# Correlation of Changes in The Amount of Autoantibodies to The Receptors of Neurotransmitters In The Brain With The State of Hypothyroidism

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***Abstract***. ***Relevance of the topic:*** the brain is the organ with the highest sensitivity to thyroid hormone deficiency in the body. Detection of autoantibodies to neurotransmitter receptors helps in the early diagnosis of neurodegenerative processes and thus in explaining changes in brain function and mental disorders in hypothyroidism. ***Purpose of the research:*** in experimental hypothyroidism serum glutamate receptor (Glu-R), dopamine receptor (DA-R), GABA-receptor (GABA-R), opiate receptors (m-OR), serotonin receptor (Ser-R), acetylcholine receptor ( Chol-R) and b-endorphin (b-end) to determine the effect of L-thyroxine and neuroprotectors on changes in autoantibodies. ***Materials and Methods:*** To achieve the goal in the study, the condition of hypothyroidism was modeled by injecting mercazolyl at a dose of 2.5 mg / 100 g into the stomach of 21 white rats for 21 days. The animals were divided into 6 groups: Group I - intact; Group II - 21-day hypothyroidism, Group III - 30-day hypothyroidism, Group IV - rats with hypothyroidism treated with L-thyroxine, Group V - L-thyroxine and rats treated with "neuromac", Group VI - L-thyroxine and " somazina "treated hypothyroid rats. pharmacotherapy was carried out for 10 days. The amount of autoantibodies to Glu-R, DA-R, GABA-R, m-OR, Ser-R, Chol-R and b-end in the serum of rats was determined by the method of immunoenzyme analysis "ELI-N-Test" (Russia). Serum levels of T3, T4 and TTG hormones, body weight and temperature were determined. The figures were statistically processed. Results: In experimental hypothyroidism, the amount of autoantibodies to neurotransmitter receptors increased reliably relative to intact group values on day 21 (group II) and day 30 (group III). Decreased levels of autoantibodies were found in the serum of treated animals. At the same time, L-thyroxine was more effective when used with neuroprotectants. ***Conclusion:*** our study has been showed that an increase in the number of autoantibodies to neurotransmitter receptors indicates pathogenetic changes in immune system function, cognitive impairment and neurodegenerative processes in hypothyroidism, and it is advisable to use a neuroprotective drug in combination with L-thyroxine to correct these changes.

***Index Terms***- hypothyroidism, cerebral, serum, Glu-R, DA-R, GABA-R, m-OR, Ser-R, Chol-R, b-end, neurotropic autoantibodies.

## I. INTRODUCTION

It is known that thyroid dysfunction is currently one of the most common diseases among endocrine diseases. The majority of these diseases are hypothyroidism, which is important both medically and socially. Hypothyroidism occurs with damage to all tissues and organ systems of the body (1), especially due to the high sensitivity of the brain to thyroid hormone deficiency, damage to the central nervous system (CNS) is higher [2]. Thyroid hormones are necessary to ensure CNS activity, development and stability throughout a person's life. Therefore, an increase or decrease in the norm of these hormones is harmful to the brain. In adults, hypothyroidism can lead to neurodegenerative processes along with cognitive impairment [3; 4]. Hypothyroidism can lead to encephalopathy, polyneuropathy, myopathy, epilepsy and other diseases [5]. Although the early stages of nervous system injury in hypothyroidism are not clinically significant, subsequent inability to concentrate, memory loss, depression, and cognitive impairment can lead to profound neurodegenerative diseases [3; 4].

It is known that autoimmune mechanisms also play an important role in the pathogenesis of neurodegenerative diseases. Changes in the parameters of autoantibodies to antigens of the nervous system indicate early signs of disturbances in the specific structure of nerve tissue [6]. Recent studies suggest that specific antibodies are involved in the modulation of the function of physiologically active substances such as neurotransmitters, neuropeptides and hormones. Underlying immune system dysfunction and brain injury are autoimmune processes directed against nerve tissue antigens. In a number of neurodegenerative diseases, a correlation was found between dysfunction of the neurotransmitter system and induction of autoantibodies to them [7; 8; 9]. Changes in the amount of neurotropic autoantibodies indicate the activity of the immune system and the intensity of neurodegenerative or neuroplastic processes.

