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Dopaminergic Projection to the Nucleus Accumbens Mediates the Memory-Enhancing Effect of Angiotensins in Rats

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WINNICKA, M. M. *Dopaminergic projection to the nucleus accumbens mediates the memory-enhancing effect of angiotensins in rats.* PHARMACOL BIOCHEM BEHAV **62**(4) 625–630, 1999.—It has been shown that the facilitatory effect of angiotensin II (AII) and its 3–7 fragment [AII(3–7)] on cognitive processes is mediated by the dopaminergic system. In the present study, the involvement of dopaminergic projection to the nucleus accumbens (NAS) and to the nucleus septi lateralis (NSL) in the expression of the positive effect of AII and AII(3–7) on the retrieval of passive avoidance after bilateral 6-OHDA induced lesions to NAS and NSL was evaluated. To protect noradrenergic neurons from destruction by neurotoxin, rats were pretreated intraperitoneally with 25 mg/kg of desmethylimipramine, an inhibitor of noradrenaline uptake, 30 min before surgery. Both peptides were given intracerebroventricularly, at the dose of 1 nmol each, 15 min before the retention testing. Bilateral 6-OHDA lesions to NAS totally abolished, and to NSL did not affect, the positive effect of angiotensins on recall of information in a passive avoidance situation. Moreover, bilateral 6-OHDA lesions to NAS but not to NSL significantly attenuated the locomotor activity of rats in an open-field test. Nevertheless, it had no essential significance on the evaluation of the influence of the disruption of the dopaminergic endings in both structures on the facilitatory effect of angiotensins on retrieval process. These results suggest that the dopaminergic projection to NAS, but not to NSL is involved in the expression of the facilitatory effect of AII and AII(3–7) on memory motivated affectively evaluated in a passive avoidance situation. © 1999 Elsevier Science Inc.

Angiotensin II Angiotensin II(3–7) Nucleus accumbens Nucleus septi lateralis 6-OHDA lesions Passive avoidance Locomotor activity Rats

THE presence of a separate renin–angiotensin system within the mammalian brain complete with the precursors and enzymes necessary for the formation and deactivation of the physiologically active forms of angiotensin was supported in many investigations (8,10–12). In view of the presence of angiotensin II (AII)-immunoreactive neurons in distinct brain areas, including the mesolimbic system, and wide distribution of AII-immunoreactive fibers within all levels of the brain (21), it has been proposed that this peptide plays a neurotransmitter role in the central nervous system.

The increasing evidence supports the involvement of AII in cognitive processes. In 1973, Graeff et al. (13) reported enhancement of lever-pressing behavior after intraseptal application of AII in water-deprived rats. Braszko and co-workers in numerous experiments (4–6) have demonstrated that intracerebroventricular (ICV) administration of 1 nmol of AII and its fragments facilitated acquisition in active conditioning trials and retention in a passive avoidance situation. According to Braszko et al. (6) the 3–7 fragment of AII [AII(3–7)] appears to be the shortest molecule possessing psychotropic activity comparable to AII, and is devoid of the pressor activity evidence by the parent hormone. Also, Wright et al. (40) have shown that the 3–8 fragment of AII (AIV) at the ICV dose of 1 nmol improved recall in a step-through passive avoidance task. The latter authors suggest that facilitatory effect of angiotensin peptides is connected with the recently discovered AT_4 receptor subtype, which preferentially binds AII(3–8) and AII(3–7) (26). Recently, Braszko et al. (3) reported that AII and its 3–7 fragment improved also recognition, but not spatial memory in rats.

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There is support for the notion that the brain renin–angiotensin system exerts some of its physiological roles via brain dopaminergic pathways, i.e., release of certain hormones (22,24,29), regulation of body temperature (14), and drinking responses to AII (9). In our laboratory it also has been found that the facilitatory effect of AII on memory appears to be mediated by central monoamine systems, because it can be abolished by pimozide, a dopaminergic receptor antagonist, and attenuated by phentolamine, an α-adrenergic receptor antagonist (38). Moreover, bilateral 6-OHDA–induced lesions of dopaminergic projection to the central amygdala abolished the facilitatory effect of AII and AII(3–7) on the retrieval of information in a passive avoidance situation (32,37) and on the recognition memory (33), and bilateral destruction of dopaminergic endings in the CA4 field of the hippocampus attenuated the facilitatory effect of both angiotensins on the retrieval process of a passive avoidance behavior (35,37). Recently, we have found that dopaminergic projection to the nucleus accumbens (NAS) is involved in the expression of the improving effect of angiotensin peptides on recognition memory in rats (36).

