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## PHYSIOLOGICAL ASPECTS OF RAT ACTIVITY, THEIR ANXIETY AND MEMORY AFTER ADMINISTRATION OF FULL GABA<sub>A</sub>-RECEPTOR COMPLEX AGONIST PROPOXAZEPAM

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*Встановлено дію 7-бром-5 (о- хлорфеніл) -3-пропокси-1,2-дигідро-3Н-1,4-бенздіазепін-2-ону (пропоксазепаму) при його тривалому введенні у різних дозах справляє виражений вплив на поведінкові реакції, тривожність і пам'ять щурів, а також на їх м'язовий тонус, що важливо з огляду на головні (протисудомний та анальгетичний) фармакологічні ефекти цієї речовини.*

*Метою дослідження була порівняльна оцінка виразності та тривалості впливу на вищі психічні функції та функції підтримання м'язового тонусу і координацію рухів центральної нервової системи щурів введення впродовж 10 діб пропоксазепаму у дозах 2; 5 та 10 мг/кг).*

*Матеріали та методи.* Дослідження проведено на 40 щурах лінії Wistar масою 220–290 г. Психофізіологічний стан тварин оцінювали методом “відкритого поля”, формування просторової робочої і довготривалої пам'яті у радіальному восьмирукавному лабіринті, м'язову релаксацію, порушення рівноваги і координації рухів – методом обертового стрижня. Статистична обробка виконувалася у Microsoft Excel 2016 з пакетом AtteStat 12.

*Результати дослідження.* При порівнянні показників тестів «відкрите поле», «радіальний лабіринт» та «ротород» у груп тварин, яким вводилися різні дози сполуки було виявлено, що в цілому, зазначені параметри при дозах 2 мг/кг та 5 мг/кг достовірно підвищуються стосовно тварин контрольної групи, але не відрізняються залежно від величини цих доз. Щодо дози 10 мг/кг, то у більшості випадків (окрім ротород-тесту) її введення децю знижувало досліджувані показники.

*Висновки.* Введення препарату в дозах 2, 5 та 10 мг/кг призводить до зниження тривожної поведінки тварини, що також супроводжується вираженим дозозалежним негативним впливом на витривалість, координацію і пам'ять тварин. Введення препарату в дозі 10 мг/кг погіршувало здатність тварин до навчання і знижувало пам'ять. Зазначене необхідно враховувати при клінічних дослідженнях сполуки

*Ключові слова:* пропоксазепам, рухова і пошукова активність, референтна і робоча пам'ять

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### 1. Introduction

There are several approaches to studying animal behaviour. Their use makes it possible to understand how behaviour helps an animal to adapt and survive in nature, or inherited an act of behaviour, or how the animal's nervous system works, or how the animal learns. In general, the driving force behind animal behaviour is environmental uncertainty and disturbance / stress. It is believed that each type of activity of animals is carried out when reaching the optimal level of arousal. Both insufficient and excessive arousal reduce efficiency. The disorder increases in an unknown and uncontrolled environment, but the animals themselves are able to change both the uncertainty of the environment and the level of their excitement. It is hypothesized that the optimization of the level of excitation is a universal mechanism of animal behaviour [1]. This is quite successfully used in biomedical research, which makes it possible to find a way to treat a behavioural problem or, conversely, to find behaviour that could be judged on the pathology. The latter is widely used in the testing of innovative drugs. Changes in the psychophysiological state in experimental animals, in particular – rats, are manifested not only in the form of behavioural features in various tests, but also reflected in

the form of neurochemical transformations. 1,4-Benzodiazepine derivatives are modulators of excitation in experimental animals and in the treatment of patients and can therefore be used to clarify some neurophysiological aspects of the emotional and mnemonic components of behaviour. In the biomedical sciences to clarify the indicators of such components of behaviour, there are appropriate terms:

1. Anxiolytic action – reducing feelings of emotional stress, depression, anxiety, fear, irritability and other manifestations of neurosis, psychopathic states and autonomic dysfunction.

