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AIDA INFLUENCES BEHAVIOR IN RATS PRETREATED WITH BACLOFEN

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AIDA influences behavior in rats pretreated with baclofen. H. CAR, A. NADLEWSKA, R. OKSZTEL, K. WIŚNIEWSKI. Pol. J. Pharmacol., 2001, 53, 245–252.

The influence of the blockade of group I metabotropic glutamate receptors (I mGluRs) by AIDA on some behavioral effects of rats pretreated with baclofen, an agonist of GABA-B receptor, was investigated using behavioral tests: the open field, the passive avoidance response and the elevated "plus" maze.

Baclofen, applied intraperitoneally (*ip*) at a dose of 0.25 mg/kg, increased the number of crossed fields and bar approaches in rats in the open field test, and prolonged the time spent in the closed arms, shortened the time spent in the open arms and decreased the number of entries to the open arms in the elevated "plus" maze, but did not affect retrieval in the passive avoidance response.

AIDA administered intracerebroventricularly (*icv*) alone at a dose of 100 nmol reduced crossings and rearings in the open field test, however, it had no effect on retrieval in the passive avoidance situation, nor did it show any influence in the elevated "plus" maze. AIDA given 15 min after baclofen significantly decreased mobility of rats (in the case of crossings to the level observed when AIDA was given alone), i.e. AIDA changed the effects of baclofen in the open field test. We also noted significant impairment of retrieval in rats pretreated with baclofen, which later received AIDA. AIDA significantly reduced the effect of baclofen on this memory process. In the elevated "plus" maze test, AIDA did not influence the behavior of rats pretreated with baclofen in comparison with the group treated with baclofen alone.

Key words: *baclofen, AIDA, retrieval, elevated "plus" maze, locomotor activity, rats*

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INTRODUCTION

The balance of inhibitory and excitatory synaptic transmission plays an important role in proper functioning of the central nervous system (CNS). Literature data [16] indicate similarities and interaction between metabotropic glutamate receptors (mGluRs) and -aminobutyric acid type B (GABA-B) receptors. mGluRs together with GABA-B receptors belong to the same superfamily of G-protein--coupled receptors [27].

Baclofen, a derivative of the inhibitory neurotransmitter GABA, is a selective agonist of GABA-B receptors in the brain stem, dorsal horn of the spinal cord and other CNS sites [13]. Baclofen has the effects either on inhibition or excitation of neuronal activity [38]. The activation of pre- and postsynaptic GABA-B receptors affects the induction of long-term potentiation (LTP) that may underlie the formation of some types of learning and memory [12, 26]. There are some reports that baclofen has an influence on cognitive processes [5, 18], impairs memory in humans [33], disturbs retention and does not change the consolidation of inhibitory avoidance task in rats [4].

mGluRs are also implicated in LTP and in learning and memory formation [2, 10, 29–31]. There is a specific role of I mGluRs in certain types of synaptic plasticity and spatial learning [2]. Group I mGluRs include $mGluR_1$ and $mGluR_5$ which are positively coupled to phosphoinositide hydrolysis/Ca^{2+} mobilization [10, 27]. AIDA is a selective $mGluR_1$ antagonist, and posseses a potential role in the hippocampus-dependent forms of learning. The blockade of class I mGluRs may enhance short-term memory under certain learning conditions [8]. AIDA improves short-term and impairs long-term memory in a spatial task in rats [7]. It also is considered antinociceptive in several models of persistent pain [24, 27].

In our present study we investigated the effects of AIDA on some behavioral activity of baclofen.

MATERIAL and METHODS

Subjects

Male Wistar rats of laboratory strain, weighing 160–180 g, were used. The animals were fed standard diet and housed in plastic cages (50 × 40 × 20 cm), 10 animals per cage, in an air-conditioned and temperature-controlled (22°C) room under a 12 h light/dark cycle beginning at 7.00 h. Food and water were freely available. All experiments were carried out in a quiet, diffusely lit room (25 W bulb, 2 m away from an animal, indirect light) between 8.00 h and 12.00 h.

