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DIFFERENCE IN HORMONAL RESPONSE OF MALE AND FEMALE MICE UPON L-THYROXIN AND PROPYLTHIOURACIL TREATMENT

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Abstract

Objective. To elucidate the relationship of the activity of hypothalamic-pituitary thyroid hormone axis upon experimental modulation of hyper- or hypothyroid status on female and male organism.

Methods. The study was performed on virgin 30 mature male mice and 33 mature female mice of the inbred line C3H-A. On male and female mice a model of experimental hyperthyroid and hypothyroid status was reproduced by the administration to L-thyroxin and propylthiouracil, accordingly. The blood samples from animals were assayed for TSH, T₄ (total) and prolactin.

Results. In the hyperthyroid male mice, the level of T₄ (total) was significantly higher as compared to the hypothyroid and control groups. No difference in the level of TSH and prolactin was found between the hyperthyroid and the hypothyroid groups. In the hypothyroid female mice, the level of TSH and T₄ (total) was significantly lower and the level of prolactin was significantly higher as compared to the hyperthyroid and the control groups.

Conclusion. The male and female mice responded in different ways upon the administration to L-thyroxin and propylthiouracil on the level of TSH, T₄ (total) and prolactin.

Keywords: hyperthyroid and hypothyroid status, hormones, L-thyroxin, propylthiouracil, C3H-A mice

РАЗЛИЧИЕ В ГОРМОНАЛЬНОМ ОТВЕТЕ У САМОК И САМЦОВ МЫШЕЙ ПРИ ВОЗДЕЙСТВИИ L-ТИРОКСИНА И ПРОПИЛТИОУРАЦИЛА

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Резюме

Цель. Изучить дальнейшую взаимосвязь в активности гормонов гипоталамо-гипофизарно-тиреоидной оси в женском и мужском организме при экспериментально вызванном гипо- и гипотиреозе у лабораторных мышей.

Методика. Исследование было проведено на 33 девственных самках и 33 самцах инбредной линии C3H-A мышей. На животных была воспроизведена модель экспериментального гипер- и гипотиреозидного состояния при использовании L-тироксина и пропилтиоурацила, соответственно. У животных были взяты образцы крови для анализа на ТТГ, Т₄ (общий) и пролактин.

Результаты. У гипертиреозидных самцов уровень общего Т₄ был значительно выше как по сравнению с гипотиреозидной, так и контрольной группой. У самцов никаких различий между уровнем ТТГ и пролактина обнаружено не было. У самок в гипертиреозидной группе уровень ТТГ и общего Т₄ был значительно ниже, а уровень пролактина был значительно выше по сравнению с гипертиреозидной и контрольной группами. У самок в гипертиреозидной группе уровень общего ТТГ был значительно выше по сравнению с гипотиреозидной и контрольной группами. Никаких различий по уровню ТТГ и пролактина не было обнаружено между гипер- и гипотиреозидной группами.

У самок в гипотиреодной группе уровень ТТГ и общего Т₄ был значительно ниже по сравнению, а уровень пролактина значительно выше как в сравнении с гипертиреодной, так в сравнении с контрольной группами.

Заключение. Самки и самцы мышей по разному реагируют на применение L-тироксина и пропилтиоурацила, что регистрируется по уровню ТТГ, общего Т₄ и пролактина.

Ключевые слова: гипер- и гипотиреодный статус, гормоны, L-тироксин, пропилтиоурацил, мыши линии СЗН-А

