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**GARBUZNEAC ANASTASIA**

# LEARNING AND MEMORY OF RATS WHEN CONSUMPTING STREPTOMYCETES BIOMASS

***165.01. Physiology of humans and animals***

**Abstract of the doctoral thesis in biological sciences**

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The thesis was developed on the basis of the Institute of Physiology and Sanocreatology, Moldova State University, the Institute of Microbiology and Biotechnology, Technical University of Moldova, the Doctoral School of Natural Sciences, Moldova State University.

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**CONTENTS**

## GENERAL CHARACTERISTICS OF THE THESIS

**Relevance of the work.** The study of learning and memory at different levels of organization, despite its long history, remains one of the central sections of both neurophysiology and fundamental science in general. Learning is a complex process of forming new behavior, and its comprehensive study is important for understanding the mechanisms of the nervous system. Neurological memory is a vital process that ensures the adaptation of a living organism to the external environment, adaptive changes in behavior, in the work of neural networks, in the molecular subcellular structure. Learning and memory are closely related, having fundamental significance for a living organism [3, 8].

In accordance with the concept of mental health, learning processes are considered as processes of the formation of psychofunctional and evaluative-executive systems [31, 33]. According to the concept of sanogenic memory, memory is a mental process of adequate reflection of reality through memorization (imprinting, consolidation), storage (preservation, provision), recognition and subsequent reproduction of objective information, sensations, emotions, movements, knowledge of previous experience, determining creative and sanogenic life activity, objective analysis and interpretation of events, phenomena, organization of rational daily activities, orientation in time, space, subjective and objective world in accordance with the real situation [34].

Identifying the causes of premature aging of the brain, accompanied by disruption of cognitive processes, including memory, and finding ways to prevent it have become especially relevant at present. Poor nutrition, stress, adverse environmental impacts, diseases that activate free-radical processes contribute to early aging of the body. As a result of these processes, humanity has become much more likely to encounter pathologies that are accompanied by neurodegenerative processes, such as Alzheimer's, Parkinson's, etc. [4, 15, 23], they are progressing rapidly, especially in developed countries [24], and some of the most important reasons for the increase in the prevalence of cognitive neuropsychiatric disorders are chronic psychogenic stress, stressful lifestyle and abrupt changes in the living conditions of modern man [32, 33].

One of the promising areas of prevention and correction of cognitive pathology at the initial stages of neurodegenerative diseases is the complex use of neuroprotectors with different targets or drugs that combine nootropic activity with neuroprotective properties. In this regard, one of the ways to solve the problem of premature memory loss is to search for substances with neuroprotective and antioxidant properties that affect various neuronal formations of the brain involved in learning and memory processes [4, 11]. Sanocreatological approaches to increasing the sanogenicity of the body and preventing early degradation of functions, including mental ones, include obtaining sanogenic substances of natural origin [32].

In recent years, data have been obtained indicating the influence of metabolites of the biomass of certain strains of streptomycetes and their components on the ability to prevent neurodegeneration provoked by oxidative stress, and their importance as powerful neuroprotective substances under conditions of lipid peroxidation induction has been demonstrated [6, 18]. Currently, a number of secondary metabolites synthesized by strains of streptomycetes are known to have significant antioxidant properties [4, 6, 17, 18]. Moreover, some of the metabolites of streptomycetes have the ability to stimulate neuritogenesis, influencing the ultrastructural organization of various neuronal formations in the brain [13, 21], and the differentiation of neural stem cells [2].

Despite the increasing number of reports on the impact of streptomycete waste products on neuronal processes, their impact on animal behavior has been little studied. It was previously found that long-term consumption of culture fluid and, in particular, biomass of *Streptomyces massasporeus* CNMN-Ac-06 and *Streptomyces fradiae* CNMN-Ac-11 strains isolated from the soils of the central part of the Republic of Moldova by white rats of both sexes facilitates the development of defensive conditioned reflexes and contributes to an increase in the speed of

targeted motor reactions [16, 35, 36]. When studying the effect of secondary metabolites of *Streptomyces avermectilis* and *Streptomyces lincolniensis* avermectins doramectin and ivermectin on the behavioral reactions of white rats, their anxiolytic effect was revealed, in particular. Using the methods of "Open field", "Elevated plus maze", and "Conflict behavior" it was found that in therapeutic doses, secondary metabolites of streptomycetes reduce the level of anxiety and stress, protect rats from the convulsive effects of pentylenetetrazole and picrotoxin [20].

The study of cognitive processes in animals using sensitive, reliable neurobehavioral tests is a particularly important source of information about their changes that occur under the influence of food or pharmacological drugs, and has an undeniable advantage over *in vitro* models, allowing us to accurately assess their ability to learn, perceive space, preserve a memory trace, and identify the presence of disturbances in the activity of certain parts of the brain [7, 14].

Based on the literature data, it is reasonable to assume that the streptomycete biomass contains secondary metabolites capable of stimulating and supporting neuronal processes underlying learning and memory. In particular, one of these metabolites is benzastatins, which demonstrate powerful antioxidant and neuroprotective activity [9]. In this regard, it was decided to use para-aminobenzoic acid (PABA) when cultivating streptomycetes on a nutrient medium, which is the starting material for the synthesis of benzastatins, alkaloids of various groups, some of which are among the most common and powerful antioxidants with neuroprotective properties [1, 10].

**The purpose of the research** is to study the learning and memory characteristics of white rats under conditions of long-term consumption of biomass of *Streptomyces massasporeus* CNMN-Ac-06 and *Streptomyces fradiae* CNMN-Ac-11 strains isolated from the soils of the central part of the Republic of Moldova.

To achieve this goal, the following **tasks** were set:

– to study the biosynthetic properties of *Streptomyces massasporeus* CNMN-Ac-06 and *Streptomyces fradiae* CNMN-Ac-11 strains, cultured on media of different compositions, to obtain biomass, presumably having the greatest effect on learning and memory;

– to study the dynamics of body weight, fertility of white rats and development of rat pups under the influence of streptomycete biomass;

– to study the features of learning and memory of white rats under conditions of long-term consumption of biomass of the strains *Streptomyces massasporeus* CNMN-Ac-06 and *Streptomyces fradiae* CNMN-Ac-11, cultured on the complex nutrient medium SP-I;

– to study the features of learning and memory of white rats under the influence of the biomass of the *Streptomyces massasporeus* CNMN-Ac-06 strain, grown on the SP-I medium with the addition of para-aminobenzoic acid.

**Research hypothesis:** the stimulation of the processes of conditioned reflex and spatial learning, activation of working memory and an increase in the duration of storage of memory traces in white rats is possible by consuming the biomass of local strains of streptomycetes *Streptomyces massasporeus* CNMN-Ac-06 and *Streptomyces fradiae* CNMN-Ac-11, and the addition of para-aminobenzoic acid to the nutrient medium for cultivating streptomycetes can lead to an increase in the effectiveness of the biomass in relation to learning and memory processes.

**Scientific novelty:** The stimulating effect of streptomycete biomass on the process of spatial learning and memory of white rats in the eight-arm radial maze and the Morris water maze has been revealed for the first time. It has been found for the first time that the addition of PABA to the nutrient medium significantly enhances the stimulating effect of the biomass on conditioned reflex and spatial learning and memory. New data have been obtained on the features of the effect of streptomycete biomass on conditioned reflex learning and memory in rats of different ages, indicating its neuroprotective effect. New data have been obtained on the stimulating effect of streptomycete biomass cultivated on a nutrient medium with the addition of PABA on body weight and fertility, which have been patented. A new nutrient medium for culturing the *S. massasporeus* CNMN-Ac-06 strain is proposed, improving its biosynthetic properties, the development of which has been completed by patenting.

**The scientific problem solved in the dissertation:** consists in obtaining new scientifically substantiated knowledge about the features of conditioned reflex and spatial learning and memory in white rats under conditions of their consumption of biomass of local strains of streptomycetes as a food additive using a complex of physiological (behavioural), biochemical and microbiological methods, which led to the establishment of a significant stimulating effect of biomass on the studied cognitive processes and made it possible to demonstrate the promise of strains *S. massasporeus* CNMN-Ac-06 and *S. fradiae* CNMN-Ac-11 for the purpose of obtaining new biologically active substances with neuroprotective and nootropic properties, as well as to propose a new nutrient medium for cultivating streptomycetes with the addition of PABA, the use of which makes it possible to increase the effectiveness of biomass in relation to learning and memory processes.

**Fundamentally new results for science and practice:** based on modern physiological (behavioural), microbiological and biochemical methods, fundamentally new results were obtained on the influence of streptomycete biomass on the learning and memory processes of white rats, as well as on the presumed presence of secondary metabolites with pronounced neuroprotective and antioxidant properties in streptomycete biomass.

**Theoretical significance:** The results obtained expand and deepen scientific understanding of the peculiarities of the processes of conditioned reflex and spatial learning and memory under the influence of biologically active substances of microbial origin with neuroprotective and neurostimulating properties.

**The applicative value of the work:** The results obtained demonstrate the promise of further studies of the strains *S. massasporeus* CNMN-Ac-06 and *S. fradiae* CNMN-Ac-11 with the aim of isolating and identifying biologically active substances with neuroprotective and nootropic properties. A new nutrient medium for the cultivation of the *S. massasporeus* strain CNMN-Ac-06 with the addition of PABA was obtained, with the help of which its biosynthetic properties were improved and the stimulating effect of biomass on the processes of learning and memory was enhanced. The results obtained demonstrate the possibility of obtaining new drugs based on the biomass of local strains of streptomycetes in order to stimulate weight gain and fertility of farm animals.

**Implementation of scientific results:** The results were introduced into the educational process of the Faculty of Geography and Natural Sciences of T.G. Shevchenko Tiraspol State University. 2 patents and 4 medals at international innovation exhibitions were received.

**Approval of scientific results:** The dissertation materials have been presented at the following international conferences: 24th International Pushchino School-Conference of Young Scientists „Biology – Science of the 21st Century" (Pushchino, 2020); Microbial Biotechnology Conference (Chișinău, 2022). Conferences with international participation: International Conference on Scientific Practice and Participation in the International Conference „Instrument for the Development of Scientific Research and Societal Cooperation" (Chișinău, 2021); Life sciences in the dialogue of generations: connections between universities, academia and business community (Chișinău, 2022, 2023). Republican conferences: Tendințe contemporane ale dezvoltării științei: viziuni ale tinerilor cercetători (Chișinău, 2019, 2020); Metodologii contemporane de cercetare și evaluare: Ştiinţe biologice şi chimice, Ştiinţe fizice şi matematice, Ştiinţe economice (Chişinău, 2021); Conferința Ştiinţifică Naţională, consacrată jubileului de 95 ani din ziua naşterii academicianului Boris Melnic (Chișinău, 2023).

The dissertation materials were tested at the International Innovation Exhibitions: European exhibition of creativity and innovation "Euroinvent" (Iași, 2023); The 27th international exhibition of inventics "INVENTICA" (Iași, 2023); Salonul Internațional de Invenții și Inovații „TRAIAN VUIA" (Timișoara, 2023); Salonul Internațional al Cercetării științifice, Inovării și Invenții (Cluj-Napoca, 2023), in which 4 Medals were received.

**Author's contribution.** The dissertation is based on the materials of research on learning and memory of white rats under the influence of streptomycete biomass, carried out by the author for the period 2018-2023, the author formulated a scientific problem, set a goal and objectives, analyzed the research results, formulated general conclusions and practical recommendations.

**Publications on the topic of the thesis.** On the topic of the dissertation, 23 scientific works were published (including 3 without co-authors): articles in scientific journals from the Web of Science, SCOPUS database - 3, articles in scientific journals from the National Register of specialized journals - 1, publications in the materials of international scientific conferences - 10, in the materials of national scientific conferences with international participation - 3, articles in the materials of national scientific conferences - 4, patents - 2.

**The volume and structure of the thesis.** The dissertation is presented on 125 pages of the main text, which includes: annotation (in Russian, Romanian and English), introduction, 6 chapters, general conclusions, recommendations, 5 appendices. The work contains 5 tables, 47 figures and a list of references, including 192 titles.

**Keywords:** white rats, conditioned reflex and spatial learning, working and long-term memory, streptomycetes, biomass, para-aminobenzoic acid, amino acids, lipids.

## THESIS CONTENT

**THE INTRODUCTION** highlights the relevance, scientific and practical significance of studying the processes of learning and memory, including under the influence of streptomycete metabolites, and indicates the purpose and objectives of the study, the methodological and scientific-theoretical basis of the work and its scientific novelty.

## 1. MODERN CONCEPTS OF THE MECHANISMS OF NEUROLOGICAL MEMORY, BIOLOGICALLY ACTIVE SUBSTANCES SYNTHESISED BY STREPTOMYCETES AND THEIR INFLUENCE ON LEARNING AND MEMORY PROCESSES

An analysis of scientific publications and a synthesis of accumulated knowledge in the field of neurochemical and molecular mechanisms of various types of memory from a neurophysiological point of view, as well as modern scientific data on the physiological effects of streptomycete metabolites and, in particular, their influence on neuronal processes underlying learning and memory were carried out.

