Research in Pharmaceutical Sciences, April 2009; 4(1): 33-42
Received: Nov 2008
Accepted: Jan 2009

School of Pharmacy & Pharmaceutical Sciences
Isfahan University of Medical Sciences

Original Article

Possible involvement of angiotensin-II and its receptors in experimental anterograde and retrograde amnesia

Kamal Kishore

Department of Pharmacy, M.J.P. Rohilkhand University, Bareilly-243006, (Uttar Pradesh), India.

Abstract

Angiotensin-II is a multifunctional hormone that regulates blood pressure, plasma volume, neuronal functions, electrolyte balance, thrust and various other vital mechanisms. It acts through its receptors AT_1 and AT_2. The involvement of angiotensin-II and its receptors in cognition is still ambiguous. Therefore, the present study was designed to investigate the effect of angiotensin-II (2 µg/3 µl, i.c.v.), losartan (AT_1 blocker) (20 mg/kg, i.p.) and PD123177 (AT_2 blocker) (20 mg/kg, i.p.) on scopolamine (3 mg/kg, i.p), sodium nitrite (75 mg/kg, i.p.) and BN52021 (15 mg/kg, i.p.) induced amnesia in mice using water maze test. All the agents were administered 30 min prior to first acquisition trial for 4 consecutive days and on the 5th day during the retrieval trial. The study indicated that losartan significantly reversed the scopolamine and sodium nitrite induced anterograde amnesia. On the other hand losartan failed to produce any significant effect on sodium nitrite and BN52021 induced retrograde amnesia. Angiotensin-II and PD123177 did not exhibit any significant effect on scopolamine, sodium nitrite and BN52021 induced amnesia. The findings suggest that anterograde amnesia of scopolamine and sodium nitrite may be mediated through AT_1 receptor subtype only. These receptors are not involved in retrograde amnesia of sodium nitrite and BN52021. The finding also indicates that the brain structures involved in learning and memory are insensitive to exogenous angiotensin-II and PD123177 or have very less density of angiotensin receptors particularly AT_2 subtype.

Keywords: Angiotensin-II; losartan; PD123177; Amnesia; Water maze

INTRODUCTION

Memory is a faculty by which sensations, impressions, and ideas are stored and recalled, where learning is a process by which brain acquires new information about the events occurring in the given surroundings (1). Amnesia is a severe disruption of memory without any deficit in learning, intelligence, attention, perception or judgment (2). There are two major classes of amnesia i.e. anterograde and retrograde amnesia (3). The anterograde amnesia is impairment to store new memories; where retrograde amnesia is a failure to retrieve old memories (2). Angiotensin-II (A-II) and its two distinct receptors known as AT_1 and AT_2 are widely distributed in mammalian brain (4-6), particularly in the areas involved in the regulation of various behavioural activities including learning and memory (7,8). Renin-angiotensin system (RAS), enzymes and peptides which are necessary for the biosynthesis of angiotensins have also been recognized in the mammalian brain (9,10). RAS and its modulators are involved in neurological disorders related to learning and memory impairment (11,12) and Alzheimer's diseases (13). Antihypertensives which produce their action through modulation of RAS, angiotensin converting enzyme inhibitors (14,15) and A-II blockers are reported to improve cognitive impairment in dementia (16), Alzheimer's (17-20) and elderly patients (21,22). A-II (23) and its fragments i.e. A-IV (3-8) have been noted to play a critical role in memory enhancement (24-29). The hippocampus has the highest concentration of A-II, significantly more than plasma extracts (5). Microinjection of A-II in CA1 hippocampus region also reported to attenuate learning and memory (30,31). Long-