As in our earlier study (34) NAS-lesioned rats stayed on the illuminated platform, in a step-through passive avoidance situation, much longer than sham-operated controls, the contribution of dopaminergic projection to this structure in the facilitatory effect of AII in this test was impossible for the evaluation. Because Ader et al. (1) have argued that the time spent by rats on the platform is directly proportional to the intensity and duration of the stimulus, a weaker stimulus (0.25 instead of 0.5 mA) was used in the present study.

Therefore, in the present study the involvement of the dopaminergic projection to NAS and to the nucleus septi lateralis (NSL) in the facilitatory effect of AII and AII(3–7) on retrieval of information in a passive avoidance situation was evaluated in rats.

METHOD

Animals

Male Wistar rats, after 5 days of acclimatization to the laboratory conditions, were used. On the day of surgery 7-week-old rats weighed 160–165 g, and 10 days later at the time of behavioral testing they weighed 180–185 g. The rats were housed in plastic cages (50 × 40 × 20 cm), eight animals per cage, in the temperature-controlled room (22°C) with a 12 L:12 D cycle beginning at 0700 h. Food and water were freely accessible.

Surgery

The rats were anesthetized with chloral hydrate, and were placed in a Kopf stereotaxic apparatus with tooth bar 5 mm above the interaural line. The skull was exposed, and burr holes 1.5 mm in diameter were drilled above the appropriate coordinate targets. The coordinates (in mm), anterior (A) from the bregma, lateral (L) to the midline, and below (V) the skull surface were selected with the aid of the atlas of König and Klippel (17) at A: 3.0, L: 1.0, and V: 6.7 for NAS, and at A: 1.5, L: 0.7, and V: 5.5 for NSL, respectively. Each site was infused with 1 μl of 0.9% NaCl containing 8 μg of 6-OHDA (6-Hydroxydopamine Hydrochloride, Sigma, St. Louis, MO). The neurotoxin was dissolved in a vehicle solution containing 5 mg/ml of ascorbic acid, to prevent oxidation of 6-OHDA, and injected over 10 min through a stainless steel cannula (o.d. = 0.3 mm) at the rate of 0.1 μl/min. The cannula was left in place for an additional 5 min after the end of the infusion. Twenty-eight randomly selected rats received 6-OHDA to NAS and 28 to NSL; the remaining 26 and 28 sham-operated control rats underwent the same procedure except that they received only the vehicle solution to NAS and NSL, respectively. Thirty minutes before surgery rats were pretreated with an intraperitoneal injection of 25 mg/kg of desmethylimipramine (Desipramine Hydrochloride, Sigma, St. Louis, MO), an inhibitor of norepinephrine (NE) uptake, which has been shown to protect NE neurons from destruction by 6-OHDA (7). After 6-OHDA infusions, an additional burr hole, 0.5 mm in diameter, was drilled into each rat's skull 2.5 mm laterally and 1 mm caudally from the point of intersection of the bregma and the superior sagittal suture on the right side of head for the ICV injection. Behavioral testing started after a 10-day recovery period. AII (Angiotensin II, free base Sigma) and AII(3–7) (Angiotensin II fragment 3–7, free base, Sigma), dissolved in 5 μl of 0.9% NaCl were given ICV in a dose of 1 nmol per rat each, 15 min before the recall testing in a passive avoidance situation. The ICV injections were made manually into the right ventricle with a Hamilton syringe, using a removable KF 730 needle 4.5 mm long, according to the technique described earlier (6). NaCl (0.9%) received nine lesioned to NAS and nine lesioned to NSL rats; eight and nine sham-operated to NAS and to NSL rats, respectively. All groups of rats injected with AII lesioned and sham-operated to NAS and to NSL consisted of nine rats. AII(3–7) was injected into 10 lesioned to NAS and NSL rats and to 9 and 10 sham-operated to NAS and NSL rats, respectively.

Behavioral Tests

Passive avoidance. Passive avoidance performance was studied in a one learning trial, step-through passive avoidance situation (1), which utilizes the natural preference of rats for a dark environment. The apparatus consisted of an illuminated platform attached to a large dark compartment. After a 2-min habituation in the dark, the rats were placed on the platform and were allowed to enter the naturally preferred dark compartment. Two more trials, with a 2-min interval, were given on the following day. At the end of the second trial, an inescapable scrambled electric footshock (0.25 mA for 3 s) was delivered through the grid floor of the dark compartment. Retention of a passive avoidance behavior was tested 24 h after the single learning trial by measuring the latency to reenter the dark compartment up to a maximum of 300 s.

