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Effect of MPEP on rat's behavioral activity in experimental episodes of hypoxia

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ABSTRACT

Purpose: The influence of the selective antagonism of metabotropic glutamate receptor subtype 5 ($mGluR_5$) by MPEP (2-methyl-6-(phenylethynyl)-pyridine) on some behaviors was tested in control groups of rats and in rats exposed to short-term hypoxia once or to repeated episodes of hypoxia.

Material and Methods: We used the following methods: the open field test, the passive avoidance test and the object recognition test. Experimental hypoxia was produced by placing rats in a glass chamber flushed with a mixture of 2% O_2 in N_2.

Results: MPEP applied intravenously (IV) at the dose of 1 mg kg^{-1} significantly enhanced locomotor and exploratory activity, impaired acquisition, but improved consolidation and retrieval in the passive avoidance situation and did not alter rats' activity in the object recognition test. The single short-term hypoxia significantly inhibited motility of rats and profoundly impaired acquisition, consolidation and retrieval processes, but the positive effect of MPEP on retrieval was preserved. Hypoxia also did not influence the activity of rats in the object recognition object. The repeated episodes of short-term hypoxia were induced for five consecutive days and it also inhibited motility of rats, but did not change consolidation and retrieval processes. The episodes of hypoxia significantly diminished the beneficial effect of MPEP on consolidation and retrieval, and also the enhancement of locomotor and exploratory activity. MPEP, used in rats subjected to the single or the repeated episodes of short-term hypoxia, did not change recognition memory.

Conclusion: MPEP used before the single episode of hypoxia only, had beneficial effect on retrieval.

Key words: 2-methyl-6-(phenylethynyl)-pyridine, locomotion, passive avoidance, recognition memory, hypoxia, rats

INTRODUCTION

The major excitatory neurotransmitter glutamate acts by stimulation both ionotropic (iGluRs) and metabotropic receptors (mGluRs). mGluRs linked to G-proteins are classified in three distinct groups (I, II and III) on the basis of their sequence homology, effector coupling and pharmacology. Group I mGluRs include the $mGluR_1$ and $mGluR_5$ subtypes, which are positively coupled to phospholipase C and phosphoinositol hydrolysis [1]. $mGluR_5$ is generally located postsynaptically in the striatum, nucleus accumbens, olfactory tubercle, hippocampus and cerebral cortex. $mGluR_5$ is specifically expressed in pyramidal cells in CA1-CA4 areas of the hippocampus and granule cells of the dentate gyrus [2].

Pharmacological evidence implicates that glutamatergic transmission plays a major role in biochemical events underlying learning and memory processing. mGluRs are strongly involved in synaptic plasticity of various brain structures, and mGluRs are very important in some learning and memory processes [3].

MPEP (2-methyl-6-(phenylethynyl)-pyridine) is a potent, selective, non-competitive and systemically active antagonist of the $mGluR_5$ [4]. Literature data have shown that MPEP influences acute nociceptive transmission [5], exhibits dose-dependent anxiolytic-like effects [6], is neuroprotective [7] and also protects rat hepatocytes against hypoxic damage [8].

A number of mGluR antagonists have been tested in models of focal or global ischemia with the aim of reducing post-ischemic neuronal damage [9]. Non-selective antagonists

of group I mGluRs could reduce neuronal death in *in vitro* models of cerebral ischemia [10].

Hypoxic/ischemic brain injury is a serious clinical problem. Hypoxia produces disturbances in excitatory and inhibitory neurotransmission. Our previous studies have proved that short-term hypoxia impaired retrieval and consolidation processes in the passive avoidance situation. In our earlier study under hypoxic conditions, MPEP, had beneficial effect on retrieval in the passive avoidance situation [11].

The aim of this study was to investigate the influence of MPEP, the selective antagonist of $mGluR_5$, on some behaviors in rats subjected to experimental repeated episodes of hypoxia.

MATERIAL AND METHODS

Animals

The study was conducted on white, male Wistar rats weighing 160-180 g. The animals were fed on "Murigran" standard diet and housed in group cages in an air-conditioned room (humidity 50-60%) under 12h light/ 12h dark cycle beginning at 7.00 h. All experiments were carried out between 8.00 h and 12.00 h. It was from 9-12 animals in each experimental group.

The experimental procedures applied in this study were in compliance with the Board for Ethical Affairs and Supervisions over Research on Animals and Individuals, Medical University of Białystok.

