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Experimental Investigation of Acute and Delayed Renal Effect of Exogenous Thyroxine

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Abstract

Introduction: Normally, thyroid hormones are important regulators of metabolic processes in mammals.

Aim: To study the renal function of rats in a single dose of thyroxine, as well as analysis of remote renal effects of experimental hyperthyroidism.

Materials and methods: The study used inbred male rats massing 200-250 g, the experimental hyperthyroidism caused a 10-day daily intragastric sodium salt of thyroxine, suspended in 1% of starch gel. Thyroxine produced by Berlin Chemie (Germany) was administered to 20 micrograms per 100 g of body mass. The function of the kidneys of rats were studied under conditions of induced diuresis induced by water stress, 24 h after the single purpose of thyroxine, 24 h after the completion of the 10-day administration of the hormone, as well as 14 days after completion of the 10-day administration of the hormone. A control group of animals using appropriate age and body mass euthyroid male rats treated with the gel containing no hormone.

Results: Studies have shown that under conditions of water stress within 24 h after a single injection of thyroxine (Table 1) there is no significant variation in urine output, expressed in absolute values per 100 g of body mass of the animal, as well as the ratio of urine to the volume fluids (relative diuresis).

Conclusions: It is shown that the duration of the appointment in rats' thyroxine promotes the further strengthening potassuresis. The magnitude of the glomerular filtration rate is reduced, and the rates of sodium excreted by the kidneys are quite moderate.

1) Found that 14 days after cessation of thyroxine to rats is not observed significant variations in the values of glomerular filtration rate and potassium excretion by the kidneys, however, the rate of sodium excreted by the kidneys clearly exceed the benchmarks.

2) Found that a single injection of thyroxine to rats has no effect on the magnitude of diuresis, but induces a distinct increase in sodium excretion by the kidneys, stimulates potassuresis and lowers the glomerular filtration rate.

Keywords: Homeostasis; Kidney; Rat; Experimental hyperthyroidism; Thyroxine

Introduction

Normally, thyroid hormones are important regulators of metabolic processes in mammals [1,2]. With the ability to regulate transcription of specific proteins, iodothyronine ensure the maintenance of optimal level of metabolic processes [3,4]. Furthermore, the results of modern studies show direct evidence of the importance of the role of thyroid hormones in the processes of adaptation to the adverse geophysical factors [5]. In the literature discussed ways of involving iodothyronine formation in response to changes in the parameters of homeostasis [4,6,7].

However, the flow of thyroid diseases are accompanied by violations of water-salt metabolism, pathophysiological mechanisms which require further study [8,9,10]. Published research results underscore the relevance of the analysis renotrop effects of thyroid hormones, as well as provide direct evidence for regular changes of homeostatic kidney function in hyperthyroidism [8,9,11]. Some review publications suggests that the symptoms characteristic of thyreopathology, including renal, can be eliminated by successful correction of the thyroid status of the organism [9,11,12]. Thus, the findings presented in the cited sources suggest that pathological changes in the synthesis and secretion of thyroid hormones due to hypo-or hyperfunction of the secretory epithelium of the thyroid gland, the main cause that determines the dynamics of changes of the kidneys and the intensity of the renal manifestations symptoms, accompanying thyreopathology. Therefore, efficient treatment of the underlying disease creates a favorable background correction dysfunction of internal organs, including kidneys. Meanwhile, in the literature, there are some reports that the restructuring of the kidney is registered within the first few hours after a single dose of an animal of exogenous thyroxine [13], with chronic experimental hyperthyroidism can cause irreversible structural changes of renal parenchyma, not only resolves the correction of thyroid status [11,14].

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The aim of presented work was to study the renal function of rats in a single dose of thyroxine, as well as analysis of remote renal effects of experimental hyperthyroidism.

