

# Changes in the functional activity of the hypothalamic-pituitary-adrenal axis in rats of both sexes with Guerin's carcinoma against the background of hypothyroidism

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## Abstract

The hypothalamic-pituitary-adrenal axis (HPA) makes the body's response to various stress factors, interacting with the thyroid and gonadal axis.

**The aim** of our work was to study the effect by induced hypothyroidism on changes in the functioning of the HPA axis in rats with Guerin's carcinoma of both sexes.

**Materials and methods.** The experiment was performed in white outbred rats of both sexes. Hypothyroidism was induced in animals by medication for 30 days with Mercazolil, and then Guerin's carcinoma was transplanted (the main group). The reference groups covered animals with the independent growth of Guerin's carcinoma and with independent hypothyroidism, as well as intact animals (the normal conditions). On day 18 of the tumor growth, the animals were sacrificed, and, using standard ELISA kits, in the serum and the homogenates of the adrenal glands, the tumor and the perifocal zone, the level of cortisol was determined; in the homogenates of the hypothalamus we measured the concentration of CT-releasing hormone (CRH) and in the pituitary gland the concentration of ACTH.

**Results.** Induced hypothyroidism both in males and females caused adrenal insufficiency. The growth of Guerin's carcinoma increased the level of CT-releasing hormone in males by 9.6 times and cortisol in the adrenal glands in females and males by 1.3 times and 2.3 times ( $p < 0.05$ ), respectively. In the main group females and males we revealed a decrease in the level of CT-releasing hormone of the hypothalamus by an average

of 1.4 times, ACTH in the pituitary gland by 1.5-1.8 times, but an increase in the cortisol concentration in blood and the adrenal glands only in males by an average of 1.5 times ( $p < 0.05$ ). Only in males of the main group in the tumor and its perifocal zone, the content of cortisol increased by 5.9 times and 1.6 times ( $p < 0.05$ ), respectively.

**Conclusion.** The HPA axis has a gender-specific response to the growth of a malignant tumor, both in its independent growth variant and against the background of hypothyroidism, which in its independent variant causes adrenal insufficiency.

## Keywords

Guerin's carcinoma, Tumor, Hypothyroidism, CT-releasing hormone, ACTH, Cortisol

## Imprint

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## Introduction

All regulatory axes: the hypothalamic-pituitary-thyroid (HGT), hypothalamic-pituitary-gonadal (HPG) and hypothalamic-pituitary-adrenal (HPA) axes work in their close interaction, as a result of which some changes in thyroid hormone levels can affect the production and circulation of glucocorticoids, as well as the function of the hypothalamus and the pituitary [1,2]. Thus, thyrotropin-releasing hormone (TRH) of the hypothalamus stimulates the secretion not only of TSH, but also ACTH, which complements the mechanisms of the relationship between the thyroid and glucocorticoid axes [3].

The HPA axis plays a central role in coordinating the neuroendocrine adaptation of the stress response and in synchronizing the peripheral circadian clock [4]. The three main hormones involved in the regulation of HPA are corticotropin-releasing hormone

(CT-releasing hormone, CRH) produced by neurons in the paraventricular nucleus of the hypothalamus, adrenocorticotropin (ACTH) secreted by corticotrophic cells of the anterior pituitary gland, and glucocorticoid hormones produced by the adrenal glands [5, 6]. Corticosteroids have a negative feedback effect on the secretion of ACTH and CT-releasing hormone into the bloodstream [4].

Glucocorticoids act practically on all tissues, mobilizing energy reserves, improving the cognitive function and increasing the cardiovascular activity, while suppressing the immune, reproductive and digestive functions. In a short-term period, some stress-related increases in the glucocorticoid levels lead to favorable physiological and behavioral changes necessary for an acute stress response. Unfortunately, a long-term elevation of glucocorticoid levels caused by chronic stress can have detrimental health consequences [7].

Women tend to make a stronger neuroendocrine response to acute stress, as evidenced by their elevated levels of CT-releasing hormone and ACTH compared with men after exposure to a range of stressors of various modalities [8]. On the other hand, the response to various psychological stimuli also depends on the gender, and, as a result, in men, neuroticism is associated with greater activity of the HPA axis, while in women, its activity may be reduced [8].

It is known that the growth of a malignant tumor has a significant and often sex-dependent effect on the body's regulatory axes [9]. Moreover we previously found that induced hypothyroidism had an inhibitory effect on the growth of Guerin's carcinoma and S45 sarcoma only in the females, but not in the males [10, 11].

