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PATHOPHYSIOLOGICAL ANALYSIS OF MODULATION OF GABA RECEPTOR ACTIVITY IN EXPERIMENTAL ALZHEIMER'S DISEASE

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Key words: *Alzheimer's disease, carbacetam, behavioral response, memory.*

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Resume. *The annual increase in the number of older people in the world leads to the fact that diseases associated with human aging are becoming increasingly relevant. Existing and new data indicate a significant role of the GABA-ergic system in the mechanisms of Alzheimer's disease. In particular, it is known that the use of GABA-ergic compounds is associated with improved cognition. Some of the nootropics counteract the neurotoxicity of β-amyloid through the activation of GABA-ergic neurotransmission and themselves exhibit anti-amyloidogenic effects, which leads to a decrease in its deposition. Nevertheless, there are still many unclear questions, the answers to which could contribute to the prevention and treatment of the pathology.*

Objective *of the work was to study the effect of carbacetam, as a modulator of GABA receptors, on behavioral response of rats of different ages with scopolamine induced Alzheimer's disease.*

Material and methods*. The experiments were conducted on nonlinear albino mature and old male rats. Alzheimer's disease was simulated by scopolamine hydrochloride (Sigma, USA) introduced intraperitoneally (i/p) in the dose of 1 mg/kg of the body weight once a day for 27 days. On the 28th day, carbacetam was introduced intraperitoneally at a dose of 5 mg/kg once a day during 14 days. The functional state of the central nervous system was assessed by the behavioral response of rats in "open field" and conditioned passive avoidance reflex (CPAR) tests. The results were processed statistically by means of the t-Student criterion. The differences were considered statistically confident with p≤0,05.*

Results. *Based on our research, we established that carbacetam positively changes indicators of motor, orientation-learning activity, emotional reactions and vegetative behavior in rats with Alzheimer's disease. An increased latent period of entrance into the dark block after the introduction of carbacetam reflects effective maintenance of the conditioned passive avoidance reflex to electric painful stimulation. It demonstrates the improvement of cognitive function of rats of different ages with Alzheimer's disease promoted by the new endogenic modulator of the GABA-ergic system.*

Conclusion. *Modulation of GABA receptors with carbacetam confirms the suggestion concerning their role in the mechanisms of adaptation, learning activity and memory in rats of different age with experimental Alzheimer's disease.*

ПАТОФІЗІОЛОГІЧНИЙ АНАЛІЗ МОДУЛЯЦІЇ АКТИВНОСТІ ГАМК-РЕЦЕПТОРІВ ПРИ ЕКСПЕРИМЕНТАЛЬНІЙ ХВОРОБІ АЛЬЦГЕЙМЕРА

Є.П. Дрезналь, Т.І. Кметь

Ключові слова: *хвороба Альцгеймера, карбацетам, поведінкові реакції, пам'ять.*

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Резюме. *Щорічне збільшення у світі кількості людей старшого віку призводить до того, що захворювання, пов'язані зі старінням людини, набувають все більшої актуальності. Існуючі та нові дані свідчать про значну роль ГАМК-ергічної системи в механізмах розвитку хвороби Альцгеймера. Зокрема відомо, що використання ГАМК-ергічних сполук пов'язане з покращенням пізнання. Деякі з ноотропів протидіють нейротоксичності β-амілоїду через активацію ГАМК-ергічної нейротрансмісії та самі по собі виявляють антиамілоїдогенну дію, що призводить до зниження його відкладення. Тим не менш, залишається багато незрозумілих питань, відповіді на які могли б сприяти профілактиці та лікуванню патології.*

Original research

Мета роботи *– вивчення впливу карбацетаму, як модулятора ГАМК-рецепторів, на поведінкову реакцію щурів різного віку зі скополаміноіндукованою хворобою Альцгеймера.*

Матеріал і методи*. Експерименти проводили на нелінійних білих статевозрілих і старих самцях щурів. Хворобу Альцгеймера моделювали скополаміну гідрохлоридом (Sigma, США), який вводили внутрішньоочеревинно (в/п) у дозі 1 мг/кг маси тіла 1 раз на добу протягом 27 днів. На 28-му добу внутрішньочеревно вводили карбацетам у дозі 5 мг/кг 1 раз на добу протягом 14 днів. Функціональний стан центральної нервової системи оцінювали за поведінковою реакцією щурів у «відкритому полі» та тестами умовного рефлексу пасивного уникнення. Результати обробляли статистично за допомогою t-критерію Стьюдента. Відмінності вважали статистично достовірними при p≤0,05.*