## 2. MATERIALS AND METHODS OF STUDY

The object of the study were 246 white Wistar rats (144 males and 102 females) aged from 2 to 6.5 months (young) and aged from 12 to 16.5 months (old), kept in standard vivarium conditions with free access to water and food, 12/12-hour light and darkness, taking into account the recommendations of the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes [26].

The biomass of two streptomycete strains isolated from the soils of the central part of the Republic of Moldova and stored in the National Collection of Non-Pathogenic Microorganisms of the Institute of Microbiology and Biotechnology was used to feed the animals: *Streptomyces massasporeus* CNMN-Ac-06 and *Streptomyces fradiae* CNMN-Ac-11. Animals of the experimental groups, starting from the age of 2 months (young) or 12 months (old), received dried biomass of *Streptomyces massasporeus* CNMN-Ac-06 or *Streptomyces fradiae* CNMN-Ac-11 strains, cultivated on nutrient media of various compositions, daily at a dose of 250 mg/kg of body weight as a food supplement to the standard diet for 90 days. Animals of the control groups received a standard diet without added biomass during the same period of time.

The productivity of streptomycete strains depends on the composition of the nutrient medium. To determine the most productive strain in terms of the amount of biomass required for animal feed, as well as in terms of lipid composition (total lipids and lipid fractions), the studied strains were cultivated on three different nutrient media (g/l): M-I (corn flour – 20.0, yeast – 0.5, $CaCO_3$ – 0.15, pH 7.0-7.2); SP-I (corn flour – 20.0, soy flour – 10.0, NaCl – 0.5, $CaCO_3$ – 1.0, pH 7.0-7.2); SP-III (corn flour – 20.0, soy flour – 10.0, NaCl – 0.5, $CaCO_3$ – 1.0, $K_2HPO_4$ – 3.0, pH

7.0-7.2) [5, 30]. Extraction of intracellular lipids from the biomass was carried out using the Folch method [4]. The qualitative and quantitative composition of lipids was determined by thin-layer chromatography on Sorbfil plates and by the densitometric method [19].

In order to study the contribution of the antioxidant neuroprotective activity of streptomycete metabolites – benzastatins to the neurophysiological effects of biomass, nutrient media with the addition of PABA, which is the starting material for the synthesis of benzastatins, were used during the cultivation of streptomycetes [9]. The *Streptomyces massasporeus* CNMN-Ac-06 strain was cultivated on the SP-I nutrient medium containing different amounts of PABA (1 – 0.685; 2 – 1.37; 3 – 2.74 g/l) and a comparative study of the amount of biomass, total lipids, lipid fractions and amino acids was performed depending on the PABA content in the nutrient medium compared to the control (standard SP-I medium).

To determine the amino acid composition of the biomass of the *Streptomyces massasporeus* CNMN-Ac-06 strain, cultivated on a medium with the addition of PABA, the ion exchange chromatography method was used on an AAA-339 M "Microtehna" amino acid analyzer [25].

The toxicological properties of the biomass of streptomycete strains cultivated on a nutrient medium containing and not containing PABA [29] were studied, as well as its effect on the dynamics of body weight, fertility of white rats and postnatal development of rat pups. The body weight of the animals was recorded every 7 days on electronic laboratory scales A-2500 from Axis (Poland). The body weight studies were carried out both under normal physiological conditions and under heat stress. Animals that were subjected to heat stress were kept daily for 2 weeks in a room where the air temperature was +34+36°C for 4 hours.

To study the process of conditioned reflex learning with aversive reinforcement under the influence of streptomycete biomass, the method of developing a conditioned reaction of active avoidance (CRAA) of an electrocutaneous pain stimulus was used [27]. Rats were trained using the method of bilateral active avoidance in a shuttle chamber. In order to study the processes of conditioned reflex memory and extinction of the conditioned reflex, the dynamics of the latent period of the avoidance reaction (LPAR) were determined. The dynamics of LPAR were studied on the 5th, 10th, 15th, 20th, 30th and 45th days after the experiment on developing conditioned reflexes of active avoidance.

In order to study spatial learning and memory under the influence of streptomycete biomass, the behavioral setup "Eight-arm radial maze" (EARM) (with food reinforcement) and the modern and well-proven in laboratories of various countries "Morris water maze" (MWM) technique were used [7, 12, 14]. These techniques allow us to study the processes of spatial learning and memory (working and long-term), where working memory is considered as an operational component of short-term memory. An important indicator of the learning and testing process in EARM is: the average spatial memory score (ASMS) with different duration of the delay phase (DP) of 30 s and 10 min. On the 30th day of the experiment, spatial long-term memory was assessed. Using the MWM, we studied the duration of the latent period during which the rat found the platform and climbed onto it (LP, s) and the length of the path the animal traveled from the place where it was placed in the water to the platform (PT, cm), and determined the time spent in each sector (%). On the 5th, 9th and 30th days of the experiment, we assessed the activation of spatial long-term memory and the duration of retention of memory traces.

The obtained data were statistically processed by the ANOVA method using Student's t-test.

## 3. STUDY OF BIOLOGICALLY ACTIVE SUBSTANCES CONTAINING THE BIOMASS OF *STREPTOMYCES MASSASPOREUS* CNMN-AC-06 AND *STREPTOMYCES FRADIAE* CNMN-AC-11 STRAINS USED IN EXPERIMENTS TO STUDY LEARNING AND MEMORY PROCESSES

The studied strains were cultivated on three complex liquid media, the composition of which is presented above. The results of the conducted studies showed that when cultivating the strain *S. fradiae* CNMN-Ac-11 on the nutrient medium SP-III, the biomass yield is significantly

higher than on the media M-I and SP-I (by 1.61 and 1.52 times, respectively). At the same time, the strain *S. massasporeus* CNMN-Ac-06 has the highest biomass yield when cultivated on the nutrient medium SP-I (Table 3.1).

**Table 3.1. Formation of biomass and total lipids in strains *S. fradiae* CNMN-Ac-11 and *S. massasporeus* CNMN-Ac-06 during cultivation on complex media**

| **Nutrient medium** | ***ADB, g/l*** | | ***Total lipids, % of ADB*** | |
|---|---|---|---|---|
| **Strain** | ***Streptomyces fradiae* CNMN-Ac-11** | ***Streptomyces massasporeus* CNMN-Ac-06** | ***Streptomyces fradiae* CNMN-Ac-11** | ***Streptomyces massasporeus* CNMN-Ac-06** |
| M-I | 5,95±1,26 | 10,56±1,29 | 8,76±1,02 | 11,96±0,29 |
| SP-I | 6,09±2,60 | 11,53±0,83** | 15,85±0,49*,** | 19,52±0,45*,** |
| SP-III | 9,61±0,28*,** | 9,86±0,49* | 12,76±0,26* | 13,52±0,67 |

*Note:* * – significant differences between SP-I and/or SP-III compared to M-I (P<0.05), ** – significant differences between SP-I and SP-III (P<0.01-0.05)

When determining the proportion of total lipids in the absolutely dry biomass (ADB) depending on the cultivation medium, it was found that their highest content in the biomass of both the *S. fradiae* CNMN-Ac-11 strain and *S. massasporeus* CNMN-Ac-06 was observed in the SP-I medium (significantly compared to M-I and SP-I), and the lowest on the M-I medium (Table 3.1).

The results of the study of lipid fractions (phospholipids, sterols, triglycerides, etc.) showed that the greatest amount of phospholipids (as a percentage of total lipids), which play an important role in the transmission of nerve impulses and synaptic plasticity, which are important parameters of memory processes, was noted during the cultivation of the *S. fradiae* CNMN-Ac-11 strain on SP-I and SP-III media (11.11±1.87 and 11.96±1.12%, respectively), and the *S. massasporeus* CNMN-Ac-06 strain on SP-I medium (12.15±0.98%).

Thus, the results of the experiments showed that the complex nutrient medium SP-I to the greatest extent contributes to the increase in the amount of biomass of the strains *S. fradiae* CNMN-Ac-11 and *S. massasporeus* CNMN-Ac-06, the content of total lipids in it, and, what is especially important, to the increase in the amount of such a physiologically important lipid fraction as phospholipids. Therefore, the complex nutrient medium SP-I was selected for further studies.

In order to study the contribution of the antioxidant neuroprotective activity of streptomycete metabolites – benzastatins to the neurophysiological effects of biomass during the cultivation of the *S. massasporeus* CNMN-Ac-06 strain, the SP-I nutrient medium with the addition of PABA in three concentrations was used: 0.685, 1.37 and 2.74 g/l. As a result of the studies, it was established that the addition of PABA to the nutrient medium in all concentrations, especially 1.37 g/l, contributes to an increase in the amount of biomass, and the addition of PABA in doses of 1.37 and 2.74 g/l approximately equally contributes to an increase in the content of total lipids in the biomass (Table 3.2).

**Table 3.2. Accumulation of biomass and lipids by the strain *S. massasporeus* CNMN-Ac-06 when cultivated on the complex medium SP-I with the addition of PABA**

| ***Cultivation medium*** | ***Biomass*** | | ***Total lipids*** | |
|---|---|---|---|---|
| | ***ADB, g/l*** | ***% of control*** | ***Lipids, g/l*** | ***% of control*** |
| *1) SP-I – (control)* | 7,99±1,12 | - | 1,48±0,19 | - |
| *2) SP-I + PABA (0,685 g/l)* | 10,91±1,07* | 136,54* | 1,49±0,14 | 100,84 |
| *3) SP-I+ PABA (1,37 g/l)* | 24,99±1,1* | 312,76* | 1,96±0,08* | 132,28* |
| *4) SP-I+PABA (2,74 g/l)* | 15,41±0,78* | 192,86* | 1,85±0,12* | 124,94* |

*Note:* * – significant differences compared to control (P<0.05).

Figure 3.1 shows that when PABA is added to the SP-I nutrient medium in concentrations from 0.685 to 2.74 g/l, the ratio of lipid fractions changes. The proportion of phospholipids increases at the maximum concentration of PABA, the proportion of sterols and triglycerides increases when PABA is added in any of the above concentrations, and to the greatest extent at a PABA concentration of 1.37 g/l.

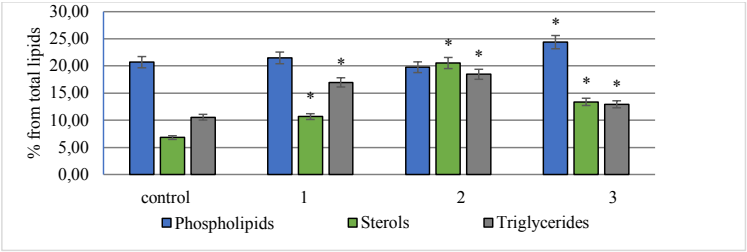


**Fig. 3.1. The amount of the main lipid fractions of the biomass of the *S. massasporeus* CNMN-Ac-06 strain after cultivation on the complex medium SP-I with the addition of PABA.** Along the abscissa axis of the cultivation medium: 1 – SP-I (control); 2 – SP-I + PABA 0.685 g/l; 3 – SP-I+ PABA 1.37 g/l; 4 – SP-I+PABA 2.74 g/l, *– reliable differences compared to the control (P<0.01-0.05)

We have conducted studies of the amino acid content in the biomass of the *S. massasporeus* CNMN-Ac-06 strain when culturing on the complex nutrient medium SP-I with the addition of PABA. Until now, the lipid and amino acid composition of the streptomycete biomass, the change in its amount when PABA is added to the nutrient medium have not been studied.

The analysis of the amino acid content (16 amino acids were identified) in the biomass of the *S. massasporeus* CNMN-Ac-06 strain showed that the amount of amino acids, which are especially necessary according to modern concepts for learning and memory processes, increased compared to the control when PABA was added to the cultivation medium in three concentrations (0.685, 1.37 and 2.74 g/l): aspartic acid (by 32.48±2.01, 63.69±1.75 and 64.09±1.12%, respectively), threonine (by 48.54±1.47, 57.28±1.09 and 28.15±2.68%, respectively), proline (by 15.38±2.13, 46.39±1.78 and 39.17±1.42%), respectively), phenylalanine (by 30.30±1.78, 31.06±1.32 and 11.36±2.12%, respectively). The arginine content increased with the addition of PABA at a dose of 1.37 and 2.74 g/l (by 31.48±2.12 and 42.59±1.68%, respectively), and glutamic acid and glycine increased with the addition of PABA at 1.37 g/l. Analysis of the arginine content showed a tendency to increase with the addition of PABA at 0.685 g/l to the medium, and cysteine - with the addition of PABA at a dose of 0.685 and 2.74 g/l. As a result, it can be concluded that the SP-I nutrient medium with the addition of PABA at 1.37 g/l is the best for obtaining biomass with an optimal amino acid composition in the study of learning and memory processes.