Taking into account the fact that the main regulatory axes of the body are interconnected, participate in the maintenance of homeostasis under various pathological conditions, and their response to stressful effects and the growth of malignant tumors can be gender-specific, **the aim of our work** was to study the effect produced by induced hypothyroidism on changes in the functioning of the HPA axis in rats of both sexes with Guerin carcinoma.

## Materials and methods

The experiment was performed in 110 white outbred rats of both sexes with a individual body weight of 150–180 g. The animals were delivered by the Federal State Budgetary Institution Scientific Center for Biomedical Technologies at the Federal Medical and

Biological Agency (Andreevka branch, Moscow region). Laboratory animals were kept under the natural light conditions with free access to water and food. Work with animals was conducted in accordance with the rules of the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes (Directive 86/609/EEC) as well as in accordance with the International Guiding Principles for Biomedical Research Involving Animals and Order No. 267 "Approval of the rules of laboratory practice" dated June 19, 2003, issued by the Ministry of Health of Russia. Animals were manipulated in a box in compliance with the generally accepted rules of asepsis and antisepsis. Reference: Record No. 25/129 dated 27.10.2021 prepared by our Ethics Committee.

In our research work, we used a strain of Guerin's carcinoma, supplied by the Federal State Budgetary Institution "The Russian Cancer Research Center named after N.N. Blokhin" at the Ministry of Health of Russia. Material for transplantation was obtained from donor rats on days 12-16 of the tumor growth. Transplantation of Guerin's carcinoma to animals was carried out by standard subcutaneous injection of a tumor suspension under the skin of the right shoulder blade in a volume of 0.5 ml of cell suspension at a dilution of 1:10 in saline.

White outbred rats of both sexes received for 30 days a pharmacopoeial thyreostatic drug Merkazolil ("Akrikhin" Russia) 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, but however deterioration in the appearance of the skin and hairline, lethargy and drowsiness were recorded. Hypothyroidism in the animals was confirmed by determining the content of total thyroxine and thyroid-stimulating hormone in the blood serum, by radioimmunoassay using standard kits (Immunotech, Czech Republic) 30 days after taking the thyreostatic agent. The animals of each sex were divided into groups, each having 15 females and 15 males, as listed below: the main group covering the animals, which after reproduction of persistent hypothyroidism were subcutaneously transplanted with Guerin's carcinoma; reference group No. 1 covering the animals with hypothyroidism; reference group No. 2 covering the animals without hypothyroidism, with the independent growth of Guerin's carcinoma; the intact animals (10 females and 10 males) were considered as those showing the respective physiological norm.

The animals were decapitated (reference group No. 2 and the main group) after 18 days of the growth of Guerin's carcinoma. In 1% homogenates of the pituitary, the hypothalamus, and the adrenal glands, in blood serum and in 10% homogenates of the tumor and perifocal zone, the level of CT-releasing hormone (Cusabio, China), ACTH and cortisol (Immunotech, Czech Republic) was determined using standard ELISA and RIA methods.

Statistical analysis of the results was performed with the Statistica 10.0 software package. The data obtained were analyzed for their compliance of the distribution of signs with the normal distribution law using the Shapiro-Wilk test (for small samples). Comparison of quantitative data in groups was conducted with the use of the Student's t-test and Mann-Whitney test. Table data are presented as  $M \pm m$ , where M is the arithmetic mean, m is the stan-

dard error of the mean;  $p < 0.05$  was taken as the level of statistical significance.

**The results** of the study showed that in the intact animals, the content of CT-releasing hormone in the hypothalamus had certain gender differences: in the females it was 1.4 times higher than that recorded in the males. However, the contents of ACTH in the pituitary gland and blood and cortisol in the adrenal glands and in blood had no significant gender differences (see Table 1 given herein).

The influence made by hypothyroidism, the growth of inoculated Guerin's carcinoma and their combination had different effects on the studied parameters of the HPA axis.

Hypothyroidism in female rats caused a decrease in the level of CT-releasing hormone in the hypothalamus by 1.3 times, of ACTH in the pituitary gland by 1.4 times, of cortisol in the adrenal glands by 1.8 times

Table 1

Indicators of the HPA axis in the central and peripheral organs in rats with the growth of Guerin's carcinoma against the background of hypothyroidism