*****Corresponding author: Kamal Kishore
Tel. 0091 9412148058, Fax. 0091 581 2524232
Email: kamalbareilly@yahoo.co.in

term potentiation (LTP), a frequency dependent mechanism of learning and memory, has been studied extensively in the hippocampus (32). The hippocampal A-II (33-35) and specific receptor analogues of A-II are reported to block LTP (36) and selectively impair olfactory and spatial learning (37), indicating that LTP is related to important cognitive processes through RAS. Moreover, antagonist action at AT_1 or AT_2 sites may exhibit cognitive enhancing effects (38-40). On the other side, the involvement of AT_1 and AT_2 receptors modulators (losartan and PD123177, respectively) in cognition was not confirmed in the study of Shepherd et al. (41), but Kerr and his coworkers (42) suggested that A-II blocks memory consolidation through a mechanism involving activation of AT_2 receptors. It has been suggested that endogenous A-II does not participate in the consolidation of long-term memory (42). Brain renin angiotensin system retention impairment was also documented (43). Tchekalarova et al. (44) also reported contradictory findings of brain angiotensin in learning and memory. These reports created a doubt, about the role of A-II and angiotensin receptors (AT_1 and AT_2) in cognition. Thus, the present study was designed to investigate the effect of AT_1 and AT_2 receptor agonists, losartan (AT_1 receptor blocker) and PD123177 (AT_2 receptor blocker) on experimental amnesia developed by scopolamine, sodium nitrite and BN52021 in mice, using water maze test (45).

MATERIALS AND METHODS

Animals

Swiss albino mice (2-3 months of age, 28-36 g) of either sex procured from the Laboratory Animal Resource Section, Division of Animal Genetics, Indian Veterinary Research Institute, Izatnagar-243022. The ratio of male and female mice kept equal in each group to minimized the effect of sex difference on memory. They were provided with 12 h light and dark cycle, free access to water and standard laboratory diet (Kisan feed Ltd, Mumbai). All the animals were naive to water maze. The experiments were conducted between 10.00 to 17.30 h in a semi-sound proof laboratory. The research was conducted under the guidelines of "Committee for the Purpose of Control and Supervision of Experiments on Animals" (CPCSEA), Ministry of Social Justice and Empowerment, Government of India, New Delhi. The experimentation was carried out with prior approval of the Ethical Committee; vide registration no-453/01/a/CPCSEA.

Drugs and solutions

All drug solutions were freshly prepared prior to use. The solution of A-II (Sigma chemicals, USA) was prepared in saline. PD123177 (DuPont, Merck Pharmaceutical Company, Washington, USA) was dissolved in 0.5 ml of 1 M sodium hydroxide, neutralized with 0.1 N hydrochloric acid up to pH 7.4 and final volume was made with normal saline. The solution of losartan potassium (Cipla India Ltd), sodium nitrite (s.d. fine chemical Ltd.) and scopolamine (Merck KgaA, 64271 Darmstadt, Germany) was prepared in distilled water. BN52021 (Gift by Dr. P. Braquet, Institut Henri beaufour, France) was dissolved in 0.5 M dimethylsulfoxide (DMSO) (Spectrochem, Pvt. Ltd, Mumbai).

Apparatus

The water maze test was used to determine escape latency time (ELT) and time spent (TS) for all animals. Food and water deprivation is not required in this test as required in other models. Water maze consists of a circular pool, made of a galvanized iron sheet having a diameter of 150 cm and a height of 45 cm. The pool was filled with water up to a height of 30 cm and water was made opaque with commercially available white color and maintained at 25 °C. The pool was hypothetically divided into 4 equal quadrants with the help of two threads fixed at right angle to each other, on the rim of the pool. A platform (11 cm^2) of 29 cm height, was placed in the centre of one of these four quadrants i.e. target quadrant (TQ). The platform was submerged 1 cm below the water surface. Utmost care was taken not to change the relative location of water maze with respect to

any object serving as a visual clue in the laboratory.