2. The sedative effect of reducing aggression or agitation and with increasing dose of the compound that causes it, sleep occurs.

### 2. Literary review

In a wide range of drugs, special attention is paid to potential neurotropic agents, among which a prominent place is occupied by 1,4-benzodiazepine derivatives. They enhance the action of the neurotransmitter gamma-aminobutyric acid (GABA) on the GABA receptor, causing sedative, hypnotic, anxiolytic, anticonvulsant, muscle relaxant and analgesic effects. These properties make ben-

zodiazepines useful in the treatment of anxiety, insomnia, agitation, seizures, muscle spasms and alcohol withdrawal syndrome. In addition, benzodiazepine drugs are used as pharmacological analyzers of neurophysiological processes, including behavioural responses of experimental animals. An innovative compound created at our institute – propoxazepam, 7-bromo-5 (o-chlorophenyl) -3-propoxy-1,2-dihydro-3H-1,4-benzodiazepin-2-one is characterized by anticonvulsant [2], analgesic [3] and anti-inflammatory [4] action. We proved [5] that the mechanisms of the analgesic effect of propoxazepam involve the dopaminergic system, NMDA receptors, alpha-1 adrenoceptors, as well as GABA receptors. Regarding the mechanism of anticonvulsant action of propoxazepam, it is due to its interaction with GABA- and glycine receptors [2, 6]. The compound is considered a promising drug and undergoes the necessary preclinical trials, so it is important to determine its possible side effects, which will prove the safety of use in the future. Thus, we have already shown [7] that acute (3, 7 and 14 days) and subchronic (90 days) oral administration of propoxazepam does not cause any clinical signs of toxicity or mortality in mice and rats. The LD<sub>50</sub> value of propoxazepam was higher than 5000 mg/kg, and the observed adverse effect level is considered to be 4000 mg/kg per day for both mice and rats, which refers to the fifth category of non-toxic substances according to GHS [8].

Propoxazepam also has no detrimental effect on the stomach under conditions of acute, subacute and chronic administration and does not change the eating behaviour and general activity of animals, which is evidence of the safety of this compound, in particular, for the gastrointestinal tract [9].

Propoxazepam in doses of 10; 100; 250; 500 and 1000 µg / ml do not induce gene mutations in the Ames test on *Salmonella typhimurium* strains TA 98 (mutations by type of frame shift) and TA 100 (point mutations such as base pair replacement). In this regard, the presence of carcinogenic properties associated with genotoxicity in compounds is also unlikely [10].

Neurophysiological aspects of motor, emotional and mnemonic components of behaviour are manifested in a single continuum and are anxiolytic, sedative, hypnotic and muscle relaxant actions in the administration of benzodiazepines [11]. Unfortunately, it is impossible to separate one effect from another in one drug, which is the main limitation of the use of benzodiazepines in medical practice. Therefore, it could be assumed that propoxazepam has all these pharmacological properties. In previous studies [12], we proved that a single administration of propoxazepam to rats in moderate doses (0.15 and 1.5 mg / kg) did not cause significant changes in motor activity and tentative exploratory behaviour of animals, determined by the method of open field, in comparison with animals of the control group. Studies of the anxiolytic and anxiogenic effects of propoxazepam, which were performed on mice according to the method of the elevated plus maze, also did not show probable changes.

Based on the fact that propoxazepam may be used in much higher dosages in the future and for a long time it was necessary to determine the effect of the compound on locomotor activity, orientation and emotional activity in the open field model, and on anxiety in the test of the elevated plus maze, which allows to detect both anxiolytic

and anxiogenic effects. On the other hand, such data expand our knowledge of the mechanism of propoxazepam action.

### 3. The purpose and objectives of the study

In this regard, the aim of this study was to determine the effect of propoxazepam with its long-term administration in different doses on the behavioural responses, anxiety and memory of rats, as well as on their muscle tone, which is important given the main (anticonvulsant and analgesic) pharmacological effects. Experimental study of neurophysiological disorders and the dynamics of their recovery allows to assess their severity and duration, and can also be used to determine the effectiveness and justification of the use of pharmacological correction in rehabilitation measures in patients.