Surgery

Under light ether anesthesia, a round piece of skin 7 mm in diameter was cut off the rat's head and the underlying skull surface was cleaned off the soft tissue. Two burr holes of 0.5 mm in diameter were drilled in the rat's skull, 2.5 mm laterally and 1 mm caudally from the point of intersection of bregma and the superior sagittal suture on both sides of the head [14]. After 48 h of recovery, the wound was completely dry and the animal behaved normally. The intracerebroventricular (*icv*) injections of AIDA were made freehand into the lateral cerebral ventricles with a 10 l Hamilton syringe, using a removable KF 730 needle 4.5 mm long. This procedure allowed lowering the tip of the needle about 0.5 mm below the ceiling of the lateral cerebral ventricle. It was relatively nontraumatic as the animal, gently fixed in the left hand of the experimenter, was usually quiet and no vocalization occurred. The injection volume was 5 l administered for over 1 min. After termination of each experiment, all animals were sacrificed, their brains were removed, and the sites of injection were verified macroscopically after brain sectioning. Animals with inappropriate injection sites were not considered for analysis.

Drugs

AIDA (Tocris Cookson) was dissolved in 0.9% NaCl (pH 7.4) and administered into the lateral ventricle of the brain (*icv*) [14] at a dose of 100 nmol per rat in the volume of 5 l [7], 15 min after administration of baclofen and 15 min before placing animals in the open field or in the elevated "plus" maze, and testing drug influence on the retrieval process in the passive avoidance situation [22]. (–) Baclofen (Polfa, Starogard Gdański) was dissolved in 0.9% NaCl (pH 7.4) and administered intraperitoneally (*ip*) at a dose of 0.25 mg/kg [34, 35] 30 min before examination of the animals' behavior in the open field test or in the elevated "plus" maze and the passive avoidance learning. Saline (0.9 % NaCl) (Polfa, Poznań) was administered *icv* in the volume of 5 l at the same time as

AIDA or *ip* at a dose of 1 ml/kg at the same time as baclofen.

Behavioral testing

Locomotor and exploratory activity. The open field test was used to estimate the locomotor (crossings) and exploratory (rearings, bar approaches) activity of rats. The apparatus consisted of a square 100 × 100 cm white floor, which was divided by 8 lines into 25 equal squares, and surrounded by white walls, 47 cm high. Four plastic bars (designed as objects of possible interest), 20 cm high, were located at four different line crossings in the central area of the floor. A single rat was placed in the centre of the floor and following 1 min of adaptation, crossings, rearings, and bar approaches were counted manually for 5 min. The crossings of the square were counted when the animal crossed the line with all four paws and the bar approaches were considered when the rat directed its head toward the bar, approached and touched it with its nose.

Passive avoidance response training. The response was induced using the one-trial-learning method of Ader et al. [1]. The apparatus consisted of a 6 × 25 cm platform illuminated with a 25 W electric bulb connected through a 6 × 6 cm opening with a dark compartment (40 × 40 × 40 cm). The floor of the cage was made of metal rods, 3 mm in diameter spaced at 1 cm. The investigation took advantage of the natural preference of rats to stay in dark compartments. The test lasted 3 days. On the first day, after 2 min of habituation in the dark compartment, the rats were placed on the illuminated platform, allowed to enter the dark compartment and then immediately removed. Two similar trials, at an interval of 2 min, were carried out on the second day. After the first trial rats were allowed to stay in the dark compartment for 10–15 s. At the end of the second trial, when a rat entered the dark compartment it received an inescapable footshock (0.25 mA, 3 s) delivered through the grill floor of the dark compartment (learning trial). Retention of passive avoidance was checked 24 h later by measuring the latency to re-enter the dark compartment up to a maximum of 300 s.

Elevated "plus" maze. The maze (constructed of grey colored wooden planks) consisted of two open arms, 50 cm (length) × 10 cm (width), and two enclosed arms, 50 cm (length) × 10 cm (width) × 40 cm (height), covered with a removable lid, so that the open or closed arms were opposite to each other. The maze was elevated to a height of 50 cm from the floor. Ten minutes after the second injection, a naive rat was placed for 5 min in a pretest arena (60 × 60 × 35 cm, constructed from the same material) prior to exposure to the maze. This step allows the facilitation of exploratory behavior. The experimental procedure was similar to that described by Pellow et al. [28]. Immediately after the pretest exposure rats were placed in the centre of the elevated "plus" maze facing one of the open arms. During the 5 min test period the following measurements were taken: the number of entries into the open and closed arms and the time spent in the open and closed arms. An entry was defined as entering with all four feet into one arm. An increase in open arm entries and increase in time spent in the open arms is indicative of potential anxiolytic activity, as rats naturally prefer the closed arms.

