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Contemporary comprehensive approaches to assessing the effectiveness of experimental model of neurodegenerative disorders with cognitive status changes

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Aim of the study was to characterize the locomotor and cognitive aspects of the behavior of experimental rats under intracerebroventricular colchicine administration in the open field test and the 8-arm radial maze, as well as identify a set of behavioral features of experimental animals that emerged during the study.

Materials and methods. The study was conducted in two stages on 20 male Wistar rats aged 10–11 months. The first stage involved assessment of initial locomotor activity and cognitive functions in all intact rats. At the next stage, the rats were divided into two experimental groups (n = 10): the first group with intracerebroventricular injection of physiological NaCl solution, and the second group with intracerebroventricular injection of colchicine. In 14 days after the surgery, repeated recording of locomotive and cognitive activity indicators was performed.

Results. The locomotor activity characteristics did not statistically differ between the animals before the surgical procedures and the rats of the first group. However, in the second group, the activity indicators were significantly higher than in the respective pre-surgery rats. In the intergroup comparison of the rats that entered the second stage of the experiment, it was found that among all the investigated parameters, only the indicator of high activity duration was significantly higher in the second group compared to the first group. At the same time, the animals in the second group showed significant cognitive impairments compared to the first group, as indicated by significantly lower memory index values, the number of correct entries into the maze arms, and a significantly longer time to make the first correct entry into the maze arm.

Conclusions. Intracerebroventricular administration of colchicine to experimental rats is accompanied by increased locomotor activity and impairment of cognitive functions. The administration of a physiological solution is not accompanied by a statistically significant increase in locomotor activity, but it demonstrates a clear tendency to increase, which may indicate a certain influence of the procedure itself. The applied pharmacological model of neurodegeneration with subsequent comprehensive assessment of animal behavior in an open field and an 8-arm radial maze is legitimate and can be used to study the early development of neuroinflammation, neuroapoptosis, and synaptogenesis disorders in the experiment.

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Сучасні комплексні підходи до оцінювання ефективності експериментальної моделі нейродегенеративних порушень зі змінами когнітивного статусу

М. В. Данукало, Ю. М. Колесник, О. В. Ганчева

Мета роботи – охарактеризувати локомоторні та когнітивні аспекти поведінки експериментальних щурів на тлі інтрацеребровентрикулярного введення колхіцину у тесті «відкрите поле» та восьмирукавному лабіринті, а також визначити їхні поведінкові особливості, що виникли під час дослідження.

Матеріали та методи. На 20 щурах самцях лінії Wistar віком 10–11 місяців у 2 етапи дослідили локомоторну активність у тесті «відкрите поле» та когнітивні функції у восьмирукавному радіальному лабіринті. На першому етапі в усіх інтактних щурів зафіксували вихідні показники. На наступному етапі щурів поділили на 2 експериментальні групи: перша – з інтрацеребровентрикулярним введенням фізіологічного розчину NaCl (n = 10); друга – з інтрацеребровентрикулярним введенням колхіцину (n = 10). Через 14 днів після оперативного втручання повторно фіксували показники локомоторної та когнітивної активностей.

Результати. Характеристики локомоторної активності статистично не відрізнялися у тварин до оперативного втручання та щурів першої групи. Натомість у тварин другої групи показники активності вірогідно перевищували відповідні параметри щурів до оперативного втручання. При міжгруповому порівнянні щурів, що залучені до другого етапу експерименту, встановили: з-поміж усіх параметрів, що вивчали, у тварин другої групи вірогідно більшим був лише показник часу високої активності порівняно зі щурами першої групи. Разом із тим, у тварин другої групи виявили значні когнітивні порушення порівняно з тваринами

першої групи. Про це свідчили вірогідно нижчі показники індексу пам'яті та кількості правильних входів до рукавів лабіринту, а також вірогідно більший час затримки першого правильного входу в рукав лабіринту.