Recently, the study of postsynaptic and presynaptic membrane receptor activity in endocrine diseases, including thyroid disease, has been the focus of researchers 'interest. The pathogenetic and diagnostic significance of autoantibodies to neurotransmitter receptors has also not been studied. Thus, the

immunological aspect of the pathogenesis of hypothyroidism is one of the main problems to be addressed in neuroimmunopathology. Disorders of neurodegenerative receptor activity, indicating neurodegenerative processes in thyroid hormone deficiency, correction with L-thyroxine and neuroprotective drugs "neuromak" and "somazina" have not been resolved.

## II. The purpose of the study

In experimental hypothyroidism, serum glutamate receptor (Glu-R), dopamine receptor (DA-R), GABA-receptor (GABA-R), opiate receptors (m-OR), serotonin receptor (Ser-R), acetylcholine receptor (Chol- R) to determine the effect of L-thyroxine and neuroprotectors on changes in autoantibodies to vab-endorphins (b-end).

## III. Materials and Methods

*Research material.* In order to restore the activity of receptors for neurotransmitters in experimental hypothyroidism, the drug "somazina" was selected in combination with the thyroid hormone-containing drug L-thyroxine, and the drug "neuromak" for comparison. Somazina - (citicoline equivalent), Spain «FERRER Internacional, S.A.» is a product of a pharmacological company. This drug is a neuroprotective, nootropic substance intended for use in cerebral circulatory disorders and cerebral ischemia. Neuromac (citicoline equivalent) is a product of the Uzbek pharmaceutical company Radix NPP. This drug is a neuroprotective, nootropic substance and is intended for use in cerebral circulatory disorders and cerebral ischemia.

*Research design.* The study used 120 adult white rats weighing 180-220 g without standard white rats in the central vivarium of the Interdepartmental Research Laboratory of Higher Education in Tashkent Medical Academy. All animal studies were conducted in accordance with WHO recommendations for working with experimental animals and adherence to precautionary measures. To achieve the goal, the state of hypothyroidism was modeled by injecting mercazolyl (thiamazole equivalent, Pharmaceutical company Zdorovye, LLC Ukraine) into the stomach of white rats for 21 days at a dose of 2.5 mg / 100 g [10]. This model is widely used in experimental studies as a classical model of thyroid dysfunction. The formation of hypothyroidism was confirmed by monitoring body temperature and general condition of the animals, as well as changes in thyroid hormones. No animal deaths were observed. From day 21, the experimental rats were divided into 6 groups:

**Group I** – intakt.

**Group II** – 21 days hypothyroidized modeled rats.

**Group III** –30 days hypothyroidism modeled rats.

**Group IV** – Rats treated with 3 μg / kg L-thyroxine for 10 days after 21 days.

**Group V** – Rats treated with 3 μg / kg L-thyroxine and the neuroprotector "neuroma" for 10 days after day 21.

**Group VI** – Rats treated with 3 μg / kg L-thyroxine and somazine neuroprotector after 21 days.

On the appropriate days of the study, the rats were decapitated in a cold room with a temperature of 0° - + 2°C. After decapitation, the blood of the animals was collected. The collected blood was then left at + 4°C for 30 min, centrifuged at 3000 rpm, and blood serum was collected.

*Research methods:*

*1. Determination of T3, T4 and TTG hormones.* Serum thyroid hormones: thyrotropic hormone (TTG), thyroxine (T4) and triiodothyronine (T3) were determined by enzyme-linked immunosorbent assay using the Eliza test kit from Human (Germany). Units of measurement of these hormones: TTG - mlU / l; T3 was given in pg / ml, T4 - in pmol / l / ml.

*2. Detection of autoantibodies to neurospecific proteins using the linked immunosorbent assay method ELI-N-Test.* Neurotransmitter receptors in serum using the ELI-N-Test kit (Russia) by the method of immunoenzyme analysis: glutamate receptor (Glu-R), dopamine receptor (DA-R), GABA-receptor (GABA-R), opiate receptors (m- OR), serotonin receptor (Ser-R), acetylcholine receptor (Chol-R), and β-endorphin (β-end) were classified as G-class neurotropic autoantibodies [6; 7].

