THE EFFECT OF EHRLICH'S ASCITIC CARCINOMA ON THE FUNCTION OF MOUSE THYROID

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It was noted in a number of experimental and clinical studies that the development and growth of malignant neoplasms inhibited the functional activity of the thyroid [1-6, 8, 10-12]. However, the mechanism of inhibition of the thyroid by tumors had not been elucidated.

The present work has been devoted to the study of the mechanisms of the inhibiting effect of the tumor on the thyroid gland.

EXPERIMENTAL METHODS

Experiments were conducted on adult nonpedigreed male white mice weighing 20-24 g. The mice were infected with Ehrlich's ascitic carcinoma.

The tumors were transplanted by means of either intraperitoneal or subcutaneous injection of 0.3 ml of ascitic fluid containing tumor cells.

The condition of the functional activity of the thyroid was determined by absorption of I^{131} which was injected subcutaneously in doses of 1 μC. The animals were killed 4 h following injection of the isotope. The thyroid glands were removed and I^{131} absorption was determined (as percentage of the dose injected) on a scintillation counter "Volna." The results obtained were treated statistically using the analysis of variance.

RESULTS

Using the absorption of I^{131} as our criterion, we became convinced that the development of intraperitoneally transplanted Ehrlich's ascitic carcinoma led to a statistically significant lowering of the functional activity of the thyroid gland. The inhibition of the functional activity of the thyroid increased in proportion to the degree of development of the tumor (Table 1).

Following subcutaneous inoculation of Ehrlich's carcinoma, the development of the tumor was not accompanied by an accumulation of ascitic fluid. The receptive area was also altered. However, in these cases also the growth of Ehrlich's carcinoma led to an inhibition of the functional activity of the thyroid glands of the infected animals (Table 2).

A comparison of results of experiments represented in Tables 1 and 2 shows that the irritation of the interoceptive apparatus of the peritoneum by the accumulating ascitic fluid was not of a decisive importance in the pathogenesis of inhibition of the thyroid function, since a similar inhibition was noted in mice inoculated with Ehrlich's carcinoma subcutaneously, and in which the development of the tumor was not accompanied by an accumulation of the fluid.

When Ehrlich's carcinoma is transplanted, a quantity of ascitic fluid is introduced together with tumor cells; the fluid is the medium in which tumor cells live. Thus, the question arose, as to the significance of tumor cells and of cell-free ascitic fluid in the phenomenon of inhibition of thyroid glands in mice infected with Ehrlich's car-

TABLE 1. Absorption of I^{131} by Thyroid Glands of Mice Infected with Ehrlich's Ascitic Carcinoma, Transplanted Intraperitoneally (M ± m)

Animal group	No. of animals	Absorption of I^{131} (% of dose)	P (compared with the control)
Intact animals (controls)	10	34.2 ± 2.5	–
First day after transplantation	19	9.5 ± 0.7	< 0.001
Fifth day after transplantation. . . .	20	16.5 ± 1.4	< 0.001
Twelth day after transplantation . .	20	10.3 ± 1.0	< 0.001

TABLE 2. Absorption of I^{131} by Thyroid Glands of Mice Following Subcutaneous Transplantation of Ehrlich's Carcinoma (M ± m)

Animal group	No. of animals	Absorption of I^{131} (% of dose)	P (compared with the control)
Intact animals (controls)	19	27.7 ± 2.3	–
Fifth day after transplantation. . . .	15	16.4 ± 2.3	< 0.001
Tenth day after transplantation. . .	17	21.4 ± 1.8	< 0.05
Twentieth day after transplantation.	19	7.2 ± 0.5	< 0.001

TABLE 3. The Effect of Tumor Cells and of Cell Free Ascitic Fluid on the Absorption of I^{131} by Thyroid Glands of Mice (M ± m)

Animal group	Experimental procedure	No. of animals	Absorption of I^{131} by thyroid glands (% of dose)	P (compared with controls)	P (in comparison with groups)
1st	Injection of tumor cells	16	13.3 ± 1.4	< 0.001	> 0.05 (1st and 3rd)
2nd	Injection of cell free ascitic fluid	16	6.2 ± 0.8	< 0.001	< 0.001 (1st and 2nd)
3rd	Injection of normal saline	16	16.0 ± 1.9	< 0.001	< 0.001 (2nd and 3rd)
4th	Intact animals (controls).	19	27.7 ± 2.2	–	–

cinoma. In order to answer this question, the ascitic fluid was centrifuged and the tumor cells and the supernatant fluid were separated from each other. The cells were washed twice in normal saline, and cell suspensions in normal saline were injected intraperitoneally in the same volumes as before into normal animals. Cell free ascitic fluid in the same volume was injected into intact animals of the 2nd group. The 3rd group of mice received normal saline intraperitoneally, and the 4th group of intact animals served as controls. Twenty hours after the beginning of the experiment all the animals were injected subcutaneously with I^{131} and were killed 4 h later (Table 3).

The analysis of results presented in Table 3 led to the following conclusions: the irritation of the peritoneum by normal saline produced some inhibition of the function of the thyroid; injection of ascitic fluid-free Ehrlich's carcinoma cells produced a similar inhibiting effect as by saline; injection of cell-free ascitic fluid produced a statistically significant and much more pronounced inhibition of the thyroid function. This inhibiting effect of the cell-free ascitic fluid was probably due to the presence in it of metabolic products of tumor cells. Thus the results of this experiment showed that the thyroid-inhibiting substance was present in the ascitic fluid.

We found that heating of the cell-free ascitic fluid in a boiling water bath for 2-5 minutes destroyed its antithyroid properties. Injection of the heat treated ascitic fluid into mice did not result in the reduction of I^{131} absorption by the thyroid gland.

It was noted that substances precipitated from the cell-free ascitic fluid by absolute alcohol were able to inhibit the thyroid function (Table 4).

TABLE 4. Effect of Substances Precipitated by Absolute Alcohol from Cell-Free Ehrlich's Ascitic Fluid on the Absorption of I^{131} by Thyroid Glands of Mice (M ± m)

Experimental procedure	Number of animals	Absorption of I^{131} by thyroid glands (% of dose)	P
Injection of normal saline	9	18.4 ± 1.7	< 0.01
Injection of the precipitate	10	11.4 ± 0.9	

The results of the mentioned experiments have shown that an antithyroid factor was present in Ehrlich's carcinoma ascitic fluid. This factor is thermolabile, can be precipitated by absolute alcohol and is probably a protein or a polypeptide. Being a product of metabolism of tumor cells, this factor enters into the humoral medium of the organism and produces an inhibition of the thyroid function.

The thyroid-inhibiting substance cannot be related to the "toxohormones" described by Grinshtein [7] and by numerous other workers including Nakahara and Fukuoka [9]. Unlike the "toxohormones" which are heat stable, the factor discovered by us is a heat labile compound.

SUMMARY

The ascitic fluid of Ehrlich's carcinoma contains a factor capable of an antithyroid effect, which is evidenced by a sharp decrease in the I^{131} absorption of the thyroid gland. This factor is thermolabile, is cooled with absolute alcohol, and is apparently of a protein or polypeptide nature. As a metabolic product of tumor cells it enters the humoral media of the body and inhibits the thyroid function. The secretion by tumor cells of a substance inhibiting the thyroid function is regarded as a specific manifestation of one of the mechanisms by which the tumor influences a definite system in the body. This substance cannot be attributed to the group of "toxohormones" because, as distinct from the latter, which has thermal stability, it is a thermolabile compound.

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