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Review Article

Study of analgesic activity and effects of new dipharmacophores – nebracetam and cyclooxygenase-2 inhibitors derivatives on the cognitive abilities of rats

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Abstract

Introduction: The aim of the present study was to research the analgesic activity and effect of new dipharmacophore compounds consisting of substances with proven therapeutic activity, namely nebracetam–ibuprofen (**NRIP**), nebracetam–dexibuprofen (**NRDIP**), nebracetam–niflumic acid (**NRNFA**), and nebracetam–mefenamic acid (**NRMFA**), on the cognitive abilities of rats.

Materials and methods: The experimental study was performed in 110 Wistar rats (male/female ratio 50/50%), weighing 180–200 g, and 50 laboratory mice (male/female ratio 50/50%) weighing 18–22 g. The study of the analgesic activity was carried out using the acetic acid writhing test and the hot plate test. The effect on the cognitive abilities of rats was studied using the pattern recognition test in a model of neurotrauma caused by a drop-weight.

Results and discussion: It has been shown that the administration of dipharmacophores nebracetam–ibuprofen (**NRIP**), nebracetam–dexibuprofen (**NRDIP**), nebracetam–niflumic acid (**NRNFA**) as well as nebracetam–mefenamic acid (**NRMFA**) in the tested dosages leads to a statistically significant ($p<0.05$) analgesic action in acetic acid writhing tests and hot plate tests. At the same time, the analgesic activity of the compounds has been shown to conjoin with a statistically significant influence on cognitive functions in the experimental animal groups after simulating a neurotrauma.

Conclusion: The dipharmacophore compounds studied in the present research, having analgesic and nootropic effects, can be used as effective and safe analgesics and can also be used for the treatment and prevention of pain syndrome, enhancing the cognitive abilities of healthy people in complicated professional conditions.

Keywords

NSAID, nootropic drugs, nebracetam, COX-2, dipharmacophores, analgesic activity, cognitive abilities, laboratory animals.

Introduction

According to statistics from health services and leading pain specialists in many developed countries of the world, millions of people suffer from pain syndrome, which changes their physical and emotional states, reduces the quality of life and their ability to work. Chronic pain is associated with significant impairments in the level of social and labor adaptation (Goldberg et al.2011). In most cases, chronic pain syndrome is accompanied by depression, causes negative emotional experiences. According to the WHO, pain syndrome is known to be one of the leading causes (from 11.3% to 40%) of primary care physician visits (Gureje et al. 2001). Among neurological patients, chronic pain syndrome is diagnosed in about 52.5% of them (Mäntyselkä et al. 2001). Failure to cope with pain has important detrimental biological consequences, including, but not limited to, cardiovascular pathologies (hypertension, myocardial ischemia), reduced physical activity leading to deterioration of joints and muscles, and various physiological manifestations and psychological consequences of stress caused by an aversive condition (Joshi and Ogunnaike 2005; Ong et al. 2007; Dunwoody et al. 2008).

Today, pain and inflammation are known to be closely linked to each other. Pain is caused by all those proinflammatory agents that lead to hyperalgesia through activation of the corresponding receptors expressed by the nociceptive terminals (Bruni et al. 2018). Non-steroidal anti-inflammatory drugs (NSAID), for example cyclooxygenases (COX-1 and/or COX-2) inhibitors (Yaksh and Wallace 2011; Atkinson et al. 2013) and opiates (Yaksh and Wallace 2011), are used to treat inflammation-induced pain. For nerve injury conditions, therapy includes antidepressants that block the uptake of monoamines (amitriptyline, duloxetine, venlafaxine) (Sindrup et al. 2005; Finnerup et al. 2010; Mika et al. 2013), drugs that act via sodium channel blockade (lidocaine, carbamazepine) (Dworkin et al. 2007; Wiffen et al. 2014), via change in calcium channel activity (ziconotide, gabapentin) (Wiffen et al. 2013; Wiffen et al. 2014) or by increasing extracellular levels of gamma-aminobutyric acid (GABA) (tigabine) (Dalby 2003; Todorov et al. 2005) and, to a lesser extent, opioids (Yaksh and Wallace 2011) and local anesthetics (lidocaine, capsaicin for patients with cutaneous allodynia and hyperalgesia) (Derry et al. 2014; Smith and Brooks 2014).

