

## EXAMINATION OF THE INFLUENCE OF 3,5-DHPG ON BEHAVIORAL ACTIVITY OF ANGIOTENSIN II

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The effects of the class I metabotropic glutamate receptor (mGluR) stimulation on the behavioral activity of angiotensin II (Ang II) was investigated in the present study. The experiments were performed on adult male Wistar rats. Stimulation of the group I of mGluR receptors was evoked by *icv* injection of (S)-3,5-dihydroxyphenylglycine (3,5-DHPG) at the dose of 0.01 and 1 nmol per rat. Fifteen minutes later, the animals were given *icv* solution containing 1 nmol of Ang II. Memory motivated affectively was evaluated in passive avoidance and active avoidance responses (CARs). Moreover, the speculative influence of the treatment on anxiety and motor activity was tested in elevated plus-maze and in open field, respectively.

We observed that both compounds did not have statistically significant influence on motor activity of rats in open field test. However, 3,5-DHPG at the dose of 0.01 nmol given alone and combined with Ang II tended to increase locomotor activity. 3,5-DHPG, given alone, significantly facilitated consolidation process in a passive avoidance situation (only at the dose of 0.01 nmol) but had no influence on acquisition and recall of information. Examination of the influence of 3,5-DHPG on the acquisition and extinction of CAR proved that it did not alter acquisition and extinction of these responses. In the elevated plus-maze, 3,5-DHPG had anxiogenic-like profile. Ang II, as repeatedly shown before, greatly increased passive avoidance latency, rate of acquisition of CARs and decreased their extinction. On the other hand, Ang II induced anxiolytic-like effect in elevated plus-maze. The pre-treatment of rats with 3,5-DHPG tended to attenuate behavioral effects of the Ang II administration.

**Key words:** *angiotensin II, 3,5-DHPG, learning, memory, metabotropic glutamate receptors, rat*

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## INTRODUCTION

In addition to the classic cardiovascular [4] and water/electrolyte balancing [11] functions of the brain angiotensins [12, 33], several reports indicate that angiotensin II (Ang II), angiotensin IV (Ang IV) and its other fragments may participate in the mechanisms of learning and memory and interfere with cognitive function [6, 7, 16, 31, 34]. The underlying mechanisms accounting for such behavioral activity of Ang II may be due to angiotensin-evoked stimulation of the other neurotransmitter systems in the central nervous system. Related to this, it has been shown that the beneficial influence of Ang II on learning and memory processes can be blocked by pre-treatment with NMDA ionotropic glutamate receptor antagonists [32]. It may suggest that the behavioral effects of Ang II may be mediated by endogenous glutamate system. Since metabotropic glutamate receptors (mGluRs) besides ionotropic ones are involved in some effects of glutamatergic system on learning and memory [21], the role of this receptor family in Ang II-evoked enhancement of cognitive functions required elucidation.

The mGluRs can be subdivided into three groups [9, 29]: class I comprising mGluR 1 and mGluR 5 acting *via* phospholipase C and inositide hydrolysis, class II including mGluR 2 and mGluR 3, and class III composed of mGluR 4, mGluR 6, mGluR 7 and mGluR 8, which inhibit adenylyl cyclase and reduce cyclic AMP synthesis [25, 27]. Behavioral investigations have supported that class I mGluRs are important in learning and memory processes [9, 15, 22]. Therefore, in this study we have investigated an influence of (S)-3,5-dihydroxyphenylglycine (3,5-DHPG), a selective agonist for class I mGluR [17, 26], on behavioral activity of Ang II in rats.

## MATERIALS and METHODS

### Subjects

Male Wistar rats of laboratory strain, weighing 160–180 g were used. They were housed in cages (55 × 40 × 20 cm), 8 animals per cage, at room temperature with a 12 h light-dark cycle beginning at 7.00 a.m. Food and water were freely accessible. The experimental procedures applied in this study were in compliance with the Board for Ethic Af-

fairs and Supervision over Research on Animals and Individuals, Medical Academy of Białystok.

### Surgery and experimental procedure

Under light ether anesthesia, two burr holes, 0.5 mm in diameter, were drilled in the skull 2.5 mm laterally and 1 mm caudally from the point of intersection of a bregma and the superior sagittal suture on the both sides of the head [14]. After 48 h of recovery, the wound was completely dry and the animal behaved normally. The *icv* injections were made freehand into the lateral cerebral ventricle with a 10  $\mu$ l Hamilton syringe, using a removable KF 730 needle 4.5 mm long. It was relatively non-traumatic as the animal, gently fixed with the left hand of the experimenter, was usually quiet and no vocalization occurred. The injection volume was always 5  $\mu$ l administered over 3 s. At the end of each experiment a rat was sacrificed and the sites of injections were verified microscopically after brain sectioning. The data obtained in animals with incorrect injections were not included in the final analysis.