Indicators	CT releasing hormone (CRH) Hypothalamus (ng/g tissue)	ACTH Pituitary gland pg/g tissue	ACTH Serum pg/mL	Cortisol Adrenal gland nM/g tissue	Cortisol Serum nM/g tissue
Females					
Intact animals	$0,33 \pm 0,02$	$80,6 \pm 2,97$	$4,55 \pm 0,26$	$35,78 \pm 2,36$	$47,9 \pm 2,46$
Hypothyroidism	$0,25 \pm 0,02$ $P_1 - 0,0178$	$58,7 \pm 2,91$ $P_1 - 0,0000$	$5,96 \pm 0,42$ $P_1 - 0,0086$	$19,7 \pm 1,3$ $P_1 - 0,0000$	$8,6 \pm 0,71$ $P_1 - 0,0000$
Guerin's carcinoma	$0,37 \pm 0,02$	$69,0 \pm 3,18$ $P_1 - 0,0126$	$7,22 \pm 0,64$ $P_1 - 0,0005$	$47,67 \pm 3,19$ $P_1 - 0,0056$	$59,8 \pm 3,45$ $P_1 - 0,0090$
Main group	$0,26 \pm 0,02$ $P_1 - 0,0426$ $P_3 - 0,0014$	$52,5 \pm 2,14$ $P_1 - 0,0000$ $P_1 - 0,0001$	$2,39 \pm 0,21$ $P_1 - 0,0000$ $P_2 - 0,0000$ $P_3 - 0,0000$	$39,6 \pm 2,73$ $P_2 - 0,0000$	$55,7 \pm 3,24$ $P_2 - 0,0000$
Males					
Intact animals	$0,23 \pm 0,02$ $P_4 - 0,0009$	$79,9 \pm 7,1$	$6,12 \pm 0,38$ $P_4 - 0,0020$	$28,1 \pm 2,16$ $P_4 - 0,0230$	$52,43 \pm 6,14$
Hypothyroidism	$0,28 \pm 0,018$ $P_1 - 0,0424$	$39,76 \pm 2,5$ $P_1 - 0,0000$ $P_4 - 0,0000$	$4,77 \pm 0,39$ $P_1 - 0,0193$ $P_4 - 0,0479$	$16,7 \pm 1,57$ $P_1 - 0,0002$	$29,4 \pm 2,66$ $P_1 - 0,0018$ $P_1 - 0,0000$
Guerin's carcinoma	$2,2 \pm 0,18$ $P_1 - 0,0000$ $P_4 - 0,0000$	$46,0 \pm 2,3$ $P_1 - 0,0000$ $P_4 - 0,0000$	$60,86 \pm 4,44$ $P_1 - 0,0000$ $P_4 - 0,0000$	$65,32 \pm 7,04$ $P_1 - 0,0000$ $P_4 - 0,0000$	$88,1 \pm 7,01$ $P_1 - 0,0018$ $P_4 - 0,0000$
Main group	$0,16 \pm 0,015$ $P_1 - 0,0029$ $P_2 - 0,0000$ $P_3 - 0,0015$	$44,4 \pm 2,0$ $P_1 - 0,0000$ $P_4 - 0,0105$	$6,7 \pm 0,62$ $P_2 - 0,0137$ $P_3 - 0,0000$ $P_4 - 0,0000$	$44,25 \pm 3,33$ $P_1 - 0,0003$ $P_2 - 0,0000$ $P_3 - 0,0115$	$78,95 \pm 4,47$ $P_1 - 0,0016$ $P_2 - 0,0000$ $P_4 - 0,0002$

Notes: significant differences compared with the following: 1 – with intact animals; 2 – group with hypothyroidism; 3- group with Guerin's carcinoma; 4 – with females of the similar group.

and in serum by 5.6 times, but at the same time it increased in blood the ACTH level by 1.3 times ( $p<0.05$ ), compared with the intact animals (see Table 1 herein).

In the males with hypothyroidism, we did not reveal a change in the level of CT-releasing hormone in their hypothalamus, while we recorded a decrease in the level of ACTH in the pituitary gland and in blood by 2 times and 1.3 times, respectively, and a reduction in the cortisol concentrations in the adrenal glands and blood, by 1.7 times and 1.8 times ( $p<0.05$ ), respectively, compared with the indices in the intact animals.

In the females with independently developing Guerin's carcinoma, the level of CT-releasing hormone in the hypothalamus and ACTH in the pituitary gland had no significant differences with those recorded in the intact animals, however, ACTH in blood exceeded the norm by 1.6 times, and cortisol in the adrenal glands by 1.3 times ( $p<0.05$ ), without significant changes therein in blood.

In the males, the growth of Guerin's carcinoma was accompanied by an increase in the level of CT-releasing hormone in the hypothalamus by 9.6 times, but however by a decrease in the ACTH concentration in the pituitary gland by 1.7 times ( $p<0.05$ ), probably due to the active release thereof into the bloodstream, since the level of ACTH in blood was 9.9 times higher than the normal value. Also, an increase in the level of cortisol in the adrenal glands and blood by 2.3 times and 1.7 times ( $p<0.05$ ), respectively, was found.