Procedure

Acquisition trials

Manually each mouse was placed in water maze apparatus for 4 consecutive days and 4 trials were conducted on each day. Each trial was conducted with an interval of 5 min and each trial was started from the midpoint of peripheral wall of each quadrant (Q) with animal facing towards the wall of water maze. The mice were allowed to swim for 120 s. After locating the hidden platform, the mice were permitted to remain on it for 10 s before returning to the home cage. Mice that fail to locate the hidden platform within 120 s were placed on it by hand and scored as 120 s. The time spent to locate the hidden platform (placed in Q2 i.e. TQ) was noted down and was termed as ELT. Mean of the four-escape latency times was calculated for each day. This mean was used as an index of acquisition or learning. Starting position on each day to conduct four acquisition trials was changed as follows:

Day 1:	Q1	Q2	Q3	Q4
Day 2	Q2	Q3	Q4	Q1
Day 3	Q3	Q4	Q1	Q2
Day 4	Q4	Q1	Q2	Q3

Retrieval trials

On the 5th day, platform was removed. Mouse was placed in water maze and allowed to explore the maze for 120 s. Each mouse was subjected to four such trials and each trial was started from different quadrant. Mean time spent in TQ in search of missing platform was noted down. It was taken as an index of retrieval of memory.

Intracerebroventricular administration

Intracerebroventricular (i.c.v.) administration was performed under ether anesthesia. A microlitre syringe (Hamilton, Bonaduz, Switzerland) was employed for i.c.v. injection. The injection site was 2 mm either to right or left from the midpoint on a line drawn through the anterior base of ears. Injections were performed randomly into right or left ventricle. To ascertain that drugs were administered exactly into the cerebral ventricle, approximately 20% mice were injected with 3 µl of diluted patent blue and their brains were cut into slices of about 3 mm thickness to examine macroscopically.

Experimental protocol

Thirty groups of mice (n=10) were used. A-II (2 µg/3 µl) was administered through i.c.v. injection. Other pharmacological agents, losartan (20 mg/kg), PD123177 (20 mg/kg), scopolamine (3 mg/kg), sodium nitrite (75 mg/kg), and BN52021 (15 mg/kg) and their vehicles (normal saline, 10 ml/kg), distilled water (10 ml/kg), and 0.5 M DMSO (10 ml/kg) were administered intraperitoneally (i.p.), 30 min before the first acquisition trial for 4 consecutive days and 30 min before the first retrieval trial only on the 5th day. A-II, losartan and PD123177 were administered 5 min after the administration of scopolamine, sodium nitrite and BN52021, respectively.

Statistical analysis

All the results were expressed as the mean ± S.E.M and statistically interpreted by using one-way analysis of variance (ANOVA) followed by Dunnett's test. A value of $P<0.05$ was considered statistically significant.

RESULTS

The effects of scopolamine, sodium nitrite and BN52021 on learning and memory.

In control (normal saline treated) group, ELT was significantly decreased with consecutive learning trials on day 2, 3, 4 as compared to its means of day 1(Fig. 1a-4a). The TS by the mice in the TQ i.e. Q2 in search of missing platform was significantly higher as compared to TS in the other quadrants Q1, Q3, Q4 during retrieval trials (Fig. 1b-4b). Anterograde administration of scopolamine, sodium nitrite attenuated the decrease in ELT during the learning trials for 4 consecutive days (Fig. 1a). On the other hand, retrograde administration of scopolamine did not produce any marked effect on higher TS in TQ. But sodium nitrite significantly decreased the TS in TQ for searching the missing platform

during the retrieval trials (Fig. 1b). Anterograde administration of platelet activating factor (PAF) antagonist BN52021 did not produce any significant effect on decrease in ELT during the learning trials for 4 consecutive days (Fig. 1a). Moreover, retrograde administration of BN52021 significantly decreased the TS in TQ for search of missing platform during the retrieval trials (Fig. 1b).

The effects of A-II on scopolamine, sodium nitrite and BN52021 induced amnesia.