To achieve this goal, the following tasks were set:

1. To analyze the effect of propoxazepam on motor and exploratory activity of rats by a method that allows to simultaneously observe the behaviour of the animal in the open field and to assess the exploratory reflex.
2. Evaluate with the method of radial arm maze change in the spatial working and long-term memory of animals under the action of the compound.
3. To determine by the method of the rotating rod "rotarod" the occurrence of muscle relaxation, imbalance and coordination of movements in rats, on the background of the introduction of propoxazepam.

### 4. Materials and methods of the research

The study was conducted in accordance with Directive 2010 / 63EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes, as well as with the national "Common Ethical Principles for Animal Experiments" (Ukraine, 2001).

The study was performed on 40 Wistar rats aged 6 months weighing 220–290 g. The animals were in standard vivarium conditions (12-hour light cycle, temperature 22 °C). For experiments, animals were subjected to food deprivation, reducing by 15–20 % the daily intake of food for 24 hours before the experiment, but with free access to water. In order to tame, the rats before the experiment was held in his hands for 2–3 minutes for 5 days, which facilitated subsequent experimental studies.

*Research scheme.* The animals were divided into 4 groups:

- 1) 10 animals that underwent intragastric administration of solvent (control) in a volume of 1 ml;
- 2) 10 animals treated with intragastric administration of propoxazepam at a dosage of 2 mg/kg;
- 3) 10 animals treated with intragastric administration of propoxazepam at a dosage of 5 mg/kg.
- 4) 10 animals treated with intragastric administration of propoxazepam at a dosage of 10 mg/kg.

The administration was performed once a day at 10:00 in a vivarium for 10 days.

*Determination of motor and exploratory activity.* The psychophysiological status of rats was determined by the open field test using a device that allows to simultaneously observe the behaviour of the animal in the open field (arena size 80x80x35cm) and assess the exploratory reflex.

The animal was placed in the middle of one of the sides with its snout against the wall, after which it was allowed to move freely around the arena for 8 minutes. We evaluated the total travelled distance, total activity, percentage of activity and inactivity, number of freesings and entering the center, travelled distance near the wall and in the central part of the arena, vertical exploratory activity (the number of rearings on the hind legs near the wall and in the center), number of short and long grooming, the number of defecation and urination acts.

The experiments eliminated the possibility of external and internal visual, olfactory and auditory stimuli. The behaviour of the animals was recorded with a special colour video camera SSC-DC378P (Sony, Japan). The video file was analyzed using Smartv 3.0 software (HarvardApparatus, USA).

*Evaluation of reference and working memory.* The radial eight-sleeved maze LE760 (AgnTho's, Sweden) was used to assess the formation of spatial working and long-term memory under the control of the hippocampus [13, 14]. This method of testing is based on the use of the instinct of rodents to explore new places in combination with food reinforcement. Throughout the experiment, in order to activate the search behaviour, the daily diet was reduced by 15–20 %.

From the first day of drug administration, the animals were placed in the central part of the labyrinth, which consisted of 4 closed rays and 4 open ones, the feeders of which contained 200 mg of food pellets. The combination of open and closed rays was individual and constant for each animal. For the next 5 days, the animal learned to find food using external visual landmarks. Training was conducted for 10 minutes or until the animal found all four food sources. After the experiment, the animal received a daily diet. On the 10th day of administration of the compound, the animal was placed in a radial labyrinth with eight open arms, 4 of which had food placed in it according to the usual scheme for the animal. We evaluated the reference memory (general long-term understanding of the structure of the maze and the location of food formed in the animal during training) and the number of errors of the reference memory (first visits to a previously closed beam in which the animal never found food), and working memory (short-term idea of the animal about the location of food in a particular experiment) and the number of errors in working memory (re-visiting the beam in which the animal has previously found or did not find food). In addition, we evaluated the travelled distance and overall motor activity.