The success of pain management is limited by a lack of understanding of the molecular mechanisms underlying its transmission and perception. Therefore, a promising direction in the field of creating new drugs is the search for biologically active substances with anti-inflammatory and analgesic activities. A combination therapy using agents with different treatment sites, biological targets and non-overlapping profiles of adverse reactions and adverse events can provide an improved therapeutic effect in the treatment of pain syndrome (Chaparro et al. 2012).

We believe that to solve this problem, it is best to use a combined drug therapy to simultaneously affect various sites of pathogenesis and ways of producing nociceptive sensations. Since using NSAID has become almost inevitable in today's setting, the relatively safe use of these drugs is the goal of pain pharmacotherapy. To achieve this goal, it is necessary to clearly understand the molecular mechanism and signaling pathways involved in NSAID therapy. In addition, it has been shown today that chemical modification of NSAID by pharmacophore modification aimed at reducing their toxic effects and improving their bioavailability without compromising therapeutic effects is an effective strategy to search for new analgesics. Extensive studies have been conducted to analyze NSAID effects at the molecular level, which has resulted in the development of novel combination drugs in the form of NSAID prodrugs with increased efficacy (Bindu et al. 2020).

The aim of the present study was to research the analgesic activity and effect of new dipharmacophore compounds consisting of substances with proven therapeutic activity, namely nebracetam–ibuprofen (**NRIP**), nebracetam–dexibuprofen (**NRDIP**), nebracetam–niflumic acid (**NRNFA**), and nebracetam–mefenamic acid (**NRMFA**), on the cognitive abilities of rats.

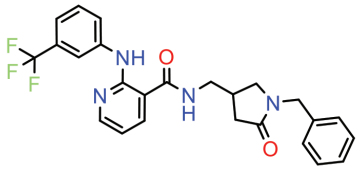
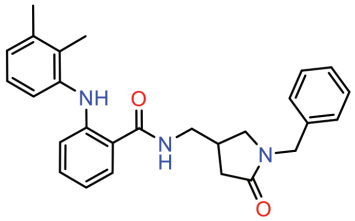
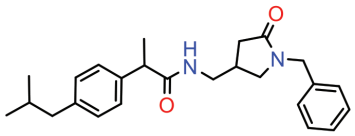
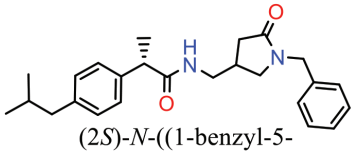
Materials and methods

The experiment and vivisection was performed at the Center for Preclinical and Clinical Studies of Belgorod State National Research University in strict compliance with *The Rules of Laboratory Practice*, approved by Order No.708n of the Ministry of Health of the Russian Federation of 23.08.2010 and with *The European Convention for the Protection of Vertebrate Animals Used for Experiments or for Other Scientific Purposes* (Directive2010/63/EU). The experimental studies were approved by the Bioethical Commission of Belgorod State National Research University (Minutes №15/10 of 29.10.2021).

Experimental animals

The experimental study was performed in 110 Wistar rats (male/female ratio 50/50%), weighing 180–200 g and 50 laboratory mice (male/female ratio 50/50%) weighing 18–22 g. The animals were kept in accordance with the rules of laboratory practice for preclinical studies on the territory of the Russian Federation. The animals were kept under the standard conditions according to the sanitary rules on the organization, equipment and maintenance of experimental biological clinics (vivariums) No. 1045–73, approved by the Ministry of Health of the USSR on 06.04.1973 and GOST R 53434-2009. The individually ventilated cages (Tecniplast S.p.A., Italy) designed for keeping small laboratory animals. The bedding was sawdust, sterilized by ultraviolet irradiation. Special pellet feed for small laboratory rodents and

Table 1. Laboratory codes, names and chemical structures of dipharmacophoric compounds

Code	Substance	Structure
NRNFA	nebracetam–niflumic acid	 *N*-((1-benzyl-5-oxopyrrolidin-3-yl)methyl)-2-((3-(trifluoromethyl)phenyl)amino)nicotinamide
NRMFA	nebracetam–mefenamic acid	 *N*-((1-benzyl-5-oxopyrrolidin-3-yl)methyl)-2-((2,3-dimethylphenyl)amino)benzamide
NRIP	nebracetam–ibuprofen	 *N*-((1-benzyl-5-oxopyrrolidin-3-yl)methyl)-2-(4-isobutylphenyl)propanamide
NRDIP	nebracetam–dexibuprofen	 (2*S*)-*N*-((1-benzyl-5-oxopyrrolidin-3-yl)methyl)-2-(4-isobutylphenyl)propanamide

pre-treated water disinfected with UV irradiation were used. In each cage, microclimate was created and supported by an individual ventilation system. All the animals had been acclimatized and quarantined for at least 10 days before the experiment.