Drug administration

MPEP (Tocris Cookson, UK) was IV administered through the tail vein at the dose of 1mg kg^{-1} [5]. Control rats received saline (0.9% NaCl, Polfa Poznań) iv at the dose of 1ml kg^{-1}.

Hypoxia induction

Hypoxia was produced by placing rats in a glass chamber flushed with a mixture of 2% O_2 in N_2 [12] until respiratory arrest, after which they were immediately transferred to atmospheric air.

Single short-term hypoxia was induced 20 min before placing animals in the open field test and 20 min before the first trial (T1) in the object recognition test. In the passive avoidance situation, hypoxia was induced on the second day 20 min before training, or immediately after completion of training, or 20 min before on the third day, when we determined the effect of hypoxia on acquisition, consolidation or retrieval, respectively.

The repeated episodes of hypoxia were induced every day for five consecutive days and after two days without hypoxia MPEP was administrated and tests were performed.

Behavioral tests: Passive avoidance response training.

The response was induced using the one-trial-learning method of Ader et al. [13]. The apparatus consisted of a 6 x 25 cm platform illuminated with a 25 W electric bulb, connected through a 6 x 6 cm opening with a dark compartment (40 x 40 x 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 immediately removed. Two similar trials, at an interval of 2 min, were carried out on the second day. After the first trial, the rats were allowed to stay in the dark compartment for 10-15 s. In the second trial, when a rat entered the dark compartment it received a foot shock (0.25 mA, 3 s) delivered through the metal rods. The presence of the passive avoidance was checked 24 h later. The rats were placed on the illuminated platform once more and the latency to enter the dark compartment was measured, with a cut off time of 300 s. To determine the effect of drug treatment on retrieval, MPEP was administered on the third day 20 min before retention test. MPEP was given either immediately after the completion of induction of passive avoidance on the second day in order to test an effect on consolidation or 20 min before training to determine an effect on acquisition.

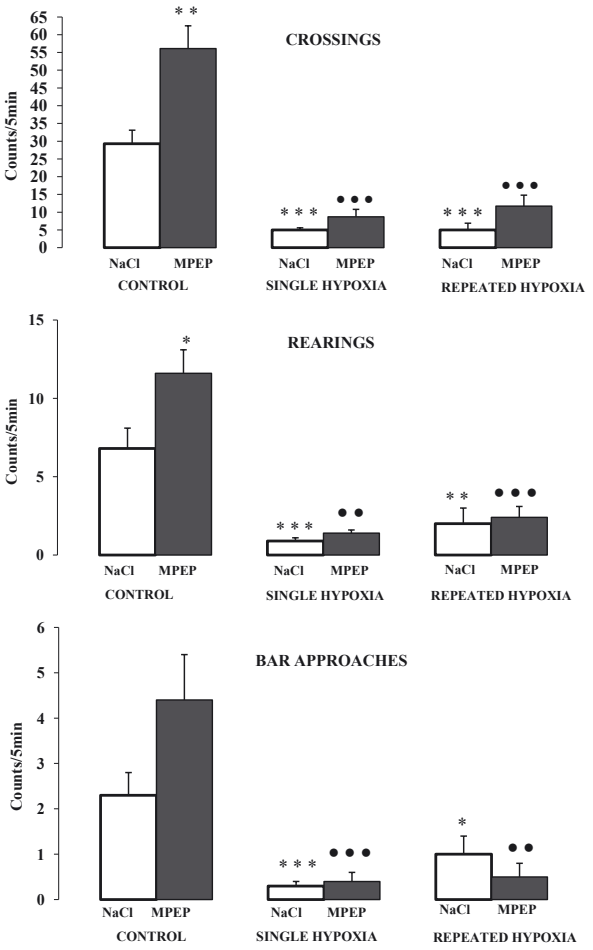
Locomotor and exploratory activity

The open field test was used for estimation of locomotor activity of rats. The apparatus consisted of a square with a 100 x 100 cm white floor, which was divided by 8 lines into 25 equal squares, and surrounded by white wall, 47 cm high. Four plastic bars, 20 cm high, were located at four different line crossings in the central area of the floor. A single rat was placed inside the apparatus for 1 min of adaptation. Subsequently, crossings, rearings, and bar approaches were counted manually for 5 min. MPEP was given 20 min before the test.