Pre-antigenic components are incubated into the sorbed tablet cells by instillation of diluted control and analyzed serum to establish a balance between free and bound antibodies to the corresponding antigens. When the contents of the cell are lost, a solution of conjugate containing peroxidase-containing autoantibodies is added and sorption of conjugate molecules in proportion to the amount of bound autoantibodies occurs. The unbound conjugate is lost and an enzymatic reaction of peroxidase with hydrogen peroxide in the presence of chromogen (tetramethylbenzidine) is performed to determine peroxidase activity. The color intensity of the chromogen is proportional to the concentration of antibodies in the sample under study. When the peroxidase reaction is stopped with a stop-reagent, the optical density is determined and the immunoreactivity is determined for the serum being analyzed according to the formula. In this case, the amount of autoantibodies to the receptors of the studied neurotransmitters (immunoreactivity) is normally in the range of -20% ... + 10%, and an increase or decrease in these values is an anomalous indicator.

*Methods of statistical analysis.* The results were statistically processed using a package of analytical application programs for statistical processing and drawing of images Excel and Origin Pro 8.6 (Microsoft, USA). Statistical reliability was calculated according to the Student t-criterion.

## IV. Results

*Effect of L-thyroxine and neuroprotectors on changes in body temperature and weight in the experimental model of hypothyroidism.* The study found a decrease in temperature and an increase in body weight in rats modeled for hypothyroidism (Fig. 1). In all of the treated groups, these indicators approached the normative values.

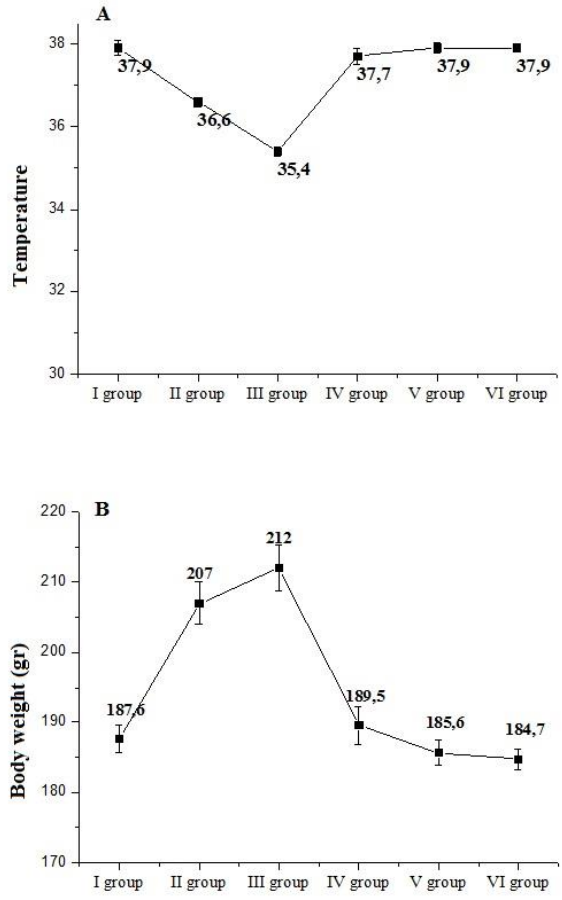


**Figure 1. Changes in body temperature (A) and body weight (B) in experimental hypothyroidism.**

*Effect of L-thyroxine and neuroprotectors on changes in thyroid hormone levels in experimental hypothyroidism.* The results for determining the thyroid status in the serum of rats in experimental hypothyroidism are presented in Table 1. The table shows that in experimental hypothyroidism, an increase in TTG levels and a decrease in T3 and T4 hormones were observed. On day 21 of the study, TTG levels increased 1.93 times relative to the intact group, while T3 and T4 hormones decreased 2.09 and 3.21 times, respectively. On day 30 of the study, TTG levels increased 3.73-fold compared to the intact group, while T3 and T4 decreased 5.13-fold and 6.4-fold, respectively. In all of the treated groups, a decrease in TTG levels, an increase in T3 and T4 hormone levels, and an approach to normal values were found. The results obtained to determine body weight, temperature, and thyroid status prove that the experimental hypothyroidism model was correctly selected.