Characteristics of test compounds

New dipharmacophoric compounds investigated in the present study were synthesized by the interaction of nebracetam with acidic non-steroidal anti-inflammatory substances (ibuprofen, dexibuprofen, niflumic acid, mefenamic acid) according to the method described in our patent (Pokrovskii et al. 2021) and reported in Table 1.

The choice of doses of the dipharmacophores has been substantiated by us earlier (Slyusarenko et al. 2021).

Study of analgesic activity in the test "acetic acid writhing's"

The analgesic effect of non-narcotic analgesics is most pronounced in tissue inflammation. Pain is known to be an integral component of the inflammatory process. The acetic acid writhing test is among the most common in assessing the analgesic activity of non-narcotic analgesics. The pain reaction in this test is due to the activation of the biosynthesis of prostaglandins as a result of moderate short-term irritation of the peritoneum with a weak acetic acid solution. The first stage of a screening analysis of the analgesic activity was carried out on an experimental model of the acetic acid writhing test. Writhings were caused by intraperitoneal administration of a 0.75% acetic acid solution at a dose of 1 ml/100 g of body weight of an experimental animal. The writhing count was started 15 minutes after the administration of acetic acid and was carried out for the following 30 minutes. The test preparations were administered intragastrically, 30 minutes before intraperitoneal administration of the acetic acid solution at the doses shown in Table 2. An equivalent amount of solvent (1% starch solution) was administered to the animals in the control group. The effect was recognized by a reduced number of writhings in comparison with the animals of the control group, calculating it by the following formula:

$$\frac{C_k - C_o}{C_k} \times 100\%$$

where C_o and $C_к$ – are the number of writhings after and before administration of the drug, respectively.

Table 2. Doses of Test Compounds Used in a Series of Experiments to Determine Analgesic Activity in the Acetic Acid Writhing Test

Experimental groups	Dose	Number of animals in each group.
Control	0.1 ml/100 g	10 (5 males, 5 females)
NRNFA	102 mg/kg	10 (5 males, 5 females)
NRMFA	102 mg/kg	10 (5 males, 5 females)
NRIP	102 mg/kg	10 (5 males, 5 females)
NRDIP	102 mg/kg	10 (5 males, 5 females)

Study of analgesic activity in the hot plate test

The hot plate test is used to measure the threshold of pain sensitivity in mice and rats. The standard hot plate heating range in the test is between 50 °C and 55 °C. The animals of experimental groups are placed on the surface of the heated plate and manifestations of painful behavior are fixed (Kumae et al. 2011).

The nociceptive response involves withdrawing or licking the fore paw, withdrawing or licking the hind paw, leans or jumps. Among all these behaviors, withdrawing the hind paw is more reliable, since the front paw is involved in other actions, such as grooming, due to which the fore paw will not constantly contact the hot plate.

In the present study, the animals of the experimental groups were placed on a hot plate Hot-Plate LE7406 (Panlab Harvard Apparatus, Spain), heated to 55 °C, and the time was recorded in seconds until the moment of withdrawing/licking the hind paw, bouncing and rearing at the cylinder wall. The experimental groups are shown in Table 3. The animals of the control group were given an equivalent amount of solvent (1% starch solution).

Table 3. Doses of Test Compounds Used in a Series of Experiments to Determine Analgesic Activity in a Hot Plate Test

Experimental groups	Dose	Number of animals in each group.
Control	0.1 ml/100 g	10 (5 males, 5 females)
NRNFA	222 mg/kg	10 (5 males, 5 females)
NRMFA	222 mg/kg	10 (5 males, 5 females)
NRIP	222 mg/kg	10 (5 males, 5 females)
NRDIP	222 mg/kg	10 (5 males, 5 females)

In each series of the experiments, the mice were exposed to a hot plate four times, bounded by a glass cylinder with a diameter of 13 cm and a height of 17 cm for 60 seconds at the intervals of 5, 15, 30 and 45 minutes after administration of the preparation. During the first exposure, the animals were on the plate for 1 minute; during the second and third exposures – for 1.5 minutes; during the fourth exposure, the animals were kept on the surface of the plate until they jumping onto the edge of the cylinder, but for a maximum of 5 minutes. The time of withdrawing the paw, the time of licking the paw, the time of rearing on the hind paws and the time of jumping onto the edge of the cylinder were recorded.