Introduction

The state of physiological functions of the whole organism, its vital activity and adaptation to various changes in the surrounding and internal environment is controlled by neurohumoral mechanisms. The main place in the implementation of those mechanisms belongs to hormones [1]. The main purpose of hormones is to fine-tune the intensity of metabolic processes. This ensures the constancy of homeostasis. Hormones control the higher integrative functions of the brain interacting with neurotransmitter systems [20]. Multifunctional relationships of hormones with the nervous system provide the formation of mental status, emotions, behavior and memory [25, 34]. Violation of the endocrine balance contributes not only to metabolic disorders [36], but the appearance and development of disorders in behavior [26]. It can be assumed with a high degree of certainty that both the regulation of metabolic changes and the cognitive function of the brain depend on the functional activity of the hypothalamic-pituitary-thyroid system [8, 22]. The insufficiency of functional activity of this system can significantly affect the developing organism and lead to a violation of embryogenesis which in its turn further leads to mnemonic and behavioral disorders [2]. A number of diseases lead to a pathology of the thyroid gland [21, 32]. For example, it is shown that autoimmune thyroiditis is one of the most common diseases in children and adolescents. This is the most common cause of acquired hypothyroidism in childhood and adolescence [33].

It has been established that thyroid hormone deficiency leads to a slowing of metabolic processes and weight gain. Otherwise an excessive level of these hormones of the peptide origin contributes to increased metabolism and weight loss [11, 35]. By the condition of the skin it is also quite possible to recognize people suffering from hypo- or hyperfunction of the hypothalamic-pituitary-thyroid system [18, 31]. The experimental data obtained show that the hypothalamic-pituitary-thyroid system is closely related to the hypothalamic-pituitary-adrenal system. The effect of thyroid hormones on the secretion of melanocyte-stimulating hormone was detected in fish. In experimental hyperthyroidism in carp (*Cyprinus L.*) in the middle part of the pituitary gland an increase in the level of α -melanocyte-stimulating hormone and mRNA of proopiomelanocortin was observed. Whereas the basal level of cortisol in the blood plasma was decreased [14]. At the same time a clinically relevant problem is currently the relationship between the activity of thyroid gland and prolactin. Hyperprolactinemia occurs in a third of children with subclinical hypothyroidism and is considered an important indication for treating subclinical hypothyroidism in children [28]. It is also a well-known fact that hyperprolactinemia is strongly associated with osteoporosis.

Pharmacological intervention by dopamine agonists reverses the bone loss [24]. Wherein the level of thyroid hormones can be normal but the level of thyroid-stimulating hormone is lowered [4]. In pregnant rats which received excessive amounts of iodine the level of prolactin decreased. At the same time the pups dramatically lost weight [10]. Thus despite some progress in studying the relationship between the hypothalamic-pituitary-thyroid axis and prolactin much remains unclear. In this regard we carried this study in inbred C3H-A mice of both sexes to elucidate further the regulatory activity of hypothalamic-pituitary-thyroid axis under the experimental impact.

Methods

The study was performed on 30 mature male and 33 mature virgin female mice of the inbred line C3H-A. The animals were obtained from the nursery «Rappolovo, leningradskaya oblast'». At the beginning of the study the age of laboratory animals was 40±0 days, their weight – 18-20 g. The experiment was being performed for 22 weeks from January 29 till the 1st of July of 2018 year. After receiving from the nursery before the experiment began the animals underwent an 18-day adaptation period during which the behavior and general condition of each animal was evaluated twice a day. Males and females were kept in

separate cages and in each case were randomly divided into three groups. In males the three groups were formed equally and each included 10 animals – hyperthyroid, euthyroid (control) and hypothyroid. In females the three groups were formed as follows: hyperthyroid, euthyroid (control) and hypothyroid – 15, 8 and 10 animals, respectively. The animals were maintained at constant temperature ($23\pm 1^\circ\text{C}$), 12:12-h light-dark cycle schedule and on standard food ration and water *ad libitum*. On males and females of the first group a model of experimental hyperthyroid status was reproduced [16]. For this purpose, the animals were intraperitoneally injected L-thyroxin in the dose of 200 μg per 100 g of weight. L-thyroxin was diluted with physiological saline to a concentration of 0.01% and administered throughout the experiment every other day with the volume of each injection being about 40 μl . On animals of the second group a model of experimental hypothyroid status was reproduced. The water in the reservoir was replaced with a 0.5% solution of propylthiouracil. According to the calculated data each animal received approximately 1.9-2.2 mg of propylthiouracil per 100 g of body weight per day. The mice of the third group made up the control group. For the correctness of the experiment the animals of the second and third groups were injected with 40 μl of 0.9% saline once every two days. By the 22nd week of the experiment all animals were decapitated and murine blood was received *ex tempore*.