Anterograde administration (before training) of A-II did not produce any significant effect on ELT during the learning trials for 4 consecutive days (Fig. 2a). Moreover, retrograde administration (after training) of A-II also did not produce any significant effect on TS in TQ by the mice for searching the missing platform during the retrieval trials (Fig. 2b). Anterograde administration of A-II, 5 min after

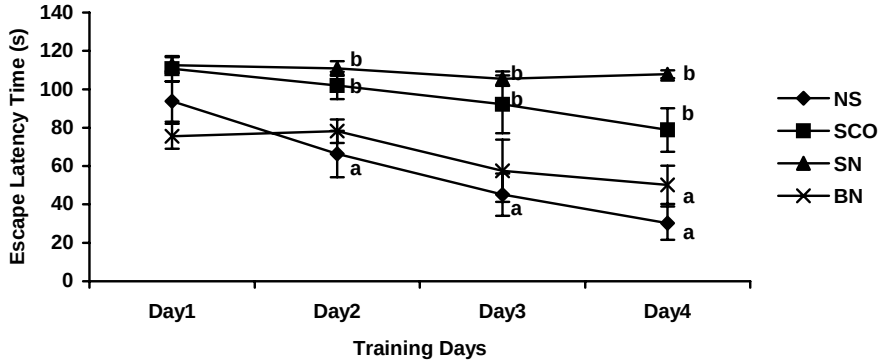

Fig. 1a. Effect of scopolamine, sodium nitrite and BN52021 on learning. Escape latency time (ELT) was recorded for 4 consecutive days i.e. day1 to day 4. Each value of ELT is a mean value of 4 consecutive learning trials conducted on each day with a gap of 5 min. NS represents normal saline (10 ml/kg i.p.), SCO represents scopolamine (3 mg/kg i.p.), SN represents sodium nitrite (75 mg/kg i.p.) and BN represents BN52021 (15 mg/kg i.p.) administered 30 min before the learning trials conducted from day 1 to day 4. n=10, a = P<0.05 vs. ELT recorded on day 1 for respective group. b = P<0.05 vs. ELT recorded in control group for the same day.

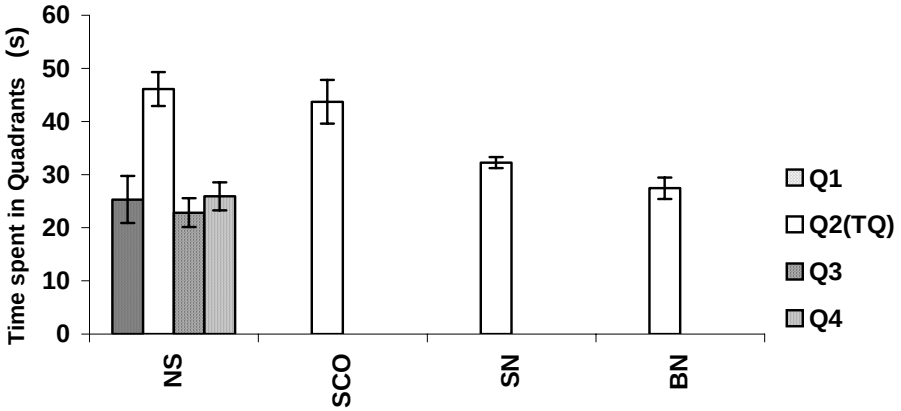

Fig. 1b. Effect of normal saline (control group), scopolamine, sodium nitrite and BN52021 on memory. NS represents normal saline (10 ml/kg i.p.), SCO represents scopolamine (3 mg/kg i.p.), SN represents sodium nitrite (75 mg/kg i.p.) and BN represents BN52021 (15 mg/kg i.p.) administered 30 min before retrieval trial conducted on day 5. Q1, Q2 (TQ), Q3 and Q4 represent quadrant one, two (target quadrant), three and four, respectively. Each blank bar represents mean value of TS in TQ in search of missing platform recorded during 4 consecutive retrieval trials conducted on day 5. n=10, a = P<0.05 vs. TS in other quadrants i.e. Q1, Q3 and Q4 in normal saline treated control group. b = P<0.05 vs. TS in TQ in control group.

scopolamine administration and 25 min before the learning trials, did not produce any significant effect on scopolamine induced attenuation of decrease in ELT during the learning trials (Fig. 2a). Anterograde administration of A-II, 5 min after sodium nitrite administration and 25 min before the learning trials, did not produce any significant effect on sodium nitrite induced attenuation of decrease in ELT during the learning trials (Fig. 2a). A-II also did not produce any significant effect on sodium nitrite induced attenuation of higher TS in TQ by the mice to search the missing platform during the retrieval trials on the 5th day (Fig. 2b). Retrograde administration of A-II, 5 min after BN52021 administration and 25 min before the retrieval trials, did not produce any significant effect on BN52021 induced attenuation of higher TS by the mice in TQ to search of missing platform during the retrieval trials (Fig. 2b).

