EFFECT OF CHLORPROMAZINE ON THYROID FUNCTION AND THYROTROPIC FUNCTION OF THE PITUITARY IN RATS WITH INDUCED TUMORS

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Thyroid function is inhibited and the thyrotropic function of the pituitary increased in rats with tumors induced by 9,10-dimethyl-1,2-benzanthracene. Administration of chlorpromazine to normal animals inhibits its absorption of I^{131} by the thyroid and stimulates production of thyrotropic hormone by the pituitary. Chlorpromazine has no such effect in rats with tumors.

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Many investigations have been made of the endocrine system of animals during tumor development. Investigation of the thyroid of animals with tumors and of cancer patients has shown that in most cases tumor development is accompanied by inhibition of thyroid function [3, 5, 8, 9, 11, 13, 17-20].

The object of the present investigation was to study the mechanisms lowering the thyroid function of animals with induced tumors. For this purpose the system regulating thyroid function was influenced by chlorpromazine, which lowers the activity of the reticular formation and inhibits the function of the neurosecretory nuclei of the hypothalamus, thereby depressing endocrine gland function [6, 7].

EXPERIMENTAL METHOD

Tumors were induced in a group of male rats weighing 120-140 g with 9,10-dimethyl-1,2-benzanthracene (DMBA). The carcinogen was injected subcutaneously in the dorsal region in a dose of 2 mg/100 g body weight. Refined sunflower oil was used as solvent. Six months after injection of the carcinogen, the animals which had developed sarcomas were divided into 2 groups. Group 1 (9 rats) received chlorpromazine in a daily dose of 5-7.5 mg/100 g body weight in 2 intramuscular injections (Expt. 1), while the animals of group 2 (8 rats) received no chlorpromazine (Expt. 2). Control rats received an injection of the solvent only at the same time as the experimental animals received the carcinogen. Some of these animals (10 rats) received chlorpromazine along with those of experiment 1 (control 1), and the rest (10 rats) received no chlorpromazine (control 2).

The state of the thyroid was judged from structural (index of cell height of the thyroid epithelium and relative weight of the thyroid glands) and functional (absorption of radioactive iodine given 4 h before sacrifice by the thyroid gland) indices. I^{131} absorption was determined by the PS-5M "Volna" scintillation dosimeter and expressed as a percentage of the injected dose. The thyroids were fixed in Zenker-formol and embedded in celloidin-paraffin, and sections were stained with azan.

The thyrotropic function of the pituitary was determined by a biological test based on the character of the thyroid response of guinea pig. injected with pituitary homogenates of the groups of rats to be studied. The "index of cell height" of the thyroid epithelium was determined at the same time.

The numerical results were subjected to statistical analysis.

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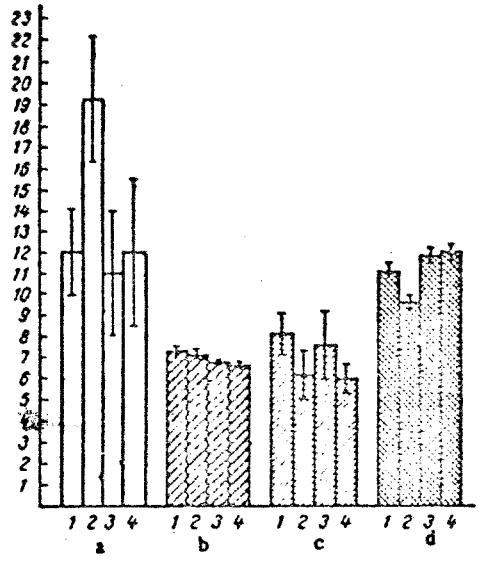

Fig. 1. Indices of thyroid function and thyrotropic function of the pituitary of experimental and control rats receiving chlorpromazine. 1) Control 1; 2) control 2; 3) experiment 1; 4) experiment 2. a) Absorption of radioiodine by the thyroid (in %); b) index of cell height of thyroid epithelium (in μ); c) relative weight of thyroids (in mg); d) thyrotropic function of pituitary. Height of thyroid epithelium of recipient guinea pigs (in μ).

EXPERIMENTAL RESULTS

It may be concluded from a comparison of the results of experiment 2 and control 2, shown in Fig. 1, that the development of induced tumors is accompanied by inhibition of thyroid function and an increase in the thyrotropic function of the pituitary.

Data in the literature regarding the possible inhibition of thyroid function in animals with induced tumors [4, 12] were thus confirmed. The thyrotropic function of the pituitary of these animals, judging by the absence of reports in the accessible literature, was evidently investigated now for the first time.