The test also used the test of the rotating rod “rotarod” (Ugo Basile, Italy), which allows to objectively assess the presence of muscle relaxation, imbalance and coordination of movements [15].

Statistical analysis of the results was performed using Microsoft Excel 2016 with the statistical processing package AtteStat 12. To assess the probability of differences in the study groups used the Kraskel-Wallis test with Dunn's correction. Differences at  $p < 0.05$  were considered probable.

## 5. Research results

Systemic response to stress, which is aimed at its elimination or reduction, is accompanied by changes in be-

havioural, autonomic, motor, sensory, cognitive and other body functions. Behaviour under stress is an integral part of its overall component. In this case, the violation of the response of animals occurs in the direction of extreme states of excitement – inhibition of the central nervous system and fits into a single scale of ethological activity: stress – fear – anxiety – depression. General and special behavioural tests are used to study qualitative and quantitative indicators of behaviour. One of these is the open field test, which allows to detect significant disorders in the neuromuscular, sensory and autonomic systems of the body and to assess the more subtle functional changes associated with individual and social behaviour of animals. This method is a good solution due to the simplicity of its implementation as it does not require prior training of animals, in contrast to the tests with preconditions. It is based on the natural opposition in animals of two motivations – the study of a new environment and the avoidance of potentially dangerous places, which allows us to assess changes in anxiety levels by changing the ratio of behavioural reactions, reflecting the predominance of motivation.

The most difficult task in the study of behavioural reactions of experimental animals is the unambiguous interpretation of the data. Their complexity is due to the fact that the interpretation of different authors of the same behavioural reactions of rodents in the open field does not always coincide, depending on the objectives of a particular experiment, its organization, the method of presenting the test to animals.

In our studies of animal behaviour in the open field test the following indicators were used: overall activity, high activity and inactivity and their duration. General activity is all types of animal movement per unit time. The computer program used allows you to identify the structure of the component of total activity (high activity and lack of activity, i.e. inactivity). Changes in the activation patterns in the amygdala, the limbic region associated with fear and anxiety, are found between low and high activity when passing the “open field” test, and are associated with the contextual conditionality of fear [16]. This is due to the level of expression of c-fos protein in the limbic system as a whole. The increase (percentage) of high activity indicates the absence of anxiety and fear in the animal and its high psycho-emotional status. Such a significant increase in high activity is manifested against the background of amphetamines and antidepressants, which leads to side effects such as anxiety and disorientation, as well as an increase in such indicators as “number of entries”, as in the case of ecstasy, sertraline and fluoxetine [17]. A high percentage of low activity and, in particular, inactivity is directly associated with the manifestation of depression, which occurs in conditions of dopamine deficiency or low affinity of dopaminergic receptors of the meso-limbic system. Changes in the structure of total activity also depend on the 5HT1A / 5HT2A receptor ratio [18]. The presence of fear or depression implies a longer stay of rats near the wall of the device as there is more darkening of the space (an indicator – an increase in the distance near the wall). The indicator of “freezing” is an indicator of anxiety, “free distance” and “number of entrances to the center” demonstrate high cognitive activity of animals, as well as the absence of anxiety, fear and depression [19].

When evaluating the specific indicators of the experimental model open field it was found that the introduction of propoxazepam has a pronounced dose-dependent effect (Table 1). Thus, in the case of a dosage of 2 mg/kg there was a statistically significant increase in the total activity of rats (by 65.33 %). Moreover, there was a significant change in the structure of activity, namely a statistically significant decrease in the duration (by 59.5 %) and the number of episodes (by 54.6 %) relative to the criterion of lack of activity (inactivity). The percentage of high and low activity in this group had no significant differences, but we noted a steady upward trend. As for the sign, the travelled distance by the animals, in the conditions of receiving a dose of 2 mg/kg did not lead to a statistically significant increase. At the same time, the animals of this group statistically significantly increased the travelled distance in the central part of the arena by 9 times in absolute numbers and 8 times in relative numbers. Also in this group, we noted a statistically significant increase in vertical search activity (an increase in the number of racks near the wall in 2 times), which together with an increase in overall activity can be seen as a decrease in learning ability, as the rat makes excessive “extra” movements and requires more time to learn a new condition.