### Drugs

Ang II (Sigma) at the dose of 1 nmol and 3,5-DHPG at the dose of 0.01 and 1 nmol per rat were injected into the lateral cerebral ventricle as a freshly prepared saline solution. The *icv* injections were given 30 min (for 3,5-DHPG) and 15 min (for Ang II) before the open field and elevated plus maze tests or before learning trial on the first day in acquisition of CAR, the trial on the 2nd day of the experiment in acquisition stage and on the 3rd day of the test in recall of the passive avoidance situation. In consolidation of avoidance responses 3,5-DHPG was injected immediately after the trial and Ang II was given 15 min later on the 2nd day of the experiment in passive avoidance situation and on 5th training day in consolidation of CARs. The control rats received 0.9% NaCl (saline) *icv*.

### Behavioral studies

All behavioral experiments were carried out in a quiet, diffusely lit room (25 W bulb, 2 m away from an animal, indirect light) between 9.00 and 14.00 p.m. with each group equally represented at the times of testing. Rats were randomly allocated to treatment groups and used only once. Passive avoidance responses were selected to estimate acquisition, consolidation and recall of memory. To

investigate the process of learning we employed tests of acquisition and consolidation of CARs. Moreover, the putative influence of the treatment on anxiety and motor activity was tested in elevated plus-maze and in open field, respectively.

### ***Open field***

Locomotor and exploratory behavior was measured in open field, which was a square white floor measuring  $100 \times 100$  cm divided by 8 lines into 25 equal squares and surrounded by a wall 47 cm high [3]. Four plastic bars, 20 cm high, were designed as the objects of possible interest and located at four intersections of the lines in the central area of the floor. Following 1 min of adaptation, crossings, rearings and bar approaches were counted manually for 5 min.

### ***Passive avoidance behavior***

Passive avoidance behavior was studied in a one trial learning, step-through situation [1], which utilizes the natural preference of rats for dark environment. After 2 min of habituation to the dark compartment the rat was placed on an illuminated platform and allowed to enter the dark compartment. On the second day, the guillotine door was closed behind the animal immediately after it entered the dark compartment. After the second entering, the animal received electric footshock (0.25 mA, AC, 2 s) *via* the grid floor (learning trial). The rat was then returned to its home cage and placed back into the holding room. Acquisition, recall and consolidation of the passive avoidance response was tested 24 h later by placing the animal on the platform and measuring latency to re-enter the dark compartment to a maximum of 300 s.

### ***Conditioned avoidance responses***

CARs were studied in a shuttle-box ( $60 \times 28 \times 24$  cm) divided into two equal parts by a wall 6 cm wide and 8 cm high, with an opening in the middle of its length [3]. A buzzer (45 dB, 2,000 Hz, conditioned stimulus, CS) was sounded for 5 s. If the rat did not make a positive (+) CAR, i.e. move to the other compartment within 5 s, a 1 mA AC scrambled electric shock (unconditioned stimulus, US) was delivered through the box floor, which was made of stainless steel rods 4 mm in diameter and spaced at 18 mm intervals. The US was terminated when the animal escaped to the other compartment of the box. CAR consolidation training consisted of

5 daily 20-trial sessions and on the 5th day, rats were injected drugs. One week and 2 weeks after the injection rats were tested. Acquisition of CARs consisted of 3 daily 10-trial sessions. After 3 training days the chosen rats were investigated in 5 daily 20-trial sessions. The number of (+) CARs was recorded every day and expressed as the percentage of the total number of trials. The intertrial interval varied randomly between 30 and 60 s. The grid floor was kept clean throughout training sessions.

### ***Elevated plus-maze***

The maze (constructed of grey colored wooden planks) consisted of two open arms, 50 cm (length)  $\times$  10 cm (width) and two closed arms, 50 cm (length)  $\times$  10 cm (width)  $\times$  40 cm (height), covered with a removable lid, such that the open or closed arms were opposite to each other. The maze was elevated to a height 50 cm above the floor. Thirty minutes (for 3,5-DHPG) and 15 min (for Ang II) after drug injection a rat was placed for 5 min in a pre-test arena ( $60 \times 60 \times 35$  cm constructed of the same material) prior to the exposure to the maze. This step allows the facilitation of exploratory behavior. The experimental procedure was similar to that described by Pellow et al. [19]. Immediately after the pre-test 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 into one arm with all four feet. An increase in closed arm entries and increase in time spent in closed arms is indicative of potential anxiogenic activity.

### **Statistics**

The results of experiments were analyzed by a one-way ANOVA followed by Newman-Keuls test, except for the passive avoidance behavior which was assessed with a nonparametric Mann-Whitney U-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.

## RESULTS

### Influence of 3,5-DHPG on Ang II activity in the open field

We observed that none of the tested drugs influenced significantly locomotor activity of rats measured by the number of crossings, rearings and bar approaches in this test (calculated by ANOVA) (Fig. 1). However, 3,5-DHPG at the dose of 0.01 nmol given alone and combined with Ang II tended to increase all the above parameters.