Thus, optimization of the complex nutrient medium SP-I by adding PABA promotes an increase in the biomass yield of the *S. massasporeus* CNMN-Ac-06 strain, the content of total lipids, phospholipids and sterols in it, and also leads to an increase in the content of amino acids, including those especially necessary for learning and memory processes. The greatest efficiency in relation to the formation of biomass, total lipids, their fractions and amino acids is demonstrated by the addition of PABA at a dose of 1.37 g/l.

## 4. INFLUENCE OF STREPTOMYCETES BIOMASS ON BODY WEIGHT GROWTH, FERTILITY OF WHITE RATS AND DEVELOPMENT OF RAT PUPS

The studies were conducted to study the subchronic toxicity of the biomass of the strains *S. fradiae* CNMN-Ac-11 and *S. massasporeus* CNMN-Ac-06, cultivated on the nutrient medium SP-I, as well as the strain *S. massasporeus* CNMN-Ac-06, cultivated on the medium SP-I with the

addition of PABA. The biomass was given in a mixture with feed in a therapeutic dose (250 mg / kg body weight) and a dose three times higher than the therapeutic, for 90 days. The results of the studies showed that the biomass of the studied strains did not have a negative effect on the clinical condition of white rats, no changes in behavior were found compared to the control receiving a standard diet. No deaths of animals throughout the experiment, as well as deviations and features in the structure of the organs of white rats were detected during pathomorphological examination. The coefficients of the mass of the internal organs of white rats did not differ significantly from the control indicators, which indicates the absence of any toxic effect of the biomass of streptomycete strains on the animal organism and their good tolerance.

When studying the dynamics of body weight under conditions of consumption of streptomycete biomass by white rats of both sexes, it was found that under normal physiological conditions, the weight gain of male rats consuming the biomass of the strains *S. massasporeus* CNMN-Ac-06 (BM1) and *S. fradiae* CNMN-Ac-11 (BM2) was significantly higher compared to the control on the 5th-6th and 8th weeks of the experiment (Fig. 4.1). In animals consuming the biomass of the strain *S. massasporeus* CNMN-Ac-06, cultivated on a medium containing 1.37 g/l PABA (BM1PABA1), the weight gain was significantly higher on the 2nd-3rd and 6th-10th weeks of the experiment compared to animals of both the control group and BM1 (Fig. 4.1). While in rats consuming the biomass of the *S. massasporeus* strain CNMN-Ac-06, cultivated on a medium containing 2.74 g/l PABA (BM1PABA2), weight gains were higher only on the 4th and 9-10th weeks of the experiment compared to the control and BM1 groups. Studies of the body weight dynamics of female rats consuming the biomass of streptomycete strains cultivated both on a standard nutrient medium and with the addition of PABA showed similar results to those in male rats.

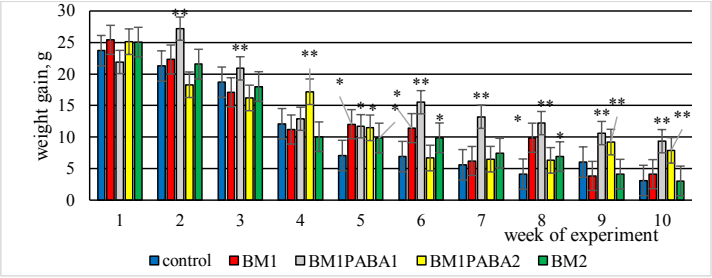


**Fig. 4.1. Dynamics of weight gain in male white rats when consuming biomass of the strains *S. massasporeus* CNMN-Ac-06 and *S. fradiae* CNMN-Ac-11, cultured on standard nutrient medium SP-I and nutrient medium containing PABA, under normal physiological conditions,** * – significant differences compared to the control (P<0.01-0.05), ** – significant differences compared to BM1 (P<0.01-0.05)

Under stress conditions (weeks 3-4 of the experiment), weight gains in animals consuming BM1 and BM2 decreased to a lesser extent than in the control, while weight gains in animals consuming *S. massasporeus* CNMN-Ac-06 strain biomass with feed, cultured on a medium containing PABA, were significantly higher under stress conditions than in animals of the groups consuming the biomass of streptomycete strains without PABA, indicating an increase in their body resistance to heat stress. In the post-stress period (weeks 5-10 of the experiment), weight gains in animals consuming BM1PABA1 and BM1PABA2 were approximately equally higher than in animals of the control group and BM1, thereby contributing to a more intensive restoration of physiological capabilities after exposure to unfavorable environmental conditions. At the same time, the weight gain of BM1 was significantly higher in the 7th and 9th weeks of the experiment compared to the control, and BM2 – only in the 6th week (Fig. 4.2).

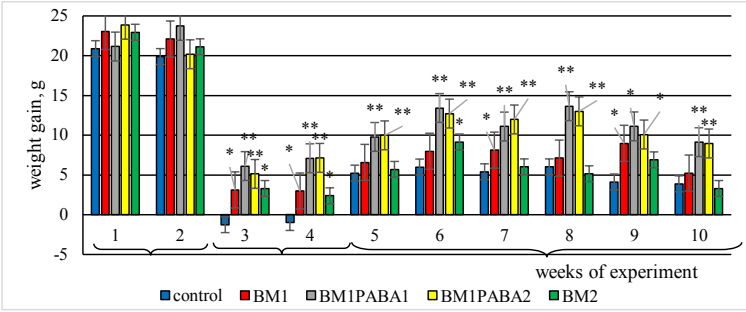


**Fig. 4.2. Dynamics of weight gain in male white rats when consuming biomass of the strains *S. massasporeus* CNMN-Ac-06 and *S. fradiae* CNMN-Ac-11, cultured on standard nutrient medium SP-I and nutrient medium containing PABA, under heat stress conditions,** * – significant differences compared to the control (P<0.05), ** – significant differences compared to BM1 (P<0.05)

When studying the effect of streptomycete biomass on the fertility of white rats, it was found that adding the biomass of the *S. massasporeus* CNMN-Ac-06 strain, cultivated on a nutrient medium containing PABA at a dose of 1.37 g/l (BM1PABA1), to the main diet contributed to a significant increase in their fertility, a decrease in postnatal mortality of rats, and an increase in the body weight of rats after birth and during the first 6 weeks of their postnatal development (Table 4.1).

**Table 4.1. Reproductive function indices of white rats and development of rat pups when consuming biomass of strains *S. massasporeus* CNMN-Ac-06 and *S. fradiae* CNMN-Ac-11, cultured on standard nutrient medium SP-I and nutrient medium containing PABA**

| Indicators studied | Animal groups | | | |
|---|---|---|---|---|
| | ***Control*** | ***BM1*** | ***BM1PABA1*** | ***BM2*** |
| Number of newborn rats per female, abs. | 10,50±1,2 | 12,23±0,75 * | 13,81±0,41 * | 11,84±0,67 * |
| Fertility index, % of control | - | 116,47±1,12* | 131,52±0,68* | 107,33±0,98* |
| Postnatal mortality of rat pups after 3 weeks, abs. | 9 | 5* | 2* | 6* |
| Body weight of newborn rats, g | 4,85±1,18 | 5,71±0,75 * | 6,90±0,62 * | 5,98±0,54* |
| ***Dynamics of body weight of rat pups, g*** | | | | |
| 1 week | 7,12±0,78 | 9,44±0,60 * | 11,80±1,2 * | 8,58±0,64 * |
| 2 weeks | 11,20± 1,02 | 15,71±0,98* | 18,49±0,96 * | 14,81±0,76* |
| 3 weeks | 18,51±0,93 | 26,31±1,09 * | 32,14±1,02* | 24,78±0,98 * |
| 4 weeks | 30,53±1,53 | 35,40±2,30 | 53,43±1,77 * | 37,13±1,90* |
| 5 weeks | 54,90±2,02 | 65,13±3,02 | 78,01±3,24 * | 64,21±3,13 |
| 6 weeks | 74,08±3,78 | 88,57±4,54 * | 99,10±6,18 * | 86,71±3,98 * |

*Note:* * – significant differences compared to control (P<0,05)

Thus, consumption of biomass of *S. massasporeus* CNMN-Ac-06 and *S. fradiae* CNMN-Ac-11 strains by white rats, cultivated on the SP-I nutrient medium, promotes an increase in body weight gain and fertility. Addition of PABA to the nutrient medium promotes a more significant increase in body weight gain both under normal physiological conditions and under heat stress compared to the control and the biomass obtained by culturing streptomycete strains on a standard nutrient medium, and also promotes a significant increase in the fertility of white rats, a decrease in postnatal mortality of rat pups, and an increase in the body weight of rat pups after birth and during the first 6 weeks of their postnatal development.

## 5. COMPARATIVE EFFECT ON LEARNING AND MEMORY TRACE RETENTION OF THE BIOMASS OF *STREPTOMYCES MASSASPOREUS* CNMN-AC-06 AND *STREPTOMYCES FRADIAE* CNMN-AC-11 STRAINS, GROWN ON THE COMPLEX NUTRIENT MEDIUM SP-I

The studies of the process of conditioned reflex learning with aversive reinforcement in a shuttle chamber were performed on white male rats of different ages (young and old). Analysis of the results of the CRAA development showed that in young animals of both experimental groups that consumed the biomass of the strains *S. massasporeus* CNMN-Ac-06 (BM1) or *S. fradiae* CNMN-Ac-11 (BM2), stimulation of the conditioned reflex activity was observed, which, in general, confirms the data obtained earlier at the Institute of Physiology and Sanocreatology on the positive effect of the metabolites of the studied strains of streptomycetes on the process of CRAA development in white rats [35, 36]. The use of BM1 leads to an increase in the number of CRAA in young rats on days 4-6 and 8-10 of the experiment compared to the control, while when rats consume BM2, the proportion of conditioned reflexes is significantly higher from days 3 to 10, as well as on days 12 and 14 of the experiment (Fig. 5.1). It should be especially noted that the use of BM2 as a food additive contributes to achieving a 100% level of CRAA production on days 12 and 14 of the experiment.

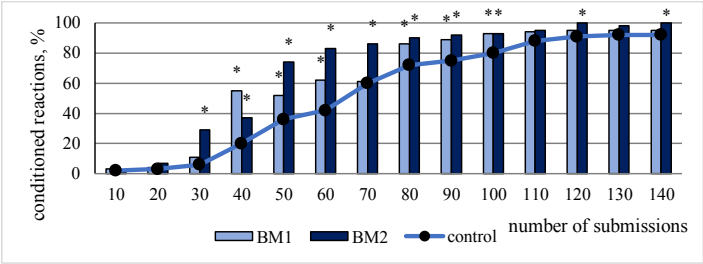


**Fig. 5.1. Dynamics of conditioned reflex learning with aversive reinforcement in young rats with long-term consumption of biomass of strains *S. massasporeus* CNMN-Ac-06 (BM1) and *S. fradiae* CNMN-Ac-11 (BM2),**
* – reliable differences compared to the control (P<0.05)

According to the results obtained, CRAA is developed much more slowly in old animals than in young animals (Fig. 5.2). Thus, on the 5th day of the experiment, the proportion of conditioned reflex runs in the total number of young rats in the control group was 36%, while in old animals it was 5%; on the 10th day, young animals achieved 80% of the level of conditioned reflex development, while in old animals it was slightly more than 32%. The obtained data may indicate the development of neurodegeneration processes in old rats during this period.

A comparative analysis of the effect of animal consumption of *S. massasporeus* CNMN-Ac-06 and *S. fradiae* CNMN-Ac-11 biomass in young and old animals shows that the efficiency of both BM1 and BM2 is significantly higher in old rats compared to young ones (Figs. 5.1 and 5.2). Thus, adding BM1 to the feed of white rats leads to a more pronounced effect on the process of conditioned reflex learning in old animals compared to young animals on the 4th-9th days of the experiment (more than 2 times).

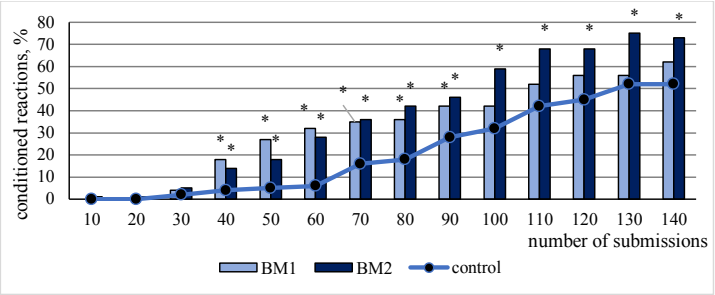


**Fig. 5.2. Dynamics of conditioned reflex learning with aversive reinforcement in old rats when consuming the biomass of strains *S. massasporeus* CNMN-Ac-06 (BM1) and *S. fradiae* CNMN-Ac-11 (BM2), *** – reliable differences compared to the control (P<0.05)

When comparing the results of BM2 efficiency obtained on young and old animals, it is evident that in old rats the effect of BM2 on the learning process is significantly more pronounced: on the 5th day BM2 increases the proportion of conditioned reflex reactions in the total number of runs in young rats by less than 2 times, and in old rats - by 4 times, on the 10th day - in young animals - by 15.6%, and in old - almost 3 times. It should be noted that in old animals BM1 affects the learning process only at the first stage of the experiment, while the effect of BM2 persists throughout the experiment. This may reflect the specific composition of the biomass of each of the studied streptomycete strains, namely the composition of metabolites that have neurophysiological effects.

