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# РЕГУЛЯТОРНІ ЗВ'ЯЗКИ ФОЛАТНОГО ЦИКЛУ І ГІПОФІЗАРНО-ТИРЕОЇДНИХ ГОРМОНІВ У ДІТЕЙ ІЗ РАЙОНІВ, ЩО ПОСТРАЖДАЛИ У РЕЗУЛЬТАТІ АВАРІЇ НА ЧОРНОБИЛЬСЬКІЙ АТОМНІЙ ЕЛЕКТРОСТАНЦІЇ

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# REGULATORY CONNECTIONS OF THE FOLATE CYCLE AND PITUITARY-THYROID HORMONES IN CHILDREN FROM AREAS AFFECTED BY THE ACCIDENT AT THE CHORNOBYL NUCLEAR POWER PLANT

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Regulation of the activity of organs and systems is the most important element of the human body. The nervous, endocrine and immune systems are distinguished as regulatory systems.

Ideas about the functioning of these systems were formulated quite a long time ago, however, at present, they continue to deepen.

In addition, it should be noted the regulatory relationships between metabolic cycles, which are poorly studied or not studied at all.

Therefore, there are problems in understanding the occurrence of pathological processes. The endocrine system is involved in the regulation of basic metabolic processes during human ontogenesis.

At the same time, it is closely connected with the central nervous system.

The basic principles of interaction between the central regulatory organs – the hypothalamic-pituitary axis and peripheral endocrine organs – the endocrine glands have been formed.

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***Мета роботи** полягає у формулюванні наукової концепції про регуляторні зв'язки фолатного циклу (ФЦ) та гіпофізарно-тиреоїдної осі на підставі результатів досліджень авторів, проведених під час обстеження дітей із районів, що постраждали внаслідок аварії на ЧАЕС.*

***Матеріали та методи:** аналітичний, бібліографічний. Матеріалами дослідження є опубліковані науково-дослідні статті авторів.*

***Результати.** У ході статистичного та кореляційного аналізу показників обміну речовин дітей із районів, що межують з ЧАЕС, було виявлено зв'язок між ФЦ та гормонами гіпофізарно-тиреоїдної вісі. Подано наукову концепцію про участь гомоцистеїну ($H_{cy}$) у регуляції гормоногенезу щитоподібної залози (ЩЗ), згідно з якою $H_{cy}$. активує у клітинах аденогіпофіза (АГ) синтез тиреотропного гормону (TSH). У свою чергу, TSH активує процес деодинації $T_4$ з утворенням $T_3$ у периферичних тканинах. При цьому $H_{cy}$. також бере участь в утворенні цистеїну – компонента коферментної частини дейодинази 5-Di, що також посилює процес утворення $T_3$, який, впливаючи на MTHFR ФЦ, посилює процес утворення CH3-MTHF і тим самим активує процес метилювання $H_{cy}$. Зниження концентрації $H_{cy}$ у крові призводить до зменшення утворення TSH у клітинах АГ. Таким чином, $T_3$ блокує синтез TSH через ФЦ, посилюючи процес метилювання $H_{cy}$.*

***Висновки.** Регуляція взаємодії між АГ та ЩЗ здійснюється за допомогою сірковмісної амінокислоти $H_{cy}$. – продукту обміну метіоніну. Продукцію THS пригнічує не $T_3$, а зниження концентрації $H_{cy}$ у крові, пов'язане з впливом $T_3$ на ФЦ. Збільшення вмісту $H_{cy}$ у крові дітей із населених пунктів поблизу ЧАЕС обумовлено мутацією генів, відповідальних за синтез основних ферментів ФЦ, а також впливом радіонуклідів, інкорпорованих в їхній організм. Стан гіпергомоцистеїнемії може бути причиною зміни гормонального обміну ЩЗ, створюючи ілюзію гіпотиреозу.*

***Ключові слова: фолатний цикл, гомоцистеїн, гормоногенез, діти, радіоактивно забруднені території.***

The main principle of their interaction is the principle of feedback [1].

Hormones produced by the adenohypophysis (AH) stimulate the production of hormones in peripheral endocrine organs.

In turn, an increase in the formation of hormones in peripheral organs blocks the synthesis of hormones in AH.

An example is the AH system – the thyroid gland (TG), in particular thyroid-stimulating hormone (TSH) and thyroid hormones.

It is generally accepted that hypertension, by producing TSH, regulates the synthesis of thyroid hormones.

TSH stimulates the synthesis of thyroxine ($T_4$) and triiodothyronine ($T_3$) in the TG. **Th4** latter, upon reaching a certain concentration, block the synthesis of TSH in AH cells.

However, it is not clear exactly how TSH synthesis is blocked (the presence of specific receptors and enzymes), as well as what hormones and other metabolites are involved in this.

