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HYPOTHYROIDISM IN THE EXPERIMENTAL MODEL OF ALZHEIMER

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Abstract:

Thyroid hormones (TG) have a wide and important range of effects in the central nervous system. Thyroid diseases are one of the main causes of cognitive impairment, including Alzheimer's disease (AD). The aim of this work was to study individual indicators of thyroid hormones in an experimental model of a neurodegenerative state with symptoms of Alzheimer's disease (MA)

Keywords: Alzheimer's disease, thyroid hormones, thyroid gland, hypothyroidism.

ГИПОТЕРИОЗ ПРИ ЭКСПЕРИМЕНТАЛЬНОЙ МОДЕЛИ АЛЬЦГЕЙМЕРА

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Аннотация
Гормоны щитовидной железы (ТГ) обладают широким и важным спектром эффектов в центральной нервной системе. Заболевания щитовидной железы являются одной из основных причин когнитивных нарушений, включая болезнь Альцгеймера (БА). Целью настоящей работы явилось исследование отдельных показателей тиреоидных гормонов на экспериментальной модели нейродегенеративного состояния с симптомами болезни Альцгеймера (МА).

Ключевые слова: болезнь Альцгеймера, тиреоидные гормоны, щитовидная железа, гипотиреоз.

Hypothyroidism is a clinical syndrome caused by a persistent decrease in the level of thyroid hormones in the body. The diagnosis of hypothyroidism is often untimely, since the symptoms detected at the initial stage are extremely nonspecific. Hypothyroidism syndrome can mimic various non-thyroid diseases, which is associated with multi-organ lesions found in conditions of thyroid hormone deficiency. To diagnose hypothyroidism, it is often sufficient to determine the concentrations of thyroid-stimulating hormone (TSH) and free thyroxine T4. Measuring TSH is considered the best way to diagnose this condition. The main goal of treatment is to

restore the normal physiological functions of all organs and systems impaired due to hypothyroidism.

The purpose of the research was to study changes in the thyroid status of animals with the administration of Mercazolil and the creation of a state of hypothyroidism, used for the development of signs characteristic of neurodegenerative diseases (AD): a decrease in the level of free thyroxine (fT4), 3,5,3′ - triiodothyronine (T3) [1].

In recent years, the relationship between Alzheimer's disease (AD) and metabolic disorders has been widely discussed. However, it remains unclear whether asthma is the direct cause of carbohydrate metabolism disorders or whether the presence of classical risk factors for type 2 diabetes mellitus (T2DM), primarily obesity, significantly increases the risk of asthma. An assessment of the separate contribution made by two factors to the development of carbohydrate metabolism disorders - 1) increase in body weight against the background of a high-calorie diet and 2) experimentally induced BA [2].

Due to the widespread prevalence of thyroid diseases, on the one hand, and stress-induced pathology, on the other, the study of the mechanisms of the anti-stress action of iodine-containing thyroid hormones is relevant.

It has been established that changes in thyroid status affect the metabolism and level of components of the central (inhibitory neurotransmitters: gamma-aminobutyric acid, glycine, dopamine, serotonin, opioid peptides) part of the stress-limiting system, which limits or neutralizes the action of the stress-releasing system. The severity of this effect is tissue specific and depends on the age and sex of the animals, as well as on the degree of thyroid dysfunction. New scientific knowledge about the activation of the central link of the stress-limiting system by iodine-containing thyroid hormones opens up the possibility of developing a new way to increase the body’s resistance to stressors by influencing its thyroid status[3]

Based on the above, the level of free thyroxine (fT4), 3,5,3′ - triiodothyronine (T3) was studied. The results of the enzyme immunoassay indicated a decrease in the functional activity of the thyroid gland to an extent sufficient to make a diagnosis of “experimental hypothyroidism.”

