# EFFECT OF 6-METHYLTHIOURACIL AND L-THYROXINE ON LIFE SPAN OF RATS WITH TRANSPLANTED CEREBELLAR GLIOBLASTOMA MULTIFORME

N. A. Spryshkova

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Administration of 6-methylthiouracil to rats with transplanted cerebellar glioblastoma multiforme prolongs the animals' life span, while injections of L-thyroxine in adequate doses cause the earlier death of the animals than in the control.

The writer has shown previously [4] that preliminary thyroidectomy prolongs the life span of rats after transplantation of a cerebellar glioblastoma multiforme. Total extirpation of the thyroid glands in rats is frequently accompanied by removal of the parathyroid glands, located on their lobes [2]. It could be assumed that the observed results of this procedure are due to removal of the parathyroids as well as the thyroid. To make absolutely sure that the prolongation of the life span of rats after transplantation of the tumor can be attributed to deprivation of thyroid hormones in the experimental animals, it is preferable to use pharmacological methods of inhibiting thyroid function.

In the present investigation the effect of 6-methylthiouracil (6-MTU) and L-thyroxine on the life span of rats after transplantation of a tumor was investigated.

## EXPERIMENTAL METHOD AND RESULTS

The dose of 6-MTU was 20 mg/100 g body weight in 0.5 ml water by mouth once daily. In one series of experiments 6-MTU was given from the moment of transplantation of tumor cells until the death of the rats, and in another series its administration began 21 days before transplantation of the tumor cells and continued until death of the animal. Groups of intact rats and rats undergoing mock operations were used as controls of nontoxicity of the dose of 6-MTU given.

## EXPERIMENTAL RESULTS

The tests carried out and method of analysis of the results are the same as were used in previous experiments [4]. The results are shown in Table 1.

In the experiments of series I administration of 6-MTU was begun after transplantation of tumor cells into the animal. These experiments were performed on rats grafted with tumor cells of the earliest (1st-4th subcultures) and later (13th-17th subcultures) generations (Table 1, groups 1-4).

In the experiments of series II, in which 6-MTU administration was began 21 days before transplantation of the tumor and continued until death of the recipient, in agreement with published data [1, 5] delay of growth and sexual development of the experimental rats was observed. For example, the weight of the control animals was 143.4 ± 13.94 g, whereas the experimental animals weighed only 97.73 ± 8.92 g.

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TABLE 1. Life Span of Rats with Transplanted Glioblastoma Multiforme and Receiving 6-MTU

| Series of experiments | Group | Number of animals | Body wt. (in g) ($M \pm t_\sigma$) | Life span (in days) | | | |
|---|---|---|---|---|---|---|---|
| | | | | $M \pm t_\sigma$ | groups compared | $m$[1] | $P$ |
| I | 1, experimental (1st-4th subculture) | 25 | 81,06±12,60 | 24,4±3,27 | 1/2 | 2,12 | 0,05 |
| | 2, control (1st-4th subculture) | 19 | 94,9±9,01 | 20,7±2,63 | | | |
| | 3, experimental (13th-17th subculture) | 16 | 80,11±9,77 | 18,25±3,73 | 3/4 | 1,37 | 0,005 |
| | 4, control (13th-17th subculture) | 31 | 104,2±12,52 | 13,77±0,83 | | | |
| II | 5, experimental | 21 | 97,73±8,92 | 16,9±2,36 | 5/6 | 1,72 | 0,02 |
| | 6, control | 10 | 143,4±13,94 | 12,6±1,51 | 5/4 | 1,053 | 0,005 |

[1]Here and in Table 2: M) arithmetic mean; $t_\sigma$) confidence interval; m) error of difference.