### Influence of 3,5-DHPG on Ang II activity in the passive avoidance behavior

Examination of the acquisition of passive avoidance responses (Tab. 1) showed that Ang II improved memory processes in the examined rats in comparison with the control group (NaCl) (ANOVA  $F_{5,67} = 2,8$ ). Mann-Whitney test gave  $p < 0.01$  for Ang II vs. NaCl. 3,5-DHPG given alone at both doses did not alter median latency in an other-

wise untreated group. In the group which received 3,5-DHPG followed by Ang II, the peptide was unable to prolong the re-entry latency.

Table 1. Influence of 3,5-dihydroxyphenylglycine (3,5-DHPG) at doses of 0.01 nmol and 1.0 nmol on angiotensin II (Ang II) activity in the acquisition of a passive avoidance responses. Control group – 0.9% NaCl (saline)

Treatment	N	Latency (s)
NaCl	13	26 (11–43)
3,5-DHPG 0.01	11	18 (5–300)
3,5-DHPG 1.0	12	14.5 (3–300)
Ang II	13	80 (12–300)**
Ang II + 3,5-DHPG 0.01	12	21 (5–300)
Ang II + 3,5-DHPG 1.0	12	19.5 (8–300)

Median latencies are given with the minimum and maximum values in parentheses. N represents number of subjects. \*\*  $p < 0.01$  vs. NaCl (ANOVA and Mann-Whitney test)

The results obtained from consolidation of passive avoidance responses are presented in Table 2

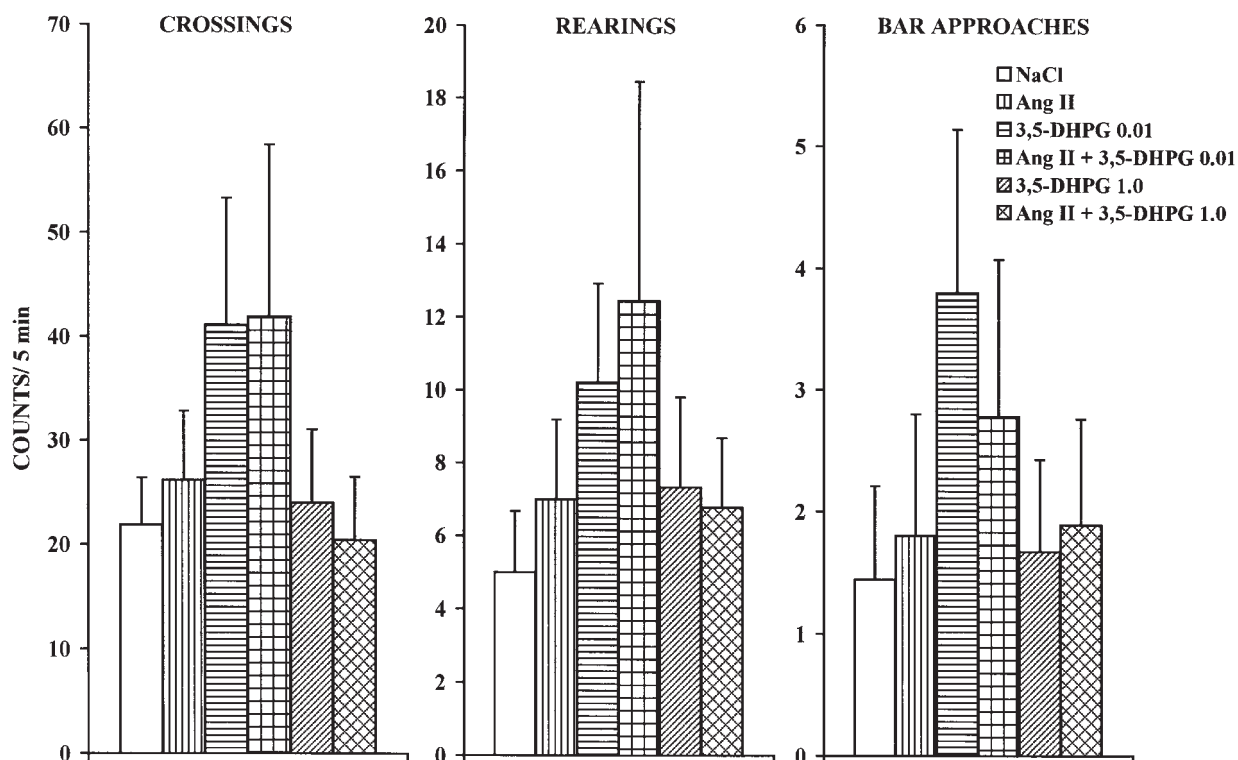


Fig. 1. Influence of 3,5-dihydroxyphenylglycine (3,5-DHPG) at doses of 0.01 nmol and 1.0 nmol on angiotensin II (Ang II) activity in the open field. Columns represent means  $\pm$  SEM of the results from 10–12 subjects. Control rats (NaCl) received 0.9% NaCl

*Table 2.* Influence of 3,5-dihydroxyphenylglycine (3,5-DHPG) at doses of 0.01 nmol and 1.0 nmol on angiotensin II (Ang II) activity in the consolidation of a passive avoidance responses. Control group – 0.9% NaCl (saline)