All blood samples were centrifuged at $1.000\times g$ for 10 min at 10°C , serum was aliquoted and stored at -70°C until shipment to AlkorBio TiroidIFA-TTG (TSH), DRG Diagnostics-T₄ (T₄ total) and AlkorBio IFA-Prolaktin assays (enzyme-linked immunosorbent assay). All kits for enzyme-linked immunosorbent assay were purchased from AlkorBio Company, St. Petersburg, Russia.

All data are reported as means \pm s.e.m. Statistical analysis was performed using Student's t-test. Differences were considered statistically significant at $P<0.05$.

Results

Male mice. As it is shown (table 1) the mean value for TSH among males of the first hyperthyroid group was 0.25 ± 0.135 $\mu\text{IU/ml}$. In the control and the hypothyroid groups, the mean values for TSH were 1.979 ± 0.940 and 0.176 ± 0.120 $\mu\text{IU/ml}$, respectively. The difference in the level for TSH was significant between the hypothyroid and the control groups at $P<0.05$. The difference in the level for TSH was also significant between the hyperthyroid and the control groups at $P<0.05$. No difference was found between the hypothyroid and the hyperthyroid males. Measuring the level of T₄ (total) immediately attracts the fact that its level in hyperthyroid female mice is significantly higher than in the other groups. This fact is evident because that group received L-thyroxine. So the difference is significant relative to the control group and the group administered to PTU at $P<0.001$ for both cases. The difference for T₄ (total) was also revealed between the control group and the hypothyroid one at $P<0.05$. If we compare the results between the hyperthyroid group and the hypothyroid one by the level of prolactin (PRL), the same trend is observed for the TSH level. No difference was detected between those groups. However, the control mice had the mean value for the level of PRL as 443.792 ± 196.226 mIU/l. The difference was significant as compared to the level of PRL for the hyper- and the hypothyroid groups at $P<0.001$ for both cases (table 1).

Table 1. The level of thyroid-stimulating hormone, thyroxin and prolactin in male C3H-A inbred mice

The experimental condition	TSH, $\mu\text{IU/ml}$	T ₄ (total), $\mu\text{g/dl}$	Prolactin, mIU/l
The hyperthyroid group (first group)	$0.257\pm 0.135^*$	$27.312\pm 0.975^{**}$	$65.411\pm 34.500^{**}$
The control group (second group)	1.979 ± 0.940	7.570 ± 0.550	443.792 ± 196.226
The hypothyroid group (third group)	$0.176\pm 0.120^*$	$4.517\pm 0.815^*$	$72.423\pm 42.500^{**}$

Notes: the difference significant at $P<0.05$ if (*) and $P<0.001$ if (**). See explanation in Results

Female mice. It is noteworthy considering the results on the level TSH in female mice that the mean value for this hormone was found to be 1.589 ± 0.369 $\mu\text{IU/ml}$ in the mice administered to PTU (table 2).