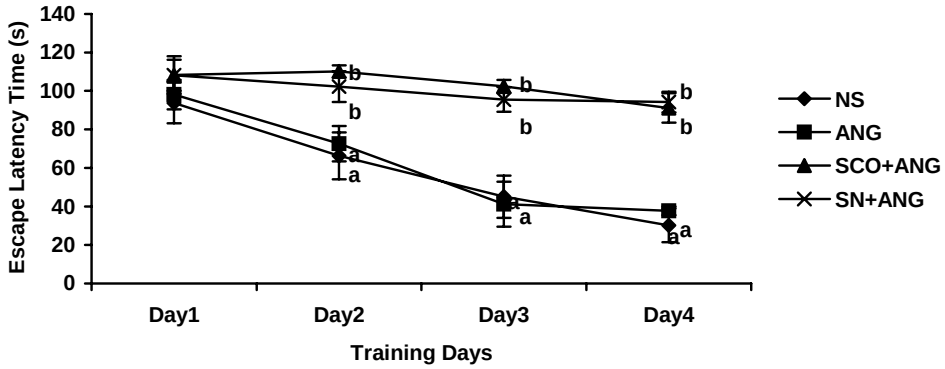

Fig. 2a. Effect of angiotensin-II on anterograde amnesia. Escape latency time (ELT) was recorded for 4 consecutive days i.e. day1 to day 4. Each value of ELT is a mean value of 4 consecutive acquisition trials conducted on each day with a gap of 5 min. NS represents normal saline (10 ml/kg i.p.), ANG represents angiotensin-II (2 µg/3 µl i.c.v.), SCO+ANG represents scopolamine (3 mg/kg i.p.) + angiotensin-II (2 µg/3 µl i.c.v.) and SN+ANG represents sodium nitrite (75 mg/kg i.p.) + angiotensin-II (2 µg/3 µl i.c.v.) administered 30 min before acquisition trials for 4 consecutive days i.e. day 1 to day 4. n=10, a = P<0.05 vs. ELT recorded on day1 for respective group. b = P<0.05 vs. ELT recorded in control group for the same day.

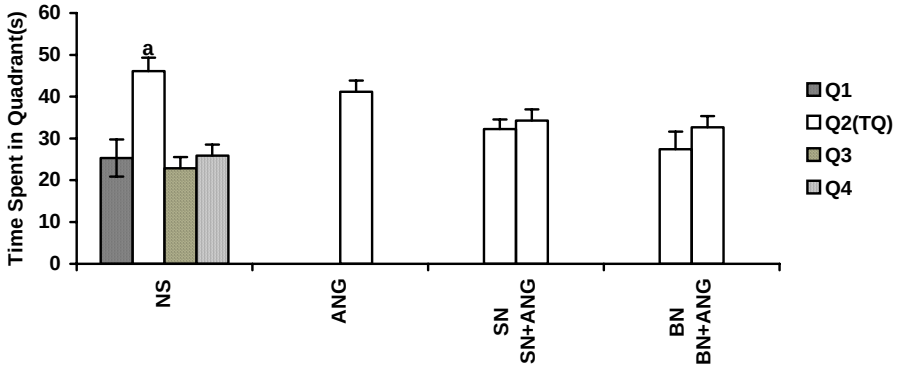

Fig. 2b. Effect of angiotensin-II on retrograde amnesia. NS represents normal saline (10 ml/kg i.p.), ANG represents angiotensin-II (2 µg/3 µl i.c.v.), SN represents sodium nitrite (75 mg/kg i.p.), SN+ANG represents sodium nitrite (75 mg/kg i.p.) + angiotensin-II (2 µg/3 µl i.c.v.), BN represents BN52021 (15 mg/kg i.p.) and BN+ANG represents BN52021 (15 mg/kg i.p.) + angiotensin-II (2 µg/3 µl i.c.v.) administered 30 min before retrieval trial conducted on day 5. Q1, Q2 (TQ), Q3 and Q4 represent quadrant one, two (target quadrant), three and four, respectively. Each blank bar represents mean value of TS in TQ in search of missing platform recorded during 4 consecutive retrieval trials conducted on day 5. n=10, a = P<0.05 vs. TS in other quadrants i.e. Q1, Q3 and Q4 in normal saline treated control group.