**Table 1**

**The amount of thyroid hormones in the experimental model of hypothyroidism (M ± m; n = 8)**

| Groups | Thyroid hormones | | |
|---|---|---|---|
| | TTG | T3 (free) pg / ml | T4 (free) pmol / l |
| I group | 0,015±0,0005 | 4,05±0,1 | 16,7±0,24 |
| II group | 0,029±0,003*** | 1,94±0,08*** | 5,2±0,32*** |
| III group | 0,056±0,004*** | 0,79±0,05*** | 2,61±0,14*** |
| IV group | 0,016±0,0008^^^ | 3,92±0,1^^^ | 14,96±0,28*, ^^^ |
| V group | 0,0168±0,0005^^^ | 3,9±0,1^^^ | 15,15±0,26*, ^^^ |
| VI group | 0,017±0,0006^^^ | 3,9±0,1^^^ | 15,11±0,32*, ^^^ |

*Note:* *** - Reliability relative to group I indicators is P<0,001; * - reliability relative to group I indicators is P<0,05; ^^^ - reliability relative to group III indicators is P<0,001.

*Changes in the parameters of autoantibodies to neurotransmitter receptors in experimental hypothyroidism and the effect of L-thyroxine and neuroprotectors on it.* Subsequent studies analyzed changes in autoantibodies relative to Glu-R, DA-R, GABA-R, m-OR, Ser-R, Chol-R, and β-end. The results showed that in experimental hypothyroidism, the amount of autoantibodies relative to neurotransmitter receptors was reliably increased compared to the intact group in rats modeled in hypothyroidism. In the drug-treated groups, the amount of autoantibodies was close to that of the intact group rats (Fig. 2).

It was noted that the immunoreactivity of all receptors in group I-intact rats was in the range of -20% ... + 10%. In group II rats modeled for 21-day hypothyroidism, all values were found to be higher than normal. The highest rates were specific to Glu-R and Ser-R, with 28.33% and 28.83%, respectively. The lowest changes were detected for the m-OR and b-end, with autoantibodies to 14.83% and 14.67%, respectively. In group III rats with 30-day hypothyroidism, the number of autoantibodies was partially reduced relative to Ser-R, while the remaining autoantibodies were increased. However, all indicators remained above the norm. The highest values are for GABA-R, Glu-R, DA-R, with an immunoreactivity of 55.5%; 48.83% and 46%, respectively.

A partial decrease in the amount of autoantibodies to neurotransmitter receptors was observed in group IV rats treated with L-thyroxine. However, the number of autoantibodies remained above the norm. Significant reductions in autoantibodies were found in group V and VI rats co-administered with neuromac and somazine L-thyroxine. However, these drugs also did not fully normalize the amount of autoantibodies. The combined effect of these neuroprotectors with L-thyroxine was more effective than the effect of L-thyroxine.