Statistical analysis

Statistical significance of the results was computed by one-way analysis of variance (ANOVA) followed by Newman-Keuls test, except for passive avoidance behavior which was assessed with Mann-Whitney ranking test. F-rations, degrees of freedom and p-values are reported only for significant differences. In all comparisons between particular groups a probability of 0.05 or less was considered significant.

This work was approved by the Ethical Committee of Medical Academy in Białystok.

RESULTS

The effect of baclofen, AIDA and baclofen with AIDA on locomotor and exploratory activity of rats in the open field test (Fig. 1)

Baclofen (0.25 mg/kg, *ip*) increased the number of crossed fields and bar approaches in rats. AIDA (100 nmol, *icv*) significantly reduced the number of crossed fields and rearings. Baclofen given with AIDA inhibited locomotor activity (crossings, rearings and bar approaches) of rats vs control and vs baclofen-treated group.

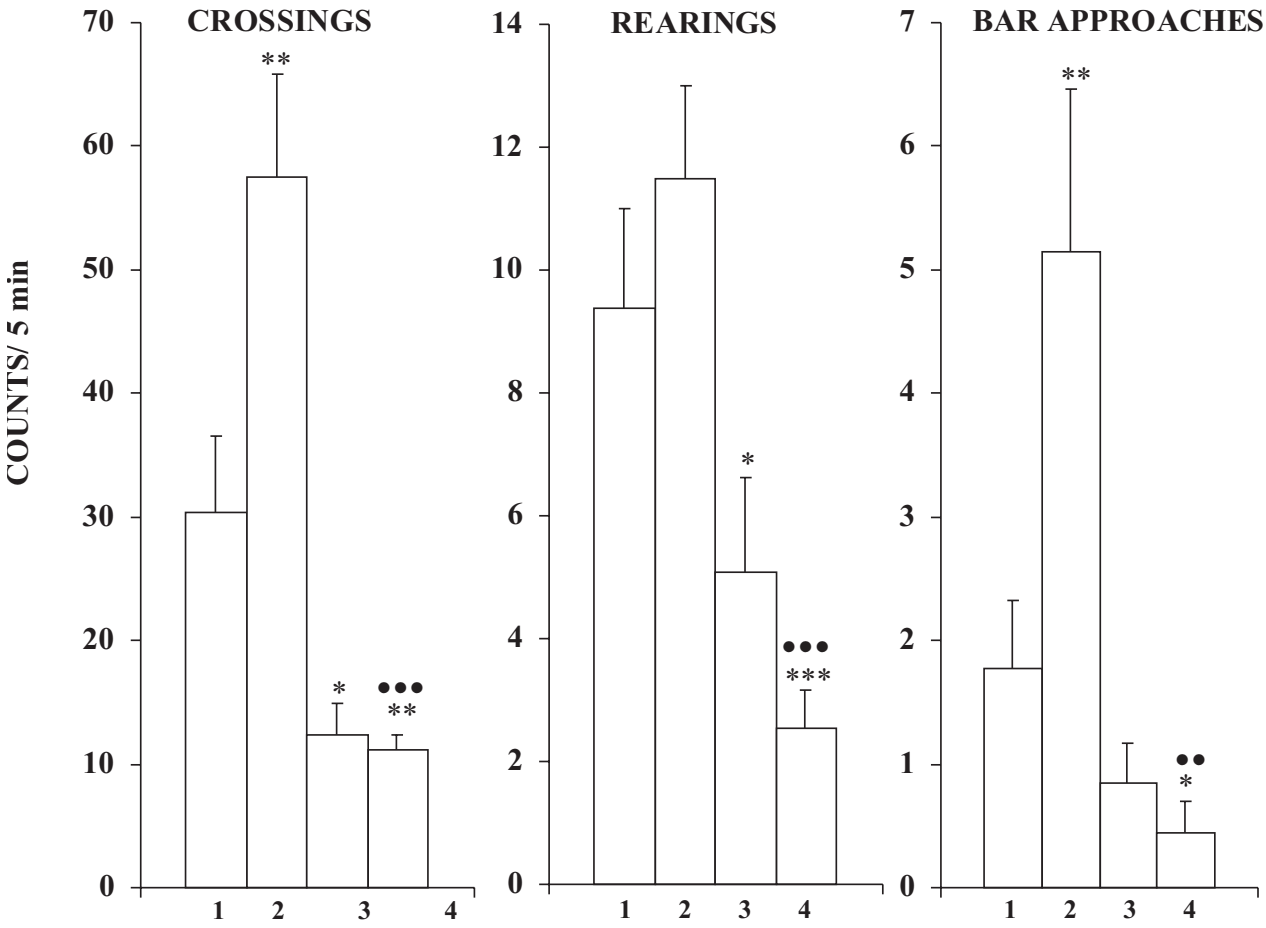

Fig. 1. The effect of 0.25 mg/kg of baclofen (2), given *ip* 30 min before testing, 100 nmols of AIDA (3), given *icv* 15 min before testing or both baclofen + AIDA (4), given at the same times and doses, on the number of crossings, rearings and bar approaches in the open field test. Control rats (1) received 0.9% NaCl *icv* or *ip*. Columns represent means ± SEM of the values obtained from 11–13 subjects. Crossings, $F(2.84) = 9.358$, * p(1–3) < 0.05; ** p(1–2,4) < 