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MORPHOLOGY AND PATHOMORPHOLOGY

Changes in Secretion of the Thyroid and Pituitary Glands with a Gradual Decrease in Deuterium Body Content

N. V. Yaglova, S. S. Obernikhin, E. P. Timokhina, V. V. Yaglov, and S. V. Nazimova

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We studied changes in the secretion of thyroid hormones and pituitary thyroid-stimulating hormone (TSH) in young mature male Wistar rats during gradual decrease in deuterium body content. The rats received deuterium-depleted water ([D]=10 ppm) instead of tap water for 21 days. As soon as after 1 day, an increase in the secretion of thyroid hormones was recorded. On day 14, secondary hypothyroidism due to a sharp decrease in TSH secretion by the pituitary gland was found. By day 21, secretion of the thyroid hormones increased, and the reciprocal dependence between the concentrations of thyroid hormones and TSH was restored. Thus, the thyroid gland showed a higher sensitivity to a decrease in the deuterium content in the body than the hypothalamic–pituitary complex. The second difference was in type of response: activation of the secretory processes in the thyroid gland and a transient decrease in the secretory activity of pituitary gland thyrotropes to a decrease in deuterium content.

Key Words: *deuterium; thyroid; pituitary; thyroid hormones*

The role of deuterium in the metabolism and physiology remains poorly understood due to insufficient studies and inconsistency of their results [1-3]. Nevertheless, there is no doubt that deuterium plays an important role in the body because it regulates cell proliferation, apoptosis, and senescence [3-5]. The least studied aspect of the biological role of deuterium is its effect on the endocrine system, the most important regulator of physiological functions. In our previous studies, we found that changes in deuterium intake (both increase and decrease) cause a pronounced response of the thyroid gland within a day [6]. These results suggest that deuterium content in the body can modulate secretory activity of the gland.

Laboratory of Endocrine System Development, A. P. Avtsyn Research Institute of Human Morphology, A. P. Petrovsky Russian Research Center of Surgery, Moscow, Russia. ***Address for correspondence:*** yaglova@mail.ru. N. V. Yaglova

Non-pharmacological correction of metabolic and functional disorders, including endocrine glands disorders, are now a promising field of research. The thyroid gland is the most vulnerable part of the endocrine system because it is very sensitive to various environmental factors, both chemical and physical [7,8]. This feature contributes to the growth of thyroid pathology, which is registered worldwide [9,10]. That is why investigations of the role of deuterium in the thyroid gland functioning is of theoretical and practical interest.

The aim of the study was to evaluate secretion of thyroid hormones and pituitary thyroid-stimulating hormone (TSH) during gradual decrease in the deuterium content in the body.

MATERIALS AND METHODS

The experiment was performed on 3-month-old male Wistar rats (n=20) weighing 200-220 g. The rats were

housed in local vivarium at room temperature and given a pelleted standard chow. Consumption of deuterium-depleted water with [D]=10 ppm (manufactured at the B. P. Konstantinov St. Petersburg Nuclear Physics Institute, National Research Center "Kurchatov Institute") instead of tap water for 21 days was used as a method of reduction of deuterium body content. The control rats (n=10) consumed distilled water with deuterium content [D]=146 ppm, identical to tap water. Body weight and amount of consumed water were measured daily. Body weight gain by the end of the experiment was 81±5 g in the control group and 71.5±5.5 g in the experimental group. The mean water intake in the control and experimental groups was 120.7±6.1 and 123.4±4.2 ml/kg, respectively. Thus, consumption of deuterium-depleted water did not affect the growth of the animals and water intake.

The blood was taken with a syringe from the caudal vein on days 1, 3, 7, 14, and 21 of the experiment. Serum concentrations of total thyroxine (T4) and its free fraction, total triiodothyronine (T3) and its free fraction, and TSH were measured by ELISA according to manufacturer's protocols (Cusabio, BioVendor).

The data were processed using Statistica 7.0 software (StatSoft, Inc.). Normally distributed quantitative data were expressed as M±SEM. Comparison of the independent groups was performed using Student's t test. The differences were significant at p<0.05.