Thus, the scheme in which the process of synthesis of thyroid hormones is directly related to AH does not reflect all the elements of the regulatory process in the pituitary-thyroid system.

Perhaps, therefore, there are problems in providing effective medical care to people with impaired thyroid status.

At the same time, it does not take into account that the largest number of active forms of thyroid hormones, $T_3$, occurs in peripheral tissues, including the liver and kidneys, during the process of deiodination of $T_4$, in which TSH participates.

In most cases, when diagnosing hypothyroidism, assessment tests are used to determine TSH and $T_4$ in the blood, completely ignoring the content of $T_3$ in the blood [2]. Taking into account the existing generally accepted scheme of the regulatory process of AH and TG, this is completely acceptable.

Even just an elevated TSH level is sufficient for this diagnosis. But what about $T_3$ – the active form of thyroid hormone?! After all, according to authoritative scientific sources, it is $T_3$ that influences the formation of TSH, exerting a genomic and post-transcriptional effect on thyroid-stimulating cells of the AH. It should be noted that the non-genomic effects of $T_3$ precede the genomic ones. At the same time, $T_3$ affects the polymerization of actin and tubulin cytoskeleton in the cells of the entire anterior pituitary gland [3].

Based on this, in the regulation of thyroid hormonogenesis, it is necessary to consider the process of $T_3$ formation in peripheral tissues, the most important producers of this hormone.

Thyroid pathology is widespread in the European part of the former USSR, including Ukraine. This was especially evident after the accident at the Chornobyl nuclear power plant (ChNPP) [4].

During the implementation of the European Commission project «Health and Ecological Programs around the Chornobyl Exclusion Zone: Development, training and coordination of health-related projects» in 2013-2017, structural chan-ges in the TG in 5.6% of cases, as well as disturbances in the production of thyroid hormones (mainly a decrease in the level of $T_4$ in the blood) in 35.5% of cases [5].

At the same time, in more than 70.0% of cases among adolescent children, a state of hyperhomocysteinemia was recorded – an increased level in the blood of the sulfur-containing amino acid homocysteine ($H_{cy}$), a metabolic product of the essential amino acid methionine (Met) [6].

This information is alarming, since hyperhomocysteinemia, occur in adults with cancer, cardiovascular pathology, and diseases of the nervous system [7-10].

A number of scientific studies have traced the connection between $H_{cy}$ and thyroid hormones. In particular, an increase in the level of $H_{cy}$ in the blood was recorded in hypothyroidism [11, 12], while a decrease in the level of $H_{cy}$ was observed in hyperthyroidism and an increase in the level of folate in the blood [13].

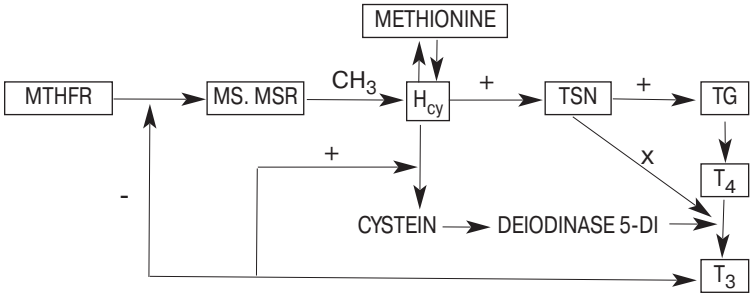
**The aim** of this work is to formulate a scientific conception about the regulatory connections of the folate cycle (FC) and the pituitary-thyroid axis based on the results of the authors' research conducted when examining children from areas affected by the Chornobyl accident.

To clarify the cause-and-effect relationship between $H_{cy}$ and the pituitary-thyroid axis in children from districts bordering the ChNPP, statistical studies of indicators characterizing the state of the FC and thyroid hormonogenesis were carried out.

In subgroups of children, aged 12-17 years old, with different genetic combinations and different levels of $H_{cy}$ in the blood (>10.0 μmol/l and ≤10.0 μmol/l), an analysis of correlations between $H_{cy}$ and

*Figura*

**Regulatory connections between the folate cycle and the pituitary-thyroid axis**





metabolic parameters reflecting the functioning of the FC, AH was carried out, the cycle of trans-sulfuration reactions, the process of deiodination of $T_4$ with the formation of $T_3$ [14-17].

The results obtained allowed the authors to formulate a scientific conception about the regulatory connections between FC and the pituitary-thyroid axis (Figure).

According to this conception, $H_{cy}$ is a regulator of the activity of AH cells, and it is its concentration in the blood that determines the intensity of production of THS by these cells, as well as, possibly, other hormones that regulate the activity of endocrine organs.

A high level of $H_{cy}$ in the blood stimulates the synthesis of THS in AH cells, as evidenced by the direct correlation between $H_{cy}$-THS in subgroups of children with genetic disorders of FC after forest fires in the Chornobyl Exclusion Zone (ChEZ) [14].