The first signs of pain irritation were withdrawing/licking paws, with the time of withdrawing/licking paws being recorded according to the criterion ”what happens first” When analyzing the pain tolerance threshold, we used the rearing-at-the-cylinder-wall/jumping indicators according to the above criterion. The criterion for the presence of the effect was the inhibition of the pain response under thermal influence manifested by the extented latent response period.

Simulation of traumatic brain injury of laboratory animals

To simulate a traumatic brain injury (TBI), this study used a drop-weight TBI model (Martynova et al. 2019; Cherevatenko et al. 2020). In this study, the following experimental groups were formed to study the effects of the compounds on the cognitive abilities of the animals (Table 4). The test compounds were administered intragastrically once a day for 7 days, starting from the day of the pathology simulation. The control animals with the neurotrauma model were injected with an equivalent amount of solvent (1% starch solution).

Table 4. Doses of Test Compounds and Comparison Preparations Used in a Series of Experiments to Determine the Pharmacological Activity of Compounds in a Model of Traumatic Brain Injury

Experimental groups	Dose	Number of animals in each group.
Intact animals	-	10 (5 males, 5 females)
TBI (Control)	0.1 ml/100 g	10 (5 males, 5 females)
NRNFA	222 mg/kg	10 (5 males, 5 females)
NRMFA	222 mg/kg	10 (5 males, 5 females)
NRIP	222 mg/kg	10 (5 males, 5 females)
NRDIP	222 mg/kg	10 (5 males, 5 females)

Study of effects of the compounds on rat cognitive abilities

On the 7th day after the induction of a traumatic brain injury, the cognitive abilities of rats were evaluated using the Object Recognition Task test. This test allows you to evaluate the preservation of spatial memory in the experimental groups. The experiment was carried out in a wooden open field (measuring 40 cm by 50 cm, wall height 50 cm). First, a habituation session was performed for 5 minutes, during which the animals freely examined the open field. At that time, there were no objects in the open field. After the habituation session, a training session was run: the rats, one at a time, examined for 5 minutes an open field in which there were 2 of the same objects (objects A1 and A2, both cubes). The objects were placed at a distance of 10 cm from the walls in 2 adjacent corners.

Short-term memory analysis (STM) of object recognition was performed 90 minutes after the training session. The animals examined for 5 minutes an open field in which there was one familiar object (A) and one new object (B, a pyramid with a square base). The recognition index was calculated by the formula TB\(TA + TB); where TA is the time spent on studying the familiar object A and TB is the time spent on studying the new object B.

Testing rats for long-term memory analysis (LTM) of object recognition was carried out 24 hours after the training session. The animals examined the open field for 5 minutes in the presence of one familiar object A and one new object C (a ball with a square base). Recognition memory was evaluated in the same way as in the short-term memory analysis. The object was examined by sniffing (the study of the object from a distance of 3–5 cm) or touching the object with the nose and/or fore paws. All the objects used in the task were of the similar texture (smooth), color (blue), and dimensions (weight, 150–200 g), but differed in shape (Barichello et al. 2014).

Statistical data processing

The statistical data were processed using Statistica 10.0 software. Shapiro-Wilk and Spiegelhalter (normtest package) normality tests were performed for the obtained data; the equality of variances was assessed using the Levene's test (lawstat package). Depending on a type of distribution and the equality of variances, the significance of the results obtained was evaluated using parametric (ANOVA) or non-parametric (Kruskal-Wallis test) one-way analysis of variance, and as a post-hoc analysis to identify intergroup differences, the Student's t-test or the Mann-Whitney test were used, respectively, with the Benjamini-Hochberg correction for multiple tests. The results were considered reliable at $p \leq 0.05$.

Results and discussion

Intraperitoneal injection of acetic acid solution into the animals of control group caused pain response in the form of writhings expressed in contraction of abdominal muscles and extension of hind limbs. The number of writhings in the control group was 31.4±0.48 (Fig. 1).