Результати. *На основі наших досліджень ми встановили, що карбацетам позитивно змінює показники рухової, орієнтовно-навчальної активності, емоційних реакцій і вегетативної поведінки у щурів із хворобою Альцгеймера. Збільшення латентного періоду входу в темний блок після введення карбацетаму свідчить про ефективну підтримку умовного рефлексу пасивного уникнення на електричне больове подразнення. Показано покращення когнітивних функцій щурів різного віку з хворобою Альцгеймера за допомогою нового ендогенного модулятора ГАМК-ергічної системи.*

Висновок. *Модуляція ГАМК-рецепторів карбацетамом підтверджує припущення щодо їх ролі в механізмах адаптації, навчальної діяльності та пам'яті у щурів різного віку з експериментальною хворобою Альцгеймера.*

Introduction. The annual increase in the number of older people worldwide results in the occurrence of diseases associated with human aging that become more and more relevant. For example, approximately 6,9 million Americans at the age of 65 and older live with Alzheimer's disease today. This amount could rise to 13,8 million by 2060 in case medical programs are not developed to prevent or treat this condition since it remains the fifth leading cause of death among the population aged 65 and older [1]. It is usually diagnosed in people over 65 years of age, but unfortunately, its prevalence and "rejuvenation" have been observed recently. Early-onset dementia accounts for up to 9% of its occurrence.

Alzheimer's disease is a multifactorial progressive neurodegenerative disease characterized by protein conformation disturbance followed by subsequent protein aggregation, dysfunction and death of brain neurons [2]. The etiology of the disease is not clearly understood; therefore, a number of theories have been suggested over the last few decades. Today, there are many hypotheses concerning the development of the disease, which form the base for a large number of strategies of therapeutic effect in progressive neurodegenerative diseases. Treatment of the pathology studies involves the use of drugs of various pharmacological groups, which, in the majority of cases, are unable to stop the progression of the brain damage process. Therefore, the search for new ways to correct the pathology focuses on preserving and possibly restoring nerve cells and neural connections, which is quite relevant.

Over the past decade, numerous scientific studies have shown that the use of GABA-ergic compounds is linked to improved cognition. Specific nootropic agents counteract the neurotoxicity of β-amyloid by activating GABA-ergic neurotransmission, and they exhibit an anti-amyloidogenic effect, resulting in a decrease in its deposits [3, 4, 5].

In particular, it is known about the role of GABA in the formation of long-term memory [6]. As well as information from our previous publications [7], where it was reported that the behavior of sexually mature rats with Alzheimer's disease in the "open field" and conditioned passive avoidance reflex (CPAR) tests after administration of carbacetam for 14 days characterizes a probable significant limitation of their signs of neurological deficit and its integral indicators. Therefore, we were interested in studying the same data in old individuals and comparing them with the results of sexually mature animals, taking into account the statistical data of the predisposition to this pathology in the elderly and to expand the understanding of the pathogenetic mechanisms of neurodegenerative processes.

Objective. Objective of the work was to study the effect of carbacetam, as a modulator of GABA receptors, on behavioral response of rats of different ages with scopolamine induced Alzheimer's disease.

Material and methods. The experiments were conducted on nonlinear albino mature and old male rats, kept under standard vivarium conditions, on well-balanced forage and with free access to water. The study was conducted keeping to the main principles of the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes (18.03.1986); the EU Directives № 609 of 24.11.1986, and the Order of the Ministry of Health of Ukraine № 690 of 23.09.2009 (Protocol № 5 of 16.12.24. of the Commission on Biomedical Ethics on compliance with the moral and legal rules of conducting medical scientific research of Bukovina State Medical University). At the beginning of the study, all the rats were divided into two groups: 1 –

control group; 2 – rats with simulated Alzheimer's disease. At the beginning of the experiment, all rats were divided into two groups: the first group was control rats; the second group was rats with a model of Alzheimer's disease, which was created by intraperitoneal (i/p) administration of scopolamine hydrochloride (Sigma, USA) at a dose of 1 mg/kg body weight once a day for 27 days [7].On the 28th day, the group of rats with simulated Alzheimer's disease was divided into two subgroups: the rats introduced to the physiological solution (saline) and the rats with i/p introduction of carbacetam in the dose of 5 mg/kg of the body weight [7].

