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CGP 42112A abolishes facilitation of recognition caused by angiotensin II and angiotensin II(3-7) in rats

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Abstract. The role of the angiotensin AT_2 receptors in some behavioural effects of angiotensin II (Ang II) and its 3-7 fragment [Ang II(3-7)], using their selective antagonist CGP 42112A, was assessed. Ang II and Ang II(3-7), given intracerebroventricularly (icv) at the dose of 1 nmole each, substantially improved object recognition memory and enhanced apomorphine (1 mg/kg) stereotypy. Pre-treatment of rats with CGP 42112A (2 μg), *per se* ineffective in all tests, abolished activity of both peptides. None of the treatments significantly changed behaviour of rats in open field. The results point to the considerable involvement of the AT_2 angiotensin receptors in the improvement of recognition memory caused by Ang II and Ang II(3-7).

Key words: angiotensin II, angiotensin II(3-7), AT_2 receptors, CGP 42112A, recognition memory, rat

INTRODUCTION

The family of peptides called angiotensins is closely linked to the regulation of cardiovascular function and body water homeostasis (Wright et al. 1988, 1989). In addition to these well known actions, angiotensins, that is angiotensin II (Ang II), des Asp^1, angiotensin II (Ang III), des-Asp^1, des-Arg^2, angiotensin II (Ang IV), des-Asp^1, des-Arg^2, des-Phe^8, angiotensin II [Ang II(3-7)] possess interesting psychoactive properties. All of the above listed peptides given intracerebroventricularly (icv) at the dose of 1 nmole increase exploration, learning, and memory in rats (Baranowska et al. 1983, Yonkov et al. 1986, Braszko et al. 1987, Wright et al. 1993).

The angiotensin receptors have been classified into two main types, AT_1 and AT_2, based on ligand selectivity, signal transduction mechanism, and structural criteria (Bumpus et al. 1991, De Gasparo et al. 1995). The G-protein coupled AT_1 receptors (Bottari et al. 1993, Heemskerk and Saavedra 1994) are responsible for the well-known effects of Ang II, such as vasoconstriction, water intake, and hormone secretion (Fregly and Rowland 1991, Hogarty et al. 1992, Timmermans et al. 1993).

Physiological role of the AT_2 receptors is not well understood. These receptors, in the rat brain, are prominently distributed in the septum, thalamus, lateral habenula, basal ganglia, locus coeruleus, superior colliculi, amygdala, ventral tegmental area, and inferior olivary nucleus (Rowe et al. 1990, Leung et al. 1991, Song et al. 1992, Heemskerk and Saavedra 1995). They are most probably involved in the autoregulation of the cerebral blood flow, vascular growth and neurosecretion (Viswanathan et al. 1991, Janiak et al. 1992, Strömberg et al. 1992). Recently, AT_2 receptor has been cloned as a seven transmembrane-domain structure (Kambayashi et al. 1993, Mukoyama et al. 1993, Tsuzuki et al. 1994) and, most probably, also acts *via* G protein modulating phosphotyrosine phosphatase activity (Bottari et al. 1993, Kambayashi et al. 1994, Takahasi et al. 1994).

We have previously found that Ang II and Ang II(3-7), the shortest Ang II fragment having psychoactive properties (Braszko et al. 1991), facilitate recognition memory (Braszko et al. 1994, 1995). In this study we searched for the involvement of the angiotensin AT_2 receptors in recognition memory. Stereotypic behaviour was used to assess the influence of our treatments on the central dopaminergic system which has previously been shown to mediate, at least in part, the Ang II facilitation of learning and memory (Wiśniewski and Braszko 1984, Winnicka et al. 1988, Winnicka 1995). Since motor performance of animals is crucial in expressing of any cognitive effects we measured locomotor and exploratory effects of all treatments in open field.

METHODS

Subjects

Male Wistar rats of laboratory strain, weighing 160-180 g, were used. They were housed in plastic cages (50 x 40 x 20 cm) 8 animals per cage, in the temperature controlled room (22 °C) on a 12 h light-dark cycle beginning at 07.00. Food and water were freely accessible.