Treatment	N	Latency (s)
NaCl	11	21 (8–65)
3,5-DHPG 0.01	10	47 (7–300)*
3,5-DHPG 1.0	11	36 (3–300)
Ang II	12	86 (13–300)**
Ang II + 3,5-DHPG 0.01	10	61 (5–300)
Ang II + 3,5-DHPG 1.0	10	16.5 (8–187)

Median latencies are given with the minimum and maximum values in parentheses. N represents number of subjects. \*  $p < 0.05$ , \*\*  $p < 0.01$  vs. NaCl (ANOVA and Mann-Whitney test)

*Table 3.* Influence of 3,5-dihydroxyphenylglycine (3,5-DHPG) at doses of 0.01 nmol and 1.0 nmol on angiotensin II (Ang II) activity in the retrieval of a passive avoidance responses. Control group – 0.9% NaCl (saline)

Treatment	N	Latency (s)
NaCl	11	12 (5–92)
3,5-DHPG 0.01	10	13.5 (5–300)
3,5-DHPG 1.0	11	18 (7–98)
Ang II	12	58.5 (12–300)*
Ang II + 3,5-DHPG 0.01	10	14 (5–300)
Ang II + 3,5-DHPG 1.0	10	18 (5–300)

Median latencies are given with the minimum and maximum values in parentheses. N represents number of subjects. \*  $p < 0.05$  vs. NaCl (ANOVA and Mann-Whitney test)

and indicate that (ANOVA  $F_{5,58} = 5$ ) Ang II alone significantly facilitated consolidation process in comparison with the control group ( $p < 0.001$ ). Although, a similar trend was present in the animals treated with 3,5-DHPG at the dose of 0.01 nmol ( $p < 0.01$  vs. control), pre-treatment of rats with 3,5-DHPG prevented stimulatory effect of the Ang II administration on consolidation.

Assessment of the recall of passive avoidance responses (Tab. 3) demonstrated that Ang II delayed re-entry to the dark compartment of the cage in comparison with the control group ( $F_{5,58} = 3.4$ ,  $p < 0.05$ ). Results obtained in groups of animals given 3,5-DHPG alone, and those injected 3,5-DHPG 15 min before Ang II were not altered in significant manner as compared with saline-treated rats.

### **Influence of 3,5-DHPG on Ang II activity in the conditioned avoidance responses**

Cumulative rates of (+) CARs in acquisition phase (Fig. 2) were significantly different in all the groups (ANOVA  $F_{5,58} = 6.85$ ). Further analysis of means by Newman-Keuls test revealed that Ang II-treated animals had significantly higher rates of acquisition of (+) CARs than the control group ( $p < 0.05$ ). Injection of both doses of 3,5-DHPG did not alter acquisition of these responses, but attenuated the facilitatory effects of Ang II in this test.

We did not observe any significant differences between all groups in the consolidation of CARs (Fig. 3) after 1 week but in the second ( $F_{5,58} = 3.2$ ) and third ( $F_{5,58} = 2.5$ ) week Ang II increased the number of (+) CARs in comparison with the control group ( $p < 0.05$ ). The injection of both doses of 3,5-DHPG alone did not induce any significant differences at any observation time as compared with saline-treated rats. Moreover, the administration of both doses of 3,5-DHPG 15 min before Ang II did not evoke any significant difference in consolidation of CARs vs. saline-treated group.

### **Influence of 3,5-DHPG on Ang II activity in the elevated plus maze**

The ANOVA showed that there were significant differences between the groups in the time spent in the closed arms ( $F_{5,54} = 21.5$ ) and open arms ( $F_{5,54} = 20.2$ ), and number of open arms entries ( $F_{5,54} = 15.2$  (Tab. 4). Post hoc analysis by Newman-Keuls test indicated that 3,5-DHPG (alone) at both doses had anxiogenic-like profile, because it increased the time spent in the closed arms ( $p < 0.001$  for a dose of 0.01 nmol and  $p < 0.01$  for a dose of 1 nmol) and decreased the time spent in the open arms ( $p < 0.001$  for a dose of 0.01 nmol and  $p < 0.01$  for a dose of 1 nmol) and the number of entries to the open arms ( $p < 0.01$ ) of the maze comparing to saline-treated group. Ang II produced few effects in plus-maze behavior. The parameters showing significant effect of Ang II treatment vs. the control were as follows: increased time spent in the open arms ( $p < 0.001$ ) and a number of entries to the open arms ( $p < 0.01$ ), and decreased time spent in the closed arms ( $< 0.001$ ) of the maze comparing to the control group. This action suggests anxiolytic-like effect of Ang II. Pretreatment with 3,5-DHPG was noted to inhibit the anxiolytic-like

