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INDICATORS OF PAIN SENSITIVITY THRESHOLD IN EXPERIMENTAL OSTEOARTHRITIS AND HYPOTHYROIDISM

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Abstract. Indicators of pain sensitivity threshold in experimental osteoarthritis and hypothyroidism. Nosivets D.S. *Diseases of the thyroid gland are an urgent problem of modern society due to a wide, constant spread of this pathology and with somatic, reproductive and mental disorders associated with these diseases. The negative effect of thyroid hormone dysfunction on the functional state of organs and systems is due to the key role of thyroid hormones in metabolic processes. It is known that metabolic disorders in diseases of the thyroid gland negatively affect the state of bone and cartilage tissue and cause the development of a number of pathological conditions among which osteoarthritis is absolutely important. However, to date, the issue of changing the pain sensitivity threshold against the background of osteoarthritis due to functional insufficiency of the thyroid gland, which is of key importance in studying the efficacy and safety of pharmacotherapy of these diseases, is not sufficiently covered. The author studied the changes in pain sensitivity threshold in rats when modeling osteoarthritis and hypothyroidism. In the work 80 rats were used, which were divided into two experimental groups – the control group (n=40) and the group of animals with experimental osteoarthritis and hypothyroidism (n=40). Experimental hypothyroidism was reproduced by enteral administration of a 0.02% solution of carbimazole, which was prepared at the rate of 5 mg per 250 ml of saline and given with a drinking ration of animals for 6 weeks. Experimental osteoarthritis was reproduced by a single intra-articular injection of 0.1 ml of monoiodoacetic acid solution into the knee joint, prepared at the rate of 3 mg of reagent per 50 μl of sterile saline. To assess the threshold of pain sensitivity in rats against the background of experimental models, the method of electrical stimulation of the rat tail was used in the standard method. The pain threshold was determined by the reaction of vocalization during electrocutaneous stimulation of the rat's tail root. Based on the data obtained, conclusions were drawn about the negative effect of the thyroid hormone deficiency on the formation of the pain response in experimental animals, which indicates a weakening of the response to nociceptive effects, is manifested by an increase in the pain threshold.*

Реферат. Показатели порога болевой чувствительности при экспериментальном остеоартрозе и гипотиреозе. Носивец Д.С. *Заболевания щитовидной железы относятся к актуальной проблеме современного общества в связи с широким, постоянным распространением данной патологии и со связанными с этими заболеваниями соматическими, репродуктивными и психическими расстройствами. Негативное влияние гормональной дисфункции щитовидной железы на функциональное состояние органов и систем обусловлено ключевой ролью тиреоидных гормонов в процессах метаболизма. Известно, что метаболические нарушения при заболеваниях щитовидной железы негативно влияют на состояние костной и хрящевой ткани и обуславливают развитие ряда патологических состояний, среди которых, безусловно, важным является остеоартроз. Однако на сегодняшний день недостаточно освещен вопрос изменения порога болевой чувствительности на фоне остеоартроза вследствие функциональной недостаточности щитовидной железы, который имеет ключевое значение при изучении вопросов эффективности и безопасности фармакотерапии этих коморбидных состояний. Автором изучены изменения порога болевой чувствительности у крыс при моделировании остеоартроза и гипотиреоза. В работе использовано 80 крыс, которые были разделены на две экспериментальные группы – контрольную (n=40) и группу животных с экспериментальным остеоартрозом и гипотиреозом (n=40). Экспериментальный гипотиреоз воспроизводили путем энтерального введения 0,02% раствора карбимазола, который готовили из расчета 5 мг на 250 мл физио-*

логического раствора и давали с питьевым рационом животных в течение 6 недель. Экспериментальный остеоартроз воспроизводили путем однократного внутрисуставного введения 0,1 мл раствора монойодуксусной кислоты в коленный сустав, который готовили из расчета 3 мг реактива на 50 мкл стерильного физиологического раствора. Для оценки порога болевой чувствительности крыс на фоне экспериментальных моделей был использован метод электрического раздражения хвоста крысы в стандартной методике. Болевой порог определяли по реакции вокализации при электрокожном раздражении корня хвоста крысы. На основании полученных данных сделаны выводы о негативном влиянии дефицита тиреоидных гормонов на формирование болевого ответа у экспериментальных животных, что свидетельствует об ослаблении реагирования на ноцицептивное влияние, которое проявляется повышением болевого порога.