Locomotor and exploratory activity. Locomotor (crossings of squares) and exploratory (rearings, bar approaches) activity was measured in an open field, which was a square 100 × 100 cm white floor divided by eight lines into 25 equal squares and surrounded by a 47-cm high wall. Four plastic bars, 20 cm high, were designed as objects of possible interest of the animals and fixed perpendicularly parallel to each other in four line crossings in the central area of the floor. Following 1 min of adaptation crossings of squares, rearings and bar approaches were counted manually for 10 min. The bar approach was considered when the rat directed its head toward the bar, approached, and touched it with the nose. The open-field test was carried out immediately after testing retention in a passive avoidance situation.

Histology

Placement of the cannula was examined histologically. At the end of behavioral testing, the rats were killed and the brains were removed and fixed in 10% formaldehyde for 7

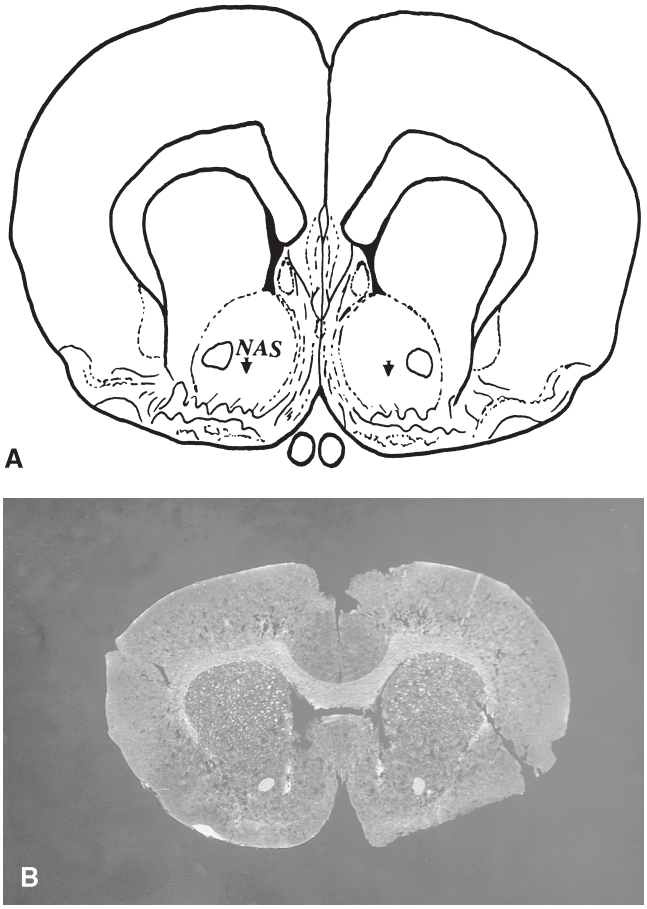

FIG. 1. Typical localization of the tip of the cannula of 6-OHDA infusions into the nucleus accumbens (NAS): (A) line drawing (arrows); (B) photomicrograph.