As evidenced by the data presented in Figure 1, the preliminary administration of the studied dipharmacophores **NRIP** (nebracetam–ibuprofen), **NRDIP** (nebracetam–dexibuprofen), **NRNFA** (nebracetam–niflumic acid) as well as **NRMFA** (nebracetam–mefenamic acid) in the studied dosages led to a statistically significant and pronounced decrease in the number of writhings after intraperitoneal administration of acetic acid solution to rats. The most pronounced analgesic activity was established in dipharmacophore **NRDIP** (13.2±1.34 writhing movements) – the number of writhings in this experimental group was significantly lower than in the control group and the group of animals receiving compound **NRNFA** (Fig. 1).

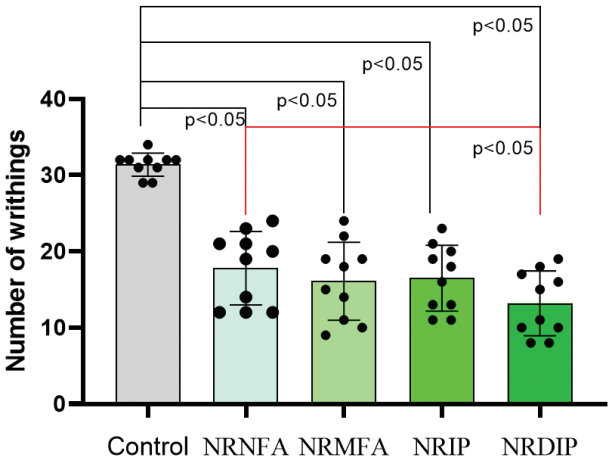


Figure 1. Influence of dipharmacophore derivatives on the number of writhings caused by intraperitoneal administration of acetic acid.

The second stage of the screening study of the pharmacological analgesic activity of the test compounds was carried out using the hot plate test. When this test was carried out in the group of control animals at the 5th minute of exposure, it was found that the latency period from placing the animal onto the surface of the heated plate to its withdrawing the paw from the surface of the hot plate was 6.1 seconds and decreased towards the 4th exposure, reaching 4.8 seconds during the fourth exposure (45 minutes from the beginning of the experiment) (Table 5).

As a result of the study, it was found that the analysed dipharmacophores had the analgesic action, statistically significantly reducing the latent period before paw withdrawing/licking, starting from the fifteenth minute of exposure (Table 5). We found the greatest analgesic activity when evaluating the latent period in the group of animals treated with dipharmacophore under laboratory code **NRDIP** (nebracetam–dexibuprofen). The latent period before paw withdraing/licking in the group of animals treated with **NRDIP** was 8.4±0.25 seconds, while in the group of the control animals this indicator was 4.8±0.25 seconds (Table 5).

Table 5. Dynamics of the Development of Analgesic Activity at the First Signs of Pain Irritation (Withdrawing Paws/Licking Paws) in Control Animals and Animals Receiving the Studied Drugs

Experimental groups	5th minute after administration	15th minute after administration	30th minute after administration	45th minute after administration
Control	6.1±0.31	4.4±0.1	4.8±0.2	4.8±0.25
NRNFA	6.2±0.24	5.9±0.15*	6.5±0.22*	7.3±0.37*
NRMFA	6.1±0.29	6.0±0.07*	6.9±0.13*	7.8±0.52*
NRIP	6.2±0.3	6.2±0.19*	7.1±0.11*	7.8±0.23*
NRDIP	6.0±0.17	6.5±0.13*	7.5±0.24*	8.4±0.25*

Note: * indicates the values at $p<0.05$ in comparison with control.

Table 6. Dynamics of Analgesic Activity on the Pain Tolerance Threshold (Rearing at the Cylinder Wall/Jumping) in Control Animals and Animals Receiving the Test Compounds

Experimental groups	5th minute after administration	15th minute after administration	30th minute after administration	45th minute after administration
Control	27.9±2.1	26.1±3.2	28.4±3.3	31.5±3.8
NRNFA	28.2±1.61	29.3±2.51	39.9±4.1*	43.8±2.5*
NRMFA	27.9±1.57	34.5±1.82*	42.5±2.74*	46.2±3.4*
NRIP	28.1±2.6	33.4±2.16*	41.2±3.8*	44.6±2.9*
NRDIP	27.4±5.2	35.2±2.5*	45.0±2.6*	49.43±3.1*

Note: * indicates the values at $p<0.05$ in comparison with control.