Object recognition test:

The apparatus was a wooden box (65 x 45 x 45cm) placed in a sound-isolated room. The procedure was similar to that described by Ennaceur and Delacour [14] and may be summarized as follows. A day before testing rats were allowed to explore the apparatus for 2 min. The experimental session comprised two trials. In the first trial (T1), two identical objects (A1 and A2), were positioned in two adjacent corners, 5 cm from the walls. During the second trial (T2) again two objects were presented, the object A' was a duplicate of the sample presented in T1 (A1) (in order to avoid olfactory traces) and one novel object (B). The novel object was placed in 50% trials in the right side and 50% trials in the left side of the box. The respective duration of T1 and T2 was 5 and 3 min. T2 started an hour after T1 trials. The basic measure was the time spent by rats in exploring objects during T1 and T2 trials. From this measure, the following variables were defined: A was the time spent exploring the objects A1 and A2 during T1. (B+A') was

Figure 1. **The effect of MPEP on number of crossings, rearings bar approaches in the open field in control and hypoxia-treated rats. Columns represent means ± SEM of the values obtained from 10-12 animals.**



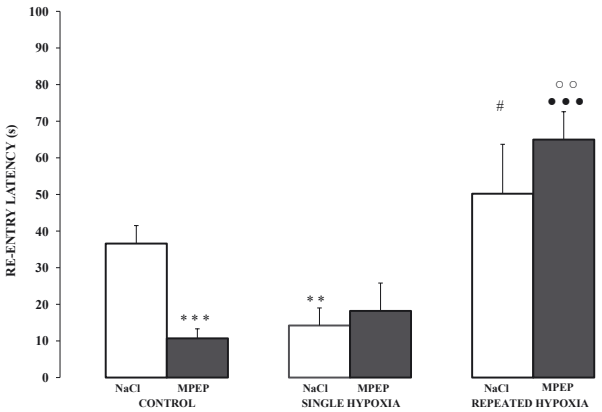
Crossings F(5.60) = 33.101; ** p< 0.01; *** p< 0.001 vs NaCl/control; ●●● p< 0.001 vs MPEP/control. Rearings F(5.60) = 20.336; * p< 0.05 ** p< 0.01; *** p< 0.001 vs NaCl/control; ●● p< 0.01, ●●● p< 0.001 vs MPEP/control. Bar approaches F(5.60) = 10.375; * p< 0.05, *** p< 0.001 vs NaCl/control; ●● p< 0.01, ●●● p< 0.001 vs MPEP/control (ANOVA and Newman-Keuls tests)

the time spent exploring the objects B and A' during T2. Object recognition was measured by the variable B-A'. Since B-A' may be biased by differences in overall levels of exploration, the variable B-A'/ B+A' was also computed. MPEP was given 20 min before the first trial T1.

Statistical analysis

The statistical significance of the results was computed by one-way analysis of variance (ANOVA) followed by Newman–Keuls tests, except for passive avoidance behavior which was assessed with Mann-Whitney ranking test. F - ratios, 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. Statistical analyses were carried out using Statistica 6 software.

Figure 2. **The effects of MPEP on acquisition of passive avoidance in control and hypoxia-exposed rats. Columns represent means ± SEM of the values obtained from 9-12 animals.**



** p < 0.01, *** p < 0.001 vs NaCl/control; ●●● p < 0.001 vs MPEP/control; # p< 0.05 vs NaCl/single hypoxia; ○○ p < 0.01 vs MPEP/single hypoxia (Mann–Whitney test)

RESULTS

The effect of MPEP on locomotor and exploratory activity of control and hypoxia-treated rats in the open-field test (*Fig. 1*)

The single and repeated hypoxia significantly decreased the number of crossings, rearings and bar approaches. MPEP significantly enhanced locomotor and exploratory activity, but both hypoxia diminished the beneficial effect of MPEP.

The effect of MPEP on acquisition of passive avoidance in control and hypoxia-treated rats (*Fig. 2*)

The single hypoxia significantly shortened the latency of entering the dark compartment in rats but repeated episodes of hypoxia did not influence the latency. MPEP also shortened the time spent on the illuminated platform. MPEP in hypoxia-treated rats did not change the latency.

The effect of MPEP on consolidation of passive avoidance in control and hypoxia-treated rats (*Fig. 3*)

The single hypoxia significantly shortened the latency in rats but repeated episodes of hypoxia did not influence on the latency. MPEP prolonged the time spent on the platform, but hypoxia diminished this effect of MPEP.