The functional state of the central nervous system was studied using the "open field" and CPAR tests [8]. As is known, the "open field" test is designed to study the behavior of rodents under new stressful conditions and allows you to assess the characteristics of individual behavioral elements; the level of emotional and behavioral activity of animals; the strategy of exploratory/protective behavior and signs of neurological deficit [9]. It was carried out using a chamber with plastic walls, where the floor was divided into equal squares with holes that imitate a burrow at the intersection of lines. Rats of all groups were placed in the center of the chamber in turn and the time of the adaptation period of "immobility" – the latent period was recorded, after which their behavior was observed for 3 min. At the same time, the following indicators were recorded: motor activity – the number of crossed squares; orienting and exploratory activity – the number of vertical stands, inspection of holes; emotional reactions – grooming (washing), fecal boluses (defecation), urination (urination).

Memory was assessed using the CPAR test or the "dark-light chamber" test, which is designed to study the behavior of animals under a free choice of comfortable conditions and the state of memory processes. A chamber was used to conduct it, which consisted of a lighted and dark compartments, which were connected by an opening that imitates a burrow. The floor of the chamber in the dark compartment was electrified. Rats were placed in the light compartment. After the time spent in the lighted compartment, the rats entered the dark compartment, the opening was closed, and the rodents were stimulated with a stabilized electric current of 0.8 mA (electropain stimulation). The time of the latent period was recorded. Rats in which the latent period of entering the dark compartment exceeded 3 min and which tried to re-enter the dark compartment were removed from the experiment.

The results were processed statistically by means of the parametric t-Student criterion, nonparametric Mann-Whitney U-criterion. The differences were considered statistically confident with $p \leq 0,05$.

Results and discussion. The "open field" test makes it possible to learn the behavioral response of rats, assess the degree and dynamics of certain behavioral elements, the level of emotional-behavioral response, learning and defensive behavior of animals, the ability to remember orientation stimuli, symptoms of neurological deficiency, and locomotor stereotype. As the results of our studies, we examined carbacetam effect on the behavioral response of mature and old rats during experimental Alzheimer's disease.

Under conditions of the test, the duration of the adjacent latent period in mature rats with simulated Alzheimer's disease was 67,5 % longer (Fig. 1) than in the group of intact control. The similar period was 56,1 % longer in the group of old rats in comparison with the intact control.

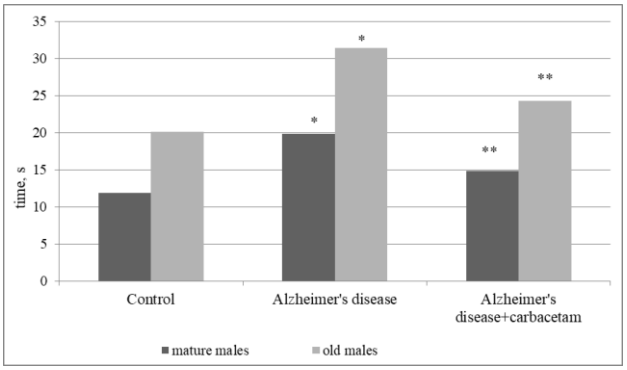

*Fig. 1. Latency period indicators of male rats of different ages with Alzheimer's disease in the «open field» test Notes: * – statistical significance in comparison of mean values with the control; **– statistical significance in comparison with the Alzheimer's disease group*

This parameter 25,2 % decreased in mature rats introduced to carbacetam during 14 days, 22,7 % – in old rats, and it did not differ reliably from that of the control. Considering the peculiarities of the test including light open space and strange surroundings, we can suggest occurrence of certain tension and behavioral changes of rats. This parameter is indicative of confusion, fear, disorientation in the strange surroundings. Moreover, mature rats demonstrate marked disorientation. Nevertheless, carbacetam introduction improves the parameter studied, especially in mature rats. It is indicative of the activation of natural adaptive reactions under the influence of modulation of GABA receptors, which play an important role in memorization processes [10].

The study of indicators of learning activity (Fig.2.) found 23,7 % decrease of motor (horizontal) activity of mature rats with experimental Alzheimer's disease and 40,2% decrease in old rats in comparison with the control group. Although, 14-day carbacetam introduction promoted increase of learning activity in both groups.