Materials and Methods

The study used inbred male rats massing 200-250 g, the experimental hyperthyroidism caused a 10-day daily intragastric sodium salt of thyroxine, suspended in 1% of starch gel. Thyroxine produced by Berlin Chemie (Germany) was administered to 20 micrograms per 100 g of body mass. The function of the kidneys of rats were studied under conditions of induced diuresis induced by water stress, 24 h after the single purpose of thyroxine, 24 h after the completion of the 10-day administration of the hormone, as well as 14 days after completion of the 10-day administration of the hormone. A control group of animals using appropriate age and body mass euthyroid male rats treated with the gel containing no hormone. Water load was performed by intragastric administration held firm and boiled tap water in the amount of 5% of body mass. Then the rats were placed in individual metabolic cages equipped for urine collection. Urinary collected within 2 hours. From the experiment, animals were withdrawn by decapitation under light ether anesthesia. Blood stabilized with heparin, and after centrifugation (3000 rpm, 15 min), blood plasma was collected for further analysis. The concentration of K + and Na + in urine was determined using the method of flame photometry. Creatinine blood plasma and urine was determined photometrically on a spectrophotometer "SF-46" (Russia) in the reaction with picric acid. Performance of creatinine clearance, absolute excretion of cations by the kidneys, taking into account the body mass of animals, as well as the magnitude of the standardized per unit volume of glomerular filtrate excretion of ions were calculated according to previously described methods [15-17].

Results

Studies have shown that under conditions of water stress within 24 h after a single injection of thyroxine (Table 1) there is no significant variation in urine output, expressed in absolute values per 100 g of body weight of the animal, as well as the ratio of urine to the volume fluids (relative diuresis).

At the same time, compared with a group of euthyroid animals, there is a moderate decrease in the values of a marker of glomerular filtration rate - Creatinine clearance. In our opinion, it is important to emphasize that 24 h after a single destination rats hormone logged more than twofold increase in the level of sodium in the urine and increased excretion of sodium by the kidneys. Along with this, in this group of rats a statistically significant increase in the value of concentration of potassium in the urine and increase the allocation of kidneys of potassium. Increased natriuresis and kaliyuresis under the influence of a single dose of thyroxine is confirmed by the results of calculations of values of kidney excretion of sodium and potassium, standardized largest excretion of endogenous creatinine. Note that these changes in renal transport of cations accompanied by two-fold increase in the values of the sodium / potassium ratio in urine compared with control values.

Table 2 presents the results of a study of kidney hyperthyroid rats 24 h after the 10-day appointment thyroxine.

Results established that the duration of the appointment of thyroxine to rats does not lead to noticeable changes in the value of diuresis. However, in this group of rats the quantity of creatinine clearance remains at a lower level compared with that in the group of euthyroid controls. It is shown that during experimental hyperthyroidism is also characterized by higher values of the concentration of sodium in the urine and increasing loss of renal cation. However, in this series of experiment the intensity of the natriuresis is markedly lower than in the group of rats exposed to occasional violations of thyroid status of an organism a single injection of thyroxine. Given the relatively low rates of natriuresis in experimental hyperthyroidism, we calculated the rates of sodium excretion by the kidneys, standardized by the value of glomerular filtration rate, reflecting the degree of functional activity of the tubular epithelium. The calculation results showed a significant

Investigated options	Control, (N = 15)	Hyperthyroidism, (n=15)
Diuresis, ml/h/100 g of body mass	2.0 ± 0.1	2.1 ± 0.1
Relative diuresis, %	80.8 ± 3.4	82.7 ± 3.9
Creatinine clearance, µl / min	609 ± 23	413 ± 19 p<0.01
The concentration of sodium in the urine, mmol / l	0.21 ± 0.03	0.56 ± 0.08 p<0.01
Sodium excretion, µmol for 2 hours	0.84 ± 0.10	2.30 ± 0.18 p<0.01
The concentration of potassium in the urine, mmol / l	4.87 ± 0.19	6.62 ± 0.22 p<0.01
The excretion of potassium, µmol for 2 hours	19.68 ± 0.36	27.81 ± 0.28 p<0.01
Sodium / potassium ratio of urine, units.	0.051 ± 0.008	0.102 ± 0.019 p<0.01
Sodium excretion standardized to creatinine excretion per 100 g of body mass	0.30 ± 0.01	0.49 ± 0.03 p<0.01
The excretion of potassium standardized by creatinine excretion per 100 g of body mass	2.28 ± 0.10	3.17 ± 0.09 p<0.01

n - Number of observations

p - Index of the reliability of intergroup differences

Table 1: Performance of the kidneys of rats 24 h after a single dose of thyroxine in the amount of 20 micrograms per 100 g of body mass (M ± m).