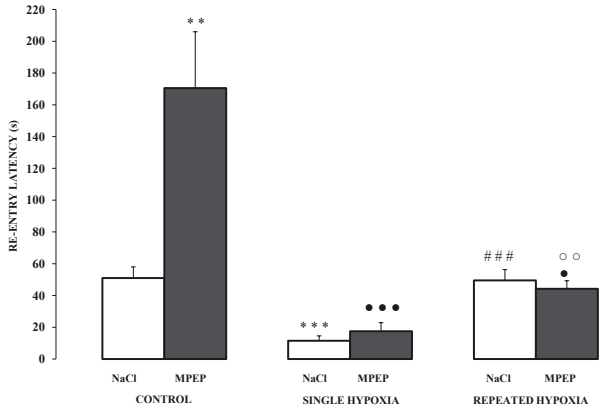
The effect of MPEP on retrieval of passive avoidance in control and hypoxia-treated rats (*Fig. 4*)

The single hypoxia significantly shortened the time before entrance into the dark compartment, but repeated episodes of hypoxia did not influence this time. MPEP significantly prolonged the latency and this effect was preserved after the single hypoxia.

The effect of MPEP on recognition memory in control and hypoxia-treated rats (*Tab. 1*)

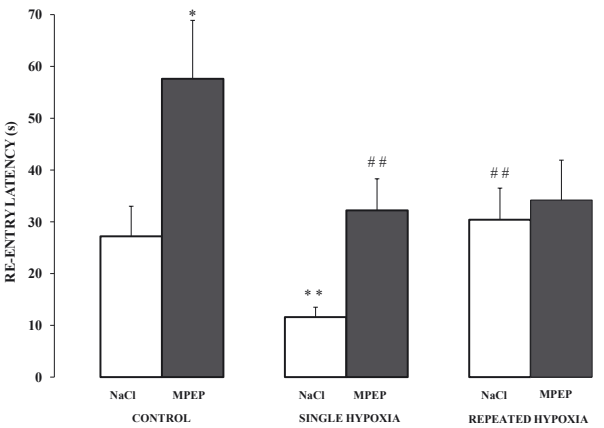
In the object recognition test, the was no significant difference among all experimental groups in any computed variables, indicating that MPEP and hypoxia had no effect on recognition memory.

Figure 3. **The effects of MPEP on consolidation of passive avoidance in control and hypoxia-exposed rats. Columns represent means ± SEM of the values obtained from 9-12 animals.**



** p < 0.01, *** p < 0.001 vs NaCl/control, ● p < 0.05,●●● p < 0.001 vs MPEP/control; ### p< 0.001 vs NaCl/single hypoxia; ○○ p < 0.01 vs MPEP/single hypoxia (Mann–Whitney test)

Figure 4. **The effects of MPEP on retrieval of passive avoidance in control and hypoxia-exposed rats. Columns represent means ± SEM of the values obtained from 9-12 animals.**



* p < 0.05, ** p < 0.01 vs NaCl/control, ## p < 0.01 vs NaCl/single hypoxia (Mann-Whitney test)

Table 1. **Effect of MPEP on object recognition memory.**

Variable (s)	Treatment					
	Control		Single hypoxia		Repeated hypoxia	
	NaCl	MPEP	NaCl	MPEP	NaCl	MPEP
B–A'	11.0(3.485)	11.7(2.261)	3.5(3.219)	0.9(0.640)	12.4(2.809)	2.4(1.424)
A	26.0(6.27)	31.9(3.96)	36.7(6.37)	30.2(2.85)	45.8(9.55)	29.7(4.40)
B+A'	22.0(3.73)	23.5(4.29)	27.3(4.92)	6.1(3.55)	24.6(4.29)	17.2(4.06)
B–A'/ B+A'	0.44(0.09)	0.53(0.08)	0.16(0.14)	0.25(0.28)	0.51(0.05)	0.22(0.18)

Table presents means ± SEM (in parentheses) of the values obtained from 9-10 rats of each experimental group (ANOVA and Newman-Keuls).

DISCUSSION

In our present experiments, we observed that MPEP, the selective antagonist of $mGluR_5$, administrated *iv* at the dose of 1 mg kg^{-1} impaired acquisition, improved consolidation and retrieval in the passive avoidance situation. The single short-term hypoxia, but not repeated episodes of hypoxia impaired memory processes. MPEP attenuated a retrieval deficit induced by hypoxia and had no effect on hypoxia–evoked impairment of consolidation. MPEP in hypoxia-treated rats did not change the acquisition in passive avoidance.

According to some data, the inhibition of I $mGluR_5$ blocks induction of hippocampal LTP (long-term potentiation) and learning in various experimental models [15]. $mGluR_5$ knockout mice exhibited inhibition of LTP in CA1 and dentate gyrus, and they showed impairment of acquisition. The systemic blockade of class I mGluRs may also enhance short-term memory [16].