Висновки. Інтрацеребровентрикулярне введення колхіцину експериментальним щурам супроводжується підвищенням локомоторної активності та погіршенням когнітивних функцій. Введення фізіологічного розчину не супроводжується статистично значущим підвищенням показників локомоторної активності, проте демонструє чітку тенденцію до їх зростання; це може свідчити про певний вплив власне процедури. Застосована фармакологічна модель нейродегенерації з наступним комплексним оцінюванням поведінки тварини у відкритому полі та восьмирукавному лабіринті є придатною, може бути використана під час дослідження раннього розвитку процесів нейрозапалення, нейроапоптозу, порушень синаптогенезу в експерименті.

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Intracerebroventricular (ICV) administration of colchicine, particularly into the lateral ventricles of the brain, is currently considered as one of the methods for modeling neurodegeneration in laboratory animals [1]. According to research, the primary mechanisms leading to neuronal death involve irreversible axonal transport blockade, accompanied by neuroinflammation, mitochondrial dysfunction in neurons, impaired synaptogenesis, and glial activation [2,3]. Additionally, it has been demonstrated that the neurotoxic effect of colchicine is also realized through alterations in the expression levels of neuropeptide genes in the brains of rats [4].

It should be noted that in experiments, selective sensitivity of neurons of various brain structures to colchicine introduced into the lateral ventricles has been repeatedly demonstrated. Notably, one of the most sensitive groups of neurons to colchicine toxic effect are the cholinergic neurons in the basal brain region [5,6]. The latter play a crucial role in the formation of higher cognitive functions, and their impairment is characteristic of the early stages of Alzheimer's disease [7]. It is essential to emphasize that under the mentioned method of neurotoxin administration, there was a predominance of neurodegeneration in specific brain regions, including the hippocampus, frontal cortex, amygdala, and striatum. These structures are pivotal for cognitive function too [1]. These findings have led researchers to consider ICV colchicine administration as one of the ways to model sporadic dementia of Alzheimer's type in animals [8,9].

The mentioned method of pharmacologically induced neurodegeneration potentially offers several advantages over a large number of corresponding genetically determined animal models. Primarily, this is because in the latter case, it's challenging to track the initial stages of the disease and control the extent of neuronal damage. In contrast, pharmacologically induced neurodegenerative conditions allow for this, as there is a "starting point" (the time of neurotoxin administration) and a dose-dependent effect of colchicine-induced damage [8]. This is important since neurodestruction in several brain structures, including cholinergic ones, is observed in the preclinical stages of various age-related neurodegenerative diseases and leads to progressive afferent cortical cholinergic denervation [10,11,12]. In such cases, there is an opportunity for in-depth study of key neurochemical aspects of neurodegeneration precisely in the preclinical stage.

Cognitive testing in mazes is essential for verifying the development of cognitive deficits in experiments. There are currently a wide variety of maze designs and research methodologies available [13,14]. However, the diversity of these mazes requires the researcher to have a clear understanding of which specific cognitive process can be investigated in each particular maze and which indicators will most accurately characterize it [14].

It is worth noting that different approaches to modeling cognitive impairments in experimental animals will lead to unique patterns and relationships of changes in the described characteristics. Therefore, based on all the above, it is logical to assume that in experimental animals exposed to ICV colchicine administration, due to the nature of the neurotoxin's impact and the emergence of "specificity in behavioral changes", conducting maze experiments requires a distinct approach and necessitates the verification of cognitive impairments in each specific case.

Aim

Therefore, the aim of this study was to characterize the locomotor and cognitive aspects of the behavior of experimental rats under intracerebroventricular colchicine administration in the open field test and the 8-arm radial maze, as well as identify a set of behavioral features of experimental animals that emerged during the study.

Materials and methods

The experiment involved 20 male Wistar rats, aged 10–11 months, with a weight range of 250–350 grams. All rats were housed under standard vivarium conditions at the Training medical and laboratory center of Zaporizhzhia State Medical and Pharmaceutical University. The research received approval from Zaporizhzhia State Medical and Pharmaceutical University Bioethics Committee and was conducted in strict accordance with the national "General Ethical Principles for Conducting Experiments on Animals" (Ukraine, 2001), which align with Directive 2010/63/EU of the European Parliament and of the Council dated September 22, 2010, titled "On the protection of animals used for scientific purposes".