Investigated options	Control, n=20	Introduction of T4, n=15
Diuresis, ml/h/100 g bm	1.8 ± 0.1	1.9±0.2
Relative diuresis, %	72.3 ± 2.6	77.5±3.9
Creatinine clearance, µl / min	605±21	387±24 p<0.01
The concentration of sodium in urine, mmol / l	0.48 ± 0.03	0.65±0.04 p<0.01
Sodium excretion, µmol/h/100 g bm	0.78 ± 0.04	1.17±0.09 p<0.05
The concentration of potassium in urine, mmol / l	8.1 ± 0.6	15.3±1.2 p<0.01
The excretion of potassium, µmol / h/100 g bm	15.1 ± 0.9	30.2±2.4 p<0.01
Sodium / potassium ratio of urine, units	0.068±0.012	0.041±0.009 p<0.01
Standardized excretion of sodium, µmol / ml GF	0.0243 ± 0.0019	0.0492±0.0025 p<0.01
Standardized excretion of potassium, µmol / ml GF	0.452 ± 0.037	1.148±0.074 p<0.01

n - Number of observations

p - Index of significant differences in comparison with a control group of rats

Table 2: Indicators of renal function in rats 24 hours after the 10-day administration of T4 in the amount of 20 micrograms per 100 g of body mass (M ± m).

increase in the value of a standardized sodium excretion by the kidneys in the group of hyperthyroid animals. In addition, this group of animals we have seen a marked increase in the concentration of potassium in the urine of rats treated with thyroxine for 10-days. We emphasize that the high intensity group kaliyuresis hyperthyroid rats is confirmed by calculations of the standardized rate of excretion of potassium. Standardized excretion of potassium is rarely used indicator. In our view, the appropriateness of its use in conditions of induced diuresis is due to the fact that the volume of final urine almost completely determined by the number of tubular fluid entering the distal nephron. In the water load further reabsorption of water does not occur, but the transport of sodium and potassium is intensive enough. This is shown by comparing the concentrations of cations in the final urine and blood plasma. Therefore, standardized excretion of potassium may be an indicator of distal secretion of ions in the light of the current rate of urine in the nephron [17]. Another feature of this series of observations on the dynamics of the values of the sodium / potassium ratio of urine - its value in experimental hyperthyroidism is somewhat lower than in euthyroid rats.

14 days after the completion of the 10-day rats thyroxine was conducted a functional study of kidneys of animals. The data are presented in Table 3.

After 14 days after cessation of thyroxine is not found differences in magnitude of diuresis compared with euthyroid rats. Also, the analysis of renal function suggests a trend towards normalization of the values of creatinine clearance. Meanwhile, the most significant finding, in our opinion, is the fact that at this point in time of the experiment, a group of rats subjected to the introduction of thyroxine are saved rather high sodium levels in the urine and the observed increase in the magnitude of excretion of sodium by the kidneys. However, laboratory analysis of the content of potassium in the urine of rats treated with thyroxine, did not reveal significant changes in the level of the cation. Note also that the values of the sodium / potassium ratio of urine are not statistically significant between group differences in comparison with the control group of rats.

Discussion

Thus, our studies suggest that the use we have chosen an experimental model of violations of the thyroid status of the organism, as for a single appointment of thyroxine to rats, and in conditions of prolonged administration of the hormone, cause quite distinct shifts of the studied parameters of the kidney - decrease of creatinine clearance and increased values kidney excretion of sodium and potassium. In turn, 14 days after the cessation of hormone administration, we are seeing the trend towards normalization of glomerular filtration rate and kaliyuresis, while the rate of renal loss of sodium are stored at a sufficiently high level. In our opinion, the correct interpretation of the results require some explanation, to allow a more objective assessment of the identified changes in functional status of kidneys.