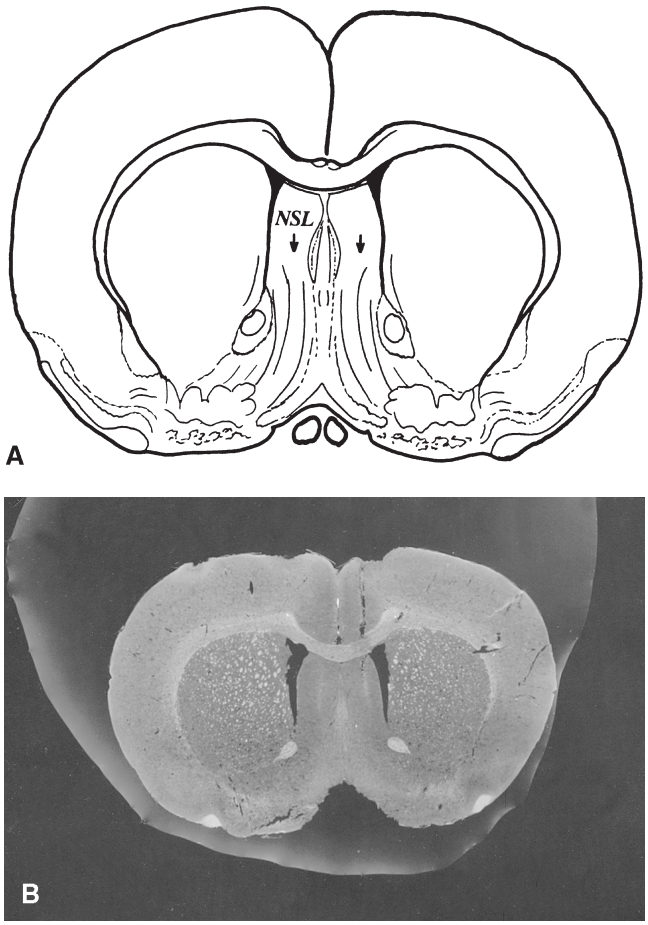

FIG. 2. Typical localization of the tip of the cannula of 6-OHDA infusions into the nucleus septi lateralis (NSL): (A) line drawing (arrows); (B) photomicrograph.

days. Subsequently, coronal sections (20 μm thick) of the cannula tract were cut using the frozen sectioning method, saving every fifth section through the lesion, mounted on slides, and stained with cresyl violet. Rats in which the cannula tip was located outside the center of target structure, and those with incorrect ICV injections were excluded from the experimental data. According to Agid et al. (2), the location of the tip of the cannula is particularly critical for reproducibility of the decrease in dopamine levels in lesioned structures. After infusion of 1 μl of 6-OHDA distribution of neurotoxin has a spherical shape with the diameter 3.0 mm. Typical localization of the tip of the cannula into NAS and NSL is shown on Fig. 1A and B and Fig. 2A and B, respectively.

Statistical Analysis

The results of the experiments were evaluated by two-way analysis of variance (ANOVA) followed by the Newman–Keuls test. *F*-ratios, degrees of freedom, and *p*-values are reported only for significant differences. In all comparisons between groups a probability of 0.05 or less was considered significant.

RESULTS

In the final analysis, 24 lesioned and 24 sham-operated to NAS, and 25 lesioned as well as sham-operated to NSL animals were included. Lesioned and sham-operated to NSL groups of rats injected with saline and AII consisted of nine rats; all the remaining groups consisted of eight rats.

The Effect of AII and AII(3–7) on Retrieval of Passive Avoidance After Bilateral 6-OHDA Lesions to NAS and to NSL (Fig. 3)

Bilateral 6-OHDA–induced lesions to NAS totally abolished the facilitatory effect of AII and AII(3–7) given 15 min before the retention testing in a step-through passive avoidance situation. The stimulating performance effect of AII and AII(3–7) was fully preserved in the sham-operated groups of rats. ANOVA of three lesioned and three sham-operated groups of rats, injected ICV with angiotensins or saline, yielded, $F(5, 42) = 157.44$, $p < 0.001$. Further post hoc comparisons between these groups, made with the Newman–Keuls test, revealed significant increase of the mean step-through latency in the sham-operated groups of rats injected with AII or AII(3–7) compared with all other groups. However, rats lesioned to NAS, injected ICV with saline, stayed almost twice the amount of time on the illuminated platform than lesioned subjects; this difference was insignificant. Lesioned to NAS rats injected ICV with AII or AII(3–7) spent the same time on the illuminated platform as lesioned saline-

injected animals. Only the sham-operated rats injected with AII or AII(3–7) stayed on the illuminated platform significantly longer than all the other groups; more than eight times longer than sham-operated animals injected with saline.

Bilateral 6-OHDA lesions to NSL did not affect the facilitatory effect of angiotensin peptides on the retrieval process in a passive avoidance situation. Again, the facilitatory effect of AII and AII(3–7) was fully preserved in the sham-operated groups of rats. ANOVA of three lesioned and three sham-operated groups of rats injected ICV with AII, AII(3–7) or saline yielded, $F(5, 44) = 66.25$, $p < 0.001$. Post hoc analysis made with the Newman–Keuls test showed that both sham-operated and lesioned rats injected ICV with AII or AII(3–7) performed significantly better than the respective sham-operated and lesioned rats injected ICV with saline.

The Effect of 6-OHDA Bilateral Lesions to NAS and NSL on Locomotor and Exploratory Activity of Rats (Table 1)

The spontaneous locomotor activity, measured by crossings of squares, was significantly ($p < 0.05$) decreased in NAS-lesioned rats but not following the NSL lesion. The exploratory activity (rearings, and bar approaches) of both lesioned to NAS and to NSL rats was comparable with exploratory activity of respective sham-operated control groups. There were no differences in locomotor and exploratory activity between angiotensins and saline-treated subgroups, both in lesioned and sham-operated to NAS and to NSL groups of rats.