Next, the effect of the preparations on the duration of the latent period to reach the pain tolerance threshold was evaluated. In the control group, the latent period to reach the pain tolerance threshold was 27.9 seconds in the first series of the experiments and 31.5 seconds at the fourth exposure. Intragastric administration of the test drugs caused an increase in the time before rearing onto the hind paws (Table 6). Overall, we observed a pattern comparable to that of the latent period analysis before licking/withdrawing paws. As a result of the study, it was found that the analyzed dipharmacophores had the analgesic activity, statistically significantly reducing the latent period before rearing onto the hind paws from the 15th minute of exposure (compounds **NRMFA**, **NRIP**, and **NRDIP**) and from the 30th minute of exposure (compound **NRNFA**) (Table 6). We found the greatest analgesic activity when evaluating the latent period in the group of animals treated with dipharmacophore under laboratory code **NRDIP** (nebracetam–dexibuprofen).

Next, we evaluated the analgesic activity on the maximum tolerated pain irritation (jumping onto the edge of the cylinder). Due to the four exposures of the study (at the 5th, 15th, 30th and 45th minutes after the introduction of the drug), we recorded the jumping time only at the 4th exposure, when the animal was on a hot plate for 5 minutes. For the intact untreated animals, the time to jumping was 127.6±10.9 seconds. Intragastric administration of the examined dipharmacophores led to a statistically significant increase in the latent period before jumping onto the edge of the cylinder (Fig. 2). The maximum latent period before jumping onto the edge of the cylinder (208.8±18.33 seconds) was recorded in the group of animals which had received dipharmacophore with laboratory cipher **NRDIP** (nebracetam–dexibuprofen).

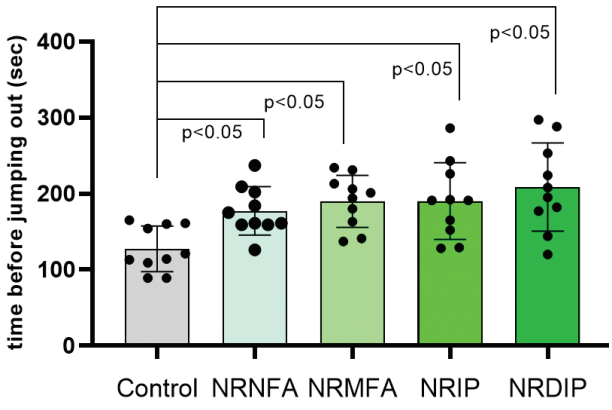


Figure 2. Effect of the examined dipharmacophores on the latent period before jumping onto the cylinder edge in the hot plate test.

Also, as part of this study, the effect of the compounds on the cognitive abilities of rats was studied against the background of simulating a traumatic brain injury. On day 7, after the pathology simulation, the Object Recognition Task study was conducted to assess the effects of the drugs on long-term memory (LTM) and short-term memory (STM) in the rats (Fig. 3). The study showed that simulations of brain injury led to an increase in the object recognition index by 1.86 and 1.7 times compared with the group of the intact animals when analyzing STM and LTM indicators, respectively. As in the previously described tests aimed at assessing the analgesic activity of the developed compounds, in this test the most active compound was a substance with laboratory code **NRDIP**. The use of **NRDIP** led

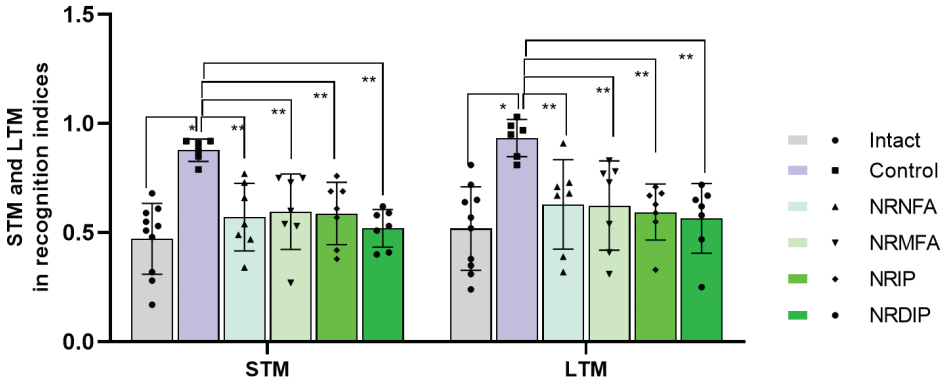


Figure 3. Effect of the studied drugs on short-term memory (STM) and long-term memory (LTM) recognition indices in rats on day 7 after simulating a traumatic brain injury.

to a decrease in the object recognition index in tests for short-term and long-term memory by more than 1.8 times (Fig. 3).