The increase in thyrotropic function of the pituitary which was discovered may be interpreted as secondary, dependent on primary inhibition of thyroid function by the same developing tumor. This inhibition may result from the injurious action of tumor metabolites both on the hypothalamic centers regulating thyroid function and directly on the thyroid cells.

Although administration of chlorpromazine, judging from the absorption of radioactive iodine (comparison of control 1 with control 2) caused inhibition of thyroid function ($P < 0.01$), the morphological picture (index of cell height and relative weight of thyroid glands) suggested some stimulation of the function of this gland (differences significant $P < 0.05$ and < 0.01). The problem of thyroid function in this particular case thus requires further investigation. In normal rats receiving chlorpromazine (control 1) a parallel increase in thyrotropic function of the pituitary was observed. These results do not agree with those obtained previously [2, 7, 15, 16], presumably because of differences in doses and in duration of administration of the preparation. However, data analogous to our own can be found in the literature [14].

We consider that the increase in thyrotropic function of the pituitary is a secondary reaction to the inhibition of iodine uptake for synthesis of the thyroid hormones by the gland as a result of chlorpromazine administration. This may explain the injurious action of chlorpromazine on the hypothalamic centers regulating the iodine metabolism of the thyroid gland.

The structural changes in the thyroid of animals receiving chlorpromazine demonstrate that under these experimental conditions the thyroid retains to some extent the ability to react to increased production of thyrotropic hormone. It may thus be postulated that the reduced incorporation of radioactive iodine in the thyroid following administration of chlorpromazine is effected via the hypothalamus, bypassing the pituitary, by a parahypophyseal or para-adenohypophyseal pathway [1, 10].

Administration of chlorpromazine to animals with tumors (Expt. 1) did not change the level of thyroid function or of the thyrotropic function of the pituitary, which had come under the influence of the developing tumor. The areactivity of this system in animals with tumors to the action of chlorpromazine was thus demonstrated.

LITERATURE CITED

1. B. V. Aleshin, Development of the Thyroid and Pathogenesis of Goiter [in Russian], Kiev (1954).
2. B. V. Aleshin and L. A. Us, Probl. Éndokrinol., No. 3, 32 (1960).
3. M. M. Alikishibekov and M. A. Andreeva, Probl. Éndokrinol., No. 5, 82 (1961).
4. V. I. Arkhipenko, In: Proceedings of the Twenty-eighth Scientific Session of Dnepropetrovsk Medical Institute [in Russian], Dnepropetrovsk (1965), p. 102.
5. V. I. Arkhipenko and A. P. Vorona, Abstracts of Proceedings of the Second All-Union Conference of Endocrinologists [in Russian], Moscow (1962), p. 37.

6. A. V. Val'dman, In: Current Problems in Pharmacology of the Reticular Formation and Synaptic Transmission [in Russian], Leningrad (1963), p. 9.
7. A. A. Voitkevich, E. I. Zubkova-Mikhailova, and I. I. Dedov, Probl. Éndokrinol., No. 3, 106 (1965).
8. P. A. Kucherenko, The Endocrine Glands and Malignant Neoplasms [in Ukrainian], Kiev (1937).
9. L. F. Larionov, Cancer and the Endocrine System [in Russian], Moscow (1938).
10. A. L. Polenov, Arkh. Anat., Gistol. Émbriol., No. 9, 3 (1962).
11. V. I. Yakovleva, Arkh. Pat., No. 3, 34 (1961).
12. J. L. Claus, T. B. Trunnel, and T. G. Llaurado, Acta Endocr. (Kbh.), 40, 548 (1962).
13. B. B. Jacobs, Proc. Soc. Exp. Biol. (New York), 104, 328 (1960).
14. U. Marinoni, G. Puricelli, S. Hukovic, et al., Endocr. Sci. Cost., 25, 332 (1958).
15. St.-M. Milcu, J. Negoescu, A. Lupulescu, et al., Stud. Cercet. Endocr., 10, 478 (1959).
16. St.-M. Milcu, J. Negoescu, N. Radian, et al., Comun. Acad. Rep. Pop. Rom., 5, 1397 (1955).
17. K. Y. Scott and M. B. Daniels, Cancer Res., 16, 784 (1956).
18. S. C. Sommers, J. Lab. Invest., 4, 160 (1955).
19. C. D. Stevens, D. H. Stewart, P. D. Meinken, et al., Cancer Res., 9, 488 (1949).
20. C. D. Stevens, D. H. Stewart, P. D. Meinken, et al., Cancer Res., 10, 155 (1950).