The preservation of the memory trace in white rats was studied by determining the dynamics of the LPAR over 45 days after the development of the CRAA. Addition of the biomass of both streptomycete strains to the feed of young animals contributes to a reduction in LPAR on the 40th and 45th days of the study to approximately the same extent. Consequently, the metabolites contained in the streptomycete biomass contribute to the prevention of forgetting processes and the improvement of memorization processes and storage of memory traces (Fig. 5.3).

The background values of LPAR in old rats of all groups did not have statistically significant differences. LPAR in old rats increased progressively, starting from the 15th day after the development of CRAA, much more intensively than in young animals, which indicates a more pronounced process of extinction of memory traces (Fig. 5.4). In old rats, when consuming BM1, reliably lower LPAR values are observed on the 30th and 45th days of the study compared to the control, and in animals receiving BM2 - throughout the experiment, starting from the 15th day. Based on these data, it can be assumed that the metabolites included in the local strains of streptomycetes help prevent premature memory extinction in old animals and maintain memory processes within sanogenic limits.

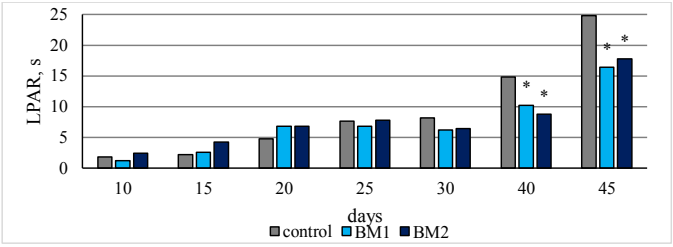


**Fig. 5.3. Dynamics of LPAR in young rats over 45 days after the development of CRAA when consuming the biomass of the strains *S. massasporeus* CNMN-Ac-06 (BM1) and *S. fradiae* CNMN-Ac-11 (BM2), *** – significant differences compared to the control (P<0.05)

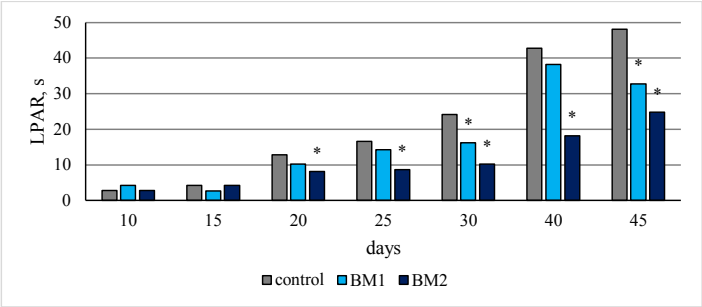


**Fig. 5.4. Dynamics of LPAR in old rats for 45 days after the development of CRAA when consuming the biomass of the strains *S. massasporeus* CNMN-Ac-06 (BM1) and *S. fradiae* CNMN-Ac-11 (BM2), *** – reliable differences compared to the control (P<0.05)

Thus, consumption of streptomycete strain biomass results in a noticeable facilitation of the process of active avoidance skill learning and improvement of conditioned reflex memory in young and, especially, old animals. As mentioned above, a number of "new" lipid peroxidation inhibitors have been isolated from various streptomycete strains and their significance as powerful neuroprotective substances under conditions of lipid peroxidation induction has been demonstrated [6, 18]. Based on this, it can be assumed that the effect of facilitating the development of defensive conditioned reflexes under the influence of streptomycete biomass recorded in the work is due to the neuroprotective action of its antioxidants in relation to the activation of free radical oxidation induced under conditions of pain stress accompanying the development of CRAA with electrocutaneous reinforcement in the shuttle chamber. This assumption is to a certain extent confirmed by the results of experiments on old animals. The fact that the efficiency of streptomycete biomass application in old animals is significantly higher than in young animals, taking into account the role of oxidative stress in the development of age-related neurodegenerative changes against the background of decreased activity of the multilevel antioxidant system of nerve cells, supports the assumption of a neuroprotective mechanism of the effects of streptomycete strain biomass metabolites on the processes of conditioned reflex activity and memory. Based on the presence of streptomycete metabolites that have the ability to stimulate neuritogenesis and differentiation of neuronal stem cells [2, 13, 21], it cannot be ruled out that the observed effect of the biomass of the studied streptomycete strains is also due to its influence on the neuronal processes underlying learning and memory.

The results of the study of spatial learning and memory under the influence of the biomass of the strains *S. massasporeus* CNMN-Ac-06 (BM1) and *S. fradiae* CNMN-Ac-11 (BM2) using the EARM with food reinforcement showed that long-term consumption of streptomycete biomass by white rats of both sexes contributes to a noticeable increase in the number of correct entries into the arms with the extraction of a food reward and a decrease in the number of errors, i.e. any incorrect entries into the arms, which leads to a noticeable increase in the average spatial memory score (ASMS), in other words, contributes to the facilitation of the learning process and the activation of working memory. It was found that the consumption of BM1 by animals increases ASMS to a greater extent compared to BM2 (Figs. 5.5-5.7), especially at the second stage of testing, after a break on days 8 and 9 (Figs. 5.5 and 5.6), which contributes to the activation of long-term memory on the 10th day of the experiment. It is interesting to note that the analysis of the dynamics of the ASMS in rats of the control and experimental groups shows that the duration of the delay phase (DP) has a significant effect on the learning process, especially on days 1–4 of the experiment. In white rats of both sexes, in almost all cases, the ASMS with a 10-min DP is significantly higher than with a 30-s DP. It is known that the use of guillotine doors causes a short-term freezing reaction, a behavior that rats usually demonstrate in stressful situations [22]. Opening and closing the EARM doors at the beginning of the testing phase could have been an

uncontrollable stressor that disrupted the rats' attention. Over 10 minutes, these stressors were spread out in time, which allowed the animals to recover from the stressful stimuli during testing. In contrast, the potentially stressful stimuli acted for a short period of time under the 30-s DP, and the rats may not have been able to fully recover from the first stressor before the subsequent stressor occurred. Attention was impaired and learning was worsened in rats under the conditions of 30 s, but not 10 min, DP. It should be noted that the effectiveness of streptomycete biomass is higher under 30 s DP compared to 10 min, and especially at the initial stage of the experiments. It can be assumed that this is due to their antioxidant effect, which contributed to the reduction of the negative effects of stress on nerve cells. However, the effectiveness of streptomycete biomass remains significant under 10 min DP, as well as at the second stage of training, after the animals have become accustomed and the stress level has decreased. This allows us to assume that the streptomycete biomass contains metabolites with antioxidant action, which have a neuroprotective effect, as well as metabolites that have the ability to stimulate neurogenesis and synaptogenesis.

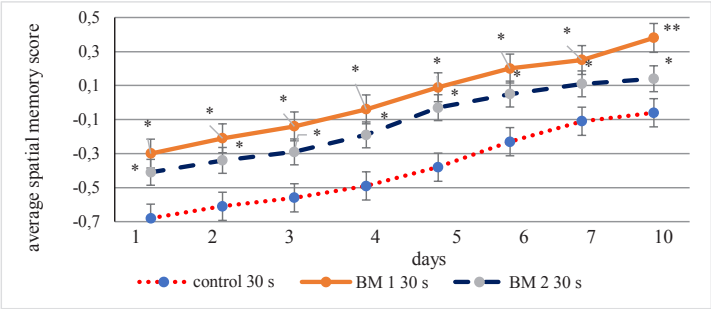


**Fig. 5.5. Dynamics of the ASMS of male rats in the EARM with a 30-s delay under the influence of the biomass of the strains *S. massasporeus* CNMN-Ac-06 (BM1) and *S. fradiae* CNMN-Ac-11 (BM2),** *– significant differences compared to the control (P<0.05), **– significant differences BM1 compared to BM2 (P<0.05)

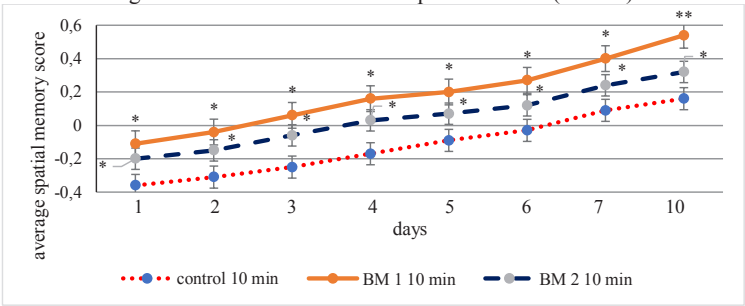


**Fig. 5.6. Dynamics of the ASMS in male rats in the EARM with a 10-min delay under the influence of the biomass of the strains *S. massasporeus* CNMN-Ac-06 (BM1) and *S. fradiae* CNMN-Ac-11 (BM2),** *– significant differences compared to the control (P<0.05). **– significant differences BM1 compared to BM2 (P<0.05)

At the stage of studying the preservation of spatial long-term memory traces 20 days after the completion of testing (on the 30th day of the experiment), it was found that the ASMS in rats of both sexes that received BM1 and BM2 was significantly higher than in the control (Fig. 5.7). Consequently, the biomass of the strains *S. massasporeus* CNMN-Ac-06 and *S. fradiae* CNMN-Ac-11 not only facilitates the learning process and activation of spatial memory, but also increases the preservation of memory traces.

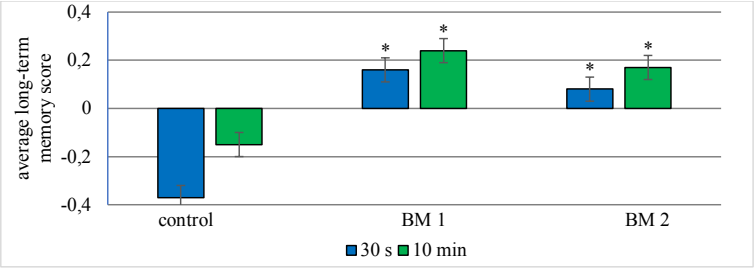


**Fig. 5.7. Dynamics of the ASMS in the EARM in white male rats under the influence of the biomass of the strains *S. massasporeus* CNMN-Ac-06 (BM1) and *S. fradiae* CNMN-Ac-11 (BM2) on the 30th day of the experiment,** * – reliable differences compared to the control (P<0.01-0.05)

Thus, studies of spatial learning and memory in the EARM showed that consumption of streptomycete biomass by white rats of both sexes facilitates the development of working memory, activation of long-term spatial memory and a decrease in the rate of memory trace extinction.

One of the widely used and well-proven methods for assessing spatial learning and memory, where, unlike associative learning, local landmarks are not required, is the EARM. This method allows us to study the processes of spatial learning and memory (working and long-term), where working memory is considered as an operational component of short-term memory. Using this test, we studied the duration of the LP, during which the rat found the platform and climbed onto it, and the length of the PT, which the animal passed from the place where it was placed in the water to the platform, and determined the time spent in each of the sectors (%). Analysis of the obtained dynamics of spatial learning and working memory indicators in the EARM - LP and PT shows their significant changes under the influence of streptomycete biomass.

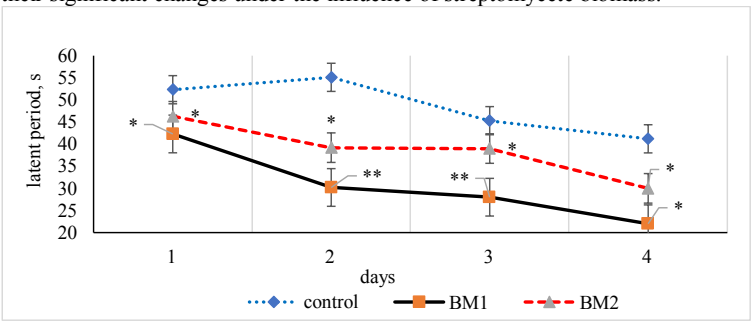


**Fig. 5.8. Dynamics of LP in male rats in the EARM under the influence of the biomass of the strains *S. massasporeus* CNMN-Ac-06 (BM1) and *S. fradiae* CNMN-Ac-11 (BM2).** * – significant differences compared to the control (P<0.01-0.05), ** – significant differences BM1 compared to BM2 (P<0.01-0.05)

It was found that long-term consumption of biomass contributes to a significant facilitation of the spatial learning process, while it was shown that the biomass of the strains *S. massasporeus* CNMN-Ac-06 and *S. fradiae* CNMN-Ac-11 contributes to varying degrees to facilitation of learning in the EARM. In contrast to BM2, BM1 already on the 1st day of training causes a reliable decrease in LP (by 20.2±6.2%), on the 2nd day of training in rats consuming BM2, LP is 29.9±4.6% lower than the control, and in rats consuming BM1 - by 45.2±5.9%, on the 3rd day, respectively - by 16.0±6.3% and by 38.2±4.9%, on the 4th day, respectively - by 27.2±5.4% and

by 46.7±4.6% (Fig. 5.8). A similar picture is observed in the study of another indicator of spatial learning in the EARM - PT (Fig. 5.9).

