South Russian Journal of Cancer 2022, Vol. 3, No. 4, P. 26-39
https://doi.org/10.37748/2686-9039-2022-3-4-3
ORIGINAL ARTICLE

CHANGES IN PATHOPHYSIOLOGY OF TUMOR GROWTH AND FUNCTIONAL ACTIVITY OF THE HYPOTHALAMIC-PITUITARY-THYROID AXIS IN RATS OF BOTH SEXES WITH THE DEVELOPMENT OF GUERIN'S CARCINOMA ON THE BACKGROUND OF HYPOTHYROIDISM

E. M. Frantsiyants, V. A. Bandovkina✉, I. V. Kaplieva, E. I. Surikova, I. V. Neskubina, Yu. A. Pogorelova, L. K. Trepitaki, N. D. Cheryarina, L. A. Nemashkalova, A. Yu. Arakelova

National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation
✉ valerryana@yandex.ru

ABSTRACT

Purpose of the study. Was to analyze changes in pathophysiological parameters of transplantable tumor growth and functional activity of the hypothalamic-pituitary-thyroid axis (HPT) in rats of both sexes with Guerin's carcinoma in presence of induced hypothyroidism.

Materials and methods. The dynamics of tumor growth and average life span were assessed in white alley rats of both sexes with Guerins carcinoma transplanted subcutaneously on the background of thyreostatic induced hypothyroidism. RIA (radioimmune assay) and ELISA (enzyme-linked immunosorbent assay) methods were used to determine levels of thyroid hormones in the blood and thyroid and tumor samples, and thyrotropin-releasing hormone (TRH) in the hypothalamus, as well as TSH in the pituitary gland. The experiment included 2 control groups: animals of both sexes with hypothyroidism (control group 1, number of rodents = 15) and animals with subcutaneously transplanted Guerin's carcinoma without hypothyroidism (control group 2, number of rodents = 15).

Results. Hypothyroidism in female rats inhibited the tumor growth and improved median survival by 1.8 times ($p < 0.05$). No such effect was observed in males of the main group. Levels of regulatory peptides of the hypothalamus and pituitary gland declined in females of the main group, while levels of TSH in the pituitary gland in males increased, despite a decrease in TRH by 3.5 times. TSH levels decreased in the thyroid and blood of animals of both sexes; however, a decrease in levels of total and free circulating thyroxine (T4 and FT4) by 1.6 times and by 2.8 times was found in the tumor, respectively; samples of Guerin's carcinoma in males of the main group remained saturated with T4 and FT4 as well as and in control group rodents without induced hypothyroidism.

Conclusions. The gender differences in the pathophysiology of the tumor development in presence of hypothyroidism, as well as changes in the functional activity of the HPT axis in experimental animals revealed in this study can probably be associated with sex hormones, which requires further study of the hypothalamic-pituitary-gonadal (HPG) axis and steroid hormones in peripheral organs and tumor samples.

Keywords:
Guerin's carcinoma, hypothyroidism, hypothalamic-pituitary-thyroid axis, thyroid hormones

For correspondence:
Valeriya A. Bandovkina – Dr. Sci. (Biol.), senior researcher of the laboratory for the study of pathogenesis of malignant tumors, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation.
Address: 63 14 line str., Rostov-on-Don 344037, Russian Federation
E-mail: valerryana@yandex.ru
ORCID: http://orcid.org/0000-0002-2302-8271
SPIN: 8806-2641, AuthorID: 696989

Funding: financing within the framework of state task No. 121031100252-6.
Conflict of interest: authors report no conflict of interest.

For citation:
Frantsiyants E. M., Bandovkina V. A., Kaplieva I. V., Surikova E. I., Neskubina I. V., Pogorelova Yu. A., Trepitaki L. K., Cheryarina N. D., Nemashkalova L. A., Arakelova A. Yu. Changes in pathophysiology of tumor growth and functional activity of the hypothalamic-pituitary-thyroid axis in rats of both sexes with the development of Guerin's carcinoma on the background of hypothyroidism. South Russian Journal of Cancer. 2022; 3(4): 26-39. https://doi.org/10.37748/2686-9039-2022-3-4-3

The article was submitted 26.05.2022; approved after reviewing 21.10.2022; accepted for publication 12.12.2022.

Южно-Российский онкологический журнал 2022, Т. 3, № 4, С. 26-39
https://doi.org/10.37748/2686-9039-2022-3-4-3
ОРИГИНАЛЬНАЯ СТАТЬЯ

ИЗМЕНЕНИЕ ПАТОФИЗИОЛОГИИ РОСТА ОПУХОЛИ И ФУНКЦИОНАЛЬНОЙ АКТИВНОСТИ ГИПОТАЛАМО-ГИПОФИЗАРНО-ТИРЕОИДНОЙ ОСИ У КРЫС ОБОЕГО ПОЛА ПРИ РАЗВИТИИ КАРЦИНОМЫ ГЕРЕНА НА ФОНЕ ГИПОТИРЕОЗА

Е. М. Франциянц, В. А. Бандовкина✉, И. В. Каплиева, Е. И. Сурикова, И. В. Нескубина, Ю. А. Погорелова, Л. К. Трепитаки, Н. Д. Черярина, Л. А. Немашкалова, А. Ю. Аракелова

НМИЦ онкологии, г. Ростов-на-Дону, Российская Федерация
✉ valerryana@yandex.ru

РЕЗЮМЕ

Цель исследования. Изучение изменения патофизиологических параметров роста перевивной опухоли и функциональной активности гипоталамо-гипофизарно-тиреоидной оси (ГГТ) у крыс обоего пола с карциномой Герена на фоне индуцированного гипотиреоза.