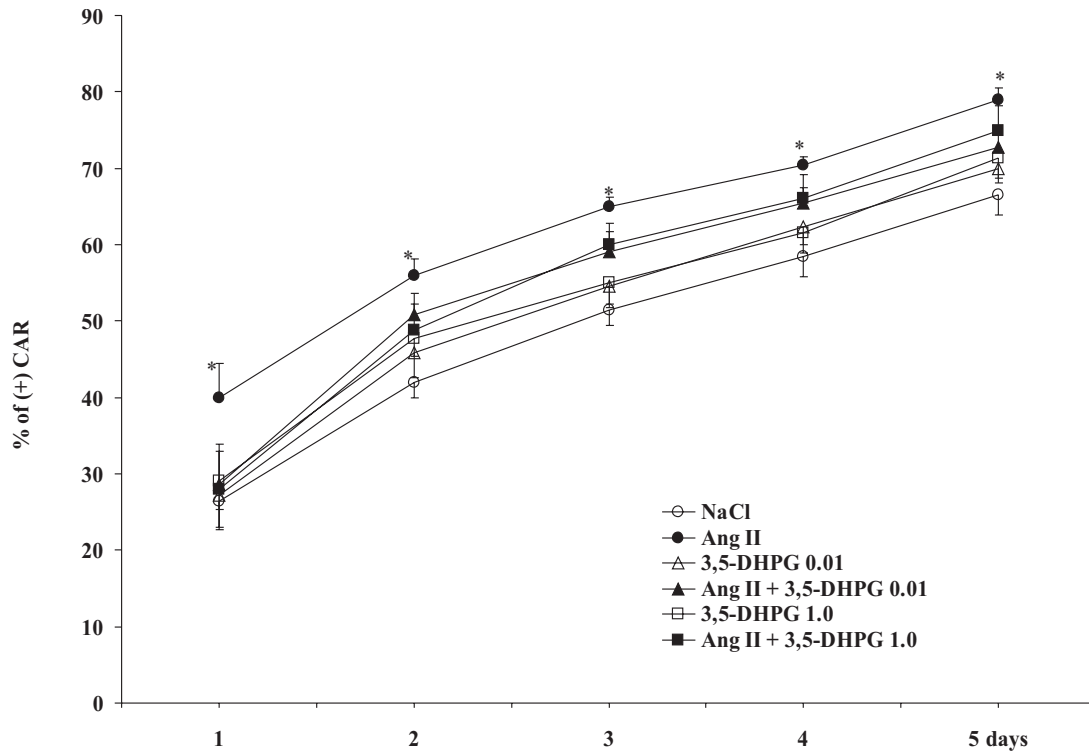


Fig. 2. Influence of 3,5-dihydroxyphenylglycine (3,5-DHPG) at doses of 0.01 nmol and 1.0 nmol on angiotensin II (Ang II) activity in the acquisition of conditioned avoidance responses (CARs). Points represent means  $\pm$  SEM of the results from 10–12 subjects. Control rats (NaCl) received 0.9% NaCl. \*  $p < 0.05$  vs NaCl (ANOVA and Newman-Keuls test)