Thus, it 19,9 % increased in mature rats and 29,8 % in old ones. Improvement of horizontal motor activity might be associated with inhibition of psychological tension in animals provided by activation of GABA receptors [11].

Further study of rats' behavior in "open field" test showed changes in orientation-learning behavior. Thus, frequency of vertical positions (rising on the hind legs) compared to the intact control (Fig.3), in mature rats with Alzheimer's disease 58,8 % decreased and 83,2 % – in old ones.

At the same time, the use of the modulator of GABA receptors promoted the increase of this indicator by 83,2%

in mature rats and 68,5 % in old rats. Studying the learning activity of rats (Fig.4.) we found that the amount of holes examined by rats with Alzheimer's disease 41,5 % decreased in mature rats and 55,6 % in the old ones compared.

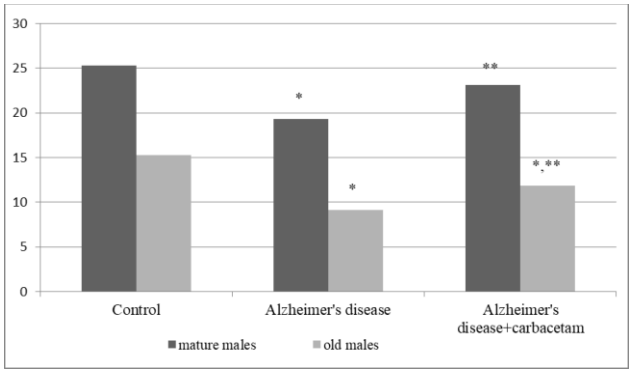

Fig. 2. Indicators of motor (horizontal) activity of male rats of different ages with Alzheimer's disease in the «open field» test
*Notes: * – statistical significance in comparison of mean values with the control; **– statistical significance in comparison with the Alzheimer's disease group*

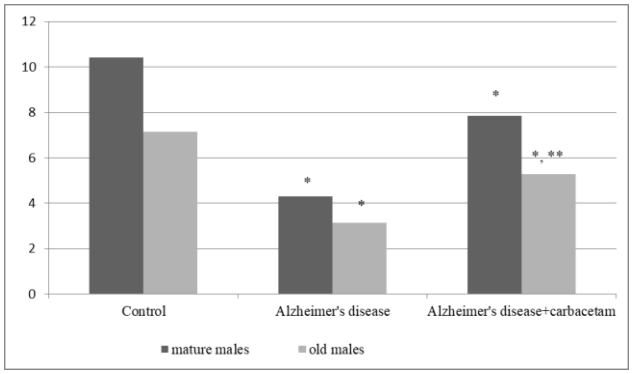

Fig. 3. Indicators of vertical (orienting) activity of male rats of different ages with Alzheimer's disease in the «open field» test
*Notes: * – statistical significance in comparison of mean values with the control; **– statistical significance in comparison with the Alzheimer's disease group*

After carbacetam correction the above indicators 32,7 and 75,0 % increased respectively. Therefore, the results obtained enable us to suggest that carbacetam is able to decrease anxiety level and improve cognitive mechanisms.

One of the constituent parts in studying the animal behavior in "open field" are emotional reactions and vegetative behavior (Fig. 5a, 5b, 5c). We analyzed the following: grooming, urination and fecal bolus reflecting the anxiety level of animals.

Thus, in the group of mature rats with Alzheimer's disease grooming 43,9% decreased and in the group of old rats it 64,3% decreased compared to the control group. At the same time, these groups demonstrated a tendency to reduce the amount of urination and fecal bolus. Under

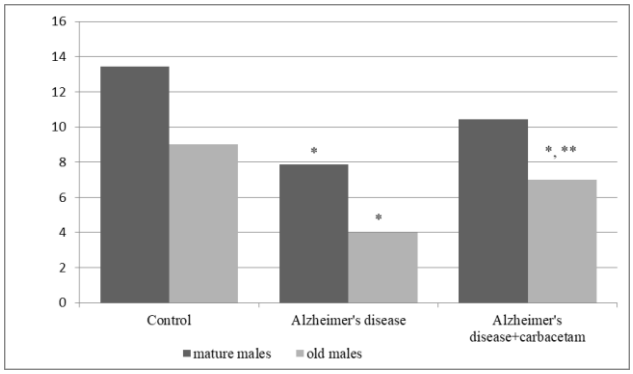

Fig. 4. Indicators of exploratory activity of male rats of different ages with Alzheimer's disease in the «open field» test
*Notes: * – statistical significance in comparison of mean values with the control; **– statistical significance in comparison with the Alzheimer's disease group.*
to the control group