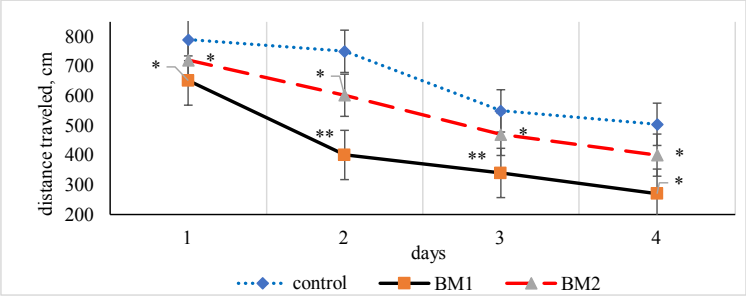


**Fig. 5.9. Dynamics of PT of male rats in EARM under the influence of biomass of strains *S. massasporeus* CNMN-Ac-06 (BM1) and *S. fradiae* CNMN-Ac-11 (BM2), *** – reliable differences compared to the control (P<0.05), ** – reliable differences BM1 compared to BM2 (P<0.01-0.05)

According to the methodology, a classic criterion of memorization was found to study the activation of long-term spatial memory – the time spent by rats in the target sector after the end of training (on the 5th day), when the platform was removed from the pool. It was found that animals that consumed streptomycete biomass spent most of their time in the target sector compared to the control, which indicates stimulation of the process of activation of long-term spatial memory, the process of consolidation of the engram. At the same time, animals that consumed BM1 and BM2 spent approximately the same amount of time in the target sector (37.2±3.5 and 40.1±4.2%, respectively) (Fig. 5.10).

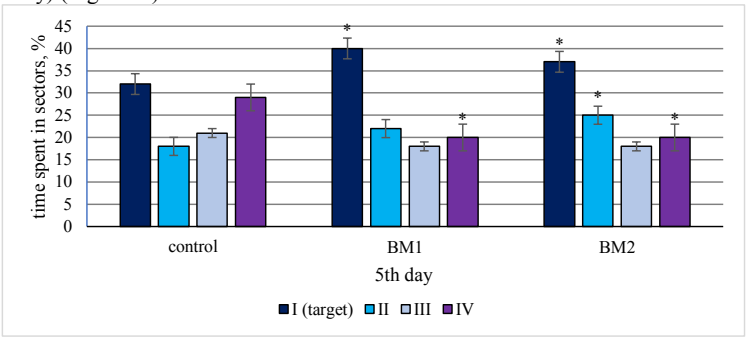


**Fig. 5.10. Duration of stay of male rats in the EARM sectors on the 5th day of testing under the influence of the biomass of the strains *S. massasporeus* CNMN-Ac-06 (BM1) and *S. fradiae* CNMN-Ac-11 (BM2), *** – reliable differences compared to the control (P<0.01-0.05)

To assess the preservation of the memory trace and, accordingly, spatial long-term memory, according to the method, the time spent by rats in the target and non-target sectors of the maze was determined on the 9th and then 30th day after the start of training. The results showed that on the 9th day of the experiment, i.e. 5 days after the end of training, rats that received BM1 and BM2 with food spent relatively more time in the target sector compared to the control and even slightly more compared to the 5th day of the experiment (45.3±3.3% and 40.1±2.8%, respectively), which indicates the preservation of memory traces and the effectiveness of streptomycete metabolites in maintaining the memory trace (Fig. 5.11).

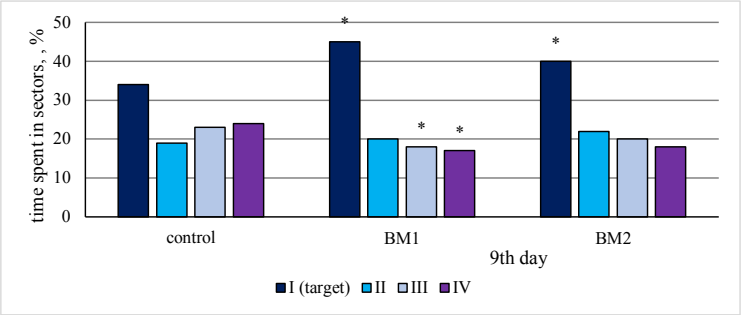


**Fig. 5.11. Duration of stay of male rats in the EARM sectors on the 9th day of testing under the influence of the biomass of the strains *S. massasporeus* CNMN-Ac-06 (BM1) and *S. fradiae* CNMN-Ac-11 (BM2), *** – reliable differences compared to the control (P<0.05).

The results of testing on the 30th day of the experiment showed that even after a long time, rats that consumed streptomycete biomass, unlike the control, retain memory traces of the platform location and are more often in the target sector of the EARM (Fig. 5.12), while the effectiveness of BM1 is greater compared to BM2. Consequently, the biomass of the strains *S. massasporeus* CNMN-Ac-06 (to a greater extent) and *S. fradiae* CNMN-Ac-11 contributes to improving the preservation of memory traces.

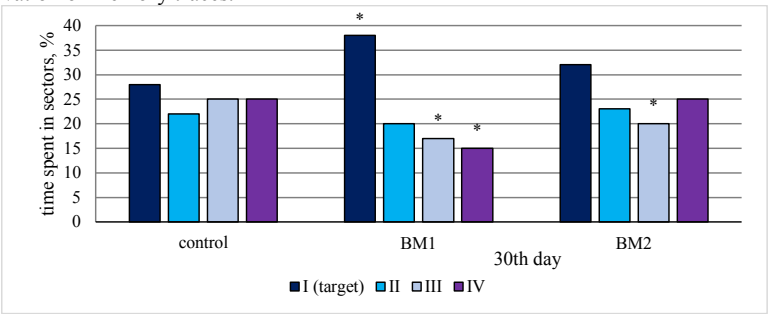


**Fig. 5.12. Duration of stay in the EARM sectors of male rats on the 30th day under the influence of the biomass of the strains *S. massasporeus* CNMN-Ac-06 (BM1) and *S. fradiae* CNMN-Ac-11 (BM2), ***– reliable differences compared to the control (P<0.05)

It should be noted that the studies of the process of spatial learning and memory of animals in the MWM, as well as in the EARM, under the influence of the biomass of the strains *S. massasporeus* CNMN-Ac-06 and S. fradiae CNMN-Ac-11 were conducted for the first time. The data obtained can indirectly demonstrate the influence of secondary metabolites of the biomass of the studied strains on certain mechanisms of learning, working and long-term memory in white rats, which is apparently determined by the different composition of the biomass of these strains. Thus, the biomass of the strains S. massasporeus CNMN-Ac-06 and, to a lesser extent, *S. fradiae* CNMN-Ac-11, contributes to a significant facilitation of the process of spatial learning of male white rats in the MWM, activation of working and long-term spatial memory, and an increase in the duration of storage of the memory trace. The effectiveness of the biomass of the studied strains in relation to learning and memory processes is obviously due to the neuroprotective effect of the antioxidants included in its composition (it is well known that swimming in the MWM model is a fairly strong stress factor for rats at the initial stage of learning [12, 14]), as well as metabolites that can stimulate and support neuronal processes underlying learning and memory, as evidenced

by the results obtained earlier at the Institute of Physiology and Sanocreatology together with employees of the Institute of Microbiology and Biotechnology [35, 36].

## 6. FEATURES OF LEARNING AND MEMORY OF WHITE RATS UNDER THE INFLUENCE OF THE BIOMASS OF THE STREPTOMYCES MASSASPOREUS CNMN-AC-06 STRAIN, GROWN IN SP-I MEDIUM WITH THE ADDITION OF PARA-AMINOBENZOIC ACID

The results of the study obtained in the study of spatial learning and memory of white rats in the EARM and MWM showed that the biomass of the *S. massasporeus* CNMN-Ac-06 strain, cultivated on the SP-I nutrient medium, to a greater extent contributes to facilitating the process of spatial learning, activating working and long-term memory and increasing the preservation of memory traces. In recent decades, it has been established that streptomycete strains synthesize a number of metabolites with pronounced neuroprotective properties, primarily due to their antioxidant activity. Some of the most powerful neuroprotectors are benzastatins [9]. In order to identify the role of benzastatins, the neurophysiological effects of biomass revealed by us, we added PABA, which is the starting material for the synthesis of benzastatins, to the nutrient medium for cultivating the *S. massasporeus* CNMN-Ac-06 strain. Therefore, for further studies of learning and memory in the shuttle chamber, EARM and MWM, the biomass of the S. massasporeus CNMN-Ac-06 strain was used when cultivated on SP-I medium with the addition of PABA.

When studying the processes of conditioned reflex learning with aversive reinforcement in a shuttle chamber, it was found that the biomass of the *S. massasporeus* strain CNMN-Ac-06, cultured on the SP-I medium containing 1.37 g/l PABA (BM1PABA1), causes a noticeable increase in the production of CRAA in rats of both sexes, both in comparison with the control (on days 3-4 and 6-15 of the experiment), and in comparison with animals that received the biomass of the *S. massasporeus* strain CNMN-Ac-06, cultured on the standard nutrient medium SP-I (BM1) (on days 3 and 6-15 of the experiment) (Fig. 6.1). Increasing the PABA content in the medium for culturing the *S. massasporeus* strain CNMN-Ac-06 to 2.74 g/l (BM1PABA2) leads to a weakening of the biomass efficiency in relation to the development of conditioned reflexes. According to the results obtained, in animals receiving BM1PABA2, CRAA are developed more slowly than BM1PABA1, but faster than in the control.

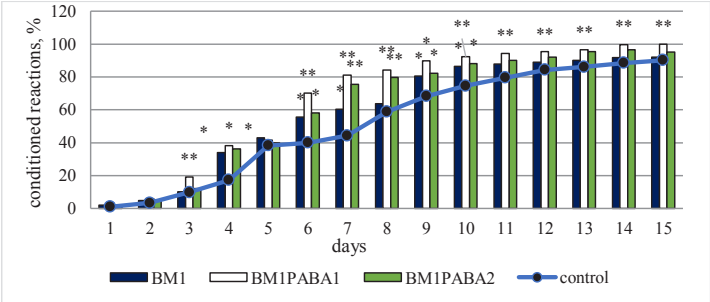


**Fig. 6.1. Dynamics of conditioned reflex learning with aversive reinforcement in males with long-term consumption of biomass of the *S. massasporeus* strain CNMN-Ac-06 grown on the SP-I medium with the addition of PABA, *** - reliable differences compared to the control (P<0.05), ** - reliable differences compared to BM1 (P<0.05)

In a study of conditioned reflex memory processes, it was found that adding PABA to the medium for culturing the *S. massasporeus* strain CNMN-Ac-06 at a dose of 1.37 g/l and, to a lesser extent, 2.74 g/l contributed to a decrease in the value of LPAR in male rats both in comparison

with the control and, in some cases, in comparison with BM1 (Fig. 6.2). Similar dynamics were also observed in female rats.

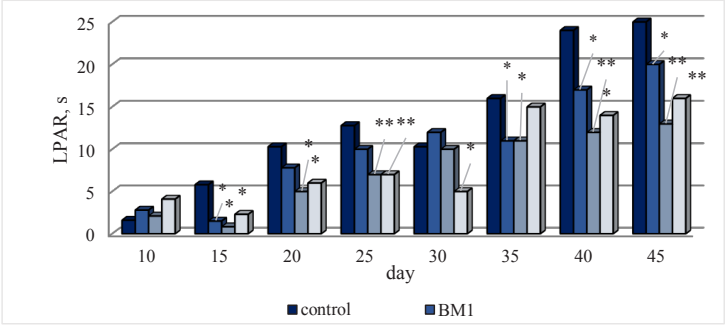


**Fig. 6.2. Dynamics of LPAR in male rats for 45 days after the development of CRAA with long-term consumption of the biomass of the *S. massasporeus* strain CNMN-Ac-06 grown on the SP-I medium with the addition of PABA, *** - reliable differences compared to the control P<0.05, ** - reliable differences compared to BM1 (P<0.05)

Thus, the addition of PABA to the nutrient medium for cultivating the *S. massasporeus* strain CNMN-Ac-06 at a dose of 2.74 g/l and, especially, 1.37 g/l causes a noticeable intensification of the development of defensive conditioned reflexes of active avoidance and contributes to an increase in the effectiveness of the biomass in relation to the processes of conditioned reflex memory and the preservation of traces of long-term memory in white rats of both sexes.

