later. The tendency for the blood corticosterone concentration of the rats to rise was evidently observable from the 6th day after transplantation of the tumor.

Histological examination of the adrenals of the rats with a developing transplanted tumor showed a high proportion of cells in the zona glomerulosa with vacuolated cytoplasm (Fig. 1). Sudanophilic material was seen in the zona glomerulosa in a somewhat greater quantity than in the animals with brain trauma. Morphological study of the thymus of these rats showed foci of destruction in the cortical layer as well as areas containing groups of confluent thymocytes with hyperchromic nuclei. Besides these changes, many macrophages carrying out phagocytosis of cells and their particles and giving a positive Brachet's reaction were seen in the cortical layer (Fig. 2). No changes were found in the thymus of the animals with brain trauma.

Investigations of the adrenals and thymus of the nontumor-bearing animals were particularly interesting from the point of view of study of antitumor resistance. The histological picture of the adrenals of these animals was indistinguishable from normal. Morphological study of the thymus revealed very marked activation of the medulla. This was very wide. Cells of the reticulo-epithelium located in the medulla were swollen and many of them had mitotic figures. Ingested particles of cells could be seen in isolated reticulo-epithelial cells. In the thymus of most animals (6 to 8 without tumors) the reticulo-epithelial cells formed continuous sheets and tubular structures, the cavities of which were filled with PAS-positive material (Fig. 3). There were also aggregations of PAS-positive material in the cytoplasm of individual reticulo-epithelial cells.

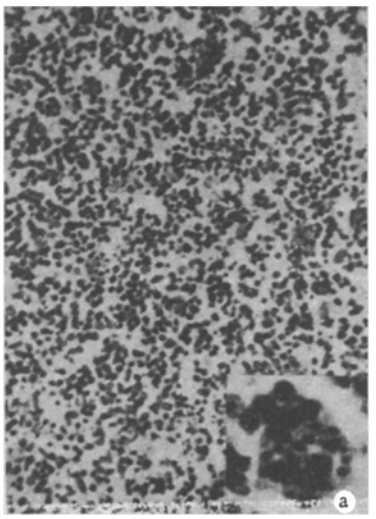

Fig. 2 Fig. 3

Fig. 2. Well-marked macrophagal response in the cortex of the thymus of a rat with a developing brain tumor: a) macrophage in the cortex of the thymus. Hematoxylin–eosin, a) immersion, 500×.

Fig. 3. Formation of epithelial structures at the boundary of the cortical and medullary layers in the thymus of a nontumor-bearing rat. Hematoxylin–eosin, 500×.

Elements of the reticulo-epithelium of the thymus are known to produce a humoral factor stimulating antibody formation [8-10]. Inhibition of the reticulo-epithelium of the thymus in the tumor-bearing animals thus lowers their immunobiological responses. On the other hand, activation of the reticulo-epithelium in the nontumor-bearing animals, together with other factors, evidently potentiated their antitumor resistance. Since depression of the reticulo-epithelium may be connected with the action of glucocorticoids on it, the sharp increase in the level of these substances during growth of the transplanted tumor must be interpreted as a negative factor. This conclusion is supported by data in the literature [3, 6, 7].

LITERATURE CITED

1. F. M. Burnet, Cellular Immunology, Cambridge Univ. Press (1969).
2. É. V. Gyulling, V. M. Kavsan, and O. F. Mel'nikov, Zh. Ushn. Nos. Gorl. Bol., No. 6, 25 (1971).
3. I. N. Dimant, M. Sh. Mil'man, G. M. Laktionov, et al., in: Tumor and Organism [in Russian], Kiev (1973), p. 112.
4. R. E. Kavetskii, Proceedings of the 1st Congress of Oncologists of the RSFSR [in Russian], Ufa (1973), p. 71.
5. Yu. A. Pankov and I. Ya. Usvatova, Publications on New Apparatus and Methods of the First Moscow Medical Institute [in Russian], Vol. 3, Moscow (1965), p. 65.
6. N. A. Spryshkova, Vopr. Onkol., No. 5, 100 (1972).
7. L. Ya. Yablonovskaya, in: Experimental Brain Tumors Obtained by Heterografting and Induction [in Russian], Leningrad (1967), p. 85.
8. J. Comsa, Path. Biol., 20, 639 (1972).
9. P. Erbesen and H. E. Christensen, Acta Path. Microbiol. Scand., 80, 5 (1972).
10. M. Kostowiecki, Z. mikr.-anat. Forsch., 76, 141 (1967).