At the same time, in peripheral tissues, a cycle of transsulfuration reactions is activated with the participation of $H_{cy}$ and serine, as well as vitamin $B_6$ as a coenzyme of cystathionine-β-synthase [14, 15].

The consequence of this process is the formation of cysteine, which, after combining with selenium, is a coenzyme of deiodinase 5-Di, which promotes the deodination of $T_4$ with the formation of $T_3$.

TSH takes an active part in this process, which also stimulates the synthesis of hormones in the TG (Figure).

Genetic mutations that reduce the activity of FC enzymes contribute to an increase in the level of $H_{cy}$ in the blood [15], and hence the formation of $T_3$.

In turn, $T_3$ stimulates methylenetetrahydrofolate reductase (MTHFR), which produces the active form of vitamin $B_9$-5-methyltetrahydrofolate ($CH_3$-MTHF). This is evidenced by the direct correlation between $T_3$ and $B_9$ [16]. An effect on $B_{12}$-methionine synthase (MS) and methionine synthase reductase (MSR) is possible. As a result, the process of $H_{cy}$ methylation is enhanced.

Thus, $T_3$, formed under the influence of a high level of Hcy, reduces the content of the latter, as evidenced by the inverse correlation relationship $T_3$-$H_{cy}$ [17].

When the stimulating effect of $T_3$ on the FC weakens or stops, the levels of $H_{cy}$ and $T_4$ in the blood begin to increase.

The strong direct association of TSH-$B_9$, in the subgroup with the major genotype A/C MTHFR:1298-C/TMTHFR:677-A/AMTRR:66, suggests that TSH is also capable of stimulating MTHFR activity and promoting $H_{cy}$ reduction [16]. However, we cannot rule out the possibility that, in this case, TSH acts on MTHFR via $T_3$.

The direct relationship between TSH and $T_3$, recorded in the subgroup with the homozygous variant of the T allele of the MTHFR polymorphism, in the overwhelming majority of cases of hyperhomocysteinemia [15], is a reflection of the influence of the pituitary hormone on the production of $T_3$ in peripheral tissues.

The inverse correlation between $T_3$ and TSH indicates a mechanism for blocking TSH production. However, at the same time, the same connection is recorded between $T_3$ and $H_{cy}$ [17].

We are inclined to believe that the relationship between $T_3$ and TSH occurs through an intermediary, which is $H_{cy}$. THS production is not suppressed by $T_3$, but by a decrease in the concentration of $H_{cy}$ in the blood associated with the effect of $T_3$ on FC.

Increased concentrations of $T_3$ are able to block the activity of reactions of the trans-sulfuration cycle ($T_3$-$B_9$ feedback) [15].

Thus, $H_{cy}$, THS and $T_3$ carry out regulatory processes between the FC and the pituitary-thyroid axis.

Based on the presented hypothesis, the higher the $H_{cy}$, the more intense the functioning of the pituitary-thyroid axis, including THS, $T_3$ and $T_4$.

A decrease in the level of $T_4$ in the blood and an increase in $T_3$ will occur with a decrease in $H_{cy}$ [17]. And a direct correlation between $H_{cy}$-$T_4$, at a level of $H_{cy}$ <10.0 μmol/l, is associated with a decrease in the content of these metabolites in the blood.

Thus, $T_3$ is a stimulator of FC in the reaction of $H_{cy}$ methylation and the formation of internal Met.

In our opinion, this is due to the need to enhance energy processes in the cells of vital organs and systems under external environmental influences, including the incorporation of $^{137}Cs$ radionuclides, which causes damage to mitochondria [15].

In this case, $T_3$ has a stimulating effect on energy supply processes, which leads to increased activity of MTHFR, MS, MSR, and therefore to an increase in the synthesis of $CH_3$-MTHF and methylcobalamin, and therefore to an increase in the process of $H_{cy}$ methylation and the formation of internal Met.

But this happens when the FC enzymes, and in particular MTHFR, are susceptible to the action of $T_3$ [17].

In the case of severe genetic disorders of FC, especially MTHFR, $T_3$ is not effective in stimulating $H_{cy}$ methylation.

Increased $H_{cy}$ concentration in the body causes chronic hormonal stress associated

with increased production of $T_3$ and cortisol [17].

At the same time, the function of many organs and systems is disrupted.

In particular, in more children from areas affected by the Chornobyl accident, heart rhythm disturbances were recorded, as well as a decrease in functional reserves and adaptive capabilities of the circulatory system [18].

Disruption of $H_{cy}$ methylation processes associated with genetic mutations of FC and external environmental influences (radiation factor) [17] can create a false effect of hypothyroidism.

In this case, the use of thyroid hormones as a therapeutic drug will not be effective, since the body already contains the active form of thyroid hormones – $T_3$.