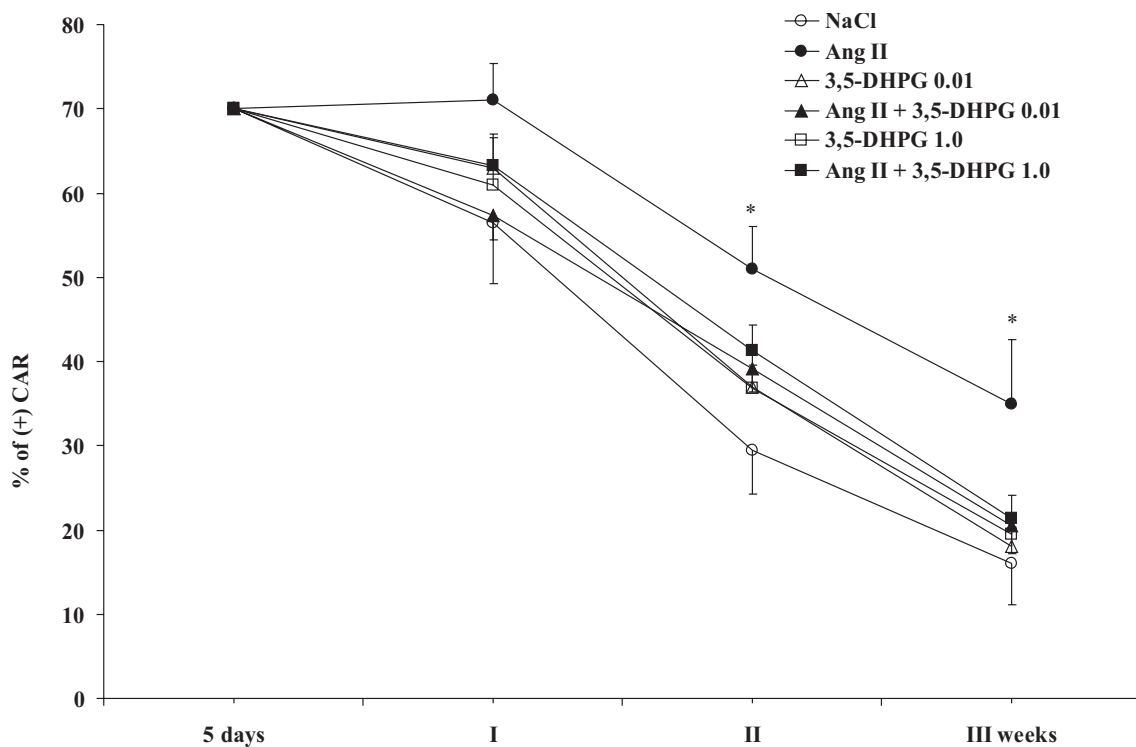


Fig. 3. Influence of 3,5-dihydroxyphenylglycine (3,5-DHPG) at doses of 0.01 nmol and 1.0 nmol on angiotensin II (Ang II) activity in the consolidation of conditioned avoidance responses (CARs). Points represent means  $\pm$  SEM of the results from 10–12 subjects. Control rats (NaCl) received 0.9% NaCl. \*  $p < 0.05$  vs NaCl (ANOVA and Newman-Keuls test)

Table 4. Influence of 3,5-dihydroxyphenylglycine (3,5-DHPG) at doses of 0.01 nmol and 1.0 nmol on angiotensin II (Ang II) activity in the behavior in the elevated plus maze. Control rats (NaCl) received 0.9% NaCl (saline)

Treatment	Time spent in the open arms (s)	Time spent in the closed arms (s)	Number of open arm entries	Number of closed arm entries
NaCl	28.6 (3.95)	267.6 (3.0)	2.2 (0.32)	2.8 (0.75)
3,5-DHPG 0.01	1.8 *** +++ (1.2)	294.3 *** +++ (1.5)	0.6 ** +++ (0.2)	1.6 (0.2)
3,5-DHPG 1.0	8.6 ** +++ (3.2)	290.4 ** +++ (3.1)	0.6 ** +++ (0.2)	2.1 (0.5)
Ang II	53.2 *** (7.3)	244.8 *** (7.3)	3.4 ** (0.3)	3.8 (0.3)
Ang II + 3,5-DHPG 0.01	12.7 * +++ (3.7)	285.8 ** +++ (3.8)	1.1 * +++ (0.3)	2 (0.3)
Ang II + 3,5-DHPG 1.0	8.5 ** +++ (3.4)	289.4 *** +++ (3.3)	0.7 ** +++ (0.2)	1.7 (0.2)

The results are presented in the table as means  $\pm$  SEM (in parentheses) of the values obtained from 10 subjects. \*  $p < 0.05$ , \*\*  $p < 0.01$ , \*\*\*  $p < 0.001$  vs NaCl; +  $p < 0.05$ , ++  $p < 0.01$ , +++  $p < 0.001$  vs Ang II (ANOVA and Newman-Keuls test)

effect of Ang II when it was co-injected with this peptide. Similarly to the rats receiving 3,5-DHPG alone, animals treated with Ang II combined with 3,5-DHPG showed anxiogenic-like responses.

## DISCUSSION

The present study was designed to investigate whether the activation of the group I mGluR by 3,5-DHPG plays a role in the Ang II-stimulated behavior. As we supposed that all cognitive effects had to be expressed by psychomotor activity, the effect of the treatments on the general locomotor and exploratory behavior was checked in open field. We observed that none of the tested compounds influenced significantly locomotor activity of rats. However, we noticed a tendency to an increase in a number of crossings, rearings and bar approaches after the administration of 3,5-DHPG at the dose of 0.01 nmol alone and combined with Ang II. This effect is in agreement with reports which indicate that mutant mice strain that does not express mGluR1 showed poor motor coordination [2, 10]. Moreover, behavioral studies in rats showed that of 3,5-DHPG caused hyperlocomotion [15, 18].

Anxiety could also be an important factor in the experiments, therefore, it was evaluated in elevated plus-maze. Estimation of the fear reactions proved that 3,5-DHPG at both doses produced anxiety enhancement in animals manifested by a decrease in entries into open arms and time spent in these arms. Unfortunately, this action could bias the results of memory testing using aversive stimulation. In contrast, the administration of Ang II increased number of entries into the open arms and the time spent in these arms, which might suggest an anxiolytic-like activity. This anxiolytic-like effect of Ang II was inhibited by pretreatment with 3,5-DHPG.