The effect of losartan on scopolamine, sodium nitrite and BN52021 induced amnesia.

Anterograde administration (before training) of losartan did not produce any significant effect on ELT during the learning trials for 4 consecutive days (Fig. 3a). Moreover, retrograde administration (after training) of losartan also did not produce any significant effect on TS in TQ by the mice for searching the missing platform during the retrieval trials (Fig. 3b). Anterograde administration of losartan, 5 min after scopolamine administration and 25 min before the learning trials, significantly reversed, scopolamine induced attenuation of decrease in ELT during the learning trials (Fig. 3a). Anterograde administration of losartan, 5 min after sodium nitrite administration and 25 min before the learning trials, significantly reversed sodium nitrite induced attenuation of decrease in ELT during the learning trials (Fig. 3a). Losartan did not produce any significant effect on sodium nitrite induced attenuation of higher TS in TQ by the mice to search the missing platform during the retrieval trials on the 5th day (Fig. 3b). Retrograde administration of losartan, 5 min after BN52021 administration and 25 min before the retrieval trials, did not produce any significant effect on BN52021 induced attenuation of higher TS by the mice in TQ to search of missing platform during the retrieval trials (Fig. 3b).

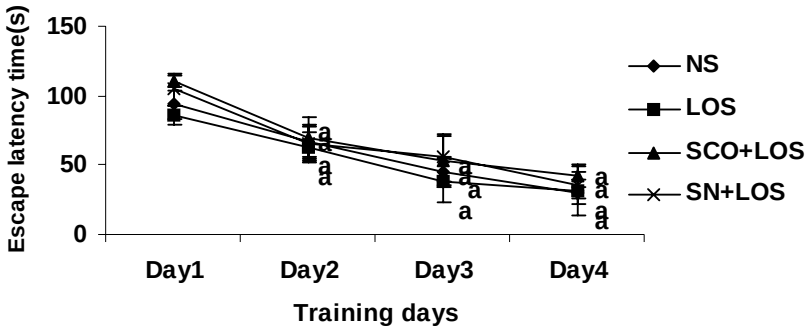

Fig. 3a. Effect of losartan (angiotensin AT_1 receptor blocker) on anterograde amnesia. Escape latency time (ELT) was recorded for 4 consecutive days i.e. day1 to day 4. Each value of ELT is a mean value of 4 consecutive acquisition trials conducted on each day with a gap of 5 min. NS represents normal saline (10 ml/kg i.p.), LOS represents losartan (20 mg/kg i.p.), SCO + LOS represents scopolamine (3 mg/kg i.p.) + losartan (20 mg/kg i.p.) and SN+LOS represents sodium nitrite (75 mg/kg i.p.) + losartan (20 mg/kg i.p.) administered 30 min before acquisition trials conducted from day 1 to day 4. n=10, a = P<0.05 vs. ELT recorded on day1 for respective group.