Материалы и методы. У белых беспородных крыс обоего пола с подкожно перевитой карциномой Герена на фоне индуцированного тиреостатиком гипотиреоза (основная группа) изучали динамику роста опухоли и среднюю продолжительность жизни, радиоиммунным и иммуноферментным методами (РИА и ИФА) определяли содержание тиреоидных гормонов в крови, щитовидной железе и в образцах опухоли, тиреотропного рилизинг гормона в гипоталамусе и тиреотропного гормона (ТТГ) в гипофизе. В эксперименте использовали 2 контрольные группы: животные обоего пола с гипотиреозом – контрольная группа № 1 (по 15 животных) и контрольная группа № 2 – самостоятельный рост опухоли – подкожная перевивка карциномы Герена (по 15 животных).

Результаты. У самок крыс гипотиреоз вызвал торможение роста перевивной опухоли и увеличение средней продолжительности жизни в 1,8 раза ($p < 0,05$). У самцов основной группы подобного эффекта не наблюдали. У самок основной группы установлено снижение уровня регуляторных пептидов гипоталамуса и гипофиза, тогда как у самцов уровень ТТГ в гипофизе повышался несмотря на снижение ТГ-рилизинга в 3,5 раза. В щитовидной железе и крови у животных обоего пола установлено снижение содержания ТГ, однако в опухоли установлено падение уровня общего и свободного тироксина (Т4 и FT4) в 1,6 раза и в 2,8 раза соответственно, образцы карциномы Герена у самцов основной группы оставались насыщенными Т4 и FT4 также, как и в контрольной, у животных без индуцированного гипотиреоза.

Заключение. Выявленные в настоящем исследовании половые различия в патофизиологии течения злокачественного процесса на фоне гипотиреоза, а также изменения функциональной активности ГГТ оси у экспериментальных животных, вероятно, могут быть связаны с половыми гормонами, что требует дальнейшего исследования гипоталамо-гипофизарно-гонадной (ГГГ) оси и показателей стероидных гормонов в периферических органах и образцах опухоли.

Ключевые слова:
карцинома Герена, гипотиреоз, гипоталамо-гипофизарно-тиреоидная ось, тиреоидные гормоны

Для корреспонденции:
Бандовкина Валерия Ахтямовна – д.б.н., старший научный сотрудник лаборатории изучения патогенеза злокачественных опухолей, ФГБУ «НМИЦ онкологии» Минздрава России, г. Ростов-на-Дону, Российская Федерация.
Адрес: 344037, Российская Федерация, г. Ростов-на-Дону, ул. 14-я линия, д. 63
E-mail: valerryana@yandex.ru
ORCID: http://orcid.org/0000-0002-2302-8271
SPIN: 8806-2641, AuthorID: 696989

Финансирование: финансирование в рамках государственного задания № 121031100252-6.
Конфликт интересов: авторы заявляют об отсутствии конфликта интересов.

Для цитирования:
Франциянц Е. М., Бандовкина В. А., Каплиева И. В., Сурикова Е. И., Нескубина И. В., Погорелова Ю. А., Трепитаки Л. К., Черярина Н. Д., Немашкалова Л. А., Аракелова А. Ю. Изменение патофизиологии роста опухоли и функциональной активности гипоталамо-гипофизарно-тиреоидной оси у крыс обоего пола с карциномой Герена на фоне гипотиреоза. Южно-Российский онкологический журнал. 2022; 3(4): 26-39. https://doi.org/10.37748/2686-9039-2022-3-4-3

Статья поступила в редакцию 26.05.2022; одобрена после рецензирования 21.10.2022; принята к публикации 12.12.2022.

INTRODUCTION

Thyroid hormones (TH) are one of the factors that have the greatest impact on the human body, and play a key regulatory role in many physiological processes, including cell growth, differentiation and metabolism [1; 2]. The synthesis and release of TH is strictly controlled by the hypothalamus– pituitary-thyroid axis (HPT axis). In response to various physiological and environmental stimuli, the neurons of the small-cell paraventricular nucleus secrete thyrotropin-releasing hormone (TG-releasing), which stimulates the anterior pituitary gland to produce thyroid-stimulating hormone (TSH). TSH, in turn, regulates all stages of growth and thyroid function. On the other hand, the products of TG-releasing and TTHare subjected to negative control with the help of TH [2].

The thyroid gland produces two main hormones: L-thyroxine (T4) and L-triiodothyronine (T3). T4 is the predominant form (more than 80 %) secreted by the gland and circulating, while T3 is considered the most active form because it binds with a much higher affinity with nuclear receptors [2; 3]. Free triiodothyronine and consolidated thyroxine (FT3 and FT4) enter cells through transmembrane carrier proteins and the most well-known mechanisms of their action are based on the regulation of transcription mediated by nuclear receptors. However, some cellular activities are initiated by THon the plasma membrane and are designated as "non-genomic" [2].

The HPT axis interacts with other regulatory axes – hypothalamic-pituitary-gonadal and adrenal. Thus, TG-releasing hormone of the hypothalamus is able to stimulate the release of prolactin, and TH hormones are able to regulate the mammotropic effects of prolactin and affect the metabolism of sex steroids [4], on the other hand, the activity of deiodinases is under the endocrine influence of sex steroids and prolactin [5].

Hypothyroidism refers to a pathological condition of thyroid hormone deficiency. The lack of adequate therapy can lead to serious adverse health consequences and, ultimately, to death [6]. Hypothyroidism is a common disease affecting about 5 % of the population, and is more common in women [7].