The most important goal of our study, however, was the investigation of the effect of activation of class I mGluRs by both doses of 3,5-DHPG on the facilitatory action of Ang II on behavior related to memory and learning processes. When we examined behavior in passive avoidance situation, we found that 3,5-DHPG (only at the dose of 0.01 nmol) significantly facilitated consolidation process but had no influence on acquisition and recall of task. These data are in line with previous observations [5, 22] and with the theory suggesting that the time of application of drugs acting on mGluRs is critical for the effect upon learning and memory [21]. Interestingly, the administration of both doses

of 3,5-DHPG 15 min before Ang II attenuated stimulatory effect of the Ang II on the stages memory formation in passive avoidance situation. In these experiment, on the contrary to injection of Ang II alone, the results obtained in the group of rats receiving 3,5-DHPG combined with Ang II were not significantly altered vs. control rats. Performance of rats during acquisition and consolidation of CARs revealed that 3,5-DHPG did not alter these responses as compared with saline-treated control animals. Similarly, rats pretreated with 3,5-DHPG and then with Ang II did not exhibit any significant alterations of acquisition and consolidation of CARs as compared with saline-treated rats, whereas Ang II given alone had obvious positive effect in this paradigm.

Behavioral evidences obtained in our study suggest that the activation of class I mGluRs by both tested doses of 3,5-DHPG led to attenuation of facilitatory effects of Ang II on memory and learning. The mechanism responsible for this influence of 3,5-DHPG is unclear. It can be assumed that weaker effects of Ang II may be linked to an unspecific action of 3,5-DHPG on behavior such as increasing locomotor activity and enhancement of anxiety. Another possible explanation of the detrimental role of 3,5-DHPG in the facilitatory effect of Ang II is that pretraining injection of mGluR agonist may induce saturated activation of class I mGluR which in turn hinders further learning [22]. Also, it is necessary to take into consideration that mGluR activation induces hyperpolarization of basolateral amygdala neurons [20], which are critically involved in the memory-enhancing effect of Ang II in rats [30]. Similarly, 3,5-DHPG reduces transmission in hippocampal CA1 area [13], while the hippocampus plays potential role in the facilitation of memory by angiotensin [35]. Moreover, the stimulation of group I mGluR has been reported to decrease currents through voltage-dependent calcium channels [8,23], whereas in Ang II signal transduction pathways, these channels are activated [24, 28].

Although this mechanism appears plausible, the degree and nature of behavioral relationships between mGluRs and Ang II is at present unclear and requires further studies.

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## REFERENCES

1. Ader R., Weijnen J.A.W.M., Moleman P.: Retention of passive avoidance response as function of the intensity and duration of electric shock. *Psychonomic Sci.*, 1972, 26, 125–129.
2. Aiba A., Kano M., Chen C., Stanton M.E., Fox G.D., Herrup K., Zwingman T.A., Tonegawa S.: Deficient cerebellar long-term depression and impaired motor learning in mGluR1 mutant mice. *Cell*, 1994, 79, 377–388.
3. Baranowska D., Braszko J.J., Wiśniewski K.: Effect of angiotensin and vasopressin on acquisition and extinction of conditioned avoidance in rats. *Psychopharmacology*, 1983, 81, 247–251.
4. Bellin S.I., Bhatnager R.K., Johnson A.K.: Periventricular noradrenergic systems are critical for angiotensin-induced drinking and blood pressure response. *Brain Res.*, 1987, 403, 105–112.
5. Bianchin M., Da Silva R.C., Schmitz P.K., Medina J. H., Izquierdo I.: Memory of inhibitory avoidance in the rat is regulated by glutamate metabotropic receptors in the hippocampus. *Behav. Pharmacol.*, 1994, 5, 356–359.
6. Braszko J.J., Kułakowska A., Wiśniewski K.: Angiotensin II and its 3-7 fragment improve recognition but not spatial memory in rats. *Brain Res. Bull.*, 1995, 6, 627–631.
7. Braszko J.J., Wiśniewski K.: Effect of angiotensin II and saralasin on motor activity and the passive avoidance behavior of rats. *Peptides*, 1988, 9, 475–479.
8. Chavis P., Fagni L., Bockaert J., Lansman J.B.: Modulation of calcium channels by metabotropic glutamate receptors in cerebellar granule cells. *Neuropharmacology*, 1995, 34, 929–937.
9. Conn P.J., Pin J.P.: Pharmacology and functions of metabotropic glutamate receptors. *Annu. Rev. Pharmacol. Toxicol.*, 1997, 37, 205–237.
10. Conquet F., Bashir Z.I., Davies C.H., Daniel H., Ferraguti F., Bordi F., Franz-Bacon K., Reggiani A., Matarrese V., Conde F. et al.: Motor deficit and impairment of synaptic plasticity in mice lacking mGluR1. *Nature*, 1994, 372, 237–243.
11. Fitzsimmons J.T.: *The Physiology of Thirst and Sodium Appetite*. Cambridge University Press, Cambridge, 1979.
12. Ganten D., Marquez-Julio A., Granger P., Hayduk R., Karsunky K.P., Boucher R., Genest J.: Renin in dog brain. *Amer. J. Physiol.*, 1971, 221, 1733–1737.
13. Gereau R.W., Conn P.J.: Multiple presynaptic metabotropic glutamate receptors modulate excitatory and inhibitory synaptic transmission in hippocampal area CA1. *J. Neurosci.*, 1995, 15, 6879–6889.
14. Herman Z.Z.: *The effects of noradrenaline on rat's behaviour*. Psychopharmacologia (Berlin), 1970, 16, 369–374.
15. Hölscher C.H., Gigg J., O'Mara S.M.: Metabotropic glutamate receptor activation and blockade: their role