TABLE 1

EFFECT OF BILATERAL 6-OHDA LESIONS TO THE NUCLEUS ACCUMBENS (NAS) AND TO THE NUCLEUS SEPTI LATERALIS (NSL) ON THE LOCOMOTOR ACTIVITY OF RATS IN "OPEN FIELD" TEST.

	Number of Counts		
Group	Crossings	Rearings	Bar approaches
Sham-operated to NAS			
Injected with 0.9% NaCl	36.24 (4.95)*	9.25 (1.35)	5.04 (0.93)
Injected with AII	38.12 (6.23)*	10.02 (1.52)	6.11 (0.92)
Injected with AII (3-7)	34.93 (4.28)*	8.96 (1.27)	4.60 (0.73)
Lesioned to NAS			
Injected with 0.9% NaCl	15.82 (2.78)	9.98 (1.03)	3.43 (0.68)
Injected with AII	15.78 (2.65)	9.27 (1.11)	5.64 (0.82)
Injected with AII (3-7)	14.24 (1.89)	6.43 (0.80)	3.77 (0.69)
Sham-operated to NSL			
Injected with 0.9% NaCl	41.26 (7.34)	13.70 (2.05)	7.34 (1.02)
Injected with AII	38.91 (5.97)	10.38 (1.86)	7.45 (0.97)
Injected with AII (3-7)	39.17 (5.74)	9.19 (1.67)	5.49 (0.83)
Lesioned to NSL			
Injected with 0.9% NaCl	32.46 (4.62)	9.22 (1.41)	5.99 (0.48)
Injected with AII	33.02 (4.66)	10.76 (1.39)	5.92 (0.60)
Injected with AII (3-7)	35.20 (5.33)	11.28 (1.82)	6.75 (0.63)

Values are means from 8-9 rats, ± SEM in parentheses. *$p < 0.05$ vs. number of crossings in all lesioned to NAS groups of rats. (ANOVA and Newman-Keuls test).

DISCUSSION

The present results point to the involvement of a dopaminergic projection to NAS, but not to NSL, in the expression of the facilitatory effect of AII and its 3–7 fragment on the retrieval process in a passive avoidance situation.

Because motor performance of animals is essential for expressing memory, their locomotor and exploratory activity was measured in an "open-field" test. Bilateral removal of dopaminergic endings from NAS but not from NSL significantly attenuated the locomotor activity of rats measured by the number of the crossings of squares. No significant group differences were observed in the number of the crossings, rearings, and bar approaches after bilateral destruction of dopaminergic endings in both structures.

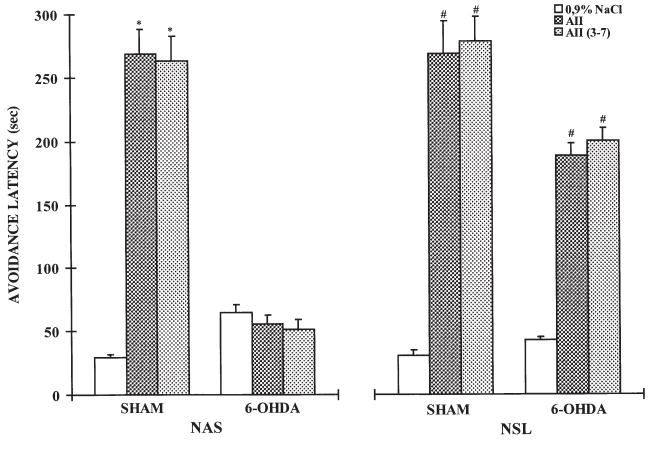

FIG. 3. Effect of AII and AII (3-7) (1 nmol ICV each) given 15 min before the retention testing in a passive avoidance situation, after bilateral 6-OHDA lesions to the nucleus accumbens (NAS) and to the nucleus septi lateralis (NSL). Columns represent means ± SEM of the values obtained from eight to nine rats, *$p < 0.01$, vs. sham-operated to NAS saline, and lesioned to NAS saline, AII, and AII(3-7)-injected groups of rats, #$p < 0.01$ vs. sham-operated to NSL and lesioned to NSL saline-injected gorups of rats (ANOVA and Newman-Keuls test).