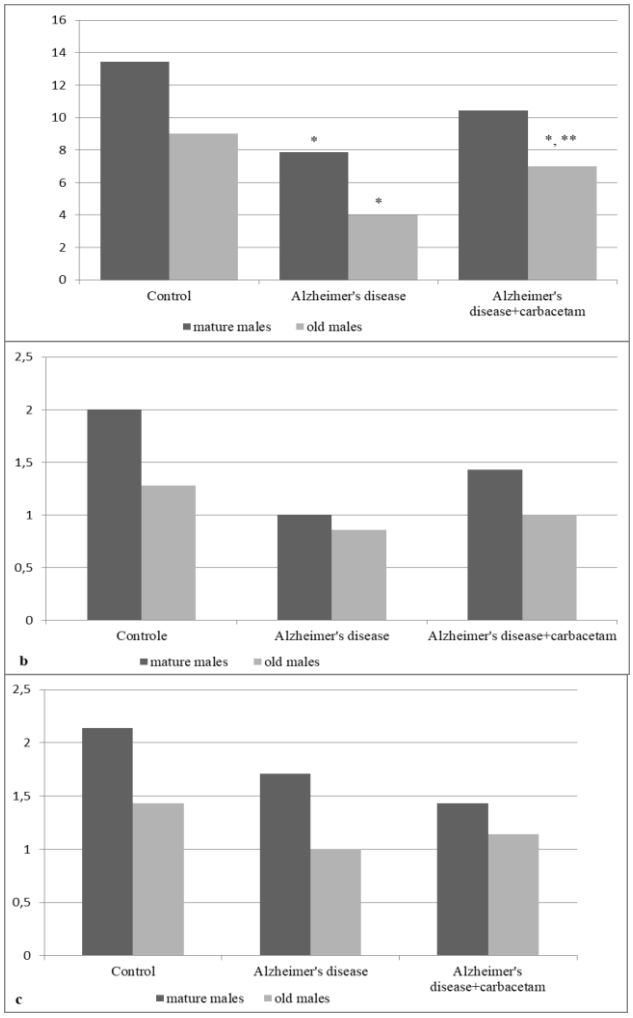

Fig. 5. Indicators of anxiety in rats in the «open field» test: a – grooming, b – urination, c – fecal boluses
*Notes: * – statistical significance in comparison of mean values with the control; **– statistical significance in comparison with the Alzheimer's disease group*

carbacetam effect, grooming indicator increased in comparison with the similar one in rats with simulated pathology. Thus, it was 64,3% higher in mature rats, and 75,5% higher in old ones. Further analysis of vegetative behavior did not find changes in urination and defecation, which in general enables to suggest that carbacetam does not produce a significant effect on emotional level of rats with Alzheimer's disease under the experimental conditions. The results obtained indicate a moderate activating effect of the modulator of GABA receptors on the emotional control system.

Considering the fact that one of the main signs of Alzheimer's disease is cognitive function, we have examined this disorder by means of CPAR test. The results of CPAR test showed that the control group of rats formed a stable reflex in response to painful simulation with electric current (Fig.6, 7). Thus, comparison of the latent period duration in rats from the control group before carbacetam introduction with the results obtained from the animals 24 hours after the first entrance of rats into the dark block determined increased interval of time in 2,8 times in mature rats and 2,1 times – in old ones. In the group of rats which got carbacetam during this period the indicator increased 1,2 times and 1,1 times respectively.