In the first stage of the research, baseline measurements of locomotor activity and cognitive status were recorded in all intact rats using an integrated system that allowed for testing in the open field and an 8-arm radial maze (LE760, PanLab Harvard Apparatus, Spain). The system was equipped with a SONY camera (Japan) and video analysis software Smart v. 3.0 (PanLab Harvard Apparatus, Spain, s/n DD347-0E6) [15]. The tests were conducted according to the methodologies described below.

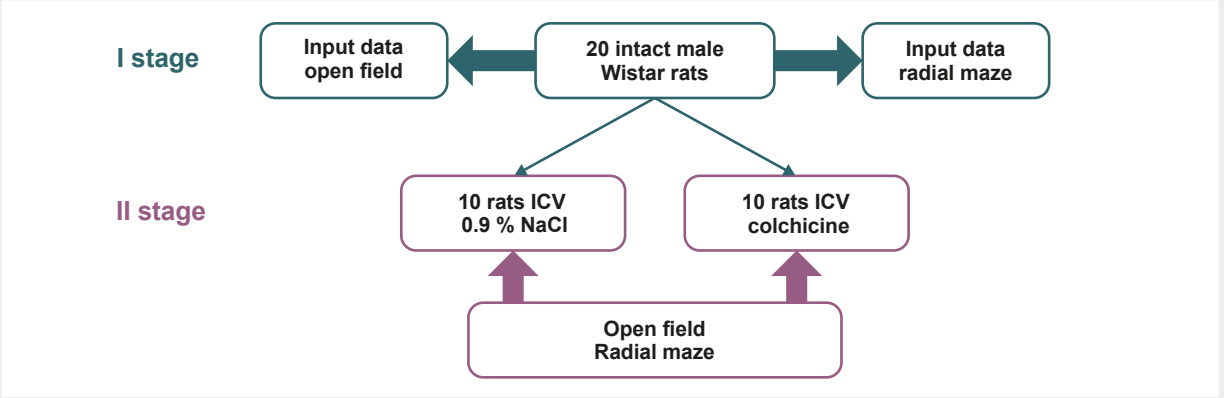


Fig. 1. Experiment design.

Table 1. Characteristics of the parameters studied in the open field test

Parameter, units of measurement	Description	Value
Duration of high, low activity, and immobility of the animal in the zone, s	Time, that animal spent at a specific level of activity in the zone of interest.	Quantitative determination of the animal's activity and its movement pattern in the open field
Distance in the zone, cm	Distance traveled by the subject in the designated zone	Quantitative assessment of animals' locomotor activity
Mean speed in zone, cm/s	Average speed of the subject in the zone of interest	Quantitative assessment of animals' locomotor activity and its movement pattern
The number of entries into the respective zone of the open field	The number of entries by subjects into the designated zones associated with the experiment. Calculated for each zone defined by the user as "zone of interest"	Assessment of the locomotor activity of the animal; Assessment of preference for a specific zone, which can be used to evaluate anxiety and exploratory activity

During the next stage, the intact rats were divided into two experimental groups, with 10 rats in each group. The first group, under "Telazol" anesthesia (0.1 ml per 100 grams of body weight), received ICV injections of a physiological saline solution (37 °C). This group served as the control group. The second group, under the same anesthesia, also received ICV injections, but in this case, it was a solution of colchicine (37 °C) (*Fig. 1*).

The methodology of open field test. The following parameters of animals' locomotor activity were calculated both in the center and in the peripheral zone using this test (*Table 1*) [16].

The calculation of the animal's activity level was performed automatically by the program based on the parameters set by the developers.

The test was conducted in an open box made of polyvinyl chloride with dimensions (width × length × height) of 80 × 80 × 20 cm. The box was positioned at a height of 1 m above the floor.

The experimental animal was placed in the center of the box, and its movements in the open field were recorded by video for 5 minutes. After each animal, the field was cleaned of feces and disinfected with a 70 % ethanol solution, and only after it had completely dried next animal placed in the field.