In our previous (34) and also in the present study, rats injected with saline and bearing NAS lesions stayed on the illuminated platform longer than saline-injected sham-operated controls. It was probably due to attenuation of locomotor activity after removal of dopaminergic endings from this structure, even though in the present study injected ICV with saline lesioned to NAS rats stayed on the illuminated platform twice as long as the sham-operated controls. Owing to the weaker stimulus delivered in the dark compartment, they spent a shorter time on the platform than lesioned to NAS animals in our previous investigation (34), so the effect of angiotensin peptides on retrieval of information was possible for the evaluation. The facilitatory effect of both angiotensins was fully preserved in sham-operated groups, but totally abolished in lesioned to NAS groups of rats.

Bilateral 6-OHDA lesions to NSL did not affect the facilitatory effect of AII and its 3–7 fragment on retrieval of a passive avoidance behavior. Both the sham-operated and the lesioned groups of rats injected with angiotensin peptides stayed on the platform significantly longer than respective saline-injected controls. This effect was comparable with the results obtained in our previous study (32), in which lesioned rats were not pretreated with desmethylimipramine to protect NE endings against destruction by neurotoxin (7). This may indicate that noradrenergic projection to this structure had no significance in the expression of cognitive properties by AII.

The importance of the mesolimbic and mesothelencephalic dopaminergic pathways in cognitive processes and other behavioral functions, such as attention and arousal, was demonstrated by Kovács et al. (18) and by Robbins and Everitt (25).

According to Kesner et al. (16), a key structure for memory motivated effectively appears to be the central amygdala. We have previously found that dopaminergic projection to this structure is involved in the expression of the facilitatory effect of AII and AII (3–7) on emotional memory evaluated in a passive avoidance situation (32,37) and on recognition memory (33). Simon et al. (28), based on a number of investigations (15,27,30,31), hypothesized that dopaminergic neurons do not have a specific role in the control of behavior, but rather facilitate the function of various forebrain structures. They suggest that the various dopaminergic pathways act in a coordinated manner, and that there are interregulations between them. It has been shown that such interregulation exist between the amygdala, NAS, and the prefrontal cortex. Dopaminergic receptor blockade and the facilitation of dopaminergic transmission in amygdala was followed by an increase, and respectively reduction, in the DOPAC peaks in NAS (23,28). Moreover, lesions of dopaminergic terminals in the amygdala reduced dopaminergic activity in the prefrontal cortex. This interregulation was confirmed by the presence of direct anatomical connections from the amygdala to the NAS (20) and to the prefrontal cortex (19). The existence of dopaminergic interregulation between the amygdala and NAS also suggests that manipulations in NAS dopamine may lead to the changes in dopaminergic activity in the amygdala.

Accumulating evidence indicates that AII exerts some of its activity like the stimulation of certain hormones release (22,24,29), the regulation of body temperature (14), and fluids balance (9) via the dopaminergic system. In our laboratory it has also been found that facilitating the cognitive processes of AII activity is, in part, mediated by the dopaminergic system (32–38). Huang and Malvin (14) hypothesizes that angiotensinergic neurons may be proximal to the dopaminergic one.

It seems to be possible that angiotensin peptides facilitate the flow of information evoking general arousal in which dopaminergic pathways are involved. The results obtained in the present study indicate that dopaminergic projection to NAS, but not to the NSL, is involved in this circuit. Because the blockade of AT_4 angiotensin receptors abolishes the facilitatory effect of AIV on cognitive processes (40), it seems to be possible that angiotensin peptides may facilitate cognitive processes by an influence on dopaminergic transmission, via the AT_4 angiotensinergic receptors in NAS, present in a high density in this structure (39). The present and the other studies (3,5–7,40) point that AII, AIII, AIV, and AII(3–7), administered at the ICV dose of 1 nmol, have very similar cognition-enhancing properties. Therefore, most probably, they all affect the common receptor site (AT_4) after being metabolized (AII and AIII) to AIV and AII(3–7).