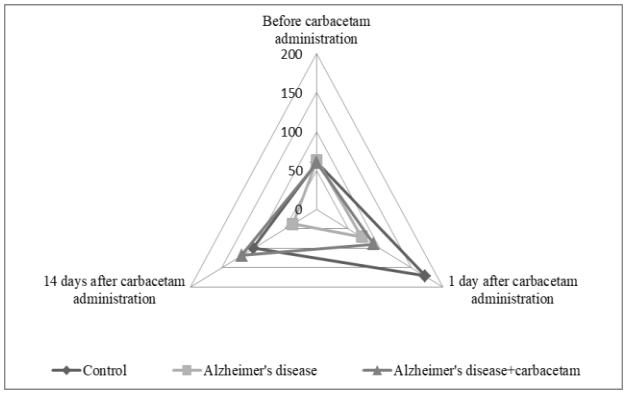

Fig.6. Effect of carbacetam on the latency period of entry into the dark compartment of mature male rats with Alzheimer's disease in the CPAR, M±m

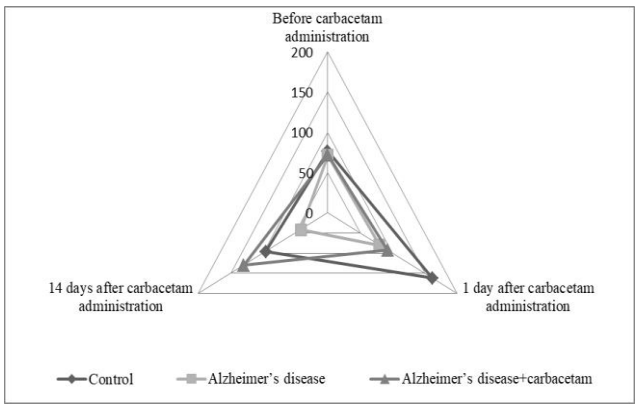

Fig.7. Effect of carbacetam on the latency period of entry into the dark compartment of old male rats with Alzheimer's disease in the CPAR, M±m

We analyzed the duration of the latent period on the 14th day after carbacetam introduction. It should be noted that in comparison with the control group, this indicator 2,6 times decreased in mature rats with Alzheimer's disease and 2,4 times in old rats. At the same time, the animals which received carbacetam presented its 3,1 time increase as compared to the groups of experimental pathology. Therefore, we can suggest memory deterioration in rats with Alzheimer's disease and its improvement after GABA receptor modulation.

Thus, during our studies we found that carbacetam produces a positive effect upon the indicators of motor, orientation-learning activity, emotional reactions and vegetative behavior of rats with Alzheimer's disease of different ages. It provides the basis for suggesting that GABA receptors play a specific role in the mechanisms of adaptation, cognitive activity, and memory. At the same time, we should admit that old rats with Alzheimer's disease presented marked changes in their behavior. The results of our study can be explained by scientific information available that age changes depend on certain neuron subpopulations and their synaptic contacts [12, 13]. A delicate balance between excitatory and inhibitory circuits is fundamental to neuroplasticity and all the aspects of brain function. Age changes in GABA signals can disturb this balance and change susceptibility to diseases, which we observe in our studies [14, 15].

The results obtained in our experiments indicating the available activating effect on locomotion and increased motor activity can be explained by a reduced level of stress and anxiety in experimental animals. It is indicative of anxiolytic properties of carbacetam due to the effect on GABA receptors. The spatial-temporal activity of GABAergic interneurons of the hippocampus is known to be crucial for the regulation of the neuron network activity associated with memory [16]. It is responsible for the maintenance of the excitatory/inhibitory balance and synchronization of activity of several populations of pyramidal neurons in the hippocampus [17]. GABA is known to participate in the formation of learned fear. Certain scientific evidence indicates that GABA-ergic system takes part both, in the formation and consolidation of conditional fear stimuli. GABA activity might be associated with other cognitive processes, including working memory and inhibition of thoughts [18].

Thus, modulation of GABA receptors realized by carbacetam confirms the suggestion about their role in the mechanisms of adaptation, cognitive activity and memory in rats of different ages with experimental Alzheimer's disease.

Conclusions. 1. In old male rats with Alzheimer's disease, according to the «open field» and CPAR tests, changes in behavioral reactions were detected: an increase in the latent period of "immobility", a decrease in motor, orientation-exploratory activity; a reduction in the latent period of entry into the dark compartment, the violations of which are more pronounced than in sexually mature individuals.

2. Carbacetam, as a modulator of GABA receptors, reduces the duration of the latent period of "immobility",

increases motor, orientation-exploratory activity and does not change the frequency of vegetative reactions - fecal boluses and defecations, which indicates a decrease in neurological deficit and its integral indicators with better results in sexually mature rats compared to these old rodents.

Prospects for further research. The obtained data encourage further study of the impact of GABA receptor modulation on the condition of other organs, which may serve as a theoretical basis for identifying opportunities for correction and prevention of neurodegenerative processes.

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