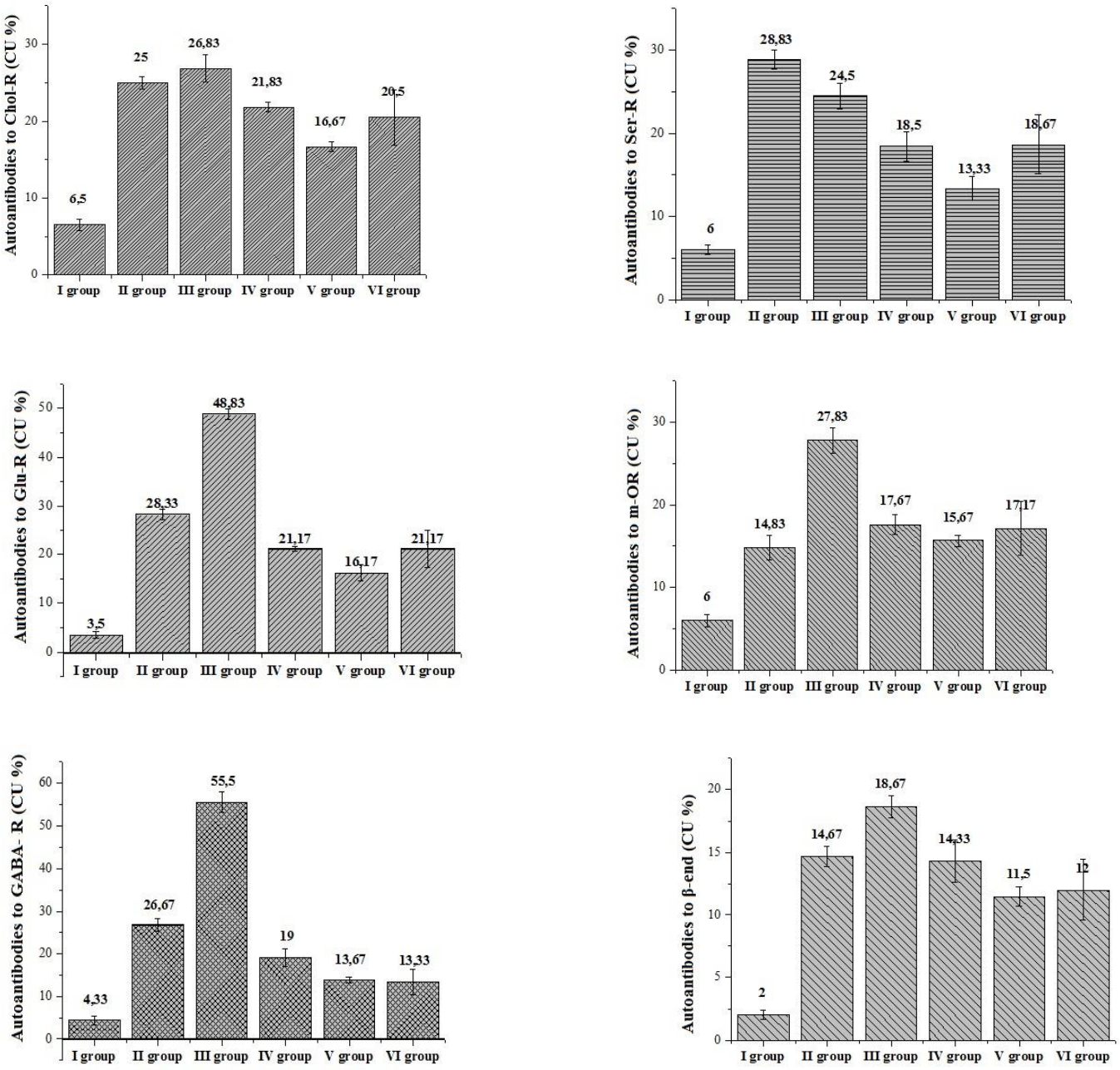


**Figure 2. In experimental hypothyroidism, glutamate receptor (Glu-R), dopamine receptor (DA-R), GABA-receptor (GABA-R), opiate receptors (m-OR), serotonin receptor (Ser-R), acetylcholine receptor (Chol-R) and autoantibodies to β-endorphins (β-end).**

## V. Discussion

Based on the results obtained, it can be said that in thyroid dysfunction exhibits metabolic, mental and neurological effects that occur with dysfunction of the neurotransmitter system in the brain. The study found that abrupt changes in experimental hypothyroidism were appropriate for GABA-R, DA-R, and Glu-R. It can be hypothesized that the increase in autoantibodies to neurotransmitter receptors in experimental hypothyroidism is associated with the acceleration of apoptosis and neurodegenerative processes in nerve cells as a result of the

neurotoxic effects of hypothyroid hormone deficiency. Determining the parameters of these autoantibodies opens the way to achieve effective results in the early diagnosis of brain damage and dysfunction in the case of hypothyroidism and the implementation of treatment and prevention measures. An interrelationship between neurotransmitter dysfunction and induction of autoantibodies to them has also been identified in various CNS diseases [11]. Prolonged hypothyroxinemia has been associated with neurological diseases such as ataxia and epilepsy [12] and an increase in autoantibodies to neurotransmitter receptors in epilepsy [8; 9] means that this condition can also occur in hypothyroidism. Our study also showed an activation of autoimmune processes in experimental hypothyroidism, indicating an increase in auto-antibodies levels relative to the receptors of various neurotransmitters.

In thyroid dysfunction, the systems of GABAergic, glutamatergic and dopaminergic neurotransmitters are disrupted. Significant changes in the activity of the cholinergic system have also been reported [3]. Cholinergic system deficiency is manifested by decreased memory and assimilation, panic, and decreased motor activity.