Table 2. The level of thyroid-stimulating hormone, thyroxin and prolactin in female C3H-A inbred mice

The experimental condition	TSH, $\mu\text{IU/ml}$	T ₄ (total), $\mu\text{g/dl}$	Prolactin, mIU/l
The hyperthyroid group (first group)	$0.323\pm 0.105^{**}$	$26.35\pm 1.810^{**}$	$102.760\pm 0.0140^*$
The control group (second group)	$0.912\pm 0.191^*$	9.444 ± 0.880	298.655 ± 48.444
The hypothyroid group (third group)	$1.589\pm 0.369^*$	$5.162\pm 0.603^{**}$	$408.439\pm 70.943^{**}$

Notes: the difference significant at $P<0.05$ if (*) and $P<0.001$ if (**). See explanation in Results

This value was significantly higher relatively to the control and the hypothyroid groups at $P<0.05$ and $P<0.001$, respectively. A significant difference was also detected between the control group and the hypothyroid one at $P<0.05$. No surprises were identified by the level of the total T_4 among the groups studied. The mean value of total T_4 was higher in hyperthyroid female mice at 26.35 ± 1.81 $\mu\text{g/dl}$. As is expected the significant difference was registered between the hyperthyroid group and the control and the hypothyroid groups at $P<0.001$ for both cases. The mean value of PRL level assayed in the group administered to PTU was 408.439 ± 70.943 mIU/l whereas it was 102.76 ± 0.014 mIU/l in third group of female mice. So the significant difference between the hypothyroid group and the hyperthyroid one was evident at $P<0.001$. It is noteworthy that no difference was found between the second and the third groups of female mice. Meanwhile the difference for PRL was elucidated between the control and the hyperthyroid groups at $P<0.05$.

Male and female. Comparing the results for TSH, T_4 (total) and PRL the attention is drawn to the fact that the level of T_4 (total) was higher in the control group of female mice as compared to the one of male mice at $P<0.05$ (table 3).

Table 3. The comparative data for the level of thyroid-stimulating hormone, thyroxin and prolactin in male and female C3H-A inbred mice

The experimental condition		TSH, $\mu\text{IU/ml}$	T_4 (total), $\mu\text{g/dl}$	Prolactin, mIU/l
The hyperthyroid group (first group)	male	0.257 ± 0.135	27.312 ± 0.975	65.411 ± 34.500
	female	0.323 ± 0.105	26.35 ± 1.810	102.760 ± 0.0140
The control group (second group)	male	1.979 ± 0.940	7.570 ± 0.550	443.792 ± 196.226
	female	0.912 ± 0.191	$9.444\pm 0.880^*$	298.655 ± 48.444
The hypothyroid group (third group)	male	0.176 ± 0.120	4.517 ± 0.815	72.423 ± 42.500
	female	$1.589\pm 0.369^{**}$	5.162 ± 0.603	$408.439\pm 70.943^{**}$

Notes: the difference significant at $P<0.05$ if (*) and $P<0.001$ if (**). See explanation in Results

The significant difference between the male and female mice of the hypothyroid groups was detected at $P<0.001$. The same level of significant difference was elucidated for the level of prolactin in the hypothyroid groups.

Discussion of results

TSH is expressed in the thyrotrophs of the anterior pituitary gland, which in turn induces the synthesis and release of thyroid hormones by the follicular cells of the thyroid gland. Thyroxine is the predominant secretory product of the thyroid gland, whereas only 20% of the circulating T_3 are secreted directly by the thyroid. In the periphery T_4 is deiodinated supplying roughly 80% of the circulating triiodothyronine. Reciprocally, synthesis and release of T_4 and T_3 are inhibited when hormone levels in plasma exceed a pre-set level.

It is considered that hypothyroidism increases synthesis of TSH and thyroid hormone uptake transporters in plasma membranes of target cells and circulating TSH levels. Otherwise hyperthyroidism decreases TSH synthesis. So there is a precise physiological feedback mechanism for regulation of the level of hormones of the hypothalamic-pituitary-thyroid axis. We found that the levels of TSH and PRL were significantly decreased in the hyperthyroid female mice. The levels of TSH and prolactin were significantly increased in the hypothyroid group. So the hypothalamic-pituitary-thyroid axis of female mice responded in ordinary way upon administration to agents which either replace the functioning of the thyroid gland or inhibit its function. The hypothalamic-pituitary-thyroid axis may also control PRL secretion because lactotropic cells (lactotrophs, PRL-secreting cells) also possess receptors, for example, to thyrotropin-releasing hormone and further to TSH.