The results of the experiments on the study of spatial learning and memory in white rats of both sexes showed that the addition of PABA at a dose of 1.37 g/l (BM1PABA1) to the medium for culturing the *S. massasporeus* CNMN-Ac-06 strain led to a noticeable increase in the ASMS both in comparison with the control and in comparison with the animals that received the biomass of the *S. massasporeus* CNMN-Ac-06 strain without PABA (BM1), both with a 30 sec and 10 min DP. Interestingly, when 2.74 g/l PABA (BM1PABA2) was added to the nutrient medium, the effectiveness of the biomass in relation to spatial learning and memory was practically not significantly different from BM1 (Figs. 6.3 and 6.4, using males as an example).

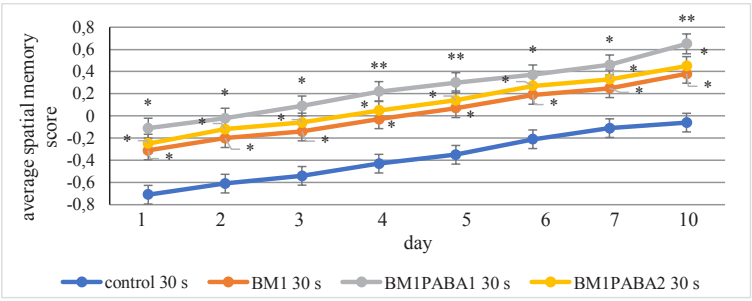


**Fig. 6.3. Dynamics of the ASMS in male rats in the EARM with a 30-s delay under the influence of the biomass of the *S. massasporeus* strain CNMN-Ac-06, cultured on the SP-I medium with the addition of PABA, ***– reliable differences compared to the control (P<0.05), **– reliable differences compared to BM1 (P<0.05)

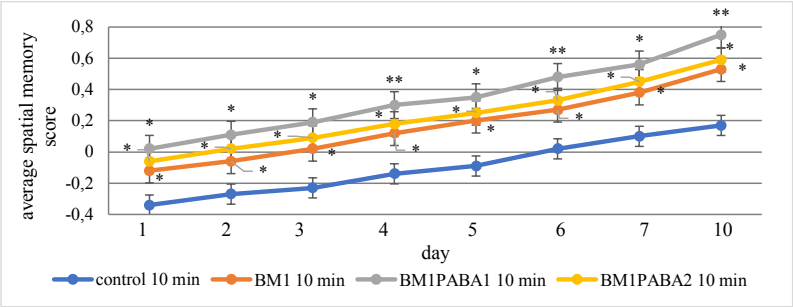


**Fig. 6.4. Dynamics of the ASMS of male rats in the EARM with a 10-min delay under the influence of the biomass of the *S. massasporeus* strain CNMN-Ac-06, cultured on the SP-I medium with the addition of PABA,** *– reliable differences compared to the control ($P < 0.05$), ** – reliable differences compared to BM1 ($P < 0.05$)

It is important to note that an increase in the PABA content in the medium for culturing the *S. massasporeus* CNMN-Ac-06 strain to 2.74 g/l leads to a decrease in the efficiency of the biomass in relation to conditioned reflex learning in the shuttle chamber. The efficiency of BM1PABA1 is significantly higher on the 10th day of the experiment (after a break on days 8 and 9) compared to the control, as well as BM1 and BM1PABA2, which indicates its stimulating effect on the activation of spatial long-term memory in white rats.

The results of the study of the preservation of long-term memory traces on the 30th day of the experiment showed that the addition of BM1PABA1 to the feed of rats leads to an increase in the ASMS in relation to the control both with a 30 sec and 10 min DP – by 0.67±0.22 and 0.63±0.35 points, respectively, and in animals receiving BM1PABA2 – by 0.51±0.45 and 0.35±0.49 points, respectively, at the same time, the addition of biomass without PABA to the feed of animals – by 0.45±0.31 and 0.29±0.53 points, respectively. Consequently, animals fed with S. massasporeus CNMN-Ac-06 strain biomass with PABA supplementation at a dose of 1.37 g/l, and to a lesser extent 2.74 g/l, demonstrated significantly better reproduction of spatial long-term memory both in comparison with the control and BM1 without PABA.

Thus, S. massasporeus CNMN-Ac-06 strain biomass, cultured on SP-I medium with PABA supplementation, significantly stimulates the learning process of white rats of both sexes in the EARM and facilitates the development of working memory, activation and preservation of long-term spatial memory both in comparison with the control and with *S. massasporeus* CNMN-Ac-06 strain biomass, cultured on standard SP-I nutrient medium.

The results of the study of the LP and PT indices obtained during the study of spatial learning in the MWM show that the biomass of the *S. massasporeus* CNMN-Ac-06 strain, cultured on the SP-I medium with the addition of PABA at a dose of 1.37 g/l (BM1PABA1), contributes to facilitating the process of spatial learning to a greater extent than at a dose of 2.74 g/l (BM1PABA2), as well as without the addition of PABA (BM1) (Fig. 6.5 and 6.6). When comparing the groups of animals consuming BM1 and BM1PABA2, no reliable differences in LP and PT were found, although a tendency towards their increase under the influence of BM1PABA2 is observed compared to BM1.

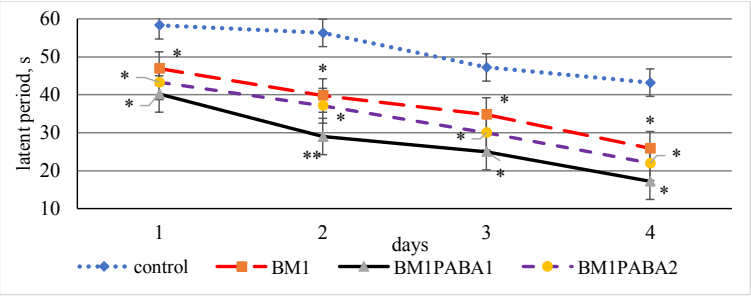


**Fig. 6.5. Dynamics of LP in male rats in the MWM under the influence of the biomass of the *S. massasporeus* strain CNMN-Ac-06, cultured on the SP-I medium with the addition of PABA,** *– reliable differences compared to the control (P<0.05), **– reliable differences compared to VM1 (P<0.05)

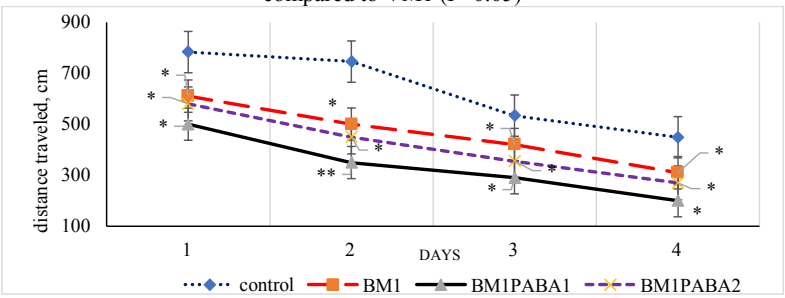


**Fig. 6.6. Dynamics of PT in male rats in MWM under the influence of the biomass of the *S. massasporeus* strain CNMN-Ac-06, cultured on the SP-I medium with the addition of PABA,** *– reliable differences compared to the control (P<0.05), **– reliable differences compared to VM1 (P<0.01-0.05)

To assess the integrity of the memory trace and, accordingly, spatial long-term memory, according to the methodology, the time spent by rats in the target and non-target sectors of the maze was determined on the 9th and 30th days of the experiment. The results showed that on the 9th day, the rats of the control group were in the target sector 30.3±2.2%, and the rats that received BM1 – 39.2±1.8%. It was found that in rats that received BM1PABA1 and BM1PABA2, the time spent in the target sector was 49.1±1.1% and 42.0±1.5%, respectively. Consequently, the animals that received BM1PABA1 with food stayed in the target sector for the longest time, which contributes to the activation of spatial long-term memory in white rats.

The results of the study on the 30th day of the experiment showed that the consumption of BM1PABA1 by male rats has a greater positive effect on the process of retention of traces of spatial long-term memory, both in comparison with the control and BM1 (Fig. 6.7). Interestingly, when comparing the groups receiving BM1 and BM1PABA2, no reliable differences were found in the time spent in the target sector, although there was a tendency for them to increase in comparison with the control.

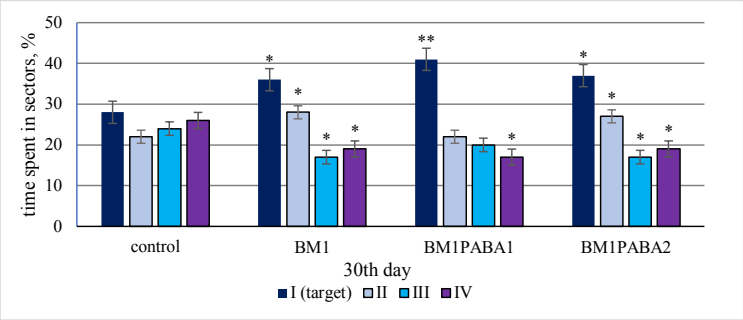


**Fig. 6.7. Duration of stay in the MWM sectors of male rats on the 30th day of testing under the influence of the biomass of the *S. massasporeus* strain CNMN-Ac-06, cultured on the SP-I medium with the addition of PABA,** *– reliable differences compared to the control (P<0.05), **– reliable differences compared to VM1 (P<0.05)

Thus, the biomass of the *S. massasporeus* CNMN-Ac-06 strain, cultivated on the SP-I nutrient medium with the addition of PABA (to a greater extent, at a dose of 1.37 g/l), contributes to a significant facilitation of the process of spatial learning, the development of working memory, the activation and preservation of traces of long-term spatial memory in white rats in the MWM, both in comparison with the control and with the biomass of the *S. massasporeus* CNMN-Ac-06 strain, cultivated on the standard SP-I nutrient medium.

## GENERAL CONCLUSIONS

The conducted research and analysis of the obtained results led to the following conclusions:

1. The biomass of streptomycetes of the *Streptomyces massasporeus* CNMN-Ac-06 and *Streptomyces fradiae* CNMN-Ac-11 strains, grown on certain nutrient media, is characterized by a high level of biologically active substances (replaceable and essential amino acids, various lipid fractions) directly involved in the regulation of plastic metabolism and psychogenic activity of the body.
2. Under the influence of the biomass of the *Streptomyces massasporeus* CNMN-Ac-06 strain, cultivated on a nutrient medium containing para-aminobenzoic acid at a concentration of 1.37 g/l, there is a significant increase in body weight gain, resistance to heat stress, fertility, as well as an improvement in the development of the offspring of white rats to a greater extent than under the influence of the biomass of the streptomycete strains *Streptomyces massasporeus* CNMN-Ac-06 and *Streptomyces fradiae* CNMN-Ac-11, cultivated on the standard complex medium SP-I.
3. A comparative study of the neurophysiological effects of the biomass of the streptomycete strains *Streptomyces massasporeus* CNMN-Ac-06 and *Streptomyces fradiae* CNMN-Ac-11, cultured on the complex medium SP-I, showed that they have varying degrees of influence on learning processes, activation of short-term memory and retention of memory traces; a more pronounced effect on conditioned reflex learning and memory is exerted by the biomass of the strain *Streptomyces fradiae* CNMN-Ac-11, and on spatial learning and memory – by *Streptomyces massasporeus* CNMN-Ac-06.
4. Long-term consumption of streptomycete biomass has a more pronounced effect on the processes of formation of new behavior, stimulation of conditioned reflex learning and the duration of storage of a long-term memory trace in old animals compared to young ones.
5. Intensification of the processes of conditioned reflex and spatial learning, activation of working memory, prolongation of the preservation of traces of long-term memory are more pronounced under conditions of consumption by white rats of the biomass of the *Streptomyces massasporeus* CNMN-Ac-06 strain, cultivated in a nutrient medium with the addition of para-

aminobenzoic acid at a concentration of 1.37 g/l, compared to the biomass obtained during its cultivation in a standard nutrient medium.

6. The biomass of streptomycetes *Streptomyces massasporeus* CNMN-Ac-06 and *Streptomyces fradiae* CNMN-Ac-11 has a multifunctional effect on the body's activity: it improves not only the learning and memory processes, but also contributes to an increase in body weight gain, fertility of white rats, growth and development of offspring, which suggests further research on the identification of biologically active substances of the biomass for their use in practice.

## PRACTICAL RECOMENDATIONS

1. The biomass of the *Streptomyces massasporeus* CNMN-Ac-06 and *Streptomyces fradiae* CNMN-Ac-11 strains isolated from the soils of the central part of the Republic of Moldova can be recommended for obtaining new effective drugs with pronounced neuroprotective and nootropic properties.

2. Drugs based on the biomass of the *Streptomyces massasporeus* CNMN-Ac-06 and *Streptomyces fradiae* CNMN-Ac-11 strains can be used in animal husbandry to increase the weight gain and fertility of farm animals.