ACKNOWLEDGEMENTS

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REFERENCES

1. Ader, R.; Weijnen, J. A. W. M.; Moleman, P.: Retention of a passive avoidance responses as a function of the intensity and duration of electric shock. Psychon. Sci. 26:125–130; 1972.
2. Agid, Y.; Javoy, F.; Glowinski, J.; Bouvet, D.; Sotelo, C.: Injection of 6-hydroxydopamine into the substantia nigra of the rat. II. Diffusion and specificity. Brain Res. 58:291–301; 1973.
3. 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. 37: 627–631; 1995.
4. Braszko, J. J.; Kupryszewski, G.; Witczuk, B.; Wiśniewski, K.: Angiotensin II-(3–8)-hexapeptide affects motor activity, performance of passive avoidance and conditioned avoidance response in rats. Neuroscience 3:777–783; 1988.
5. Braszko, J. J.; Wiśniewski, K.: Effect of angiotensin II and saralasin on motor activity and the passive avoidance behavior of rats. Peptides 9:475– 479; 1988.
6. Braszko, J. J.; Własienko, J.; Koziołkiewicz, W.; Janecka, A.; Wiśniewski, K.: The 3–7 fragment of angiotensin II is probably responsible for its psychoactive properties. Brain Res. 542:49–54; 1991.
7. Breese, G. R.; Traylor, T. D.: Depletion of brain noradrenaline and dopamine by 6-hydroxydopamine. Br. J. Pharmacol. 42:88–89; 1971.
8. Fisher-Ferraro, C.; Nahmod, V. E.; Goldstein, D. J.; Finkielman, S.: Angiotensin and renin in the rat and dog brain. J. Exp. Med. 133:353–361; 1971.
9. Fitzsimons, J. T.; Setler, P. E.: The relative importance of central nervous catecholaminergic and cholinergic mechanism in drinking in response to angiotensin and other thirst stimuli. J. Physiol. 250:613–631; 1975.
10. Ganten, D.; Fuxe, K.; Phillips, M. I.; Mann, J. F. E.; Ganten, U.: The brain isorenin–angiotensin system: Biochemistry, localization, and possible role in drinking and blood pressure regulation. In: Ganong, D.; Martini, L., eds. Frontiers in neuroendocrinology, vol. 5. New York: Raven Press; 1978:61–99.
11. Ganten, D.; Hermann, K.; Bayer, C.; Unger, T.; Lang, R. E.: Angiotensin synthesis in the brain and increased turnover in hypertensive rats. Science 221:869–871; 1983.
12. Ganten, D.; Minnich, J. E.; Granger, P.; Hayduk, K.; Brecht, H. M.; Barbeau, A.; Boucher, R.; Genest, J.: Angiotensin-forming enzyme in brain tissue. Science 173:64–65; 1971.
13. Graeff, F. G.; Gentil, C. G.; Peres, V. L.; Corian, M. R.: Lever-pressing behavior caused by intraseptal angiotensin II in water satiated rats. Pharmacol. Biochem. Behav. 1:161–173; 1973.
14. Huang, B. S.; Malvin, R. L.: Dopaminergic modulation of some central actions of angiotensin II in vivo (42752). Proc. Soc. Exp. Biol. Med. 188:405–409; 1988.
15. Iversen, S. D.: Cortical monoamines and behavior. In: Descarries, L.; Reader, T. R.; Jasper, H. H., eds. Neurology and neurobiology, vol. 10. Monoamine innervation of cerebral cortex. New York: Liss; 1984:321–349.
16. Kesner, R. P.: Neurobiological views of memory. In: Martinez, J. S.; Kesner, R. P., eds. Learning and memory, 2nd ed. New York: Academic Press; 1991:499–547.
17. König, J. R. F.; Klippel, R. A.: The rat brain: A stereotaxic atlas of the forebrain and lower parts of the brain stem. Baltimore: Williams and Wilkins; 1963.
18. Kovács, G. L.; Bohus, B.; Versteeg, D. H. G.; De Kloet, E. R.; De Wied, D.: Effect of oxytocin and vasopressin on memory consolidation: Sites of action and catecholaminergic correlates after local microinjection into limbic–midbrain system. Brain Res. 75:303–314; 1979.
19. Krettek, J. E.; Price, J. L.: A direct input from the amygdala to the thalamus and the cerebral cortex. Brain Res. 67:169–174; 1974.
20. Krettek, J. E.; Price, J. L.: Amygdaloid projections to subcortical