Investigated options	Control n=20	Introduction of T4 n=15
Diuresis (ml/h/100 g bm)	1.7 ± 0.1	1.6±0.2
Relative diuresis %	68.2 ± 2.2	62.8 ± 1.8
Creatinine clearance (µl / min)	505±31	421±23
The concentration of sodium in urine (mmol / l)	0.31 ± 0.03	0.67±0.02 p<0.01
Sodium excretion (µmol/h/100 g bm)	0.49 ± 0.06	0.98±0.12 p<0.01
The concentration of potassium in urine (mmol / l)	9.5 ± 0.8	11.3±2.3
The excretion of potassium (µmol / h/100 g bm)	15.9 ± 1.9	18.3±2.9
Sodium / potassium ratio of urine (units)	0.038±0.07	0.049±0.009
Standardized excretion of sodium (µmol / ml GF)	0.021±0.002	0.048±0.007 p<0.01

n - Number of observations

p - Index of significant differences in comparison with a control group of rats

Table 3: Performance of the kidneys of rats 14 days after administration of T4 (M ± m).

First, most authors of publications on the issue of regulatory functions of the thyroid hormones are of the opinion that accompanies hyperthyroidism during excess iodine thyronines products can lead to a change in the intensity of metabolic processes in tissues, both through direct effects on metabolism and in consequence of modulation of hemodynamic parameters in the internal organs [8,9]. Note that normal thyroid hormones are considered as important regulators of metabolic processes in the body [18]. In this case, the violation of the thyroid status of the organism causes a material breach of biosynthetic mechanisms, not only in the period of growth, but also in adulthood. Study of protein and lipid metabolism using radiolabeled substrates showed that patients with diffuse thyrotoxic goitre for more than 30% of the accelerated catabolism of albumin [19]. From the position of those facts, draw attention to reports that revealed violations of metabolic processes are consistent in nature and persist long time after reaching the euthyroid state [19,20]. Meanwhile, the state transport of sodium in the kidney, demonstrating a close positive correlation with the intensity of metabolic processes in the renal parenchyma [15,21,22]. Given data on stated nature of metabolic abnormalities caused by hypothyroidism, it is possible to assume that the consequences of these shifts can have a negative impact on the transport of substances in the kidney, a sufficiently long period after the successful correction of the thyroid status of the organism. Indeed, the validity of this assumption is confirmed by the data of experimental studies indicating the need for correction of metabolic processes in experimental hyperthyroidism conducive to the normalization of renal sodium transport [10].

On the other hand, while not denying the role of metabolic and hemodynamic factors in the pathophysiological mechanisms of disorders of the kidneys in hyperthyroid status of the organism, yet we note that previous research the role of intrarenal humoral systems autoregulation in the pathogenesis of renal dysfunction, have shown that the correction of metabolism of nitric oxide [11] and the appointment of blockers of the renin-angiotensin system (RAS) may improve functional performance of the kidneys and prevent fibrosis in the renal parenchyma, registered in the group of animals receiving only iodothyronine [8,14,23]. Later, was experimentally proven leadership PAC stimulation in pathological structural changes in tissues of other internal organs in hyperthyroidism [9,14]. However, experimental results indicate that structural changes of tissues of internal organs, including kidneys, concomitant flow of hyperthyroidism, may play a major role in the pathogenesis of renal dysfunction caused by the disruption of thyroid status of the organism [8,23,24]. However, the prerequisite for the reliability of data recorded structural damage kidney tissue is a long course of experimental hyperthyroidism - about 30 days [14,23].

In addition to these factors, in our opinion, deserves the attention of information about the ability of thyroid hormones affect nephron transport sodium cations [25,26]. In in vitro experiments confirmed