3. To increase the effectiveness of streptomycete biomass in relation to learning and memory processes, as well as to increase the weight gain and fertility of animals, it is recommended to include para-aminobenzoic acid at a concentration of 1.37 g / l in the composition of nutrient media for cultivating streptomycetes.

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**2. Articles in scientific journals**

**2.1 in scientific journals from the Web of Science and SCOPUS databases**

1. **GARBUZNEAC, A.,** BYRSA, M., BURTSEVA, S., CHISELITSA, N., CHISELITA, O. Changes in lipid composition of *Streptomyces massasporeus* CNMN-Ac-06 biomass after long-term storage. In: *Mikrobiolohichnyi Zhurnal,* Kyiv, Ukraine, 2020, nr. 5 (82), p. 41-47. ISSN 1028-0987. https://www.scopus.com/authid/detail.uri?authorId=57219709787

2. ȘEPTIȚCHI, V., VASILICIUC, A., **GARBUZNEAC, A.,** LEORDA, A., MANGUL, O., BURȚEVA, S., FILIPENCO, E., TIHONENCOVA, L. Influența consumului pe termen lung al biomasei tulpinilor *Streptomyces massasporeus* CNMN-06 și *Streptomyces fradiae* CNMN Ac-11 asupra învățării și memoriei reflector-condiționate a șobolanilor albi de diferite vârste. In: *Buletinul Academiei de Științe a Moldovei. Științele vieții*. 2021, nr. 2 (344), p. 72-82. ISSN 1857-064X. https://ibn.idsi.md/vizualizare_articol/152771

3. **GARBUZNEAC,** A., BURTSEVA, S., SYRBU, T., BYRSA, M., CHISELITSA, N., CHISELITA, O. Accumulation by *Streptomyces massasporeus* CNMN-Ac-06 strain of biomass and lipids during cultivation on complex medium with 4-aminobenzoic acid. In: *Analele Universitatii din Oradea*, *Fascicula Biologie*. 2023, vol. 30, p. 82-88. ISSN 1224-5119. https://ibn.idsi.md/ro/vizualizare_articol/188828

**2.3 in scientific journals from the National Registry of specialized journals (Categoria B)**

4**. GARBUZNEAC, A.,** ȘEPTIȚCHI, V., LEORDA, A., BURȚEVA, S., BÎRSA, M. Învățarea spațială și memoria șobolanilor albi în labirintul radial cu opt brațe sub influența biomasei de streptomicete izolate din solurile Republicii Moldova. In: *Studia Universitatis Moldaviae*, 2024, nr. 1 (171), p. 116-126. ISSN 1814-3237. https://natural.studiamsu.md/wp-content/uploads/2024/06/14_Garbuzneac_et_al.pdf

**3. Articles in proceedings of scientific conferences**

**3.2 in the proceedings of national scientific conferences with international participation**

5. БЫРСА, М., БЕРЕЗЮК, Ю., **ГАРБУЗНЯК, А.,** КАРАМАН, М., ЧЕБОТАРЬ, В., БУРЦЕВА, С. Липидный состав биомассы стрептомицетов при культивировании на средах сложного состава. In: *Instruire prin cercetare pentru o societate prosperă. Universitatea de stat din Tiraspol, Facultatea biologie şi chimie, Ediția VIII,* Chișinău, 2021, vol. 1, p. 284-290. ISBN 978-9975-76-327-1.

**3.3 in the proceedings of national scientific conferences**

6. **GARBUZNEAC, A.** Historical aspects of studying the streptomyces metabolites influence on the nervous system activity. In: *Materialele Conferinței Științifice a Doctoranzilor „Tendințe contemporane ale dezvoltării științei: viziuni ale tinerilor cercetători”,Ediția a VIII-a.* 2019, p. 101-104. https://ibn.idsi.md/ro/vizualizare_articol/80734/gscholar

7. **GARBUZNEAC, A.** Compoziția lipidică a biomasei tulpinilor de streptomicete în urma cultivării pe medii complexe după păstrare îndelungată. In: *Tendințe contemporane ale dezvoltării științei: viziuni ale tinerilor cercetători, Ediția IX*, Chișinău, Republica Moldova: Tipogr. „Biotehdesign”, 2020, vol. 1, p. 187-191. ISBN 978-9975-108-66-9. https://ibn.idsi.md/vizualizare_articol/112764

8. **GARBUZNEAC, A**. Caracteristici comparative ale activităţii reflexe condiţionate a şobolanilor de diferite vârste sub influenţa biomasei tulpinilor *Streptomyces massasporeus* CNMN-AC-06 şi *Streptomyces fradiae* CNMN-AC-11. In: *Metodologii contemporane de cercetare şi evaluare: Ştiinţe biologice şi chimice Ştiinţe fizice şi matematice Ştiinţe economice, Chişinău: CEP USM,* 2021, p. 37-42. ISBN 978-9975-159-16-6. https://ibn.idsi.md/vizualizare_articol/154698

9. **GARBUZNEAC, A.,** SHEPTITSKY, V., BURTSEVA, S., BYRSA, M. Influence of long-term consumption of streptomycete biomass on conditional-reflex learning and memory in white rats of different ages. Conferința Științifică Națională, consacrată jubileului de 95 ani din ziua nașterii academicianului Boris Melnic, Chisinau. In: *CEP USM*. 2023, vol. 1, p. 57-60. ISBN 978-9975-62-496-1. https://ibn.idsi.md/vizualizare_articol/175037

**3.4 in the proceedings of international scientific conferences (abroad)**

10. БЫРСА, М., БУРЦЕВА, С., ВАСИЛЬЧУК, А., **ГАРБУЗНЯК, А.,** ЧЕБОТАРЬ, В. Антимикробная активность штамма *Streptomyces massasporeus* CNMN-Ac-06 после длительного хранения в лиофильном виде. В: *Микроорганизмы и плодородие почвы*, Киров, Россия: Вятский ГАТУ. 2022, с. 19-23.

**4. Theses in conference proceedings**

**4.1 in the proceedings of scientific conferences with international participation (Republic of Moldova).**

11. **GARBUZNEAC, A.,** BYRSA, M., BURTSEVA, S. *Streptomyces fradiae* CNMN-Ac-11 after storage by subculturing and cultivation on complex media. In*: Microbial Biotechnology, Chișinău, Republica Moldova: Artpoligraf,* 2022, vol. 5, p. 33. ISBN 978-9975-3555-6-8. https://ibn.idsi.md/vizualizare_articol/167883

**4.2 in the proceedings of national scientific conferences with international participation**

12. **GARBUZNEAC, A.,** SHEPTITSKY, V. Conditioned reflex learning and memory of white rats of different ages under the influence of the biomass of streptomycetes isolated from the soils of the Republic of Moldova. In: *Life sciences in the dialogue of generations: connections between universities, academia and business community, Chișinău, Moldova State University,* 2022, vol. 2, p. 131. ISBN 978-9975-159-80-7. https://ibn.idsi.md/sites/default/files/imag_file/131_12.pdf

13. **GARBUZNEAC, A.,** SHEPTITSKY, V. Spatial learning and memory of male and female white rats under the influence of biomass of streptomycetes isolated from the soils of the Republic of Moldova. In: *Natural sciences in the dialogue of generations. Chișinău: CEP USM*. 2023, p. 116. ISBN 978-9975-3430-9-1. https://ibn.idsi.md/sites/default/files/imag_file/57-60_58.pdf

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14. FURDUI, T., SHEPTITSKY, V., LISTOPADOVA, L, **GARBUZNEAC, A.** On the possibility of using antioxidant microelements for the maintenance of mental health. In: *Neuroscience for medicine and psychology: proceedings of the XVI International Interdisciplinary Congress.* Sudak, Crimea. 2020, p. 489-490. ISBN 978-5-317-06406-8.

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16. **ГАРБУЗНЯК, А.,** ШЕПТИЦКИЙ, В. Сравнительный анализ влияния биомассы *S. fradiae* CNMN-AC-11 и *S. massasporeus* CNMN-AC-06 на выработку оборонительных

условных рефлексов у белых крыс. В: *Биология – наука XXI века. Пущино, Россия: Пущинский научный центр биологических исследований Российской академии наук, Ediția a 24-a.* 2020, p. 229-230. ISBN 978-5-91874-901-2. https://ibn.idsi.md/vizualizare_articol/115404
17. SHEPTYTSKY, V**., GARBUZNEAC, A.,** MANGUL, O., BEREZIUC, I., VASILCIUC, A., BURTSEVA, S. Neuroprotective and nootropic effects of the products of vital activity of Streptomyces. In: *Neuroscience for medicine and psychology: proceedings of the XVIII International Interdisciplinary Congress*. Sudak, Crimea. 2022, p. 387-388. ISBN 978-5-317-06792-2
18. BÎRSA M., BURŢEVA S., SÎRBU T., **GARBUZNEAC A.,** ŞEPTIŢCHI V. *Streptomyces massasporeus* CNMN-Ac-06 – source of biologically active substances for agriculture. In: *Proceedings of the 15th Edition of European exibition of creativity and innovation „Euroinvent – 2023*". Iași, România, 2023, p. 103-104 (Medalie de argint).
19. BÎRSA M., BURŢEVA S., SÎRBU T., **GARBUZNEAC A.,** ŞEPTIŢCHI V. *Streptomyces massasporeus* CNMN-Ac-06 – source of biologically active substances for agriculture. In: *The 27rd internaţional exhibition of inventics „INVENTICA 2023*", Iași, România, 2023 (Medalie de aur).
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21. BÎRSA M., BURŢEVA S., SÎRBU T., **GARBUZNEAC A.,** ŞEPTIŢCHI V. *Streptomyces massasporeus* CNMN-Ac-06 – source of biologically active substances for agriculture. In: *Salonul Internaţional al Cercetării ştiinţifice, Inovării şi Invenţii*, ed. XXI, Cluj-Napoca, România, 2023, p. 276-277. ISSN: 3008-458X (Diploma de Excelenta și Medalie PRO INVENT).

**5. Patents**
1. BÎRSA, M., BURŢEVA, S., SÎRBU, T., **GARBUZNEAC, A.,** ŞEPTIŢCHI, V. *Mediu nutritiv pentru cultivarea tulpinii Streptomyces massasporeus CNMN-Ac-06.* Cerere de brevet Nr. Intrare AGEPI 2337.08.09.2022.
2. BÎRSA, M., **GARBUZNEAC, A.,** ŞEPTIŢCHI, V., BURŢEVA, S., SÎRBU, T. *Procedeu de hrănire a animalelor cu sânge cald*. Cerere de brevet Nr. Intrare AGEPI 2338.08.09.2022.

**ADNOTARE**

**Anastasia Garbuzneac „Învățarea și memoria șobolanilor în consumul biomasei de streptomicete", teza de doctor în științe biologice, Chișinău, 2024.**

**Structura tezei:** Lucrarea este prezentată pe 125 de pagini de text principal, constă din introducere, 6 capitole, concluzii generale și recomandări, conține 7 tabele, 48 figuri, bibliografie din 192 titluri, 5 anexe. Rezultatele obținute sunt prezentate în 23 lucrări științifice și 2 brevete.

**Cuvinte-cheie:** șobolani albi, învățare reflector-condiționată și spațială, memorie de lucru și pe termen lung, streptomicete, biomasă, acid para-aminobenzoic, aminoacizi, lipide.

**Scopul lucrării:** Studierea particularităților de învățare și memorie la șobolani albi sub influența consumului pe termen lung de biomasă a tulpinilor *Streptomyces massasporeus* CNMN-Ac-06 și *Streptomyces fradiae* CNMN-Ac-11, izolate din solul din partea centrală a Republicii Moldova.

**Obiectivele cercetării**: Studiul proprietăților de biosinteză ale tulpinilor *S. massasporeus* CNMN-Ac-06 și *S. fradiae* CNMN-Ac-11, cultivate pe medii cu diferite compoziții pentru a obține biomasă, ipotetic având cel mai mare impact asupra învățării și memoriei; studiul particularităților dinamicii masei corporale, fertilității șobolanilor albi și dezvoltării puilor de șobolan sub influența biomasei de streptomicete; studiul particularităților de învățare și memorie ale șobolanilor albi în condițiile consumului pe termen lung a biomasei tulpinilor *S. massasporeus* CNMN-Ac-06 și *S. fradiae* CNMN-Ac-11, cultivate pe mediul nutritiv complex SP-I, precum și pe mediul SP-I cu adăugarea acidului para-aminobenzoic.