Due to the pleiotropic effect of thyroid hormones, hypothyroidism can also affect the course of other diseases. The mechanism of the relationship between thyroid dysfunction of both hypo- and hyperthyroidism and the risk of cancer remains unclear, and the data of epidemiological and experimental studies are quite contradictory [8; 9]. Some studies have found that women with hypothyroidism are at a higher risk of breast cancer than women without hypothyroidism, and taking levothyroxine may reduce the risk of breast cancer in women with hypothyroidism [10]. Other studies have reported that higher levels of TSH in the blood, as a biomarker of hypothyroidism, are associated with a reduced risk of breast cancer [11]. While Khan S. R. et al. In his studies, he did not reveal a link between hypothyroidism and breast cancer (BC) [12]. Wang Y. et al. It has been reported that high serum TSH levels improve the results of treatment of head and neck cancer, glioma and breast cancer, but are associated with poor results of treatment of renal cell carcinoma [13].

At the same time, experimental data have shown that T4 and T3 have proliferative and anti-apoptotic effects on breast cancer tumor cells, regulating gene expression and stimulating estrogen-like effects [9; 14]. The role of TH in the pathophysiological mechanism of proliferation and differentiation in malignant tumor cells remains controversial, however, it is known that their elevated level may correlate with a worse prognosis of the course of the disease [15].

The increased risk of malignant neoplasms of various localizations under the influence of taking thyroid hormones for the treatment of hypothyroidism can be explained by the fact that TH increases the activation of mitochondrial function responsible for the overproduction of ROS. An increased level of ROS may be associated with increased oxidative stress in the body and the further development of cancer. Previous studies have shown that oxidative stress can disrupt cell function and, consequently, leads to a number of chronic disease conditions, including cancer and autoimmune diseases [16].

However, since the mechanisms explaining the link between thyroid dysfunction and cancer risk have not been fully determined, a new approach is needed to further study the causal relationship between them. An experimental animal model, taking into account gender, may be the best option for determining a possible biological mechanism.

The purpose of the study was to study changes in the pathophysiological parameters of the growth of

the transplant tumor and the functional activity of the hypothalamic-pituitary-thyroid axis (HPT) in rats of both sexes with Guerin carcinoma on the background of induced hypothyroidism.

MATERIALS AND METHODS

The experiment was performed on white mongrel rats of both sexes weighing 150–180 g. The animals were obtained from the Research Center for Biomedical Technologies of the FMBA (Andreevka branch, Moscow region). Laboratory animals were kept under natural lighting conditions with free access to water and food. Work with animals was carried out in accordance with the rules of the "European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes" (Directive 2010/63/EU), as well as in accordance with the "International Recommendations on conducting Biomedical research using animals" and the order of the Ministry of Health of the Russian Federation dated June 19, 2003 No. 267 "On approval of the rules of laboratory practices". Manipulations with animals were performed in the box in compliance with the generally accepted rules of asepsis and antiseptics.

The study used a culture of Guerin's carcinoma obtained from the N. N. Blokhin National Medical Research Centre of Oncology. The material for transplantation was obtained from donor rats on the 12th-16th day of tumor growth. Transplantation of Guerin's carcinoma to animals was carried out by standard injection of 0.5ml tumor suspension under the skin of the right scapula in proportions of 1:10 in saline solution.

White mongrel rats of both sexes for 30 days received the pharmacopoeial thyrostatic drug mercazolil (Akrikhin Russia) (active ingredient Thiamazole) at a daily dose of 2.5 mg/100 g of weight (the total dose was 75 mg/100 g of weight). The animals did not refuse to eat, gained weight, deterioration of the appearance of the skin and hair, lethargy and drowsiness were registered. Hypothyroidism in animals was confirmed by determining the serum content of total thyroxine and thyroid-stimulating hormone by radioimmune assay (RIA) using standard kits (Immunotech, Czech Republic) after 30 days of taking thyrostatica. Animals of each sex were divided into the following groups:

The main group, after receiving persistent hypothyroidism to study its effect on the growth of malignant tumors, groups of animals of both sexes (15 females and 15 males) were subcutaneously transplanted with Guerin's carcinoma

Control group No. 1 animals of both sexes with hypothyroidism (n = 15 females and n = 15 males

Control group No. 2 animals of both sizes (n = 15 females and n = 15 males) with subcutaneous grafting of Guerin's carcinoma in the same dose and volume as in animals from the main groups.

Intact animals of both sexes (10 pieces each).

Animals with tumor growth – control group No. 2 and the main group were decapitated after 14 days of growth of Guerin's carcinoma. Animals of control group No. 1 and intact rats were decapitated at the same time as the main group. In the blood and 10 % of tumor homogenates, perifocal zone, thyroid gland and 1 % of pituitary homogenates, the level of thyroid hormones and TSH was determined using standard kits, in 1 % of hypothalamus homogenates, the level of TG-releasing was determined by the enzyme immunoassay (ELISA) method.

In addition, in 60 rats of both sexes (15 animals each), the dynamics of tumor growth and average life expectancy were studied with the growth of Guerin's carcinoma in its own variant and against the background of induced hypothyroidism.

Statistical analysis of the results was carried out using the Statistica 10.0 software package. The data obtained were analyzed for compliance with the normal distribution law using the Shapiro-Wilk criterion (for small samples). Quantitative data in the groups were compared using the Student and Mann-Whitney t-test. The data of the tables are presented in the form of M ± m, where M is the arithmetic mean, m is the standard error of the mean, $p < 0.05$ was taken as the level of statistical significance. The obtained results were statistically processed in compliance with the general recommendations for medical research.