Procedure

Under light ether anaesthesia, a round piece of skin 7 mm in diameter was cut off the rat's head and the underlying skull surface was cleaned from the soft tissue. A 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 the bregma and the superior saggital suture on the right and left side of the head (Braszko et al. 1991). 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 ventricles with a 10 µl Hamilton syringe, using a removable KF 730 needle cut 4.5 mm from its base. 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 2 µl administered over 3 s. Upon completion of each experiment all rats were sacrificed and the sites of injections were verified microscopically after brain sectioning.

Ang II (Sigma) and Ang II(3-7) (Bachem) at the dose of 1 nmole each as well as CGP 42112A (Ciba-Geigy) at the dose of 2 µg (~ 1.5 nmole) were injected into the lateral cerebral ventricles as freshly prepared saline solutions. First injection was given to the left, and second, 5 min later, to the right cerebral ventricle. There were six groups receiving the following (left-right) injections: control (saline-saline), CGP (CGP 42112A-saline), Ang II (saline-Ang II), Ang II(3-7) [saline-Ang II(3-7)], CGP-Ang II (CGP 42112A-Ang II), CGP-Ang II(3-7) [CGP 42112A-Ang II(3-7)].

All behavioural studies were carried out in a quiet, diffusely lit room (25 W bulb, 2 m away from an animal, light-indirect) between 8.00 and 12.00 h with each group equally represented in the times of testing.

Object recognition was tested in the plastic box 62 cm long, 38 cm wide and 20 cm high covered with a wire mesh lid. The objects to be discriminated were made of glass or porcelain and existed in duplicate. Apparently they had no natural significance for rats and they have never been associated with reinforcement. Their weight was such that they could not be displaced by rats. The procedure was similar to that described by Ennaceur and Meliani (1992) and may be summarized as follows. All rats were submitted to two habituation sessions, with 1 h interval, whereby they were allowed for 3 min exploration of the apparatus. Twenty four hours later testing began. The experimental session consisted of two trials, each lasting for 3 min. In the first trial (T1), rats were exposed to two identical objects A_1 and A_2. Immediately post-trial animals were injected icv with appropriate solutions. In the second trial (T2), performed 60 min later, rats were exposed to two objects, one of which was a duplicate of the familiar object A (A'), in order to avoid olfactory traits, and a new object B. From rat to rat, the role (familiar or new object) as well as the relative position of the two objects were counterbalanced and randomly permuted during the trial T2. These precautions were taken in order to reduce object and place preference effects. The basic measure was the time spent by rat in exploring objects during the trials T1 and T2. Exploration of an object was defined as touching it with the nose. Turning around or sitting on the object was not considered as the exploratory behaviour. From this measure the following variables were defined: A, the time spent in exploring objects A_1 and A_2 in T1; A' and B, the times spent in exploring respectively, the duplicate of familiar, and the new object in T2. Object recognition was measured by the variable B - A', and total exploration in T2 by B + A'. Moreover as B - A' may be biased by the differences in overall levels of exploration, the variable B - A' / B + A' was also computed.

Immediately after object recognition test locomotor exploratory behaviour was assessed in open field which was a 100 x 100 cm white floor square divided by 8 lines into 25 equal squares and surrounded by 47 cm high wall (Braszko et al. 1987). Four plastic bars, 20 cm high, designed as objects of possible animals' interest were fixed perpendicularly, i.e. parallel to each other, in 4 line crossings in the central area of the floor. Each rat was placed in the center of the floor and following 1 min of adaptation, crossings, rearings and bar approaches were counted manually for 5 min.

Stereotypy was evaluated according to the scale described by Kennedy and Zigmond (1979): -1, quiet or asleep; 0, normal activity; 1, occasional non-directed sniffing; 2, continuous sniffing; 3, continuous sniffing on a restricted area of the cage floor; 4, as for 3 but with occasional licking; 5, continuous licking; 6, continuous licking with occasional biting; 7, continuous biting. Stereotyped behaviour was produced by an intraperitoneal injection of 1 mg/kg of apomorphine hydrochloride (Sigma) dissolved in 0.9% NaCl solution and given in a volume of 1 ml/kg immediately after second icv injection.

The results of the experiments were evaluated by analysis of variance (ANOVA) followed by Bonferroni's 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. All ratings of stereotyped behaviour for one rat were summed-up first and overall group means were then calculated.