Conclusion

The attention of practitioners and scientists around the world has been riveted for many years to the problem of treating acute and chronic pain (Dear et al. 2015). An important contribution to the development of pain control is made by analgesic and anti-inflammatory drugs; however, they are not always quite effective, and many of them have an unfavorable safety profile. The success of pain management is limited by our incomplete understanding of the molecular mechanisms underlying its transmission and perception. Therefore, a promising direction in the field of creating new drugs is the search for biologically active substances with anti-inflammatory and analgesic activities.

It is known that the mechanism of action of NSAID is associated with the inhibition of cyclooxygenase, an enzyme that catalyzes the production of prostaglandins and thromboxane. Prostaglandins mediate various physiological functions and play an important role in inflammatory and nociceptive processes (Derry et al. 2015). Inhibition of cyclooxygenase results in reduced pain, fever, platelet aggregation, and inflammatory response (Jorge et al. 2010).

We believe that the search for novel pharmacological agents for pain treatment should be carried out in the field of innovative dipharmacophore compounds having fragments with different pathogenetic and, therefore, therapeutic directions. NSAID is widely used in drug therapy of various diseases accompanied by pain or inflammation. Their widespread presence ensured the absence of side effects inherent in opiates: sedation, respiratory depression and addiction. NSAIDs are able to suppress inflammation, to reduce body temperature and pain intensity. Nootropes (neurometabolic stimulants) are drugs designed to exert a specific effect on higher mental functions. We have previously studied the pharmacological activity of a number of nootropes, cytoprotectors, and NSAIDs (Stepenko et al. 2019).

Drugs with nootropic activity are known to improve cognitive functions, such as learning and memory. Piracetam (2-oxo-1-pyrrolidine acetamide) is a nootropic drug derived from GABA, but its mechanism of action is not associated with GABA, and the exact mechanism of action remains unknown. There is evidence that the mechanism of action of piracetam is associated with the restoration of membrane fluidity and positive allosteric modulation of AMPA receptors. Considering the main possible mechanisms for implementing the antinociceptive action by nootrops, it should be noted that the pain of inflammatory genesis is characterized by sensitization of nociceptors, which leads to hyperalgesia, allodynia and increases the intensity of pain syndrome in response to stimuli that are not usually painful (Millan 1999). Inflammatory stimuli, such as carrageenan, cause activation of a cascade of inflammatory cytokines, resulting in inflammatory hyperalgesia. For example, carrageenan induces the production of TNF-α, which triggers the production of IL-1β activating the synthesis of PGE2. These inflammatory mediators are responsible for sensitizing nociceptors and activating the secondary messenger pathway (cAMP, PKA, and PKC), thereby lowering the nociceptor threshold, increasing the excitability of the neuronal membrane and facilitating activation of primary nociceptors and further impulse transmission. The chain of these events leads to hyperalgesia (Villarreal et al. 2009; Cury et al. 2011).

As part of this study, we showed that dipharmacophores containing active centers of COX-2 inhibitors and a drug from the group of racetams – nebracetam have a pronounced analgesic activity in combination with a statistically significant influence on cognitive functions in the experimental groups of animals after simulating a neurotrauma. A number of dipharmacophore compounds studied in the present study, having analgesic and nootropic effects, can be used as effective and safe analgesics and can also be used for the treatment and prevention of pain syndrome, enhancing the cognitive abilities of healthy people in difficult professional conditions. In addition, the use of the dipharmacophores studied in the present study will minimize side effects, such as potential gastritis, enteritis, gastric and duodenal ulcer, which usually occur when taking NSAID for a long time due to the presence of a carboxyl group, which is closed by forming an amide bond between the primary amine of nebracetam and the carboxyl group of acidic NSAID.

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Conflict of interests

The authors declare no conflict of interests.

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