RESEARCH RESULTS

The features of tumor growth during standard grafting of Guerin's carcinoma and grafting on the background of hypothyroidism in rats of both sexes are presented in Tables 1 and 2. Subcutaneous tumor in female rats of the main group started being deter-

mined 4 days after grafting, the tumor was grafted in 80 % of females, whereas in 20 % of female rats with hypothyroidism, Guerin's carcinoma did not reproduce. In the control group, the tumor was also detected after 4 days, the transferability was 100 %. In the females of the main group, at all stages of tumor measurement, the average volume was less than in the control group: 1.3 times after 4 days, 1.4

Table 1. Dynamics of tumor growth and survival in female rats with Guerin's carcinoma

Study timeline	Main group Hypothyroidism + Guerin's carcinoma (Tumor V, cm^3)	Control group Guerin's carcinoma (Tumor V, cm^3)
4 days	0.12 ± 0.01[1]	0.16 ± 0.06
7 days	2.28 ± 0.53[1]	3.18 ± 0.33
10 days	13.21 ± 0.93[1]	18.40 ± 2.42
14 days	27.28 ± 1.62[1]	44.76 ± 3.98
18 days	55.94 ± 5.4[1]	70.30 ± 4.78
21 days	75.73 ± 6.88[1]	107.96 ± 9.01
Baldness on the skin appearance	From day 11	Not detected
Necrotic areas appeared on the skin	Not detected	From day 14
Average life span (days)	29.3 ± 1.2[1]	18.2 ± 1.4
First lethal outcome in group	Day 24	Day 13
Last lethal outcome in group	Day 33	Day 26

Note: 1 – statistically significant differences compared to the indicators in animals of the control group $p < 0.05$

Table 2. Dynamics of tumor growth and survival in male rats with Guerin's carcinoma on the background of hypothyroidism

Study timeline	Main group Hypothyroidism + Guerin's carcinoma (Tumor V, cm^3)	Control group Guerin's carcinoma (Tumor V, cm^3)
4 days	0.04 ± 0.004[1]	0.50 ± 0.04
7 days	0.5 ± 0.002[1]	3.82 ± 0.27
10 days	7.94 ± 0.80[1]	14.74 ± 1.15
14 days	15.61 ± 1.40[1]	40.68 ± 3.81
18 days	44.90 ± 3.74	52.84 ± 5.48
21 days	72.93 ± 7.09	77.50 ± 6.25
Necrotic areas appeared on the skin	Not detected	From day 7
Average life span (days)	23.7 ± 2.1	20.0 ± 1.3
First lethal outcome in group	Day 20	Day 14
Last lethal outcome in group	Day 25	Day 24

Note: 1 – statistically significant differences compared to the indicators in animals of the control group $p < 0.05$.

times after 7 and 10 days, 1.5 times after 14 days, 1.3 times after 18 days and 1.4 times after 21 days ($p < 0.05$). At the same time, the survival rate of female rats of the main group was 1.6 times ($p < 0.05$) higher compared to rats of the control group. The first death of animals of the main group occurred 24 days later, 11 days later, compared with the first death of animals in the control group.

The study of the growth dynamics of Guerin's transfused carcinoma against the background of hypothyroidism in male rats is presented in Table 2. Subcutaneous tumor in male rats of the main group and control group in 100 % of cases began to be determined 4 days after the transfusion. In males of the main group, compared with the indicators in control animals, the average tumor volume at the stages of the experiment from day 4 to 14 was less: after 4 days by 13.3 times, after 7 days by 7.5 times, after 10 days by 1.9 times, after 14 days by 2.6 times ($p < 0.05$). However, after 18 days and after 21 days, there were no significant differences in tumor volumes. The average life expectancy of the animals had no significant differences compared to those of the males of the control group.

Taking into account the sex differences in the effect of hypothyroidism on the growth of Guerin's transfused carcinoma, we further conducted studies of the level of TH, as well as the main regulators of the HPT axis in blood and tissues. Indicators of the content of TH and TSH in the blood of rats of control and main groups are presented in Table 3.

It was found that in female and male rats with induced hypothyroidism (control group 1), the blood level of total T4 was lower than in intact animals by 7.3 times and 2 times, respectively, and TSH was increased by 1.6 times and 1.5 times. In addition, the level of total T3 was reduced by 1.3 times in male rats. At the same time, we have not established a change in the blood content of free forms of thyroid hormones in animals of both sexes.

It turned out that the growth of Guerin's carcinoma (control group 2 animals) also affected the content of thyroid hormones in the blood. Thus, in female rats with tumor growth, compared with the indicators in intact animals, the level of not only total T4 decreased by 2.0 times, but also free forms of thyroxine and triiodothyronine (FT4 and FT3) by an average of 1.4 times, despite the 1.6-fold increased content of total T3 and the absence of changes in the concentration of TSH.

In males of control group 2, a decrease in both general forms of TG was found: T4 by 4.7 times, T3 by 2.8 times, but also free forms – FT4 by 2 times

Table 3. The level of serum thyroid hormones in rats of both sexes

Группы	FT4 pMol/L	FT3 pMol/L	T4 pMol/L	T3 pMol/L	ТТГ mcIU/ml
Female					
Intact	15.73 ± 0.37	5.85 ± 0.14	61.29 ± 1.33	1.07 ± 0.06	0.085 ± 0.0015
Control 1	19.35 ± 1.20	5.82 ± 0.17	8.45 ± 0.28[1]	0.95 ± 0.07	0.14 ± 0.006[1]
Control 2	11.25 ± 0.14[1]	4.17 ± 0.11	28.12 ± 0.79[1]	1.76 ± 0.08[1]	0.07 ± 0.004[2]
Main group	8.85 ± 0.34[1,2,3]	3.5 ± 0.13[1,2]	26.70 ± 0.92[1,2]	0.55 ± 0.02[1,2,3]	0.07 ± 0.003[2]
Male					
Intact	20.11 ± 0.90	5.83 ± 0.30	75.77 ± 1.15	1.46 ± 0.07	0.083 ± 0.003
Control 1	17.18 ± 0.18	6.15 ± 0.26	38.51 ± 0.70[1]	1.11 ± 0.06[1]	0.122 ± 0.004[1]
Control 2	9.86 ± 0.44[1,2]	4.32 ± 0.19[1,2]	15.98 ± 0.64[1,2]	0.72 ± 0.03[1,2]	0.140 ± 0.005[1]
Main group	5.72 ± 0.35[1,2,3]	1.85 ± 0.08[1,2,3]	11.32 ± 0.48[1,2,3]	0.52 ± 0.03[1,2,3]	0.310 ± 0.011[1,2,3]

Note: significant differences compared to: 1 – with intact animals of the corresponding sex; 2 – with control group 1; 3 – with control group 2 ($p < 0.05$).

and FT3 by 1.3 times, against the background of an increased level of TSH by 1.8 times.