At the same time, it is necessary to regulate $H_{cy}$ metabolism, and methylated forms of folic acid and vitamin $B_{12}$ will be effective.

It should be noted that the thyroid gland of a child's body intensively accumulates $^{137}Cs$ radionuclides [15], which may be one of the reasons for the development of hypothyroidism in areas affected by the Chornobyl accident. In this case, it is also possible to increase the level of $H_{cy}$ in the blood, since the body does not produce $T_3$ in an amount capable of activating the FC enzyme system and $H_{cy}$ methylation processes. A marker of the situation is a persistently elevated level of TSH, which is not observed in hyperhomocysteinemia associated with impaired $H_{cy}$ metabolism.

**Conclusions.** The increase in $H_{cy}$ content in the blood of children from settlements located near the ChNPP is due to mutation of the genes responsible for the synthesis of the main FC enzymes, as well as exposure to radionuclides incorporated into their body.

During the correlation analysis of metabolic parameters of children from areas bordering the ChNPP, a connection was revealed between FC and hormones of the pituitary-thyroid axis.

A conception is presented about the participation of $H_{cy}$ in the regulation of hormonogenesis of the TG, according to which $H_{cy}$ activates the synthesis of TSH in AH cells.

In turn, TSH activates the process of $T_4$ deodination with the formation of $T_3$ in peripheral tissues. At the same time, $H_{cy}$ is also directly involved in the formation of cysteine, a component of the coenzyme part of deiodinase 5-Di, which also enhances the process of $T_3$ formation.

$T_3$, acting on the MTHFR FC, enhances the formation of $CH_3$-MTHF, and thereby activates the process of $H_{cy}$ methylation.

A decrease in the concentration of $H_{cy}$ in the blood leads to a decrease in the formation of TSH in AH cells.

Thus, $T_3$ blocks the synthesis of TSH, through FC, enhancing the process of $H_{cy}$ methylation.

THS production is not suppressed by $T_3$, but by a decrease in the concentration of $H_{cy}$ in the blood associated with the effect of $T_3$ on FC.

Regulation of the interaction between the pituitary gland and the TG is carried out using the sulfur-containing amino acid $H_{cy}$, a metabolic product of Met.

The state of hyperhomocysteinemia can cause changes in thyroid hormone metabolism, creating the illusion of hypothyroidism.

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*REGULATORY CONNECTIONS OF THE FOLATE CYCLE AND PITUITARY-THYROID HORMONES IN CHILDREN FROM AREAS AFFECTED BY THE ACCIDENT AT THE CHERNOBYL NUCLEAR POWER PLANT*

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***The aim*** *of this article is to formulate a scientific conception about the regulatory connections of the folate cycle (FC) and the pituitary-thyroid axis based on the results of the authors' research conducted when examining children from areas affected by the Chornobyl accident.*

***Materials and methods:*** *analytical, bibliographic. The research materials are published research articles by the authors.*

***Results;*** *During the statistical and correlation analysis of metabolic parameters of children from areas bordering the Chornobyl nuclear power plant, an association was revealed between FC and hormones of the pituitary-thyroid axis. A scientific conception is presented about the participation of homocysteine ($H_{cy}$) in the regulation of hormonogenesis of the thyroid gland (TG), according to which $H_{cy}$ activates the synthesis of thyroid-stimulating hormone (TSH) in the cells of the adenohypophysis (AH). In turn, TSH activates the process of $T_4$ deodination with the formation of $T_3$ in peripheral tissues. At the same time, $H_{cy}$ is also directly involved in the formation of cysteine, a component of the coenzyme part of 5-Di deiodinase, which also enhances the process of $T_3$ formation. $T_3$, acting on the MTHFR FC, enhances the formation of CH3-MTHF, and thereby activates the process of Hcy methylation. A decrease in the concentration of $H_{cy}$ in the blood leads to a decrease in the formation of TSH in AG cells. Thus, $T_3$ blocks the synthesis of TSH, through FC, enhancing the process of Hcy methylation.*

***Conclusions:*** *The regulation of the interaction between hypertension and the thyroid gland is carried out using the sulfur-containing amino acid $H_{cy}$, a product of methionine metabolism. THS production is not suppressed by $T_3$, but by a decrease in $H_{cy}$ blood concentration associated with $T_3$ effects on FC. The increase in $H_{cy}$ content in the blood of children from settlements located near the Chornobyl Nuclear Power Plant is due to mutation of the genes responsible for the synthesis of the main FC enzymes, as well as exposure to radionuclides incorporated into their body. The state of hyperhomocysteinemia can cause changes in thyroid hormone metabolism, creating the illusion of hypothyroidism.*

***Keywords: folate cycle, homocysteine, hormonogenesis, children, radioactively contaminated areas.***

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