The administration of the substance in a dosage of 5 mg/kg (Table 1) led to statistically significant changes in the motor activity of animals, namely a significant increase in total activity (by 77.3 %). In addition, in this group there was a significant change in the structure of activity, namely a statistically significant decrease in the duration (by 57.3 %) and the number of episodes (by 54.2 %) relative to the rate of lack of activity. As in the 2 mg/kg group, the percentage of high and low activity in this group had no significant differences, but we noted a steady upward trend.

The administration of the test substance at a dosage of 5 mg/kg did not lead to a statistically significant increase in the travelled distance, however, as in the case of general motor activity, there was a dose-dependent tendency to increase this indicator.

In addition, the animals of this group demonstrated the statistically significant increase in the travelled distance in the central part of the arena by 5.5 times in absolute numbers and 6 times – in relative numbers. There was also a statistically significant decrease in the number of acts of defecation in 3 times, which reflects the emotional component of anxious behavior.

Table 1

Behavioural reactions of rats in the open field test with different doses of propoxazepam (M±m)

Indicator	Control	2 mg	5 mg	10 mg
Total activity, cm <sup>2</sup> / s	24175.01±2839.76	39967.58±4252.68*	42862.35±3643.13 <sup>§</sup>	25089.53±3334.81 <sup>§,Δ</sup>
Duration of high activity, %	7.83±1.44	11.83±2.07	11.83±1.58	5.17±1.19 <sup>§,Δ</sup>
Duration of low activity, %	61.71±7.08	75.83±4.03	75.17±3.69	69.39±7.42
Duration of absence of activity, %	30.47±6.59	12.34±4.37*	13±4.64*	25.44±8.05
Freezing, units	284±35	129±27*	130±33*	194±43
Number of entrances to the center, units	1	2	1	1
Travelled distance, cm	4161.81±290.78	4202.03±779.1	4501.87±1064.46	3040.5±538.64
Free distance, cm	59.37±26.31	529.76±215.98*	328.8±38.72*	251.49±89.95*
Free distance, %	1.43±0.61	11.3±2.67*	8.71±1*	7.16±2.14*
Distance near the wall, cm	4102.44 ±289.55	3672.27±612.74	4173.07±1053.95	2788.71±487.6
Rearings near the wall, units	4±1	8±1*	5±1	4±1 <sup>Δ</sup>
Free rearings, units	2±1	2±1	2±1	1
Short grooming, units	2±1	1	1	1±1
Long grooming, units	1±1	1	1	1
Defecation, units	3±1	2	1 <sup>*,§</sup>	1 <sup>*</sup>
Urination, units	1±1	1	1	1

Note: \* – significant difference (p < 0.05) compared with the control group; <sup>§</sup> – significant difference (p < 0.05) in comparison with group 2 mg; <sup>Δ</sup> – significant difference (p < 0.05) compared with the 5 mg group

The administration of the substance in a dosage of 10 mg/kg led to effects that are radically different from those observed in groups with lower dosages. Thus, the overall activity of animals in this group had no significant differences with the control group. There was a tendency to decrease the duration of high activity and in-

crease low activity, however, as in other groups, animals in this group showed a decrease in the duration and number of episodes without activity, although less pronounced. However, as in the groups with lower dosage, the animals of this group probably increased the travelled distance in the central part of the arena, in this case, 4

times in absolute numbers and 5 times in relative numbers. There was also a statistically significant decrease in the number of acts of defecation in 3 times.

When evaluating the specific indicators of the method of radial labyrinth in the group of 2 and 5 mg/kg (Table 2), we found a tendency to increase both the total activity and the distance travelled. In addition, animals in these groups performed on average 3 and 4.5 times more errors in working memory compared to the control group.