Diseases of the thyroid gland belong to one of the urgent problems of modern society due to a wide, constant spread of this pathology and with somatic, reproductive and mental disorders associated with these diseases. In clinical settings, this is due to a decrease in functional dysfunction and the development of hypothyroidism (HT). Thus, among adults HT occurs in 1.5-2% of women and 0.2% of men, and at the age over 60 years – 6% and 2.5% respectively. The prevalence of HT is 0.5-2% among women in the regions with normal iodine consumption, among men it is 10 times less, and among the elderly it is between 0.4 and 2%. According to WHO, among endocrine disorders diseases yroid gland take second place after diabetes [3, 10, 12].

The negative effect of thyroid hormonal dysfunction on the functional state of organs and systems is due to the key role of thyroid hormones in metabolism. Insufficient levels of thyroid hormones in organs and tissues lead to a decrease in bone remodeling processes [5]. Therewith disorders associated with calcium metabolism do not occur in HT and bone tissue is characterized by a lower density of trabecular bone and a greater thickness of the cortical layer of bone. It is known about the decrease calcitonin levels and markers of bone formation (osteocalcin and thyroid-like factor) in serum, increased levels of calcitrol and decreased urinary excretion of pyridinoline and deoxypyridinoline, which confirms the slowing of bone resorption in HT.

The known relationship of thyroid pathology with the development of rheumatoid arthritis and systemic lupus erythematosus, diabetes mellitus, cardiovascular pathology, disorders of the gastrointestinal tract, energy metabolism, autonomic nervous system and sexual imbalances [8]. In HT, lipid peroxidation processes are activated (thyroid hormones in physiological doses have an antioxidant effect, although with their excess oxidative processes are enhanced). Also, thyroid hormones under stress in case of decrease in the reactivity of the body cause an anti-stress effect and their deficiency can contribute to increased sensitivity to stress. Deficiency of thyroid hormones causes slowing of redox processes, disorder of thermoregulation, leads to the accumulation of products of metabolism and, as a consequence, to severe functional disorders of the CNS, development of tissue dystrophy due to impregnation of tissues with mucopolysaccharides with development of myxoedema and “hypothyroid” arthropathy and myopathy. It is known that metabolic disorders in diseases of the thyroid gland negatively affect the condition of bone and cartilage tissue and cause the development of a number of pathological conditions, among which osteoarthrosis is surely important [5]. However, today the issue of changes in the threshold of pain sensitivity against osteoarthritis due to functional deficiency of the thyroid gland, which is of key importance in the study of the efficacy and safety of pharmacotherapy of this comorbid condition, insufficiently addressed [6].

The aim of the work is to study the changes in the pain threshold in experimental animals in the modeling of osteoarthritis and hypothyroidism.

MATERIALS AND METHODS OF RESEARCH

The paper used 80 white adult rats of both sexes weighing 180-230 g. The care, keeping and feeding of animals was carried out in accordance with the requirements of the normative documents in standard conditions of the vivarium of the State Establishment “DMA of Health Ministry of Ukraine”. All animals were divided into two experimental groups – control (n=40) and animals with experimental osteoarthritis and hypothyroidism (n=40).

Before the study onset, the bioethics committee of the State Establishment “DMA of Ministry of Health of Ukraine” examined and approved the study protocol, as well as all procedures related to the animals' keeping, humane treatment and their use in the experiment (in accordance with the requirements of the GLP and the European Convention on Protection of Vertebrate Animals used for research and other purposes, dated 18.03.1986).

Experimental hypothyroidism was reproduced by enteral administration of a 0.02% solution of carbimazole (medicinal agent "Espa-carb", manufactured by Esparma GmbH, Germany; in tablets of 5 or 10 mg), which was prepared at the rate of 5 mg per 250 ml of saline solution and given with drinking

ration of animals for 6 weeks [9, 11]. The adequacy of the model was confirmed by TSH, T_3 and T_4 levels in blood serum of rats.

Experimental osteoarthrosis was reproduced by a single intra-articular injection of 0.1 ml of mono-iodocetic acid solution into the knee joint, which was prepared at the rate of 3 mg of reagent per 50 μl of sterile saline [13]. The model was verified by microscopy of histological samples of the knee joints of rats [5] and changes in the corresponding biochemical markers of blood serum [4].

To assess the threshold of pain sensitivity of animals against experimental models, the method of electrical stimulation of the rat tail was used: steel needle electrodes (0.5 mm diameter) with a fixed electrode distance (10 mm) were introduced into the skin distal of 1 cm from the root of the tail. Evaluation of pain sensitivity was performed in 2-3 min. (animal calms down), 30, 60, 90 and 120 minutes after the onset of a vocal response (cheeping, vocalization) in response to electrical stimulation by ECL-1 stimulator, which gradually increased. The duration of each irritation did not exceed 1 sec. [6].