Previously, we have shown that the growth of Guerin's carcinoma against the background of hypothyroidism in the females slows down that makes its impact on a prolongation in life spans, while inhibition of the tumor growth was revealed in the males only at the initial stages after the tumor cell transplantation, then the tumor progressed rapidly, and, as a result, the life spans did not differ from the respective indicators in the group with the normal state of the thyroid gland [10].

We revealed in the females of the main group a decrease in the level of CT-releasing hormone in the hypothalamus by 1.3 times and ACTH in the pituitary gland and in blood by 1.5 times and 1.9 times, respectively. At the same time, the content of cortisol in the adrenal glands and in blood in the females of the main group did not have significant differences from the data in the group of the intact animals. In the females of the main group, the content of CT-releas-

ing hormone in the hypothalamus and that of ACTH in the pituitary gland were recorded to be 1.4 times and 1.3 times lower than in case of the independent growth of Guerin's carcinoma ( $p<0.05$ ), respectively, but did not differ from the indicators in hypothyroidism. The level of cortisol in the adrenal glands and in blood in the females in the main group was 2 times and 6.5 times higher than the data recorded in hypothyroidism, respectively, but did not have significant differences compared with the indicators in case with the independent growth of Guerin's carcinoma.

In the males of the main group, similarly to the females, found was a decrease in the level of CT-releasing hormone in the hypothalamus by 1.4 times and of ACTH in the pituitary gland by 1.8 times ( $p<0.05$ ), without significant changes in the content of ACTH in blood, compared with the intact animals. At the same time, the level of cortisol in the adrenal glands and in blood in the males of the main group exceeded the norm by 1.6 times and 1.5 times ( $p<0.05$ ), respectively. In the males of the main group, the content of CT-releasing hormone in the hypothalamus was lower than that in hypothyroidism by 1.8 times, and by 13.8 times with the independent growth of Guerin's carcinoma, while the level of ACTH did not have significant differences compared with the indicators of both reference groups. The concentration of cortisol in the adrenal glands in the males of the main group was 1.5 times lower than that noted in case with the independent growth of Guerin's carcinoma ( $p<0.05$ ), but 2.6 times higher than in hypothyroidism, while the level of cortisol in blood of the males of the main group had no significant differences compared with the data recorded under the growth of Guerin's carcinoma, and it was 2.7 times higher as against the group with hypothyroidism.

Next, we studied the level of cortisol directly in the tumor tissue and its perifocal zone and identified how induced hypothyroidism affected the indicator in question in the males and the females. In the reference group, with the independent growth of Guerin's carcinoma, the level of cortisol in the tumor was 1.4 times higher in the males ( $p<0.05$ ), and its level in the perifocal zone was 1.4 times higher in the females ( $p<0.05$ ) (see Table 2 herein).

In the main group, the cortisol levels both in the tumor and in the perifocal zone were significantly higher in the males as against the data recorded in the females: 7.6 times and 2.4 times higher, respectively.



Table 2

Content of cortisol in the tumor and its perifocal zone in rats of both sexes with Guerin's carcinoma against the background of hypothyroidism

	Tumor Reference group	Tumor Main group	Perifocal zone Reference group	Perifocal zone Main group
Females	8,54±0,57	9,33±0,92	12,26±0,99 P <sub>3</sub> -0,0029	5,98±0,42 P <sub>2</sub> -0,0000 P <sub>3</sub> -0,0025
Males	12,1±1,12 P <sub>1</sub> -0,0084	71,1±6,18 P <sub>1</sub> -0,0000 P <sub>2</sub> -0,0000	8,9±0,71 P <sub>1</sub> -0,0100 P <sub>3</sub> -0,0225	14,6±1,0 P <sub>1</sub> -0,0000 P <sub>2</sub> -0,0000 P <sub>3</sub> -0,0000

Notes: there are significant differences in comparison with the following: 1 – with females; 2 – with the reference group; 3 – with indicators in the tumor

It turned out that the content of cortisol in the tumor in the females of the main group did not have significant differences from the parameters of the reference group, and in the perifocal zone its level was 2.1 times lower (see Table 2 given herein).

On the contrary, in the males of the main group, in the tumor samples, the level of cortisol exceeded the values in the reference group by 5.9 times and that in the perifocal zone by 1.6 times ( $p < 0.05$ ).