As in the case of the open field, when assessing the specific indicators of the radial labyrinth technique, in the group of 10 mg/kg we found a tendency different

from other groups with the introduction of the drug, namely to decrease in total activity and no changes in the travelled distance in the labyrinth. Such a trend can be seen as a further decline in the ability to learn, namely to suppress this function. Animals in this group became more passive, sedative, with signs of emotional flattening and indifference and low food motivation. Obviously, the test compound at a dose of 10 mg/kg causes more pronounced than at doses of 2 mg/kg and 5 mg/kg inhibition of cognitive function of the CNS. This fact is confirmed by the number of errors in working memory detected in this experimental group – 6 times more than in the control group.

Table 2

Indicators of cognitive-mnemonic activity of rats in the labyrinth after administration of different doses of propoxazepam

Indicator	Control	2 mg	5 mg	10 mg
Total activity, cm <sup>2</sup> /s	79919.4±16558.39	82614.62±12752.79	88894.65±11472.12	76425.67±7653.79
Travelled distance, cm	2208.25±352.54	2637.67±817.36	3822.47±521.72*	2214.32±402.42 <sup>Δ</sup>
The number of reference memory errors	2	3±1	3±1	5±1
The number of working memory errors	4	13±1*	18±1*	24±3* <sup>§</sup>

Note: \* – significant difference ( $p < 0.05$ ) compared with the control group; <sup>§</sup> – significant difference ( $p < 0.05$ ) in comparison with group 2 mg; <sup>Δ</sup> – significant difference ( $p < 0.05$ ) compared with the 5 mg group

When evaluating the performance of the rotarod test (Fig. 1), we noted a clear dose-dependent tendency to reduce the length of stay of rats on a rotating rod. For a group of rats injected with 2; 5 and 10 mg/kg of compound, this figure decreased by 42, 54.3 and 76 %, re-

spectively, compared to control animals. The obtained data indicate that propoxazepam at all doses reduces the retention time on the rod of experimental rats, reflecting a decrease in the force of the clamp and increased muscle relaxation.

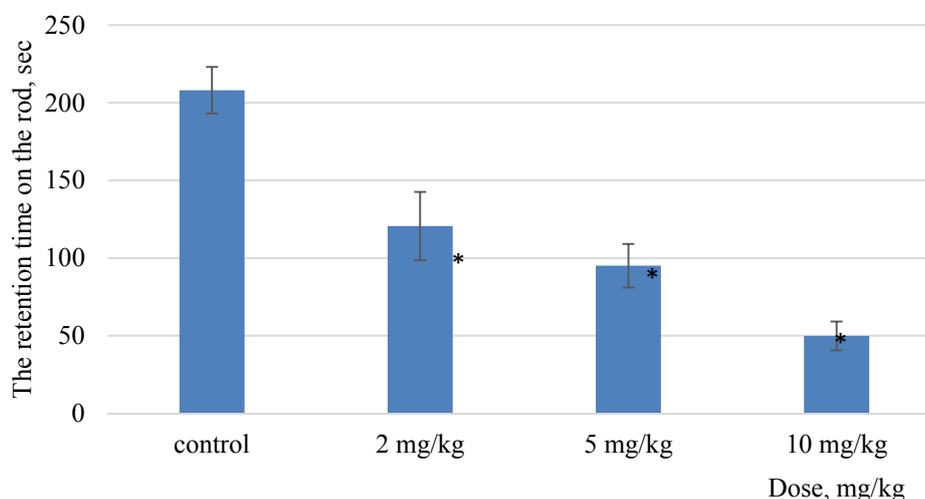


Fig. 1. The retention time on the rod and its change from the control value in the test "Rotarod" of control rats and rats after administration of different doses of propoxazepam

## 7. Discussion

In the pharmacological spectrum of propoxazepam, the analgesic effect is leading and is manifested in doses that are much lower than those that cause other neuroactive effects. However, the determination of the dose limits at which the effects that can be attributed to side effects are revealed, allow to further substantiate the most effective and safe dosing regimen in clinical trials.