The subsequent stage of the research involved digital video processing in Smart v. 3.0. To accomplish this, observation zones were first delineated: the central field (highlighted in red) and the periphery (the area between the red and blue squares) (*Fig. 2*).

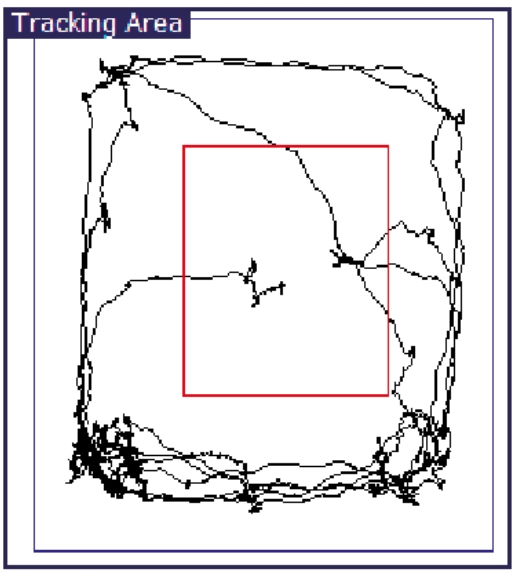


Fig. 2. Rat's tracking at the initial stage of the experiment and analysis zones in the open field test using Smart v. 3.0. The central field is highlighted in red, and the analysis boundaries are marked in blue. The area between the red and blue delineations represents the periphery.

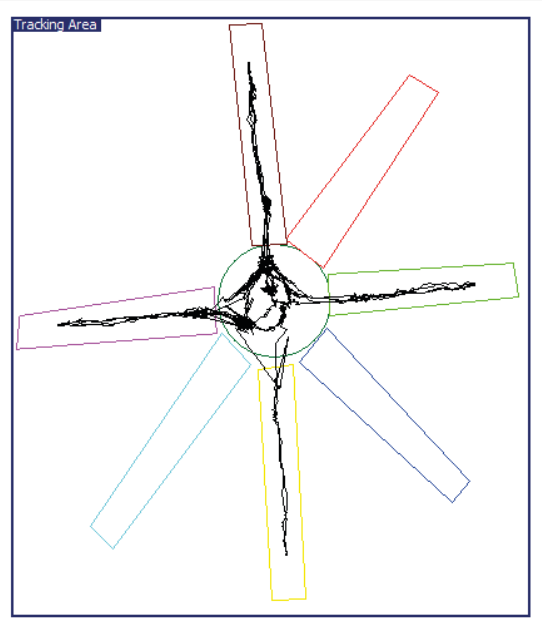


Fig. 3. Tracking of the rat during the initial stage of the experiment in the training phase and the analysis zones in the 8-arm radial maze using the Smart v. 3.0 software.

The methodology for conducting research in the 8-arm radial maze involved the Delayed Spatial Win–Shift test as a basis for assessing the cognitive status of rats. This test allows assessment of both short-term working spatial memory and long-term memory, the deficits of which were observed in the context of ICV colchicine administration by other researchers [17]. A distinctive feature of this test is the analysis of the subtest animals' ability to retain spatial information and reproduce it both during the test and after a delay period. Thus, the procedure conducted in this experiment comprised three stages: training, delay, and testing, each lasting 5 minutes.

It should be noted that before the test, the rat was adapted to the conditions of the radial maze (5 days) in compliance with several conditions, namely:

– the experiment was conducted at the same time of day to maintain stable natural lighting conditions without additional sources of light;

– access to food was restricted by 80 % during the experiment;

– the maze was cleaned with 70 % ethanol and dry wipes after each rat.

In order to form the animal's adaptation to the maze, a food reward was placed at the end of each arm. The rat was placed in the center of the maze and had the opportunity to freely explore all its arms for 10 minutes.

After the adaptation, we started the experimental phase. It began with a training stage, which involved a 5-minute recording of the rat's behavior. During this phase, the rat was placed in the center of the maze where only 4 arms had food rewards and were open, while the other arms had no rewards, and access to them was blocked by special doors with a guillotine mechanism. After the training, the delay phase (5 minutes) followed, when the rodent was removed from the maze and placed in its cage. The next stage was the testing phase, when the rat was placed in the center of the maze, and all 8 arms were open, but food rewards were placed in 4 different arms than in the training phase [18].