RESULTS

After the first day of the experiment, an increased concentration of T4 was revealed in rats that consumed deuterium-depleted water. The level of free T4, on the contrary, was decreased. The concentrations of T3 and its free form showed a slight decreased compared to the control. The TSH level was significantly reduced (Fig. 1). After 3 days, T4 and T3 serum returned to normal, but the concentrations of free hormone fractions increased significantly and exceeded the control values. The level of TSH increased significantly, but did not exceed the control one (Fig. 1).

After one week of drinking deuterium-depleted water, the level of all thyroid hormones corresponded to the values of the control group; the TSH level was below the control by 50% (Fig. 1). After 14 days, the concentration of all thyroid hormones, especially of total T4 and T3 significantly decreased in rats that consumed deuterium-depleted water; the TSH level was 3-fold lower than the control values (Fig. 1). On day 21, the thyroid status returned to normal; the concentrations of T4 and its free form, as well as T3, corresponded to the control levels, and the concentration of free T3 even exceeded the corresponding value in the control group. The TSH concentration was below the control levels (Fig. 1).

These results suggest that the thyroid gland is very sensitive to shifts in the deuterium content. The increase in the secretion of hormones by the thyroid gland in response to reduced deuterium intake observed on day 1 fully confirm our previous results [6]. It can be concluded that the thyroid gland mainly responds to changes in deuterium content in the blood and lymph, because in solid tissue these changes develop much later due to slower substitution of deuterium by protium in biopolymers [11,12]. The mechanisms of increased secretion of thyroid hormones in this case are poorly understood. It is unlikely that the enhanced release of hormones 1 day after the beginning of consumption of deuterium-depleted water could be evoked by the kinetic isotope effect, *i.e.*, an increase in the rate of cleavage of T4 and T3 residues due to the substitution of deuterium with protium in thyroglobulin molecules [13].

A gradual decrease in deuterium content in the body was found to influence the functioning of the entire hypothalamic–pituitary–thyroid axis. Reciprocal changes in the secretion of thyroid hormones and pituitary TSH up to 7 days were due to the negative feedback, but starting from the 7th day, signs of selective suppression of the secretory activity of pituitary thyrotropic cells appeared. This dysfunction could result from direct effect of deuterium depletion on cells of the adenohypophysis, or indirectly from a decreased thyroliberin secretion by the hypothalamus. This provoked the development of typical secondary hypothyroidism on day 14 in rats that consumed deuterium-depleted water. The changes in the thyroid profiles observed on day 21 attested to recovery of the pituitary gland function and the negative feedback principle. The mechanisms of restoration of the pituitary function in this case are unclear and require research.

Secretion of thyroid hormones has been shown to have circadian and infradian 3-day rhythms [14,15]. Infradian changes in hormone secretion were also observed in our study from days 1 to 7 in the control group. The free fractions of the hormones demonstrated similar fluctuations. In rats receiving deuterium-depleted water, the serum contents of total T3 and T4 were less variable. Measurements of free T4 and free T3 showed that the level of hormones available for penetration into the cells became more stable with decreasing deuterium content in the body. In the present study, no facts indicating either a possible decrease in the production of plasma binding proteins, or changes in their binding capacity were obtained. It is possible that with decreasing deuterium intake, the parameters of hormone secretion rhythmicity change,