Clinical data support such a link. Subclinical hypothyroidism with high TSH levels and even normal thyroid hormone levels is accompanied by increased PRL secretion [19]. Furthermore, hyperprolactinemia was detected in about 20% of patients with subclinical hypothyroidism and in 39-57% in overt hypothyroidism [3]. Average TSH levels were higher in hyperprolactinemic women [23, 29, 30]. Much earlier it was assumed that increased production of PRL in hyperthyroid women may be due to increased clearance of PRL in hyperthyroidism [9]. Hypothyroidism, not hyperthyroidism, may be linked to infertility although hyperthyroidism also causes menstrual irregularities. These irregularities, however, rarely lead to infertility [7]. A bit controversial results were obtained for female mice. In fact, natural differences in thyroid hormone levels in male and female have recently been elucidated in long-term

clinical study of newborn male and female [17]. So the unequal hormonal response of male and female mice treated with L-tyroxin and PTU is quite possible. For example, the level of TSH was found to be higher in the control male mice as compared to the control group of female. It may be explained in this way that thyrotropin-releasing hormone is reliably proved to be abundantly expressed in the male reproductive tract, with the highest expression being in the epidymis, prostate and testis. These tissues contain mainly so-called TRH-like peptides and a small amount (25%) of authentic TRH [15]. These peptides appear to form a paracrine network possibly regulating prostatic growth and normal growth and function of the gonads [6]. Further, TRH properly and similar peptides can stimulate higher level of TSH in male. At first glance, the results obtained by the level of hormones in response to the administration of L-thyroxin and PTU seem contradictory. They can reflect more a complicated mechanism of feedback regulation of the hypothalamic-pituitary-thyroid axis under these agents treatment. Lactotropic cells in male are developed every week. Then the hormonal imbalance provoked by L-thyroxin can just inhibit further the minimal activity of PRL-secreting cells or disrupt in male mice.

The unexpectedly low level of TSH in male mice as compared to the female ones is explained more difficult. However, the response of male mice to L-thyroxin is in natural way. There is no difference but an obvious tendency to decreasing total T_4 upon treatment by L-thyroxin exists. The particular glial cells in the third ventricle of the brain which are called tanycytes are enriched by iodothyronine deiodinase type II (DIO2). DIO2 converts T_4 into T_3 which are much more active than T_4 . There is a body of evidence that this iodothyronine deiodinase type II activity is one of main origin of T_3 for CNS [13]. But DIO2 serves to convert a variable rate of intracellular T_4 to T_3 independent of circulating in blood levels. The cytoplasmic pool of T_3 includes therefore both T_3 from the plasma and T_3 generated by DIO2. The activity of this endoplasmic reticulum enzyme can be regulated by ubiquitination and is influenced by the thyroid state (increased in hypothyroidism and decreased in hyperthyroidism) [5]. It can be one of the explanations of decreased TSH level in PTU treated male C3H-A mice. It is very probable that the feedback mechanism is disrupted for this case. But there is a good question, why the female C3H-A mice responded to PTU administration by elevated level of TSH. For this case there is another explanation. It is well established that the activity of tanycytes is under strict hormonal control. Tanycytes express a variety of estrogen receptors, and for example cultured rodent tanycytes have been shown to rapidly retract their processes when exposed to estradiol. Then the activity of tanycyte decreases and conversion of T_4 to T_3 down-regulates [12, 27].

Conclusion

The male and female mice responded in different ways upon the administration to L-thyroxin and propylthiouracil on the level of TSH, T_4 (total) and prolactin. Neuroendocrine system is very delicate entity. In spite of apparent evidence and knowledge about gender hormonal differences the nuances of hormonal regulation in male and female are still far from complete understanding and it requires further intensive study.

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