Data recording continued for four consecutive days. After this, one group of rats received an ICV injection of 3 µl of physiological saline (NaCl) into the lateral ventricles of the brain (control group). The rats of other group were administered colchicine (15 µg in 3 µL of 0.9 % NaCl solution) in the same method. All procedures were conducted under sterile conditions while the rats were under "Telazol" anesthesia.

Fourteen days after the stereotaxic surgical procedure, with ICV administration of either physiological saline (1st control group) or colchicine (2nd experimental group), the entire experiment procedure in the maze was repeated. Video tracking of the animals in the maze, followed by digital video processing, was performed using the previously mentioned Smart v. 3.0 software (*Fig. 3*).

The following parameters were investigated during the testing phase:

– the number of correct and incorrect entries into the respective arms of the maze. Re-entering the same arm was also considered an error. Based on these data, a memory index (MI) was calculated using the following formula:

$$MI = (CE - IE) / (CE + IE) \quad (1),$$

where *CE*: the number of correct entries into the arms; *IE*: the number of incorrect entries into the arms [19];

– the time elapsed from the beginning of the phase to the first correct entry into an arm (latency time), s.

The intracerebroventricular injection procedure was carried out in the surgery room for vivarium animals at the Training medical and laboratory center of Zaporizhzhia State Medical and Pharmaceutical University under sterile conditions and anesthesia using "Telazol" (containing tiletamine hydrochloride and zolazepam hydrochloride at 250 mg each in one vial) at a dose of 0.1 ml per 100 grams of the animal's body weight, administered intraperitoneally.

The ICV injections into the lateral ventricles of the rat brain were performed using a stereotaxic digital instrument World Precision Instruments (USA). The coordinates for the injections were as follows: 9.5 mm anterior to the bregma; 1.5 mm to the right of the midline and 6 mm deep.

The precise positioning of the colchicine injection site in the animal brain was performed using a stereotaxic coordinate system based on external cranial landmarks and their comparison with the images of the stereotaxic atlas of the rat brain [20].

The experimental data were processed using the Statistica software package (license number: JPZ804I382130ARCN10-J) and Microsoft Excel 7.0 (Microsoft Corp., USA). For all parameters, the following statistics were calculated: Mean (M), data dispersion and Standard Error of the Mean (m). To assess the significance of differences in the research results between the experimental and control groups of rats Student's t-test (t) was used for samples with normally distributed data or Mann–Whitney test (U) was used for samples with data that did not follow a normal distribution. A single factor analysis of variance (ANOVA) was employed to assess the memory index (MI) in the experimental

Table 2. Locomotor activity parameters in the open field test for rats in the experimental groups

Parameter, units of measurement	Before surgery, at the 1st stage		First group with ICV administration of 0.9 % NaCl		Second group with ICV administration of colhicine	
	Center	Periphery	Center	Periphery	Center	Periphery
High activity duration, s	1.53 [0.82; 3.12]	9.96 [2.13; 26.98]	5.07 [0.44; 9.84]	34.13 [22.52; 37.21]	5.46 [2.43; 7.27]	57.42 [46.79; 63.13][1,2]
Immobility duration, s	0.00 [0.00; 0.58]	180.37 [114.12; 228.96]	0.52 [0.00; 2.60]	69.96 [52.04; 109.82]	0.86 [0.00; 7.66]	64.75 [42.74; 75.66][1]
Mean speed in zone, cm/s	10.50 [7.69; 17.00]	6.69 [5.59; 8.78]	12.99 [9.79; 16.23]	9.72 [8.61; 10.95]	10.83 [9.87; 16.23]	10.32 [9.35; 12.21][1]

1: a significant difference ($p_U < 0.05$) was observed in the parameters of rats with ICV colchicine compared to animals before surgery;
2: a significant difference ($p_U < 0.05$) was observed in the parameters of rats with ICV colchicine compared to animals of the first group.

groups. After that, the probability of differences between the samples (p) was determined. Values with $p < 0.05$ were considered statistically significant, indicating that observed differences were unlikely to be random.