RESULTS

Object recognition

The time spent in exploring objects A_1 and A_2 in T1 (variable A) was comparable in all groups (Table I). Object recognition memory measured by the difference B - A' was significantly different between the groups. ANOVA yielded $F_{5,62} = 5.022$, $P<0.001$. Further post hoc comparisons made with Bonferronis test revealed a significantly better object recognition memory in rats treated with Ang II and Ang II(3-7) as compared with the saline injected control group ($P<0.01$). CGP 42112A significantly attenuated facilitating recognition memory effect of Ang II and its 3-7 fragment ($P<0.05$). Noteworthy, changes of the variable B - A' / B + A' in different groups were in the same direction as changes of the variable B - A'. This shows that object recognition scores were not biased by the differences in overall levels of exploration.

Open field

None of the applied treatments changed spontaneous locomotor and exploratory activity of rats in the open

TABLE I

Object recognition

Variables	Treatment					
	Saline	CGP	Ang II	Ang II (3-7)	CGP + Ang II	CGP + Ang II (3-7)
B-A'	-0.18 (0.63)	-0.08 (0.50)	3.64** (0.78)	3.10** (0.66)	0.83# (0.86)	0.75# (0.78)
A	19.27 (3.18)	20.33 (2.18)	17.18 (2.72)	16.05 (1.64)	19.75 (1.80)	19.17 (1.57)
B+A'	5.45 (0.98)	10.25* (1.65)	12.55* (2.31)	14.10** (1.53)	9.00 (1.42)	9.25 (1.33)
B-A'/B+A'	0.00 (0.17)	-0.03 (0.07)	0.36 (0.03)	0.20 (0.01)	0.06 (0.15)	0.04 (0.08)

The rats were given 2 μg of CGP 42112A (CGP) or saline placebo to the left lateral cerebral ventricle, then 5 min later 1 nmole of Ang II, 1 nmole of Ang II(3-7) or saline placebo to the right ventricle. For further details see text. Variables (in seconds) describe object recognition (see text). Values are means (SE in parentheses) obtained from 10-12 subjects. *$P<0.05$, **$P<0.01$ as compared with saline group, #$P<0.05$ as compared with Ang II and Ang II(3-7) group, respectively (ANOVA and Bonferroni's test).