## Discussion

In our study, we noted that in the reference group, with induced hypothyroidism in the animals of both sexes, adrenal insufficiency developed, which was expressed in a decrease in the level of ACTH in the pituitary gland, of corticosteroids in the adrenal glands and blood, as well as of CT-releasing hormone in the hypothalamus only in the females. It is known that there may be several causes of adrenal insufficiency: the primary adrenal insufficiency in case of pathology that affects the adrenal gland, the secondary adrenal insufficiency as a result from a reduction in the level of ACTH released from the pituitary gland; and the tertiary adrenal insufficiency as a result from a decrease in the level of CT-releasing hormone in the hypothalamus [12]. That is, the hypothalamic dysfunction, such as low production of TH-releasing hormone and/or CT-releasing hormone, can cause both central hypothyroidism and adrenal insufficiency through cross-talk. This, in turn, can lead to systemic complications such as heart problems and elevated cholesterol levels in case of central hypothyroidism, as well as low blood pressure and electrolyte abnormalities in adrenal insufficiency [13].

At the same time, we did not reveal adrenal insufficiency in response to the independent transplantation

of a malignant tumor; and in the males, the growth of Guerin's carcinoma was accompanied by greater activation of the HPA axis, compared with the females, in all the studied links. In our investigations, we noted an increase in the level of glucocorticoids in the adrenal glands in the animals of both sexes in response to the independent growth of Guerin's carcinoma, while the females did not reveal any changes in the synthesis of pituitary ACTH and CT releasing hormone of the hypothalamus, whereas in the males, on the contrary, we observed the activation of the hypothalamus, and a surge-type release of ACTH by the pituitary gland into blood. That is, the independent growth of Guerin's carcinoma has demonstrated its sex-specific effect on the HPA axis.

The main group of animals turned out to be the most interesting, since the rats with induced hypothyroidism, which, as it was detected, also led to central adrenal insufficiency, were transplanted with a malignant tumor, which, in its independent growth variant, initiated the activation of the HPA axis. In addition, as we have shown earlier, in the females of the main group, a significant inhibition of the tumor was revealed with a prolongation of their life spans [10]. It was found that in the main group of the animals, despite a decrease in the content of CT-releasing hormone in the hypothalamus and ACTH in the pituitary gland in the animals of both sexes, the males showed an increase in the level of cortisol both in the adrenal glands and in their blood. Attention should be drawn to the fact that in the male rats the level of CT-releasing hormone in the hypothalamus, showing an increase by more than 9 times compared with the reference in the males with independently growing Guerin's carcinoma, in the animals of the main group sharply decreased even compared with the intact animals.

Our study bears witness to the fact that there are complex mechanisms of interactions of the body's regulatory axes, as well as to the fact of a significant influence of the gender and comorbid pathology on the response of the HPA axis. We assume that the inconsistency of the data found when studying the effect of hypothyroidism in cancer patients is probably associated with a complex mechanism of an interaction between endocrine pathology and the malignant process, as well as with the gender of patients and the characteristics of the malignant tumor. In our study, only in the male rats, hypothyroidism alone, which does not change the activity of hypothalamic neurons in relation to the production of corticotropic releasing hormone, in combination with a malignant tumor, has reduced the concentration thereof in the hypothalamus. There are some studies indicating that the activation of hypothalamic neurons, the production of ACTH by the pituitary gland, as well as the glucocorticoid negative feedback of the HPA axis can have not only gender-, but also age-related differences, and also experience changes upon the influence of hormonal imbalance [14]. In addition, it has been suggested that androgens act through the androgen receptor on the production of CT-releasing hormone in the hypothalamus [15].

Probably, the reflection of changes in the central and peripheral links of the HPA axis was the content of cortisol directly in the tumor and its surrounding area, which also had certain gender characteristics in the animals of the main group. It turned out that it was precisely in the males of the main group in the tumor, as well as in its perifocal zone, that the level of cortisol increased sharply, compared with the indices in the animals of the reference group. We assume that it is the gender specifics of the response of the HPA axis to the growth of a malignant tumor in the males that made it possible for the tumor not to inhibit its growth even in the animals under the conditions of hypothyroidism, while in the females of the main group their adrenal insufficiency of central origin could be one of the reasons for the inhibition of the growth of Guerin's carcinoma under the conditions of hypothyroidism.

Thus, we found that induced hypothyroidism led to adrenal insufficiency, apparently of the central origin. However, the growth of a malignant tumor against the background of hypothyroidism resulted in the accumulation of cortisol in the tumor and its perifocal zone only in the male rats, despite the inhibition of the

synthesis of CT-releasing hormone and ACTH by the hypothalamus and the pituitary gland, apparently due to the sex specifics of the response of the HPA axis to the growth of Guerin's carcinoma.

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