TABLE 2. Effect of L-Thyroxine on Life Span of Rats after Transplantation of Cerebellar Glioblastoma Multiforme

| Nature of experiment | No. of animals | Body wt. ($M \pm t_\sigma$) | Life span in days | | | |
|---|---|---|---|---|---|---|
| | | | $M \pm t_\sigma$ | groups compared | $m$ | $P$ |
| 12.5 μg L-thyroxine before and after transplantation of tumor | 30 | 75,4±4,94 | 12,07±0,76 | 1/3 | 0,692 | 0,001 |
| 12.5 μg L-thyroxine after transplantation of tumor | 33 | 81,2±6,16 | 13,76±1,28 | 2/3 | 0,816 | 0,05 |
| Control | 40 | 82,41±6,36 | 15,70±1,06 | | | — |

The ovaries of both groups of rats weighed the same (50.99 ±8.92 mg and 49.5 ±7.94 mg/100 g body weight), but the weight of the uterus in the experimental rats was only 133.0 ± 26.73 mg compared with 152.2 ± 52.8 mg/100 g body weight in the controls.

Because it was suspected that the body levels of sex hormones differed in the experimental and control rats, an additional comparison was made of the life span of the experimental and control animals of group 4, in which the tumor was transplanted into younger, sexually immature rats.

The life span of the experimental animals in all groups of both series was significantly higher than that of the controls. Since in this case parathyroid function was not excluded, the result could be explained by a shift in the balance of thyroid hormones in the direction of deprivation. Consequently, growth of a transplanted cerebellar glioblastoma multiforme in rats and death of the animals are retarded not only after surgical exclusion of thyroid function, but also after its pharmacological blocking. It was therefore interesting to examine the effect of an excess of thyroid hormones on the course of the disease and times of death of the rats after transplantation of a glioblastoma multiforme.

To induce a state of hyperthyroidism in the rats, L-thyroxine (Reanal, batch 64,093,114) was given in a dose of 12.5 μg/100 g body weight by subcutaneous injection in 0.2 ml physiological saline once daily. This dosage of thyroxine is known to induce hyperthyroidism in rats [6]. Groups of intact rats and rats undergoing mock operations were used as controls of the toxicity of the dose of thyroxine given. One group of experimental animals received thyroxine 7 days before transplantation of the tumor cells until the animal became ill or died. The other rats received thyroxine only after transplantation of the tumor and until the day of death. The results of these experiments are given in Table 2.

The life span of the experimental animals was significantly shorter than that of the controls. Hence thyroxine, if given in a large enough dose, shortens the life span and hastens death of animals with a transplanted tumor.

When this conclusion is compared with the opposite effect of thyroidectomy and of blocking of thyroid function by 6-MTU on the life span of rats with a transplanted tumor, it is evident that the effect of the body level of thyroid hormones on development of this disease follows a regular pattern. A large increase in the body level of one thyroid hormone (thyroxine) in these animals leads to activation of the pathogenetic mechanisms and hastens death of the animals; a considerable disturbance of the balance of thyroid hormones toward deprivation or their total removal from the body causes inhibition of these mechanisms and delays death of the animals.

These facts are probably of fundamental importance in the pathogenesis of brain tumors, but because of the many-sided action of thyroid hormones in the body and because of the specific character of metabolism in the brain tissues themselves [3], no explanation can yet be put forward. These problems require further experimental study.

## LITERATURE CITED


1. A. A. Voitkevich, The Antithyroid Action of Sulfonamides and Thiourates [in Russian], Moscow (1957).
2. Ya. M. Kabak, A Textbook of Practical Endocrinology [in Russian], Moscow (1968), p. 61.
3. S. M. Leites and N. N. Lapteva, Outlines of the Pathophysiology of Metabolism and of the Endocrine System [in Russian], Moscow (1967), p. 312.
4. N. A. Spryshkova, Byull. Éksperim. Biol. i Med., No. 3, 95 (1970).
5. I. A. Éskin, Byull. Éksperim. Biol. i Med., 23, No. 4, 29 (1947).
6. S. Werner (editor). The Thyroid Gland [Russian translation], Leningrad (1963), p. 56.