a direct stimulating effect of physiologically active iodothyronine work Na^+ / H^+ -transporting protein in tubular epithelium [26]. Perhaps, under the control of thyroid hormones is the expression of Na^+ / H^+ -carriers in the nephron tubule. We found elevated levels of these proteins in the cortex of kidneys hyperthyroid rats [27]. Further investigations showed increased sodium-dependent reabsorption of inorganic phosphate [28], sulphate [29]. It is reported that the activation of sodium / proton countertransport at the apical side of the membrane proximal segment of the nephron nephrocytes in experimental hyperthyroidism enhances reabsorption cation [30]. Nevertheless, in spite of the experimentally confirmed the stimulating effect of iodothyronine on the mechanisms of tubular reabsorption of sodium in the literature provides evidence of increasing natriuresis in experimental hyperthyroidism due to metabolic disturbances in the renal parenchyma [10], as well as changes in renal hemodynamics, caused by the steady growth of intrarenal RAS activity [31]. Along with this, given the facts that, firstly, in patients with hyperthyroidism registered increased natriuresis [32]. Secondly, the increase in renal losses of sodium and chloride in experimental hyperthyroidism may be associated with changes in balance control homeostatic functions of the kidneys from some inside the organ parts of humoral control over the activities of the kidney [11,33]. In modern literature intrarenal humoral autoregulation systems play an important role in the pathogenesis of renal dysfunction and progression of renal insufficiency [34,35]. Therefore, to analyze their own research of interest, to the message that the imbalance in intrarenal humoral systems of control over the activities of the kidneys manifested during the first few hours after a single dose of an animal of exogenous thyroxine [13].

Indirect arguments in favor of this hypothesis is its own evidence that the growth of renal sodium loss in rats exposed to a single dose of thyroxine, combined with a reduction in the value of glomerular filtration and the growth kaliyuresis. Perhaps a more distinct decrease of glomerular filtration rate, and quite moderate values of sodium excretion by the kidneys, while the more intensive renal excretion of potassium in the group of animals treated with thyroxine for 10 days, compared with animals exposed to single dose of the hormone can be considered taking into account the views of that at early stages in the course of experimental hyperthyroidism, the most significant changes are observed at the tubular nephron, the cause of which has not been fully established [13]. Then, as the further course of experimental pathology, according to the authors quoted the source, leads to a reduction in renal loss osmolites, but not at the expense of increasing their tubular reabsorption, and by compensatory decrease in glomerular filtration rate.

We do not exclude that the factors that initiate the weakening of the efficiency of tubular reabsorption of sodium in early experimental hyperthyroidism can maintain its relevance and 14 days after cessation of thyroxine to rats. We also assume that a sufficiently high level of sodium excretion by the kidneys at this point in time of the experiment, on a background of minor variations in glomerular filtration rate is likely to shows that nephron epithelium, in contrast to the vascular-nephron glomerular apparatus, is more sensitive to adverse effects that accompany the disease. In addition, recognizing the relevance of structural changes of renal parenchyma in the pathogenesis of renal dysfunction caused by hyperthyroid status of the organism, we believe that at this stage, a dash of Experimental Pathology, the contribution of this factor is not determinative. The legitimacy of this conclusion is based on previously published results of pathologic examinations of kidneys of rats treated with higher daily doses of thyroxine [23]. During the studies it was found that in the initial stages of the disease, the duration of the appointment of the hormone in our experiment, recorded moderate changes proximal nephrocytes likely to indicate an increased functional activity of the epithelium. In view of the arguments, we believe that the reason for a noticeable increase in natriuresis within 14 days after administration of the hormone is on the one hand, the normalization value of glomerular filtration rate and, hence, increasing tubular load ultrafilrate. On the other hand, we do not exclude that the persistence of changes in metabolic processes proximal nephrocytes, as well as possibly an imbalance of humoral systems autoregulation of the kidney, did not allow an adequate level of efficiency of the reabsorption of sodium.

Conclusions

1. It is shown that the duration of the appointment rats thyroxine promotes the further strengthening potassuresis. The magnitude of the glomerular filtration rate is reduced, and the rate of sodium excreted by the kidneys are quite moderate.
2. Found that 14 days after cessation of thyroxine to rats is not observed significant variations in the values of glomerular filtration rate and potassium excretion by the kidneys, however, the rate of sodium excreted by the kidneys clearly exceed the benchmarks.
3. Found that a single injection of thyroxine to rats has no effect on the magnitude of diuresis, but induces a distinct increase in sodium excretion by the kidneys, stimulates potassuresis and lowers the glomerular filtration rate.

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