- in long-term potentiation, learning and neurotoxicity. *Neurosci. Biobehav. Rev.*, 1999, 23, 399–410.
16. Holy Z., Braszko J., Kupryszewski G., Witczuk B., Wiśniewski K.: Angiotensin II devoid of phenylalanine in position 8 has full psychotropic activity of the parent hormone. *J. Physiol. Pharmacol.*, 1992, 43, 183–192.
  17. Ito I., Kohda A., Tanabe S., Hirose E., Hayashi M., Mitsunaga S., Sugiyama H.: 3,5-Dihydroxyphenylglycine: a potent agonist of metabotropic glutamate receptors. *NeuroReport*, 1992, 3, 1013–1016.
  18. Mao L., Wang J.Q.: Motor stimulation following bilateral injection of the group-I metabotropic glutamate receptor agonist into the dorsal striatum of rats: evidence against dependence on ionotropic glutamate receptors. *Psychopharmacology*, 2000, 148, 367–373.
  19. Pellow S., Chopin P., Briley M.: Validation of open: closed arm entries in an elevated plus-maze as a measure of anxiety in the rat. *J. Neurosci. Meth.*, 1985, 14, 149–167.
  20. Rainnie D.G., Holmes K.H., Shinnick-Gallagher P.: Activation of postsynaptic metabotropic glutamate receptors by trans-ACPD hyperpolarizes neurons of the basolateral amygdala. *J. Neurosci.*, 1994, 14, 7208–7220.
  21. Riedel G., Reymann K.G.: Metabotropic glutamate receptors in hippocampal long-term potentiation and learning and memory. *Acta Physiol., Scand.*, 1996, 157, 1–19.
  22. Riedel G., Wetzell W., Reymann K.G.: Metabotropic glutamate receptors in spatial and nonspatial learning in rats studied by means of agonist and antagonist application. *Learn. Memory*, 1995, 2, 243–265.
  23. Sahara Y., Westbrook G.L.: Modulation of calcium currents by a metabotropic glutamate receptor involves fast and slow kinetic components in cultured hippocampal neurons. *J. Neurosci.*, 1993, 13, 3041–3050.
  24. Sayeski P.P., Ali M.S., Semeniuk D.J., Doan T.N., Bernstein K.E.: Angiotensin II signal transduction pathways. *Regul. Peptides*, 1998, 78, 19–29.
  25. Schoepp D.D., Conn P.J.: Metabotropic glutamate receptors in brain function and pathology. *Trends Pharmacol. Sci.*, 1993, 14, 13–20.
  26. Schoepp D.D., Goldsworthy J., Johnson B.G., Salhoff C.R., Baker S.R.: 3,5-Dihydroxyphenylglycine is a highly selective agonist for phosphoinositide-linked metabotropic glutamate receptors in the rat hippocampus. *J. Neurochem.*, 1994, 63, 769–772.
  27. Schoepp D.D., Johnson B.G., Monn J.A.: Inhibition of cyclic AMP formation by a selective metabotropic glutamate receptors agonist. *J. Neurochem.*, 1992, 58, 1184–1186.
  28. Summers C., Raizada M.K., Kang J., Lu D., Posner P.: Receptor mediated effects of angiotensin II on neurons. *Front. Neuroendocrinol.*, 1995, 15, 203–230.
  29. Tanabe Y., Masu M., Ishii T., Shigemoto R., Nakaniishi S.: A family of metabotropic glutamate receptors. *Neuron*, 1992, 8, 169–179.
  30. Winnicka M.M.: 6-OHDA bilateral lesions to the amygdala abolish the memory enhancing effect of angiotensin II in rats. *Pharmacol. Res.*, 1998, 38, 53–58.
  31. Wiśniewski K., Braszko J.J.: The significance of central monoamine systems in the angiotensin II (AII) improvement of learning. *Clin. Exp. Hypertension*, 1984 [A]6, 2127–2131.
  32. Wiśniewski K., Lutostańska A., Artemowicz B.: The role of NMDA receptors in the central action of angiotensin II. *Acta Physiol. Hung.*, 1996, 84, 347–348.
  33. Wright J.W., Harding J.W.: Brain angiotensin receptor subtypes in the control of physiological and behavioral responses. *Neurosci. Biobehav. Rev.*, 1994, 18, 21–53.
  34. Wright J.W., Krebs L.T., Stobb J.W., Harding J.W.: The angiotensin IV system: functional implications. *Front. Neuroendocrinol.*, 1995, 16, 23–52.
  35. Wright J.W., Miller-Wing A.V., Shaffer M.J., Higginson C., Wright D.E., Hanesworth J.M., Harding J.W.: Angiotensin II(3-8) [ANGIV] hippocampal binding: potential role in the facilitation of memory. *Brain Res. Bull.*, 1993, 32, 497–502.

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