In the females of the main group, the level of common forms of thyroid hormones in the blood was lower than in intact animals T4 2.3 times and T3 1.9 times. The concentration of FT4 and FT3 was also 1.8 times and 1.7 times lower than normal, respectively. At the same time, the T4 content was 3.2 times higher than in animals with independent hypothyroidism, but had no significant differences from the indicators in females in control 2, and the T3 concentration was 1.7 times lower compared to the indicators of control group 1 and 3.2 times lower compared to control group 2. The level of FT4 in the blood of the females of the main group was 2.2 times lower than with hypothyroidism, and 1.3 times lower than with independent tumor growth, while the concentration of FT3 in the blood was 1.7 times lower than with hypothyroidism and had no significant differences from the indicators with independent growth of Guerin's carcinoma. The TSH level in the blood of the females of the main group was 2 times lower than in animals with hypothyroidism and did not differ from the indicators in intact animals and animals with independent tumor growth.

In males of the main group, the concentration of T4 in the blood was 6.7 times lower than in intact animals, compared with hypothyroidism by 3.4 times, compared with independent tumor growth by 1.4 times. The T3 content was also lower compared to the indicators: intact animals by 2.8 times; males with hypothyroidism – by 2.1 times, with the level of animals with tumor growth by 1.4 times. As for free forms, their content in the blood of males of the main group was lower than in intact animals and in control groups No. 1 and No. 2: FT4 3.5 times, 3 times and 1.7 times, respectively, and FT3 3.2 times, 3.3 times and 2.3 times, respectively. The TSH level in males of the main group exceeded the indicators in intact animals by 3.9 times, control 1 by 2.6 times, control 2 by 2.2 times.

Further, a study was conducted of the central links of the regulation of the HPT axis, namely, the level of TG-releasing in the hypothalamus and TSH in the pituitary gland in animals of the main and control groups (Table 4).

It was found that in female rats of both the main and control groups No. 1 and No. 2, the content of TG-releasing in the hypothalamus was lower than in intact females by 2.9 times, 2.1 times and 2.2 times, respectively. It should be noted that in animals of control group 1, the concentration of TG-releasing was lower than in the main and control group No. 2 by an average of 1.4 times. Only female rats of the main group showed a decrease in the content of TSH in the pituitary gland by an average of 1.4 times compared with the intact and control group animals.

In male rats, the level of TG-releasing in the hypothalamus was lower than normal, and TSH in the pituitary gland was higher, only in animals with independent hypothyroidism and combined with tumor growth – in control group 1 and the main group – 2.2 times and 3.5 times, respectively, and 1.4 times and 1.2 times, respectively. With the independent growth of Guerin's carcinoma, no significant differences in the content of these regulatory peptides were revealed.

Table 4. The content of TSH-releasing hormone in the hypothalamus and TSH in the pituitary gland of rats with the growth of Guerin's carcinoma on the background of hypothyroidism

Groups	Female		Male	
Indicators	TH-releasing, Hypothalamus (pg/gt)	TSH pituitary (mIU/gt)	TH-releasing, Hypothalamus (pg/gt)	TSH pituitary (mIU/gt)
Intact	42.57 ± 2.24	0.28 ± 0.015	30.7 ± 1.78	0.25 ± 0.015
Control 1	14.6 ± 0.56[1,3]	0.28 ± 0.019	14.2 ± 0.64[1,3]	0.35 ± 0.012[1,3]
Control 2	20.5 ± 1.21[1,2]	0.29 ± 0.017	36.1 ± 1.22[2]	0.27 ± 0.016[2]
Main	19.26 ± 1.10[1,2]	0.20 ± 0.01[1,2,3]	8.7 ± 0.47[1,2,3]	0.31 ± 0.026[1]

Note: significant differences compared to: 1 – with intact animals of the corresponding sex; 2 – with control group 1; 3 – with control group 2 ($p < 0.05$).

Table 5. Thyroid hormone and TSH levels in the thyroid gland in rats

Группы	FT4 pM/gt	FT3 pM/gt	T4 pM/gt	T3 pM/gt	ТТГ mclU/gt
Female					
Intact	37.52 ± 2.17	45.94 ± 1.68	29.50 ± 0.97	3.59 ± 0.11	1.97 ± 0.05
Control group 1	52.95 ± 1.23[1]	91.86 ± 1.52[1]	1.22 ± 0.05[1,3]	0.07 ± 0.004[1,3]	1.57 ± 0.07
Control grou 2	61.31 ± 0.66[1]	119.61 ± 12.18[1]	9.57 ± 0.51[1,2]	1.43 ± 0.06[1,2]	1.63 ± 0.058
Main group	31.90 ± 0.65[1,2,3]	24.41 ± 0.62[1,2,3]	3.19 ± 0.17[1,2,3]	0.72 ± 0.04[1,2,3]	5.71 ± 0.13[1,2,3]
Male					
Intact	23.66 ± 0.49	21.79 ± 0.68	26.61 ± 1.06	5.37 ± 0.28	0.26 ± 0.01
Control group 1	14.21 ± 0.83[1,3]	7.94 ± 0.33[1]	9.55 ± 0.45[1,3]	0.59 ± 0.03[1,3]	1.43 ± 0.05[1,3]
Control grou 2	59.89 ± 1.14[1,2]	9.03 ± 0.37[1]	91.90 ± 1.89[1,2]	7.41 ± 0.36[1,2]	0.20 ± 0.07[1,2]
Main group	7.99 ± 0.96[1,2,3]	2.18 ± 0.14[1,2,3]	9.19 ± 0.23[1,3]	1.21 ± 0.08[1,2,3]	0.15 ± 0.004[1,2,3]

Note: significant differences compared to: 1 – with intact animals of the corresponding sex; 2 – with control group 1; 3 – with control group 2 ($p < 0.05$).