0.01; ●●● p(2–4) < 0.001. Rearings, $F(3.45) = 7.036$, * p(1–3) < 0.05; *** p(1–4) < 0.001; ●●● p(2–4) < 0.001. Bar approaches, $F(3.45) = 1.948$, * p(1–4) < 0.05; ** p(1–2) < 0.01; ●● p(2–4) < 0.01 (ANOVA and Newman-Keuls tests)

The effect of baclofen, AIDA and baclofen with AIDA on the activity of rats in the elevated "plus" maze (Fig. 2A,B; 3A,B)

Baclofen (0.25 mg/kg) given *ip* alone prolonged the time spent in the closed arms, shortened the time spent in the open arms, and decreased the number of entries to the open arms in the elevated "plus" maze. AIDA given *icv* at a dose of 100 nmol, had no effect in this test. Rats which received baclofen and AIDA together did not exhibit differences vs baclofen-treated group in the elevated "plus" maze but compared to the control they spent longer time in the closed arms and shorter time in the open arms, and showed reduced number of entries to the open arms.

The effect of baclofen, AIDA and baclofen with AIDA on retrieval in the passive avoidance (Tab. 1)

Neither baclofen (0.25 mg/kg, *ip*) nor AIDA (100 nmol, *icv*) had an effect on passive avoidance retrieval. Co-administration of baclofen with AIDA significantly shortened latency in rats, i.e. AIDA changed the action of baclofen on this process.

DISCUSSION

Our present study showed that the blockade of I mGluRs by AIDA reduced the stimulatory effects of baclofen on the GABA-B receptors in the open field test and inhibited retention of the passive