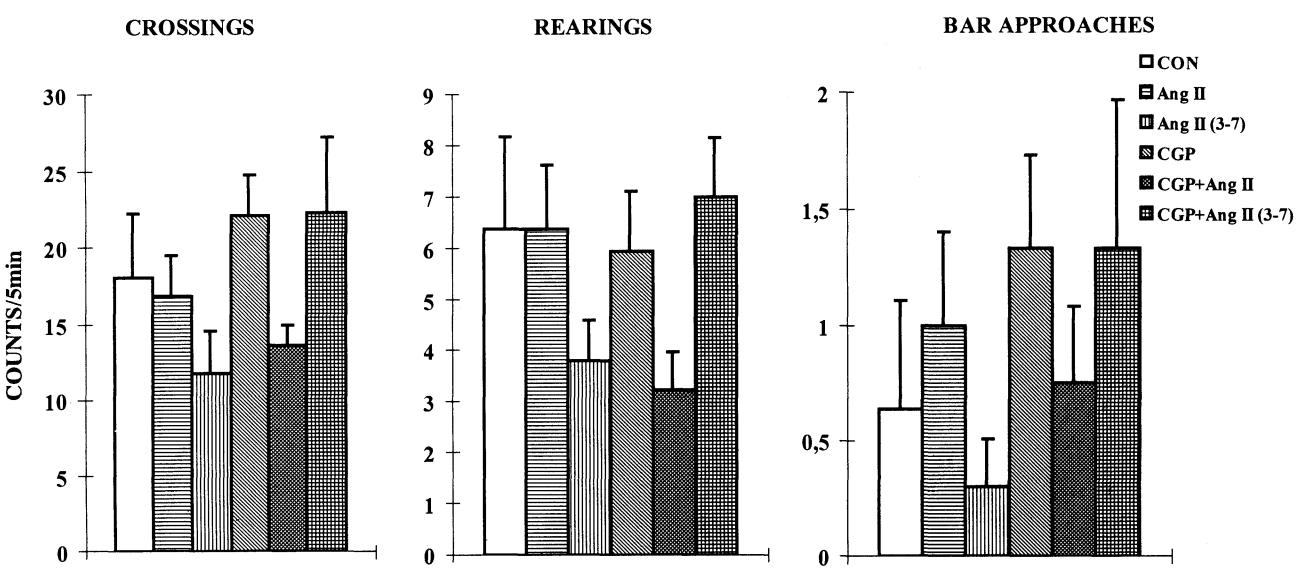

Fig. 1. Number of crossings, rearings and bar approaches in open field measured immediately after object recognition test and about 64 min after the following left-right (separated by 5 min) icv injections: saline-saline (CON), CGP 42112A-saline (CGP), saline-Ang II (Ang II), saline-Ang II(3-7) [Ang II(3-7)], CGP 42112A-Ang II (CGP+Ang II), CGP 42112A- Ang II(3-7) [CGP+Ang II(3-7)]. Columns represent means ± SEM of the values obtained from 10-12 subjects.

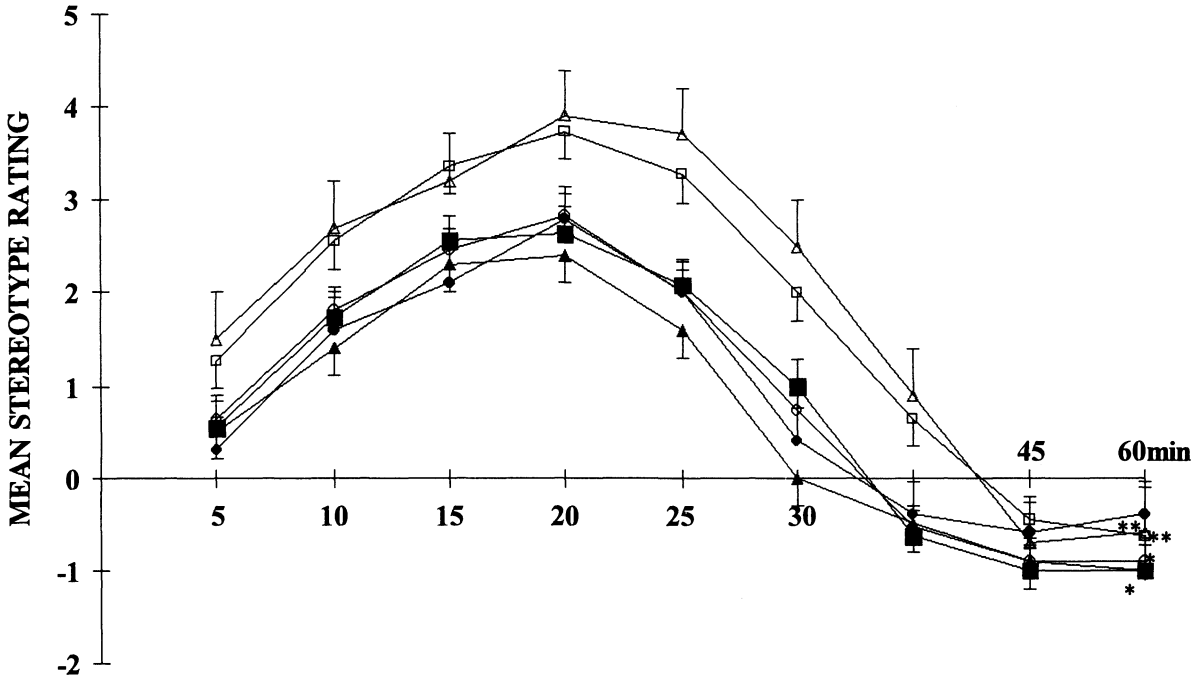

Fig. 2. Apomorphine induced (1 mg/kg, ip) stereotypy behaviour evaluated after the following left-right (separated by 5 min) icv injections: saline-saline (O), CGP 42112A-saline (●), saline-Ang II (△), saline-Ang II(3-7) (□), CGP 42112A-Ang II (▲), CGP 42112A-Ang II(3-7) (■). Columns represent means ± SEM of the values obtained from 10-11 subjects. Overall group means were statistically evaluated. $^{**}P<0.01$ vs. control group, $^{*}P<0.05$ vs. Ang II and Ang II(3-7) groups, respectively.

field estimated immediately after the object recognition test. The differences in number of crossings, rearings, and bar approaches were small and insignificant (Fig. 1).