Table 6. The level of thyroid hormones and TSH in the tumor and perifocal zone in rats with Guerin's carcinoma and hypothyroidism+Guerin's carcinoma

Groups	FT4 pM/gt	FT3 pM/gt	T4 pM/gt	T3 pM/gt
Female				
Control tumor	4.85 ± 0.23	3.88 ± 0.20	25.32 ± 0.41	0.52 ± 0.02
Control group p/zone	3.12 ± 0.16	1.18 ± 0.06	14.40 ± 0.29	0.48 ± 0.02
Main group tumor	1.73 ± 0.03[1]	2.40 ± 0.07[1]	16.11 ± 0.32[1]	0.59 ± 0.02
Main group p/zone	3.32 ± 0.11	1.30 ± 0.07	20.91 ± 0.42[2]	0.55 ± 0.02
Male				
Control tumor	1.47 ± 0.08	4.17 ± 0.14	23.83 ± 0.69	0.53 ± 0.03
Control group p/zone	4.57 ± 0.10	2.17 ± 0.055	19.61 ± 0.56	0.51 ± 0.01
Main group tumor	1.73 ± 0.06	3.12 ± 0.13[1]	20.33 ± 0.54	0.52 ± 0.03
Main group p/zone	1.41 ± 0.04[2]	0.27 ± 0.01[2]	28.20 ± 0.88[2]	0.52 ± 0.24

Note: significant differences compared to: 1 – with the tumor of the control group of the corresponding sex; 2 – with the perifocal zone of the control group of the corresponding sex ($p < 0.05$).

Next, the level of thyroid hormones and TSH in the peripheral organ – the thyroid gland was studied (Table 5).

It was found that in female rats of the control and main groups, a decrease in the level of T4 and T3 was found in the thyroid gland in varying degrees of severity, against the background of normal TSH content in the control groups and an increase of 2.9 times in the main group. The maximum decrease in the level of common forms of T4 and T3 in the thyroid gland – by 24.2 times and 51.3 times was found in control group No. 1, in female rats of control group 2 and the main group, the level of T4 and T3 was lower than the values of intact animals by 3.1 and 2.6 times and by 9.5 and 5.1 times, respectively.

Concentrations of free forms FT4 and FT3 in the thyroid gland in female rats of control group 1, despite the low level of common forms, were increased by 1.4 times and 2 times, respectively, compared with intact animals. In control group No. 2, the level of FT4 and FT3 in the thyroid gland was 1.6 times and 2.6 times higher than normal. In the main group, the FT4 content had no significant differences from the indicators in intact animals, and FT3 in the thyroid gland of females was 1.9 times lower.

In male rats with hypothyroidism independent and combined with tumor growth in the thyroid gland, a reduced content of common and free forms of thyroid hormones was also noted. Thus, the level of T4 in males of control group 1 and the main group was lower than in intact animals by an average of 2.8 times, T3 by 8.5 times and 4.3 times, respectively; the concentration of FT4 is 1.7 times and 3 times lower, respectively, and FT3 by 2.7 times and 10.3 times, respectively. With the independent growth of Guerin's carcinoma, on the contrary, the level of T4 and T3 was 3.5 times and 1.4 times higher than normal, respectively, and FT4 2.5 times. Only the FT3 content in male rats with tumor growth turned out to be 2.4 times lower than in intact animals. In males with hypothyroidism, the level of TSH in the thyroid gland was 5.4 times higher than in intact animals, whereas in the main group, the concentration of TSH, on the contrary, was 1.7 times lower.

Next, the level of thyroid hormones in the tumor and its perifocal zone was studied in animals with independent growth of Guerin's carcinoma and combined with hypothyroidism (Table 6).

It was found that in the females of the main group in the tumor, the level of total T4 was 1.6 times lower, and FT4 was 2.8 times lower, and FT3 was 1.6 times lower, compared with the samples of independently growing Guerin carcinoma. At the same time, there were no significant differences in the level of total T3 in the control and main groups.

In the perifocal zone in the females of the main group, only the level of T4 was 1.5 times higher than in the animals of the control group, and the content of T3, FT3 and FT4 had no significant differences from the indicators in the perifocal zone of the females of the control group.

In male rats of the main group, compared with the control group, the content of T4, T3 and FT4 in the tumor samples had no significant differences, and only FT3 was reduced by 1.3 times. In the perifocal zone in the males of the main group, the T4 level was 1.4 times higher, T3 had no significant differences from the indicators in the control group, while FT4 was 2.7 times lower and FT3 was 8 times lower compared to the control group.

DISCUSSION

Our studies have shown that the growth of subcutaneously transplanted Guerin's carcinoma against the background of hypothyroidism had sexual specificity: in females, the tumor was transplanted only in 80 % of cases, there was inhibition of tumor growth, the life expectancy of animals increased. In male rats, Guerin's carcinoma was subcutaneously transferred, as in the control group in 100 % of cases, some slowing of tumor growth was detected up to 14 days, but then the tumor volume increased, and life expectancy did not have significant differences from the indicators in the males of the control group. We assume that a significant increase in the average life expectancy in female rats of the main group compared with the control group may indicate a decrease in the aggressiveness of the course of the disease and be associated with a change in the functional activity of the HPT axis, both central regulatory links and peripheral, as well as directly local TG content in tumor samples. At the same time, the main group of males is of particular interest, in which, despite the presence of hypothyroidism, there was no change in the average life expectancy of animals. In connection with such sexual differences

in the course of the malignant process against the background of comorbid pathology, of course, first of all it is worth paying attention to the differences in the functioning of the HPT axis of animals of control groups No. 1.