As can be seen from the table data, the concentration of 3,5,3′-triiodothyronine (T3) in the blood serum of animals of the active group was 2.39 ± 0.19 nmol/l versus 2.48 ± 0.22 nmol/l in control animals, and in animals with MA was 2.53 ± 0.19. And the content of free thyroxine (fT4) was 82.33 ± 5.21 nmol/l and 84.72 ± 6.00 nmol/l, respectively, and in animals with MA it was 86.13 ± 7.11 nmol/l. Animals of the 3rd experimental group were administered Mercazolil at the rate of 1 mg per 100 g of body weight for 21 days. As one would expect, the animals easily tolerated such a small dose of the thyreostatic agent: no obvious deviations were noticed either in the physical status of the rats or in their behavior.

Table 1 Content of T3 and T4 in the blood serum of rats with a model of Alzheimer's disease (M±m), n=25

Groups of animals(n=25)	T3, nmol/l	T4, nmol/l
ИТп=5	2,48 ± 0,22	84,72 ± 6,00
АК n=5	2,39 ± 0,19 p > 0,05	82,33 ± 5,21 p > 0,05
МА (n=15)	2,53 ± 0,19	86,13 ± 7,11

In this group of animals, it was not possible to achieve a decrease in the level of 3,5,3′-triiodothyronine (T3) in comparison with the same indicator in the control group of animals.

The data obtained indicate that in rats with experimental local hypothyroidism in the cerebral cortex, which is apparently associated with a decrease in tissue deiodinase activity. Local asthma against the background of the euthyroid state of the body develops; a decrease in triiodothyronine in homogenates of the cerebral cortex can change the amount and modify the activity of enzymes involved in glycolysis and aerobic mitochondrial oxidation of glucose (the main energy substrate in the brain). Thus, the concentration of T3 in the blood serum of group 3 rats (MA) was 2.53±0.19 nmol/l versus 2.48±0.22 nmol/l in control animals, which indicates incomplete inhibition of the synthesis of thyroid hormones. Consequently, when using small average daily doses of Mercazolil (1 mg per 100 g of body weight) for 21 days, biochemical changes characteristic of hypothyroidism develop in the thyroid gland.

Apparently, under conditions of low doses of antithyroid drugs, the processes of peripheral deiodination of T4 are activated with the formation of more active T3.[4].

Thus, we can conclude that when Mercazolil is administered to white rats at an average daily dose of 5 mg/100 g and below for 21 days, the development of symptoms of a hypothyroid state is achieved with minimal side effects of the studied thyreostatic.

This is probably related to the decrease in glucose consumption by the brain in AD, established by a number of authors. It is known that the brain is characterized by a high level of energy metabolism, almost all brain functions are energy-dependent, in this regard, it can be assumed that the local hypothyroidism we identified is an important factor contributing to a decrease in energy production and, in connection with this, the death of neurons. The formation of ß-amyloid also plays an important role in the development of energy deficiency, since ß-amyloid is an antagonist of the insulin receptor (i.e., it reduces the flow of glucose into brain tissue), the deposition of amyloid in the vessels leads to impaired blood flow and contributes to the development of tissue hypoxia and a decrease in the delivery of energy substrates. Apparently, it is the low level of ATP that causes a decrease in the activity of acetylcholine transferase and axonal transport of acetylcholine, which is known to be the cause of the development and progression of AD. It is known that excessive phosphorylation of tau protein leads to the formation of neurofibrillary tangles, which is considered to be the leading process underlying tauopathies (including AD). In this regard, it can be assumed that an important role in the

formation of neurofibrillary tangles in AD is played by the decrease in triiodothyronine content that we identified in rat cerebral cortex homogenates.

When modeling Alzheimer's disease in rats, despite systemic euthyroidism, the cerebral cortex is in conditions of hypothyroidism, as evidenced by a decrease in triiodothyronine with a slightly increased content of thyroxine in homogenates of the cerebral cortex. In rats modeling Alzheimer's disease, there is an increase in glutamic and aspartic amino acids with a decrease in GABA, which, given the mediator role of these amino acids in conditions of central cholinergic deficiency, may be one of the important factors of metabolic disorders in this pathology. When modeling Alzheimer's disease in rats by chronic intraperitoneal administration of scopolamine, a significant decrease in the content of norepinephrine and dopamine in homogenates of the cerebral cortex is observed, which contributes to the disruption of energy metabolism and cognitive functions.

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