Results

After analyzing the results of the research on the behavior and cognitive functions of the rats, significant intergroup differences were identified both in rats' behavior in the open field test and in the cognitive status of animals following intracerebroventricular colchicine administration.

Thus, statistical analysis of the locomotor activity of experimental animals showed no significant difference between animals before surgery and rats of the first group in all the parameters studied, both in the center and on the periphery of the open field.

The studied animals demonstrated typical behavioral patterns with higher activity on the periphery of the open field, but the speed of movement per unit time prevailed in the center. In the animals of the second group, activity also prevailed in the periphery, but the speed per second in the center and periphery was almost the same (*Table 2*).

In the intergroup comparison, it was found that rats treated with colchicine injection demonstrated significant changes in the following parameters only in the periphery.

In the intergroup comparison, it was found that rats with ICV colchicine administration demonstrated significant changes in the following parameters only in the periphery of the open field:

1. High Activity duration: an increase by 576.5 % compared to the respective pre-surgical values and a 168 % increase compared to rats from the first group;
2. Immobility duration: a decrease by 35.89 % compared to the animals before the surgery but without significant changes compared to rats from the first group;
3. Mean speed: an increase of 155.3 % compared to the animals before the surgery but also without significant changes compared to rats from the first group (*Table 2*).

It should be noted that the examined parameters of rats from the second group in the center of the open field did not differ significantly from those of animals from the other comparison groups (*Table 2*).

As for other parameters of locomotor activity (duration of low activity, distance in the zone, and the number of entries into the corresponding zone of the open field), there was no significant difference between the experimental groups of rats.

The next stage of the research was to characterize the effect of colchicine on the cognitive functions of laboratory rats in the 8-arm radial maze by determining the memory index and the delay time before entering the correct arm.

According to the obtained results, the memory index in rats that received ICV of a 0.9 % NaCl solution was significantly higher than the corresponding index in the rats of the second group (based on the results of single factor analysis of variance (ANOVA) $F3.35 = 30.97$, $p < 0.05$) (*Fig. 4*).

At the same time, tracking the dynamics from the 1st to the 4th day of the experiment, it should be noted that in both examined groups, there was a tendency for the memory index to increase (*Fig. 4*). The change in the memory index is directly associated with the number of correct entries, which was on average 237.5 % higher in rats from the first group than in animals from the second group ($p < 0.05$) (*Fig. 5*).

Simultaneously with the changes in the number of correct entries into the arms and the memory index, rats from the 2nd group, compared to the control group (1st group), demonstrated a 292.8 % higher latency time from the moment of placement in the maze to entering a free arm (*Fig. 6*).

Dynamic observation of this parameter revealed that from the 1st to the 2nd day of observations, there was a tendency for a decrease in the latency time in both groups. Later, in the group of animals from the 2nd group, this parameter continued to decrease, whereas in the control rats (1st group), it remained constant (*Fig. 7*).

Thus, the provided data suggest that in rats with ICV colchicine administration, the changes observed in the open field test indicate increased locomotor activity, as well as a clear tendency to similar behavior in control animals. At the same time, the studied neurotoxin, when administered intracerebroventricularly, led to significant cognitive impairments in rats compared to animals that received a 0.9 % NaCl solution.