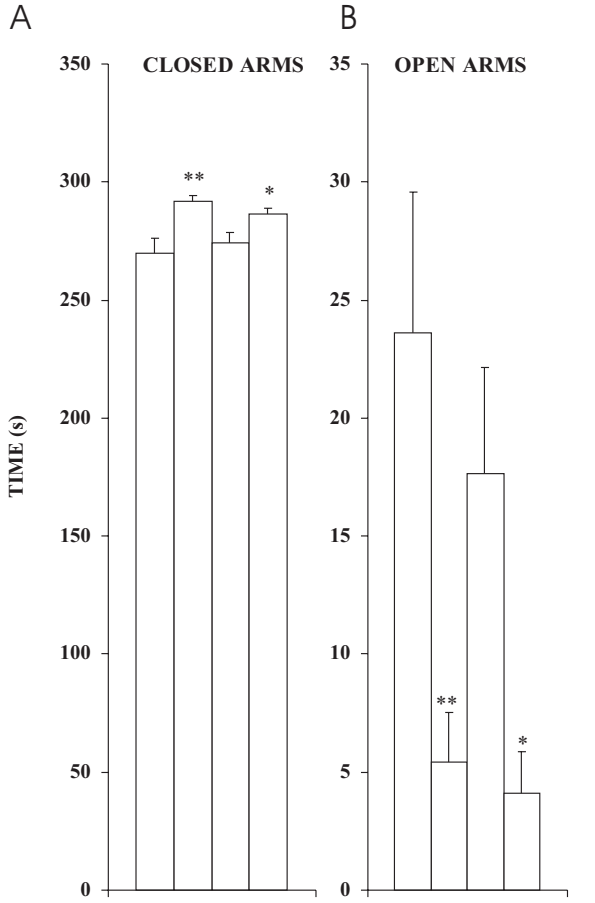

Fig. 2. The effect of saline (1), baclofen (0.25 mg/kg, *ip*) (2), AIDA (100 nmol, *icv*) (3) and baclofen with AIDA (4) on the time spent in the closed (A) or open arms (B) of elevated "plus" maze. For futher details see text. Columns represent means ± SEM of the values obtained from 9–11 subjects. A) closed arms, F (2.84) = 3.256, * p(1–4) < 0.05; ** p(1–2) < 0.01; B) open arms, F (2.84) = 3.337 * p(1–4) < 0.05; ** p(1–2) < 0.01 (ANOVA and Newman-Keuls)

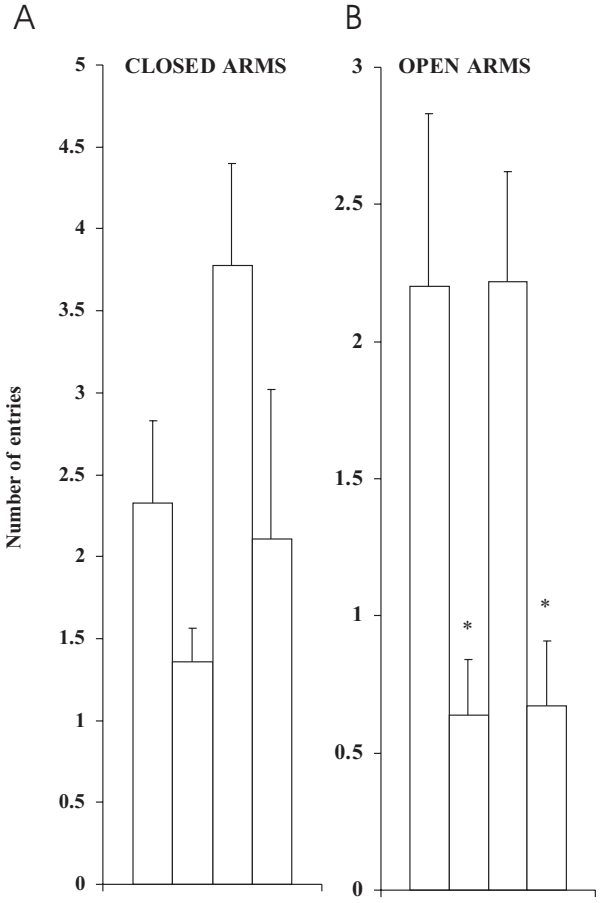

Fig. 3. The effect of saline (1), baclofen (0.25 mg/kg, *ip*) (2), AIDA (100 nmol, *icv*) (3), baclofen with AIDA (4) on the number of closed (A) or open (B) arms entries of the elevated "plus" maze. For further details see text. Columns represent means ± SEM of the values obtained from 9–11 subjects. A) closed arms, F (2.84) = 9.733, B) open arms, F(2.84) = 5.429, * p(1–2,4) < 0.05; (ANOVA and Newman-Keuls)

Table 1. The effect of baclofen, AIDA and baclofen with AIDA on retrieval in the passive avoidance situation in rats. The rats were treated *ip* with 0.25 mg/kg of baclofen, *icv* with 100 nmol of AIDA or in combination. The volume of *icv* injections was 5 l. Control rats received 0.9% NaCl *icv* or *ip*. For further details see text. Median latencies are given, with 25–75 percentiles in parentheses; *** p < 0.001 as compared with saline-treated group, •• p < 0.01, ••• p < 0.001 as compared with baclofen--treated group (Mann-Whitney test)

Treatment	n	Re-entry latency (s)
Saline	17	35.35 (12–61)
Baclofen	13	45.07 (24–67)
AIDA	15	27.40 (13–52) ••
Baclofen + AIDA	14	14.57 (5–33) *** •••

avoidance response. Baclofen enhanced the locomotor activity of rats in the open field test. There are some reports that baclofen action is dose-dependent. At very low doses it enhances the behavior related to nigrostriatal dopamine neuron activity, but at higher doses it inhibits dopamine neuron activity and receptor-mediated behavior [20, 32]. The action of baclofen on GABA-B receptors evokes the reduction of glutamate release in the spinal cord [23]. Coffey [9] reported that baclofen suppressed the release of excitatory neurotransmitters involved in monosynaptic and polisynaptic reflexes.