structures within the basal forebrain and brain stem in the rat and cat. J. Comp. Neurol. 178:225–254; 1978.
21. Lind, R. W.; Swanson, L. W.; Ganten, D.: Organization of angiotensin II immunoreactive cells and fibers in the rat central nervous system. Neuroendocrinology 40:2–24; 1985.
22. Login, I. S.; Judd, A. M.; MacLeod, R. M.: Dopamine inhibits maitotoxin-stimulated pituitary $^{45}Ca^{++}$ efflux and prolactin release. Am. J. Physiol. 250:E731–E735; 1986.
23. 23. Louilot, A.; Simon, H.; Taghzouti, K.; Le Moal, M.: Modulation of dopaminergic activity in the nucleus accumbens following facilitation or blockade of the dopaminergic transmission in the amygdala: A study by in vivo differential pulse voltammetry. Brain Res. 346:141–145; 1985.
24. McDougall, J. G.; Scoggins, B. A.; Butkus, A.; Coghlan, J. P.; Denton, D. A.; Fei, D. T.; Hardy, K. J.; Wright, R. D.: Dopaminergic modulation of aldosterone secretion. J. Endocrinol. 91:271–280; 1981.
25. Robbins, T. W.; Everitt, B. J.: Functional studies of the central catecholamines. Int. Rev. Neurobiol. 23:303–365; 1982.
26. Sardinia, M. F.; Hanesworth, L. T.; Krebs, L. T.; Harding, J. W.: AT4 receptor binding characteristics: D-amino acid- and glycine-substitutet peptides. Peptides 14:949–954; 1993.
27. Simon, H.; Le Moal, M.: Mesencephalic dopaminergic neurons: Functional role. In: Usdin, E.; Carlsson, A; Dahlström, A.; Engel, J., eds. Catecholamines: Neuropharmacology and central nervous system. Theoretical aspects. New York: Liss; 1984:293–307.
28. Simon, H.; Taghzouti, K.; Gozlan, H.; Studler, J. M.; Louilot, A.; Herve, D.; Glowinski, J.; Tassin, J. P.; Le Moal, M.: Lesion of dopaminergic terminals in the amygdala produces enhanced locomotor response to D-amphetamine and opposite changes in dopaminergic activity in prefrontal cortex and nucleus accumbens. Brain Res. 477:335–340; 1988.
29. Steele, M. K.; McCann, S. M.; Negro-Vilar, A.: Modulation by dopamine and estradiol of the central effects of angiotensin II on anterior pituitary hormone release. Endocrinology 111:722–729; 1982.
30. Taghzouti, K.; Simon, H.; Louilot, A.; Herman, J. P.; Le Moal, M.: Behavioral study after local injection of 6-hydroxydopamine into the nucleus accumbens in the rat. Brain Res. 344:9–20; 1985.
31. Taghzouti, K.; Simon, H.; Tazi, A.; Dantzer, R.; Le Moal, M.: The effect of 6-OHDA lesions of the lateral septum on schedule-induced polydipsia. Behav. Brain Res. 15:1–8; 1985.
32. Winnicka, M. M.; Boguszewicz, J.; Braszko, J.: Lesion to central amygdala abolishes angiotensin II improvement of recall in passive avoidance situation. Pol. J. Pharmacol. Pharm. 40:129–134; 1988.
33. Winnicka, M. M.; Braszko, J. J.: 6-OHDA lesions to the central amygdala abolish angiotensins facilitation of object recognition in rats. Gen. Pharmacol. 29:239–243; 1997.
34. Winnicka, M. M.; Braszko, J.; Boguszewicz, J.; Wiśniewski, K.: Effect of angiotensin II on passive avoidance performance after bilateral lesion of the nucleus accumbens septi. Pol. J. Pharmacol. Pharm. 37:897–901; 1985.
35. Winnicka, M. M.; Braszko, J. J.; Wiśniewski, K.: Effect of angiotensin II on the passive avoidance performance in rats after bilateral 6-OHDA lesions to the hippocampus and olfactory tubercle. Pol. J. Pharmacol. Pharm. 41:115–123; 1989.
36. Winnicka, M. M.; Braszko, J. J.; Wiśniewski, K.: Dopaminergic projection to the septum mediates facilitatory effect of angiotensins on recognition memory in rats. Pharmacol. Res. 36:387–394; 1997.
37. Winnicka, M. M.; Braszko, J. J.; Wiśniewski, K.: 6-OHDA lesions to amygdala and hippocampus attenuate memory enhancing effect of the 3–7 fragment of angiotensin II. Gen. Pharmacol. 30: 801–805; 1998.
38. Wiśniewski, K.; Braszko, J. J.: The significance of central monoamine synthesis in the angiotensin II (AII) improvement of learning. Clin. Exp. Hypertens. A6:2127–2131; 1984.
39. Wright, J. W.; Harding, J. W.: Brain angiotensin receptor subtypes AT_1, AT_2, and AT_4 and their functions. Regul. Pept. 59:269–295; 1995.
40. Wright, J. W.; Miller-Wing, A. V.; Shaffer, M. J.; Higginson, C.; Wright, D.; Hanesworth, J. M.; Harding, J. W.: Angiotensin II(3–8) (ANG IV) hippocampal binding: Potential role in the facilitation of memory. Brain Res. Bull. 32:497–502; 1993.