The arsenal of methods of experimental pharmacology provides an opportunity to quantify certain changes in the psycho-emotional state of animals and to characterize the direction of their manifestation. Thus, the open field test provides information on the balance of anxiety and research activity of animals. In this test, within the used doses (2–10 mg/kg), propoxazepam had a multidirectional effect on the behaviour of animals, with an in-

crease in different types of activity (total, high and low activity) along with a decrease in the number of fading (at doses of 2 and 5 mg / kg), which is an indicator of reduced anxiety and the manifestation of a certain anxiolytic effect of the compound [14, 16]. This effect is indicative of 1,4-benzodiazepine derivatives, in particular, the classic representative – diazepam, however, it is manifested at much lower doses (0.6–2.5 mg) [20]. Usually with increasing dose, the inhibitory effect of benzodiazepines is manifested, which depending on the internal activity of the compound is realized in different doses – phenazepam, in the pharmacological spectrum of which the anxiolytic effect is leading, even in doses higher than 1 mg causes inhibition of animal activity [21]. It is significant that propoxazepam shows a partial inhibition of animal activity only at a dose of 10 mg/kg and this effect is not pronounced. Together with a statistically significant decrease in emotional stress (number of defecations), this confirms the small manifestation of the neuroactive component (anxiolytic) in the pharmacological spectrum of propoxazepam, probably due to affinity for different subunits of the GABA receptor, which is a physiological basis.

The effect on memory processes (amnestic action), as one of the effects of sedation and depressant action of benzodiazepines, is also well known, but it is not manifested in all representatives to the same degree [22]. Following the administration of propoxazepam, there is a different effect on the reference (long-term) and working memory of rats – yes, constant, the reference memory is much less negatively affected (even at doses of 5 and 10 mg / kg), while working memory produces a statistically significant number of errors with a dose-dependent nature. An increase in the degree of inhibitory effect of propoxazepam is also reflected in an increase in the manifestations of muscle relaxation, which correlates with an increase in working memory errors. In general, these data suggest that the inhibitory effect of propoxazepam, although observed in the behavioural responses of animals, but, unlike other representatives of 1,4-benzodiazepine derivatives, in the pharmacological spectrum is insignificant. Although the maximum dose effect was not achieved in the study

dose range (therefore, it was not possible to determine the ED<sub>50</sub> value), the obtained data are key to selecting safe dose limits for this compound for clinical trials and more detailed study of its pharmacological spectrum components.

## 8. Conclusions

Experimental study of neurotoxic lesions with propoxazepam allows to assess their severity and duration, and can also be used to determine the effectiveness and justification of its use as a means of safe pharmacological correction of pain and convulsive syndromes. According to the results of behavioural tests, propoxazepam generally found itself as a compound with a moderate manifestation of neuroactive components in its pharmacological spectrum.

1. In the open field test, the anxiolytic effect of propoxazepam is manifested at doses of 2 and 5 mg / kg, while the inhibitory effect is observed only at a dose of 10 mg / kg.

2. In the dose range of 2–5–10 mg / kg, propoxazepam has no statistically significant effect on the function of reference memory, but working memory is more significantly affected.

3. A statistically significant effect on the coordination of animals with the introduction of propoxazepam at doses of 2–5–10 mg / kg, which is manifested in muscle relaxant action, is dose-dependent and due to increased inhibitory effect of the compound.

Thus, a comprehensive definition of indicators that characterize the state of behavioural, sensory, neuromotor and cognitive functions in experimental animals, provides an understanding of pathological processes and their regulation. Experimental study of neurotoxic lesions with propoxazepam allows to assess their severity and duration, and can also be used to determine the effectiveness and justification of its use as a means of safe pharmacological correction of pain and convulsive syndromes.

## Conflict of interest

The authors declare that they have no conflicts of interest

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