In our experiment, AIDA inhibited mobility expressed as a number of crossings, and rearings, and it changed the effect of baclofen on all parameters determined in the open field test, i.e. the effect of

the blockade of I mGluR by AIDA showed dominance over the stimulatory effect of GABA-B receptor. It is probably due to the influence on dopaminergic system and on glutamate release.

mGluRs are involved in the generation of dopamine-dependent locomotor behaviors [36, 40]. mGluRs also depress monosynaptic excitation of rat spinal motoneurons [17]. According to some data, $mGluR_1$ knock-out mice exhibited motor deficits and impaired motor learning [11]. Also Moroni et al. [24] have noticed that AIDA as the most potent and selective $mGluR_1$ antagonist causes some difficulty in the initiation of movement.

In the present experiment, baclofen used at a dose of 0.25 mg/kg had no effect on retrieval in the passive avoidance situation. Baclofen is involved in the formation of some types of learning and memory [12, 26]. In humans it impairs memory [33]. Baclofen also impairs retention and does not change the consolidation of inhibitory avoidance task in rats in dose-dependent manner [4, 6]. This agonist of GABA-B receptor is used as antispastic drug, it produces dose-dependent antinociception [37] and may be involved in antidepressant action [19, 21, 39]. Thus, baclofen cannot influence passive avoidance retrieval.

Similarly to baclofen, AIDA did not change retrieval in the passive avoidance situation. Thus, it can be assumed that the inhibition of the locomotor activity of rats by AIDA had no effect on retrieval. Blockade of mGluRs prevents induction of LTP and learning in a variety of tasks in different species [15]. Nielsen et al. [25] have suggested that learning/memory deficits may be due to selective blockade of class I mGluRs in the hippocampal formation. Christoffersen et al. [7] have reported that AIDA improves short-term and impairs long--term memory in a spatial task in rats. Moreover, I mGluRs play a significant role in the modulation of nociception [27], but when injected *icv*, AIDA has mild analgesic effects [24].

In our experiment, baclofen applied jointly with AIDA significantly impaired retrieval in comparison with the control or baclofen-treated group, and AIDA given alone. We can exclude the influence of rats' mobility after co-administration of baclofen with AIDA on retrieval in the passive avoidance situation because we observed locomotor inhibition in the open field test. Bordi et al. [3] found an indirect role of $mGluR_1$ in synaptic plasticity *via* regulation of GABA inhibition. Baclofen activates both pre- and postsynaptic GABA-B receptors. Its presynaptic activity is important for the regulation of neurotransmitter release, including excitatory amino acids [23]. Both compounds can produce analgesic effects [24, 27, 39], and this may influence activity of rats in aversely motivated behavior like passive avoidance. We also considered the effect of anxiety on the results in this test. Baclofen prolonged the time spent in the closed arms, shortened the time spent in the open arms and decreased the number of entries to the open arms in the elevated "plus" maze. AIDA did not show any influence on behavior in this maze. AIDA did not change the action of baclofen in elevated "plus" maze.

On the basis of the present experiment, it is difficult to explain this surprising outcome, as AIDA applied alone or jointly with baclofen strongly inhibited mobility in the open field test.

In conclusion, baclofen used *ip* at a dose of 0.25 mg/kg enhanced locomotor activity and exhibited anxiogenic activity but had no effect on retrieval in the present work. AIDA induced significant inhibition of rats' mobility and did not influence the activity of rats in the elevated "plus" maze. This antagonist of I mGluRs inhibited the effect of baclofen in the open field test to the level of that evoked by AIDA, while in the passive avoidance response it also inhibited baclofen retrieval, but did not change significantly the action of GABA-B receptor agonist in the elevated "plus" maze. These results suggest that the inhibition of locomotor activity of rats was strongly dependent on the blockade of I mGluRs. Aversely motivated behavior in the passive avoidance situation, such as retrieval, was significantly impaired after using AIDA. The effect of baclofen and AIDA on this process was probably a co-operation of both types of receptors.

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