Experimental hypothyroidism induced in rats of both sexes and confirmed by blood test results, with elevated TSH levels and reduced T4, was also accompanied by a decrease in the hypothalamus content of TG-releasing, without change in females, but an increase in males in the pituitary gland of TSH. At the same time, in the thyroid gland of animals of both sexes, a decrease in general forms of TG and free forms of TG was revealed only in males. That is, we can note the sexual differences in the functioning of the pituitary gland and thyroid gland in response to the effects of thyrostatics. It is known that hypothyroidism affects the female part of the population to a greater extent [17], it is possible that the experimental increase in the level of TSH in the pituitary gland in males in response to low concentrations of TG-releasing in the hypothalamus indicates a greater resistance of the male body to the effects of thyrostatics. Literature data indicate that central hypothyroidism is quite rare and equally affects both sexes, is more often associated with disorders of the pituitary gland than with the hypothalamus, but often includes both [18].

Since in our study it was found that in females, unlike males, hypothyroidism had an inhibitory effect on the growth of subcutaneously transplanted Guerin's carcinoma, in order to consider the possible mechanisms of the sexual specificity of the functioning of the HPT axis in animals with the growth of a malignant tumor against the background of hypothyroidism, it is of particular interest to analyze how the independent growth of Guerin's carcinoma affected the factors HPT axis.

Literature data indicate that under the influence of many factors, including starvation, trauma, myocardial infarction, infection, surgery, inflammation, etc. in patients with normal thyroid function, a number of thyroid hormone level disorders occur, a decrease in TG levels is noted in the blood serum, without an increase in TSH levels, aggravated with increasing severity and duration of the disease. This condition is called euthyroid weakness syndrome, euthyroid disease syndrome or low3/low4 syndrome. At the same time, a violation of thyroid hormone levels is secondary to various clinical diseases due to normal primary thyroid function [19; 20].

At the same time, the functioning of the HPT axis during the growth of malignant tumors has its own characteristics. Patients with cancer of various localizations are characterized by multidirectional changes in thyroid hormones in the blood, controlled or not controlled by TSH [21; 22]. The specificity of changes in the thyroid hormonal background in cancer patients may also be associated with the presence or absence of metastases [23] or comorbid diseases [24]. In addition, experimental studies have shown that functional changes in the HPT axis have sexual specificity. Thus, in an experiment with transfused melanoma B16/F10 mice of the C57Bl6 line, deep thyroid hypofunction with loss of pituitary control in males and normal production of common forms of TG, with a decrease in free forms of hormone in females, was revealed [25–27].

In the present study, we found that in response to the independent growth of the tumor, only female rats in the hypothalamus had a reduced level of TG-releasing, whereas in males it remained within the normal range. At the same time, in animals of both sexes, the content of TSH in the pituitary gland did not change. That is, in this case, only females were characterized by the involvement of the central link of regulation in the change in the functional activity of the HPT axis. As a result, in the thyroid gland of female tumor carriers, a decrease in the level of common, but an increase in the content of free forms of TG was revealed, whereas in males, on the contrary, an increase in the general forms of TG and FT4, but a decrease in FT3.

Despite the sex differences in the hormonal saturation of the thyroid gland, in the blood of males with Guerin's carcinoma, a decrease in the level of both general and free forms of TG was revealed, accompanied by a high content of TSH, which corresponds to clinical hypothyroidism. In females with Guerin carcinoma in the blood, against the background of normal TSH content, low T4, FT4 and FT3 values were determined, which corresponds to lowT3/lowT4 syndrome.

It is known that thyroid insufficiency syndrome is associated with systemic changes in the immune and endocrine systems. In the modern literature it is reported that its specific mechanisms mainly include changes in the metabolism of thyroid hor-

mones, secretion of TSH, protein binding TG in serum, transmembrane transport of thyroid hormones, nuclear receptors. Consequently, in low FT3 syndrome, various factors lead to an abnormal response of the body and disorders of metabolism, regulation, transmembrane transport and binding of thyroid hormone receptors [20]. Most of the literature shows that the hypothyroid state correlates with the severity of the disease, and a decrease in FT3 levels can be used as a prognostic marker of an unfavorable course of the disease [28].

Thus, we found that the studied control groups – hypothyroidism and the independent growth of Guerin's carcinoma, had a sexual specificity of changes in the activity of the HPT axis links. In response to tumor growth, the level of TG-releasing in the hypothalamus decreased only in female rats, while hypothyroidism caused a decrease in the content of the regulatory peptide in animals of both sexes. Only in males, hypothyroidism caused multidirectional changes in the level of regulatory peptides in the hypothalamus and pituitary gland (TG-releasing and TSH). Only in males, the growth of Guerin's carcinoma caused the accumulation of common forms of TG in the thyroid gland, against the background of low blood content. Therefore, of particular interest was the study of the growth of a malignant tumor against the background of hypothyroidism in animals of both sexes – the main group of our study.

In the main group, the sex specificity of changes in the activity of the HPT axis links was revealed, which was probably one of the reasons for slowing tumor growth only in females, unlike males, since it is known that thyroid hormones play a key role in the proliferation and differentiation of solid tumors [9].

In female rats of the main group, inhibition of the growth of Guerin's carcinoma on the background of hypothyroidism was revealed with a decrease in the level of not only TG-releasing in the hypothalamus, but also TSH in the pituitary gland against the background of low content of common forms of TG and FT3 both in the peripheral organ and in the blood. It should be noted that the content of TSH in the thyroid gland is sharply increased, but without entering the blood.