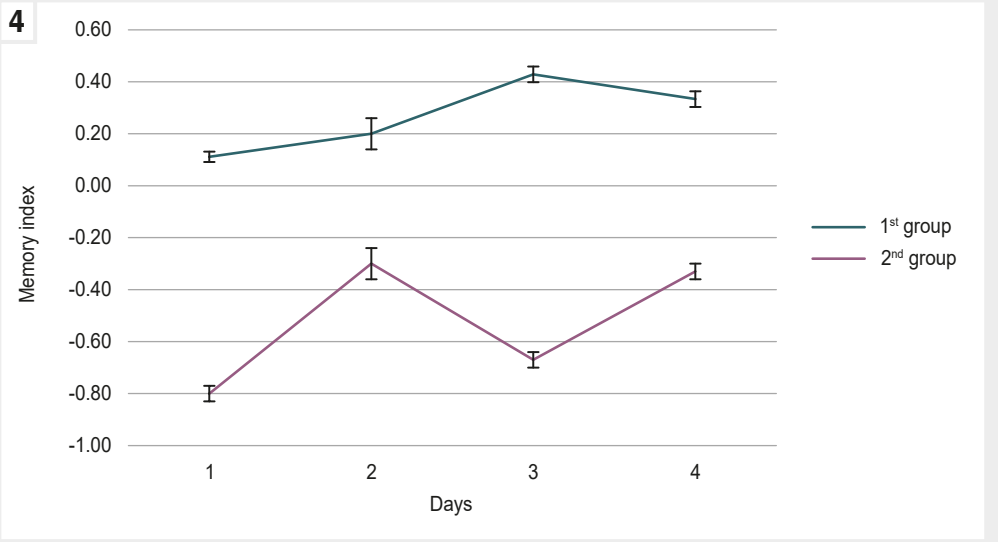
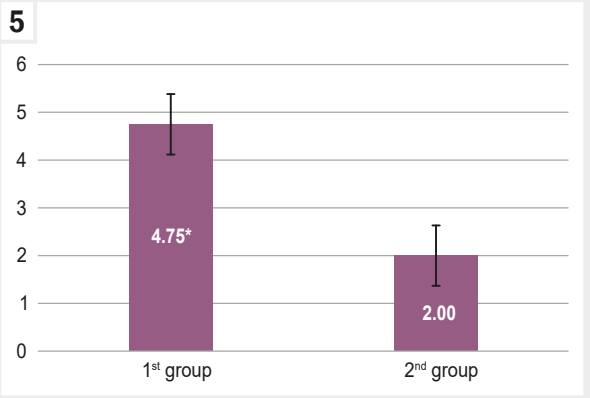


Fig. 4. Rats' memory index parameters from the first and second experimental groups.



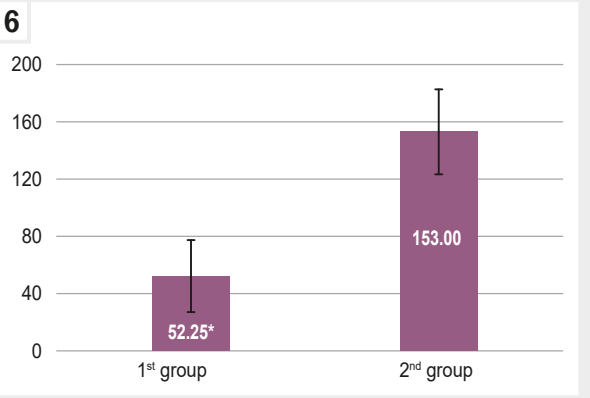


Fig. 5. The number of correct entries into the arms of the maze in rats from the 1st and 2nd groups.
***:** a significant diffetrence between the experimental groups ($p_{st} < 0.05$).

Fig. 6. Mean latency time (s) in rats from the 1st and 2nd groups.
***:** a significant difference between the experimental groups ($p_{st} < 0.05$).