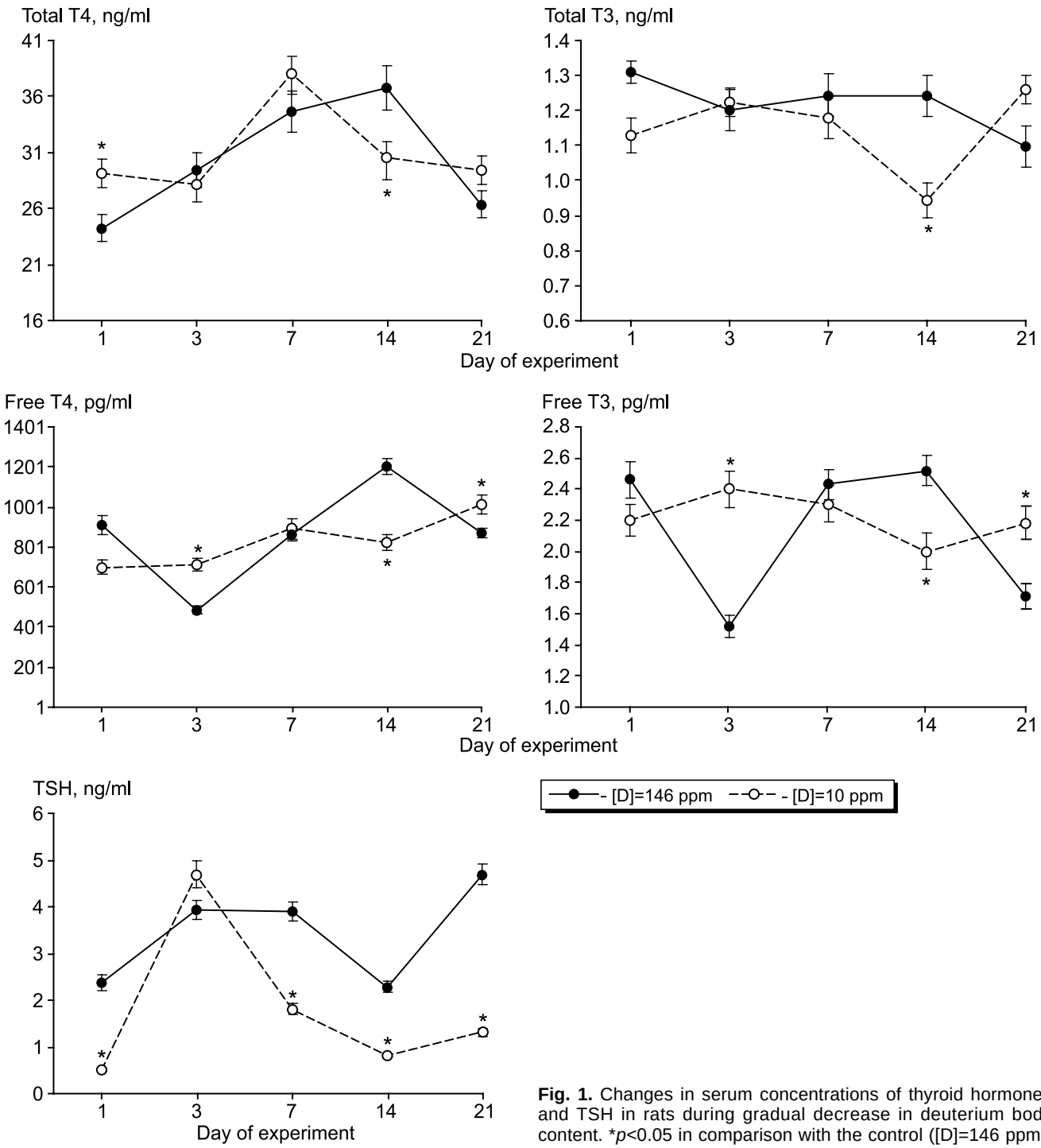

Fig. 1. Changes in serum concentrations of thyroid hormones and TSH in rats during gradual decrease in deuterium body content. *p<0.05 in comparison with the control ([D]=146 ppm).

and the lower variability in the concentrations of free fractions of thyroid hormones indicates these shifts, which requires additional studies.

Thus, the decrease in deuterium body content changes the activity of hormone secretion by the thyroid and the pituitary glands. The thyroid gland is more sensitive to deuterium depletion than the hypothalamic–pituitary complex that responded later. This indicates different sensitivity of the endocrine glands to the content of deuterium. An important difference is that deuterium depletion activates secretory processes in the thyroid gland and increases the production of hormones, whereas in the pituitary gland, on the contrary, secretory activity of thyrotropic cells transiently decreases.

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