In males of the main group, there was no inhibition of tumor growth, similar to females, while in males, against the background of a decrease in the level of TG-releasing in the hypothalamus, the level of TSH in the pituitary gland even increased. Judging by the indicators of TG and TSH in the blood of males of the main group, thyroid dysfunction by the type of hypothyroidism was aggravated, since the level of TSH in the blood increased compared to the control groups, and the content of TG decreased even more, in addition, the thyroid gland had minimal, compared with the control groups, indicators of free forms of TG and reduced, as with independent hypothyroidism, the level of T4.

There are experimental studies showing that induced hypothyroidism in rats reduces the incidence of breast cancer and tumor volume, and also increases the latent period of tumor development, but when these rats were treated with thyroxine, the anti-cancer protective effects of hypothyroidism were reversed [29].

We suggest that conflicting clinical data on the role of thyroid dysfunction on the risk of cancer of various localizations may be related to sexual specificity, as well as hormonal dependence of the tumor, which may be determined by histological structure, degree of differentiation, as well as polymorphism of various genes and many other factors. In this regard, the local saturation of thyroid hormones of the tumor and its perifocal zone, depending on the state of the HPT axis, is of interest.

In our study, it was found that in animals with independent growth of Guerin's carcinoma in tumor samples, the content of T4, T3 and FT3 in females and males was the same, and the average life expectancy did not differ. At the same time, tumor samples in males of the main group, with the growth of Guerin's carcinoma on the background of hypothyroidism, were also saturated with T4, T3 and FT4, as well as samples of the control group, whereas in females with Guerin's carcinoma on the background of hypothyroidism, a decrease in the level of T4, FT4 and FT3 was found in the tumor.

CONCLUSION

Thus, the sexual specificity of the development of the malignant process against the background of hypothyroidism was revealed, which manifested itself in the following: in female non-linear white rats with hypothyroidism, the increase in the volume of tumor nodes of Guerin's carcinoma, transplanted

subcutaneously, developed more slowly than in the control group, and the life expectancy of the animals was 1.6 times longer. In males of non-linear white rats with hypothyroidism, the increase in the volume of tumor nodes of Guerin's carcinoma, transplanted subcutaneously, did not develop evenly, in terms of up to 14 days slower, but then did not differ from the indicators of the control groups, while the life expectancy did not have significant differences. The sex differences revealed in this study during the malignant process against the background of hypothyroidism, as well as changes in the functional activity of the HPT axis in experimental animals, can probably be associated with sex hormones, which requires further investigation of the HPT axis and indicators of steroid hormones in peripheral organs and tumor samples.

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Information about authors:

Elena M. Frantsiyants – Dr. Sci. (Biol.), professor, deputy general director for science, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: http://orcid.org/0000-0003-3618-6890, SPIN: 9427-9928, AuthorID: 462868, ResearcherID: Y-1491-2018, Scopus Author ID: 55890047700

Valeriya A. Bandovkina✉ – Dr. Sci. (Biol.), senior researcher of the laboratory for the study of pathogenesis of malignant tumors, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: http://orcid.org/0000-0002-2302-8271, SPIN: 8806-2641, AuthorID: 696989

Irina V. Kaplieva – Dr. Sci. (Med.), senior researcher of the laboratory for the study of pathogenesis of malignant tumors, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: http://orcid.org/0000-0002-3972-2452, SPIN: 5047-1541, AuthorID: 734116

Ekaterina I. Surikova – Cand. Sci. (Biol.), senior researcher of the laboratory for the study of pathogenesis of malignant tumors, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: http://orcid.org/0000-0002-4318-7587, SPIN: 2401-4115, AuthorID: 301537

Irina V. Neskubina – Cand. Sci. (Biol.), senior researcher at the laboratory for the study of the pathogenesis of malignant tumors, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0002-7395-3086, SPIN: 3581-8531, AuthorID: 794688

Yuliya A. Pogorelova – Cand. Sci. (Biol.), senior researcher at laboratory of malignant tumor pathogenesis study, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: http://orcid.org/0000-0002-2674-9832, SPIN: 2168-8737, AuthorID: 558241

Lidiya K. Trepitaki – researcher at the laboratory for the study of pathogenesis of malignant tumors, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: http://orcid.org/0000-0002-9749-2747, SPIN: 2052-1248, AuthorID: 734359

Natalya D. Cheryarina – laboratory assistant at the laboratory for the study of the pathogenesis of malignant tumors, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: http://orcid.org/0000-0002-3711-8155, SPIN: 2189-3404, AuthorID: 558243

Lyudmila A. Nemashkalova – researcher at the laboratory for the study of the pathogenesis of malignant tumors, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0003-2713-8598, SPIN: 1355-8652, AuthorID: 734146

Alina Yu. Arakelova – PhD student of the department of abdominal oncology No. 1, National Medical Research Centre of Oncology, Rostov-on-Don, Russian Federation. ORCID: http://orcid.org/0000-0003-2739-1307

Contribution of the authors:

Frantsiyants E. M. – concept and design of the study;
Bandovkina V. A. – systematization and analysis of the obtained data, writing the text of the manuscript;
Kaplieva I. V. – analysis of the data obtained, scientific editing of the article;
Surikova E. I. – statistical analysis of the data obtained, interpretation of the results;
Neskubina I. V. – review of publications, technical editing of the article;
Pogorelova Yu. A. – conducting enzyme immunoassay and interpretation of the results;
Trepitaki L. K. – conducting the experimental part of the study, technical design;
Cheryarina N. D. – design of the bibliography, editing of the text of the article;
Nemashkalova L. A. – technical editing of the article;
Arakelova A. Yu. – review of publications on the topic of the article.