The exact role of $mGluR_5$ in memory is not well known. Literature data indicated effects of $mGluR_5$ antagonists that are task-specific, vary in sensitivity to the dose, vary with the type of animals used in the studies [17,18]. MPEP have influenced memory and learning processes very differently in various behavioral task [19,20]. It could depend on the time of injection of MPEP (pre-training or after training). MPEP injection into the lateral amygdale blocked the acquisition but not the consolidation and expression of conditioned fear in the same task [21]. In our experiments, low dose antagonism of $mGluR_5$ by MPEP exhibited different influences on various phases of memory formation in passive avoidance test. In previous studies we demonstrated that the administration of an antagonist of group I mGluRs, AIDA (1-aminoindan-1,5-dicarboxylic acid), or the selective antagonist of $mGluR_5$, MPEP, improved the consolidation process in a passive avoidance situation, but impaired acquisition [11]. This suggests that the antagonists of mGluR have a beneficial effect on consolidation process, but negatively affect the acquisition process. MPEP may exert antinociceptive activity [5]. The effect of MPEP could interfere with the results obtained in a passive avoidance situation, especially in acquisition process. Therefore, MPEP was administered before the learning trial and the rats were under the influence of the compound during footshock experienced in dark compartment. The antinociceptive effect of MPEP could be the reason of impairment of aquisition process.

In our study short-term hypoxia induced by 2% O_2 and 98% N_2 impaired acquisition, consolidation and retrieval in a passive avoidance paradigm [11]. It is unclear so far why hypoxia inhibited memory processes. Hypoxia disturbs the homeostasis between neurotransmitter systems [10,22]. There was an increase of the extracellular level of glutamate during hypoxia [22]. Neurotoxic effects induced by the high extracellular concentration of excitatory amino acids and free radicals lead to neuronal death. Among various regions of the brain, hippocampus, which plays a very important role in memory formation, is particularly sensitive to ischeamia and hypoxia. [22,23]. In the present our study, the repeated episodes of hypoxia did not significantly change memory and learning in the passive avoidance task. This could be due to short lasting changes in neurotransmitter systems, because our experiments had been performed two days after the last hypoxia. Maybe our experiment with repeated episodes of hypoxia is similar to a pre-conditioning phenomenon: Repeated exposure to a hypoxic environment leads to structural and functional adaptations in the rat brain. There are lots of acute effects of hypoxia on CNS, for example hemoglobin disoxygenation, increased cerebral blood volume and flow, faster capillary mean transit time, increased cerebral metabolic rate for glucose [24].

Selective blockade of $mGluR_5$ is neuroprotective. MPEP might protect erythrocytes and liver tissue against oxidative stress, it also has neuroprotective effect in cortical cultures challenged with a toxic concentration of β-amyloid peptide [7,25]. A neuroprotective potential of $mGluR_5$ antagonists has also been proved in experimental ischemic models [26].

The drug-evoked changes of locomotor activity in rats could influence the results in the passive avoidance test in our study. MPEP significantly enhanced locomotor and exploratory activity in rats. The single and repeated episodes of hypoxia inhibited this activity and diminished the enhancing effect of MPEP on locomotion in the open field test. According to some studies, effects of blockade of $mGluR_5$ by MPEP on locomotor activity in animals were dependent on the dose [6,27].

In this study we also investigated the influence of MPEP on performance in the object recognition test of rats subjected to single and repeated episodes of hypoxia. In all experimental groups of rats, there was lack of effect of MPEP and hypoxia on recognition memory. There is a model of recognition memory suggesting that information about previously encountered items is stored in a dynamic pattern of neural activity and not in a localized representation. These patterns operate in distributed neuronal networks and different networks may process different forms of recognition memory [28]. These studies indicated that two parallel-distributed neuronal networks are essential for the processing of spatial and non-spatial recognition memory in rats. There are a lot of neuroanatomical systems involved in the mediation of recognition memory. The present results demonstrated that low dose antagonism of mGluR5 and hypoxia did not significantly change recognition memory in rats.

CONCLUSIONS

In summary, episodes of hypoxia significantly diminished a beneficial effect of MPEP on consolidation and retrieval as well as an enhancement of and locomotor and exploratory activity. MPEP used in rats subjected to single or repeated episodes of short-term hypoxia, did not change the acquisition process. Single and repeated hypoxia blocks the negative effects of MPEP on acquisition. MPEP used before the single episode of hypoxia had a beneficial effect on retrieval.

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