In hypo- and hyperthyroidism, there is an increase or decrease in the amount of serotonin, an increase or decrease in the sensitivity and density of 5-$NT_1$-receptors of serotonin. In particular, the density of 5-$NT_{1A}$ and 5-$NT_2$ receptors has been studied in many studies. In particular, a decrease in the density of serotonin receptors in the cortical region of the brain has been found [13]. It can be assumed that the decrease in the density of serotonin receptors is associated with a violation of membrane integrity. As a result, subunits of these receptors appear in the blood and autoantibodies to it increase. All of these changes indicate a dysfunction of the serotonergic system and, consequently, the appearance of emotional changes in the patient.

In experimental gestational hypothyroidism, a decrease in the amount of components of the dopaminergic, GABAergic, serotonergic neurotransmitter systems in the offspring was detected [14]. Data on the effect of hypothyroidism on the system of neurotransmitters are presented in the literature. In particular, glutamate and GABA-induced neurotransmitter systems are the main excitatory and inhibitory neurotransmitter systems of CNS, and a decrease in the amount of thyroid hormones plays an important role in the dysfunction of this neurotransmitter system.

In particular, glutamate receptors are present in all areas of the central nervous system and play an important role in the normal functioning of the brain, memory and adaptation processes. In hypothyroidism, excessive secretion of glutamate and its "excitotoxicity" effect are enhanced. Excitotoxicity leads to excessive penetration of $Ca^{2+}$ ions into nerve cells by NMDA, AMPA and VGCC as a result of hyperactivation of glutamate receptors, an increase in its intracellular content leads to activation of proteases, phospholipases, nucleases, mitochondrial dysfunction, oxidative stress and oxidative stress. [15; 16]. Due to excessive secretion of glutamate, the function of NMDA receptors is impaired, these receptors are broken down into peptide fragments. Through the blood-brain barrier, destructive molecules begin to pass from the brain into the bloodstream, and activation of the immune system which produces autoantibodies to brain antigens, is observed. It is known that thyroid hormones promote the uptake of extracellular glutamate and protect nerve cells from the excitotoxic effects of glutamate [17]. In contrast, in hypothyroidism, nerve cells are damaged due to excessive secretion of glutamate. The high levels of autoantibodies to glutamate receptors identified in our studies confirm the above considerations.

It is also noted that in hypothyroidism there is an organic link between the disruption of the GABA system and brain dysfunction [18].

It has been reported that thyroid hormones protect dopamine neurons from neurotoxic effects [19]. It can be seen that in the absence of thyroid hormones, dopamine neurons are also damaged and their amount is reduced.

Thus, the increase in the number of autoantibodies to neurotransmitter receptors in hypothyroidism, identified in our study, indicates the involvement of the immune system in the mechanism of disregulation of neuroimmune interactions, addictive disorders in this disease. The mechanism of action of thyroid hormone deficiency also lies in the activation of free radical processes and imbalance of the pro- and antioxidant system. Increased production of active forms of oxygen in the brain in hypothyroidism, acceleration of peroxidation of lipids, decreased glutathione, decreased activity of superoxide dismutase and gamma-glutamyltransferase [16;20;21]. Activation of free radicalization processes leads to an increase in hematoencephalic barrier permeability and the appearance of autoantibodies to neurotransmitter receptors.

Central to hypothyroidism are decreased cognitive function, depression, slowed thinking, memory loss, drowsiness, weakness, panic, rapid fatigue, and neuropathy. In the case of hypothyroidism, the intake of thyroid hormones significantly affects the development of these mental, cognitive disorders, reducing the manifestation of neurological symptoms.

The study noted that the use of neuroprotectants in combination with L-thyroxine was more effective. Citicoline is the equivalent of both the neuromac and somazine used in our study. The neuroprotective effect of citicoline in neurodegenerative diseases has been proven [22]. The active participation of citicoline in the synthesis of phospholipids in nerve cells demonstrates a neuroprotective effect [23].

Thus, antibodies to glutamate, dopamine, GABA, opiates, serotonin, acetylcholine, and--endorphins play an important role in the pathogenesis of hypothyroidism.

## VI. Conclusion

Thus, we can conclude that the results of the study show that the increase in the number of autoantibodies relative to neurotransmitter receptors (Glu-R, DA-R, GABA-R, m-OR, Ser-R, Chol-R, β-end) is pathogenetic in immune system function. changes and cognitive impairment as a result of hypothyroidism, as well as neurodegenerative processes. In hypothyroidism, it is advisable to use a neuroprotector along with L-thyroxine to restore these disorders.

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