Stereotypy behaviour

For cumulative ratings of apomorphine stereotypy (Fig. 2) ANOVA yielded $F_{5,57} = 7.12$, $P<0.0001$. A subsequent analysis of differences between the particular groups with the Bonferroni's test revealed significantly more intense stereotypy in both peptide-treated groups than in the saline-treated control group of rats ($P<0.01$). Blockade of AT_2 receptors with CGP 42112A had not influence on apomorphine stereotypy. CGP 42112A, given before angiotensins totally abolished enhancing stereotypy effect of both peptides. The stereotypic behaviour of both groups pretreated with CGP 42112A then injected with angiotensins did not differ from saline injected control group of rats.

DISCUSSION

The present results point to the involvement of the AT_2 angiotensin receptors in the memory enhancing effect of angiotensins. They also confirm our recent findings (Braszko et al. 1995, Winnicka 1995, Braszko 1996, Winnicka and Braszko - in press) of the improvement of recognition memory after icv application of Ang II and Ang II(3-7).

The animals injected with both angiotensins explored novel, previously absent from the familiar environment, object about 3 times longer. CGP 42112A, an antagonist of AT_2 receptors, when injected icv, had no influence on the recognition of objects. The animals injected with CGP 42112A performed similarly to these injected with saline. However, pretreatment with CGP 42112A significantly attenuated beneficial effect of both angiotensin peptides on recognition memory.

As all cognitive effects have to be expressed by motor activity, the influence of applied treatments on the spontaneous locomotor and exploratory activity in open field was evaluated. No significant differences in crossings of squares, rearings and bar approaches between control and experimental groups were found. CGP 42112A which itself tended to enhance bar approaches, given before Ang II(3-7) also enhanced exploratory activity (rearings and bar approaches) lowered by the peptide. Overall, there were no statistically significant changes in

locomotor activity, making influence of motor performance on the results of cognitive tests almost improbable.

Although CGP 42112A did not influence apomorphine stereotypy itself, it totally abolished stereotypy enhancing effect of both angiotensins. It has been found previously that in expression of cognitive properties of Ang II dopaminergic system is involved. (Wiśniewski and Braszko 1984). Moreover, 6-OHDA lesions to the dopaminergic afferents in the central amygdala abolished beneficial effect of Ang II and Ang II(3-7) on recognition memory (Winnicka 1995, Winnicka and Braszko - in press).

Also, there is extensive evidence that brain renin-angiotensin system exerts some of its physiological roles *via* dopaminergic pathways (Fitzsimons and Setler 1975, Ganten et al. 1978, Reich 1984). Huang and Malvin (1988) proposed the hypothesis that angiotensinergic neuron may be proximal to the dopaminergic one. Accordingly, an inhibition of dopaminergic neurons would prevent the physiological response to Ang II. Although until now there is no evidence of AT_2 receptors located on dopamine neurones, our recent study (Winnicka and Braszko - in press) strongly suggests such a possibility. In this study we found that the bilateral removal of dopaminergic endings from the central amygdala attenuated facilitatory effect of Ang II and Ang II(3-7) on recognition memory. Considering the present results it seems possible that CGP 42112A blockade of AT_2 receptors in caudate-putamen inhibited angiotensins stimulatory effect on apomorphine stereotypy. Also, this mechanism in central amygdala could account for the attenuation of the peptides' beneficial effect on cognitive processes. Moreover, dopamine has recently been found to be necessary for the visual recognition (Hori et al. 1993).

Ang II(3-7) is one of the most effective agonist of AT_4 angiotensin receptors, described by Wright's group (Harding et al. 1992, Wright and Harding 1994). They are supposed to be almost exclusively responsible for learning and memory (Wright et al. 1993). The distribution of AT_4 receptors (high concentration in ventral tegmental area, cerebral cortex and also, however in lower concentration, in amygdala) (Wright and Harding 1995) suggests the possibility of complementary involvement of these receptors in facilitatory effect of angiotensins on recognition memory.

In conclusion, it appears that AT_2 angiotensin receptors are substantially engaged in the effects of Ang II and Ang II(3-7) in recognition memory. The distribution of these receptors in the brain areas related to sensory function (Rowe et al. 1990, Leung et al. 1991) seems to support this hypothesis.

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