**Noutatea și originalitatea științifică:** Pentru prima dată, a fost dezvăluit efectul stimulator al biomasei de streptomicete asupra procesului de învățare spațială și memorie a șobolanilor albi în labirintul radial cu opt brațe și în labirintul cu apă Morris. Pentru prima dată, s-a depistat, că adăugarea acidului para-aminobenzoic (PABA) la mediul nutritiv îmbunătățește semnificativ efectul stimulator al biomasei asupra învățării reflector-condiționate și spațiale și a memoriei. Au fost obținute date noi cu referire la particularitățile influenței biomasei streptomicetelor în raport cu învățarea reflector-condiționată și memoria la șobolani de diferite vârste. Au fost obținute noi date, privind efectul stimulator al biomasei de streptomicete cultivate pe mediu nutritiv cu adaos de PABA în raport cu masa corporală și fertilitatea, care sunt brevetate. A fost propus un nou mediu nutritiv pentru cultivarea tulpinii *S. massasporeus* CNMN-Ac-06, care îmbunătățește proprietățile ei biosintetice, a cărui elaborare a fost finalizată prin brevetare.

**Problema științifică soluționată:** consta de obținerea de noi cunoștințe argumentate științific despre particularitățile învățării și memoriei reflector-condiționate și spațiale la șobolanii albi în condițiile consumului de biomasă a tulpinilor autohtone de streptomicete ca aditiv alimentar, folosind un complex de metode fiziologice (comportamentale), biochimice și microbiologice, ceea ce a condus la stabilirea efectului stimulator semnificativ al biomasei asupra proceselor cognitive studiate și a permis demonstrarea perspicacității tulpinilor *S. massasporeus* CNMN-Ac-06 și *S. fradiae* CNMN-Ac-11 în scopul izolării și identificării substanțelor biologic active cu proprietăți neuroprotectoare și nootrope, precum și de a propune un mediu nutritiv nou pentru cultivarea streptomicetelor cu adaos de PABA, utilizarea căruia permite creșterea eficienții biomasei asupra proceselor de învățare și memorie.

**Rezultatele fundamental noi pentru știință și practică:** în baza metodelor moderne fiziologic (comportamentale), microbiologice și biochimice, s-au obținut rezultate principial noi, privind impactul biomasei de streptomicete asupra proceselor de învățare și memorie, care pot fi utilizate în obținerea substanțelor cu efect nootrop și neuroprotector.

**Semnificația teoretică:** Rezultatele obținute extind și aprofundează abordările științifice ale particularităților proceselor învățării reflector-condiționate și spațiale și ale memoriei sub influența substanțelor biologic active de origine microbiană cu proprietăți neuroprotectoare și neurostimulatoare.

**Valoarea aplicativă:** Rezultatele obținute demonstrează perspicacitatea cercetărilor ulterioare asupra tulpinilor *S. massasporeus* CNMN-Ac-06 și *S. fradiae* CNMN-Ac-11 cu scopul de a izola și identifica substanțe biologic active cu proprietăți neuroprotectoare și nootrope. A fost obținut un nou mediu nutritiv prin cultivarea tulpinii de *S. massasporeus* CNMN-Ac-06 cu adaos de PABA, au fost îmbunătățite proprietățile sale biosintetice și efectul stimulator asupra proceselor de învățare și memorie. Rezultatele obținute demonstrează posibilitatea obținerii preparatelor în baza biomasei tulpinilor locale de streptomicete în zootehnie pentru a stimula creșterea în greutate și fertilitatea animalelor.

**Implementarea rezultatelor științifice:** rezultatele sunt implementate în procesul didactic al Facultății de Geografie și Științe Naturale a Universității de Stat din Tiraspol „T.G. Șevcenco". Au fost primite 2 brevete, 4 medalii la expoziții internaționale de inovație.

## ANNOTATION

**Garbuzneac Anastasia „Learning and memory of rats when consumpting streptomycetes biomass", PhD thesis in biological sciences, Chisinau, 2024.**

**Thesis structur**e: The dissertation is presented on 125 pages, consists of an introduction, 6 chapters, general conclusions and recommendations, contains 5 tables, 48 figures, a bibliography of 192 titles, 5 appendices. The results obtained were presented in 23 scientific papers and 2 patents.

**Keywords:** white rats, conditioned reflex and spatial learning, working and long-term memory, streptomycetes, biomass, para-aminobenzoic acid, amino acids, lipids.

**Purpose:** Studying the characteristics of learning and memory of white rats under the influence of long-term consumption of biomass of the strains *Streptomyces massasporeus* CNMN-Ac-06 and *Streptomyces fradiae* CNMN-Ac-11, isolated from the soil of the central part of the Republic of Moldova.

**Objectives:** To study the biosynthetic properties of the strains *S. massasporeus* CNMN-Ac-06 and *S. fradiae* CNMN-Ac-11, cultivated in media of different compositions to obtain biomass, presumably having the greatest effect on learning and memory; to study the characteristics of the dynamics of body weight, fertility of white rats and the development of rat pups under the influence of streptomycete biomass; to study the features of learning and memory of white rats under conditions of long-term consumption of biomass of the strains *S. massasporeus* CNMN-Ac-06 and *S. fradiae* CNMN-Ac-11, cultivated on a complex nutrient medium SP-I, as well as on SP-I medium with the addition of para-aminobenzoic acid acids.

**Scientific novelty and originality:** The stimulating effect of streptomycete biomass on spatial learning and memory processes in white rats was revealed for the first time using an eight-arm radial maze and a Morris water maze. For the first time, it was discovered that the addition of PABA to the nutrient medium significantly enhances the stimulating effect of biomass on conditioned reflex and spatial learning and memory. New data have been obtained on the peculiarities of the influence of streptomycete biomass in relation to conditioned reflex learning and memory in rats of different ages. New data have been obtained on the stimulating effect of the biomass of streptomycetes cultivated on a nutrient medium with the addition of PABA in relation to body weight and fertility, which are patented. A novel nutrient medium for cultivating the strain *S. massasporeus* CNMN-Ac-06 has been proposed, improving its biosynthetic properties, the development of which has been completed by patenting.

**The solved scientific problem:** new scientific knowledge about the characteristics of conditioned reflex and spatial learning and memory in white rats when they consume biomass of local strains of streptomycetes as a dietary supplement was obtained, using a complex of physiological (behavioural), biochemical and microbiological methods, which led to the establishment of a significant stimulating effect of biomass on the studied cognitive processes and made it possible to demonstrate the promise of the strains *S. massasporeus* CNMN-Ac-06 and *S. fradiae* CNMN-Ac-11 in order to obtain new biologically active substances with neuroprotective and nootropic properties, as well as propose a new nutrient medium for the cultivation of streptomycetes with the addition of PABA, the use of which can increase the efficiency of biomass on learning and memory processes.

**Main results:** Based on modern physiological (behavioral), microbiological and biochemical methods, fundamentally new results were obtained on the effect of streptomycete biomass on learning and memory processes, which can be used in the production of substances with nootropic and neuroprotective effects.

**Theoretical significance:** The results obtained expand and deepen scientific understanding of the peculiarities of the processes of conditioned reflex and spatial learning and memory under the influence of biologically active substances of microbial origin with neuroprotective and neurostimulating properties.

**Applicative value:** The results obtained demonstrate the promise of further research on the strains *S. massasporeus* CNMN-Ac-06 and *S. fradiae* CNMN-Ac-11 with the aim of isolating and identifying biologically active substances with neuroprotective and nootropic properties. A new nutrient medium was obtained by cultivating the *S. massasporeus* strain CNMN-Ac-06 with the addition of PABA, its biosynthetic properties and stimulating effect on learning and memory processes were improved. The results obtained demonstrate the possibility of obtaining drugs based on the biomass of local strains of streptomycetes in animal husbandry to stimulate weight gain and fertility.

**Implementation of scientific results:** The results were introduced into the educational process of the Faculty of Geography and Natural Sciences of T.G. Shevchenko Tiraspol State University. 2 patents and 4 medals at international innovation exhibitions were received.

## АННОТАЦИЯ

**Гарбузняк Анастасия «Обучение и память крыс при потреблении биомассы стрептомицетов», диссертация на соискание ученой степени доктора биологических наук, Кишинэу, 2024 г.**

**Структура диссертации:** Диссертация представлена на 125 страницах основного текста, состоит из введения, 6 глав, общих выводов и рекомендаций, содержит 5 таблиц, 48 рисунков, список литературы из 192 наименований, 5 приложений. Полученные результаты были представлены в 23 научных работах, 2 патентах.

**Ключевые слова:** белые крысы, условно-рефлекторное и пространственное обучение, рабочая и долговременная память, стрептомицеты, биомасса, парааминобензойная кислота, аминокислоты, липиды.

**Цель работы:** Изучение особенностей обучения и памяти белых крыс под влиянием длительного потребления биомассы штаммов *Streptomyces massasporeus* CNMN-Ac-06 и *Streptomyces fradiae* CNMN-Ac-11, выделенных из почвы центральной части Республики Молдова.

**Задачи исследования:** Изучить биосинтетические свойства штаммов *S. massasporeus* CNMN-Ac-06 и *S. fradiae* CNMN-Ac-11, культивированных на средах разного состава для получения биомассы, предположительно, оказывающей наибольшее влияние на обучение и память; исследовать особенности динамики массы тела, плодовитости белых крыс и развития крысят под действием биомассы стрептомицетов; изучить особенности обучения и памяти белых крыс в условиях длительного потребления биомассы штаммов *S. massasporeus* CNMN-Ac-06 и *S. fradiae* CNMN-Ac-11, культивированных на комплексной питательной среде SP-I, а также на среде SP-I с добавлением парааминобензойной кислоты.

**Научная новизна и оригинальность:** Впервые выявлено стимулирующее влияние биомассы стрептомицетов на процесс пространственного обучения и памяти белых крыс в восьмирукавном радиальном лабиринте и водном лабиринте Морриса. Впервые обнаружено, что добавление в питательную среду ПАБК существенно усиливает стимулирующий эффект биомассы в отношении условно-рефлекторого и пространственного обучения и памяти. Получены новые данные об особенностях влияния биомассы стрептомицетов в отношении условно-рефлекторного обучения и памяти у крыс разного возраста. Получены новые данные о стимулирующем влиянии биомассы стрептомицетов, культивированных на питательной среде с добавлением ПАБК, в отношении массы тела и плодовитости, которые запатентованы. Предложена новая питательная среда для культивирования штамма *S. massasporeus* CNMN-Ac-06, улучшающая его биосинтетические свойства, разработка которой завершена патентованием.

**Решенная научная проблема:** состоит в получении новых научно обоснованных знаний об особенностях условно-рефлекторного и пространственного обучения и памяти у белых крыс в условиях потребления ими в качестве пищевой добавки биомассы местных штаммов стрептомицетов с применением комплекса физиологических (поведенческих), биохимических и микробиологических методов, что привело к установлению существенного стимулирующего влияния биомассы на исследуемые когнитивные процессы и позволило продемонстрировать перспективность штаммов *S. massasporeus* CNMN-Ac-06 и *S. fradiae* CNMN-Ac-11 для получения новых биологически активных веществ с нейропротекторными и ноотропными свойствами, а также предложить новую питательную среду для культивирования стрептомицетов с добавлением ПАБК, применение которой позволяет повысить эффективность биомассы в отношении процессов обучения и памяти.

**Полученные принципиально новые результаты для науки и практики:** на основе современных физиологических (поведенческих), микробиологических и биохимических методов получены принципиально новые результаты о влиянии биомассы стрептомицетов на процессы обучения и памяти, которые могут найти применение при получении веществ с ноотропным и нейропротекторным действием.

**Теоретическое значение:** Полученные результаты расширяют и углубляют научные представления об особенностях процессов условно-рефлекторного и пространственного обучения и памяти под влиянием биологически активных веществ микробного происхождения с нейропротекторными и нейростимулирующими свойствами.

**Прикладное значение:** Полученные результаты демонстрируют перспективность дальнейших исследований штаммов *S. massasporeus* CNMN-Ac-06 и *S. fradiae* CNMN-Ac-11 для выделения и идентификации биологически активных веществ с нейропротекторными и ноотропными свойствами. Получена новая питательная среда для культивирования штамма *S. massasporeus* CNMN-Ac-06 с добавлением ПАБК, улучшены его биосинтетические свойства и стимулирующий эффект биомассы на процессы обучения и памяти. Полученные результаты демонстрируют возможность получения на основе биомассы местных штаммов стрептомицетов препаратов для животноводства с целью стимуляции привесов и плодовитости.

**Внедрение научных результатов:** результаты внедрены в учебный процесс естественного-географического факультета ПГУ им. Т.Г. Шевченко. Получены 2 патента, 4 медали на международных выставках инноваций.

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**ȘCOALA DOCTORALĂ ȘTIINȚE ALE NATURII**

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**GARBUZNEAC ANASTASIA**

# ÎNVĂȚAREA ȘI MEMORIA ȘOBOLANILOR ÎN CONSUMUL BIOMASEI DE STREPTOMICETE

***165.01. Fiziologia omului și animalelor***

**Rezumatul tezei de doctor în științe biologice**

**Chișinău, 2024**

**GARBUZNEAC ANASTASIA**

# LEARNING AND MEMORY OF RATS WHEN CONSUMPTING STREPTOMYCETES BIOMASS

**165.01. Physiology of humans and animals**

**Abstract of the doctoral thesis in biological sciences**

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