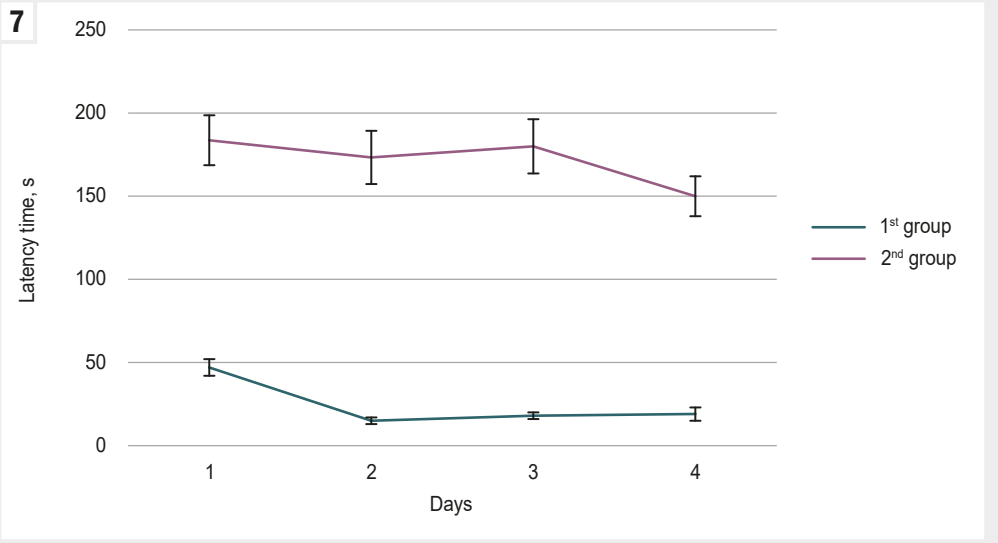


Fig. 7. Latency time parameters in rats from the 1st and 2nd groups.

Discussion

When analyzing the obtained results, it's important to consider several key components that can influence purity of the experiment. Firstly, ICV administration of colchicine is an invasive procedure, and its possible complications can potentially affect the locomotor behavior of the animals.

Additionally, the toxic effect on neurons in structures that largely contribute to the motivational component, especially appetite, in performing tasks in the radial maze may play a significant role [21].

In this regard, it's not surprising that certain contradictions can be found in the results of research by different scientists. For instance, Veerendra Kumar and colleagues claim that ICV colchicine does not lead to significant changes in the locomotor behavior of rats two to three weeks after administration [17]. In contrast, Stanley Barone Jr. and colleagues observed hyperactivity and increased aggression in animals after ICV colchicine for three weeks after injection [22]. To some extent, our results confirm these findings.

Researchers seem to draw more consistent conclusions regarding the impact of colchicine on the cognitive functions of animals. Thus, there is almost unanimous agreement that cognitive function deteriorates, that has been observed in a water maze [22], a plus-maze [17], and a radial 8-arm maze [5]. Therefore, this is consistent with the data we have obtained.

At the same time, it's difficult to ignore the clear influence of changes in locomotor activity on the results of cognitive tests in mazes. If an animal is less active, both the time-based measures (latency time to the first entry into the correct arm and the time it takes the animal to visit all correct arms) and the number of arms entered within a limited time (usually 5 minutes) will significantly differ from similar measures in hyperactive animals. In contrast, in the latter case, there is a high likelihood of the experimental rat randomly entering the correct arm.

Therefore, forming the groups of test animals for further research of cognitive status in the maze should take their activity into account. Such a comprehensive approach will allow for a more accurate analysis of colchicine-induced behavioral changes.

An essential component of testing in the radial maze is the motivation of the animal. Brenda J. Anderson and colleagues emphasized the importance of analyzing the motivational component in their research, where they restricted access to water, resulting in differing energy expenditures. This created a difference in motivation between experimental groups, making their results sensitive to group differences in this regard [23].

If we apply this to the conducted experiment, there are currently isolated studies that suggest the potential influence of colchicine on the feeding behavior of animals by damaging specific hypothalamic centers [24].

It's worth noting that the doses and method of colchicine administration in these studies differ significantly from the description provided above. Therefore, it's not possible to definitively state that intracerebroventricular administration of colchicine at a dose of 15 μg will lead to feeding behavior disturbances that affect the motivation of the animals to seek rewards in the maze.

Conclusions

1. Intracerebroventricular administration of colchicine to experimental rats is accompanied by increased locomotor activity and impairment of cognitive functions.

2. The administration of a physiological solution is not accompanied by a statistically significant increase in locomotor activity, but it demonstrates a clear tendency to increase, which may indicate a certain influence of the procedure itself.

3. The applied pharmacological model of neurodegeneration with subsequent comprehensive assessment of animal behavior in an open field and an 8-arm radial maze is legitimate and can be used to study the early development of neuroinflammation, neuroapoptosis, and synaptogenesis disorders in the experiment.

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