Statistical processing of the study results was performed using the software STATISTICA 6.1 (StatSoft Inc., serial No. AGAR909E415822FA).

RESULTS AND DISCUSSION

Pain threshold was determined by the reaction of vocalization in case of electrocutaneous irritation of the root of rat's tail. Using this criterion for the evaluation of analgesia (vocalization response to electrical irritation), "hot plate", "inflammatory process" and "tail flick" methods were given preference due to the fact that the vocal response is caused by the functioning of not only the spinal, but also the supra-segmental structures of the brain. In addition, the use of nociceptive tests such as "hot plate" and "tail flick" allows to estimate only the shift of the threshold of the response to nociceptive action and does not always make it possible to really determine the severity of analgesia, including in the presence of motor deficits in animals.

Thus, the study showed that the response of animals with hypothyroidism and osteoarthritis to pain stimulation occurred at a higher intensity of stimulation (Table).

As can be seen from the table, the value of alternating current (AC), which causes corresponding response in the form of vocalization in case of electrocutaneous stimulation of the root of the tail in intact rats was 1.76±0.09 mA, and in rats with hypothyroidism and osteoarthrosis – 2.29±0.04 mA that is, 30% higher.

Comparative characteristics of the response to pain stimulation with electric current in rats

Groups (n = 80)	Statistical values	Pain threshold of reaction (mA) in electrocutaneous irritation of tail
Control (n =4 0)	M	1,76
	m	0,09
Rats with hypothyroidism and osteoarthritis (n = 40)	M	2,29*
	m	0,04
	%	+ 30,0%

Note. * - ($p < 0.05$) compared to control.

Based on the obtained data, it can be concluded about negative affect of thyroid hormone deficiency on the state of pain response development in experimental animals. This feature can be explained by the known involvement of thyroid hormones in the processes of synthesis of proteins of the nervous system that affect neuronal differentiation and, with functional failure, cause pathological effects on the hypothalamus and cerebral cortex [1]. Metabolic hormonal disorders [11] and disregulation of the autonomic nervous system also play an important role. In clinical practice, changes caused by thyroid hormones deficiency are commonly referred to as "hypothyroid masks". In particular, inhibition and fever are characteristic signs of hypothyroidism. Thyroid hormone deficiency can affect physiological mechanisms of adaptation, including higher adaptive responses, which is associated with imbalance of autonomic regulatory mechanisms (lack of sympathetic tone and predominance of parasympathetic effects) and decreased hormone-hormonal activity. As a result of inhibition of anabolic and energy processes in the brain sub-stance. organic lesions of the central nervous system can develop and intellectual functions can be suppressed (memory defects, decrease in short-term memory span, decrease in attention, difficulties in the analysis of present events, dementia), drowsiness and sluggishness is observed. Against the back-ground of brain hypoxia caused by circulatory

disorders, seizures and impairment of consciousness, cerebellar ataxia can occur. Tendon reflexes are slowed down at the expense of relaxation phase and become inhibited due to a decrease in chronotropy, versus problems with nerve impulse conduction [2].

Therefore, with regard to data obtained it can be argued that hypothyroidism and osteoarthrosis lead to a weakening of the response to nociceptive effects, which is manifested by an increase in pain threshold.

CONCLUSIONS

1. Metabolic disorders in diseases of the thyroid gland adversely affect the whole body and condition of bone and cartilage tissue in particular, which causes the development of a number of pathological conditions, among which osteoarthrosis is surely important.
2. In laboratory animals, experimental hypothyroidism and osteoarthrosis lead to impaired response to nociceptive impact, characterized by an increase in their pain threshold.
3. The revealed features of the threshold of pain sensitivity in experimental hypothyroidism and osteoarthrosis open a new direction for finding the optimal ways of medical correction of these pathological conditions.

Conflict of interests. The author declares that there is no conflict of interest.

Prospects for further development. The work was performed on the basis of the research materials of the Department of Pharmacology and Clinical Pharmacology of the State Establishment "DMA of Health Ministry of Ukraine" on the topic "Pharmacological analysis of organ- and endothelial protection in the conditions of experimental pathological states" (State registration number 0118U006631). It is planned to further study the effect of NSAIDs and chondroprotectors on the manifestations of osteoarthrosis in concomitant hypothyroidism.

Conflict of interests. The authors declare no conflict of interest.

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