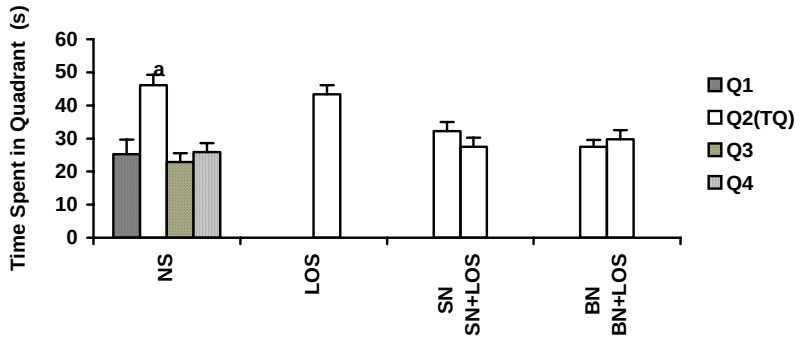

Fig. 3b. Effect of losartan (AT_1 receptor blocker) on retrograde amnesia. NS represents normal saline (10 ml/kg i.p.), LOS represents losartan (20 mg/kg i.p.), SN represents sodium nitrite (75 mg/kg i.p.), SN+LOS represents sodium nitrite (75 mg/kg i.p.) + losartan (20 mg/kg i.p.), BN represents BN52021 (15 mg/kg i.p.) and BN + LOS represents BN52021 (15 mg/kg i.p.) + losartan (20 mg/kg i.p.) administered 30 min before retrieval trial conducted on day 5. Q1, Q2 (TQ), Q3 and Q4 represent quadrant one, two (target quadrant), three and four, respectively. Each blank bar represents mean value of TS in TQ in search of missing platform recorded during 4 consecutive retrieval trials conducted on day 5. n=10, a = P<0.05 vs. TS in other quadrants i.e. Q1, Q3 and Q4 in normal saline treated control group.

The effect of PD123177 on scopolamine, sodium nitrite and BN52021 induced amnesia.

Anterograde administration (before training) of PD123177 did not produce any significant effect on ELT during the learning trials for 4 consecutive days (Fig. 4a). Moreover, retrograde administration (after training) of PD123177 also did not produce any significant effect on TS in TQ by the mice for searching the missing platform during the retrieval trials (Fig. 4b).

Anterograde administration of PD123177, 5 min after scopolamine administration and 25 min before the learning trials, did not produce any significant effect on scopolamine attenuation of decrease in ELT during the learning trials
(Fig. 4a). Anterograde administration of PD123177, 5 min after sodium nitrite administration and 25 min before the learning trials, did not produce any significant effect on sodium nitrite induced attenuation of decrease in ELT during the learning trials (Fig. 4a).

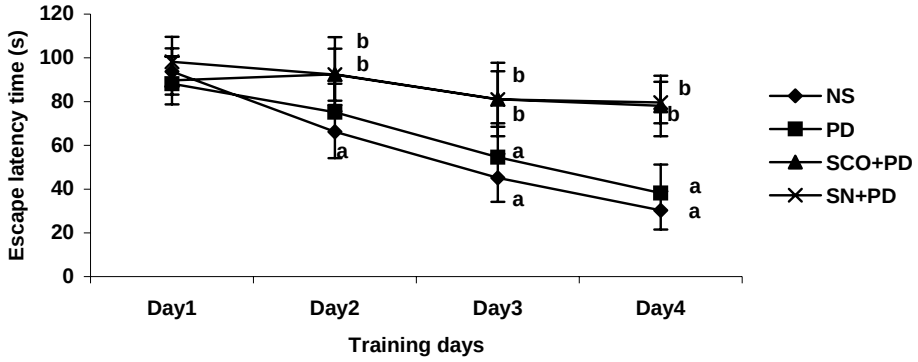

Fig. 4a. Effect of PD123177 (AT_2 receptor blocker) on anterograde amnesia. Escape latency time (ELT) was recorded for 4 consecutive days i.e. day1 to day 4. Each value of ELT is a mean value of 4 consecutive acquisition trials conducted on each day with a gap of 5 min. NS represents normal saline (10 ml/kg i.p.), PD represents PD123177 (20 mg/kg i.p.), SCO + PD represents scopolamine (3 mg/kg i.p.) + PD123177 (20 mg/kg i.p.) and SN + PD represents sodium nitrite (75 mg/kg i.p.) + PD123177 (20 mg/kg i.p.) administered 30 min before acquisition trials conducted from day 1 to day 4. n=10, a = P<0.05 vs. ELT recorded on day1 for respective group. b = P<0.05 vs. ELT recorded in control group for the same day.

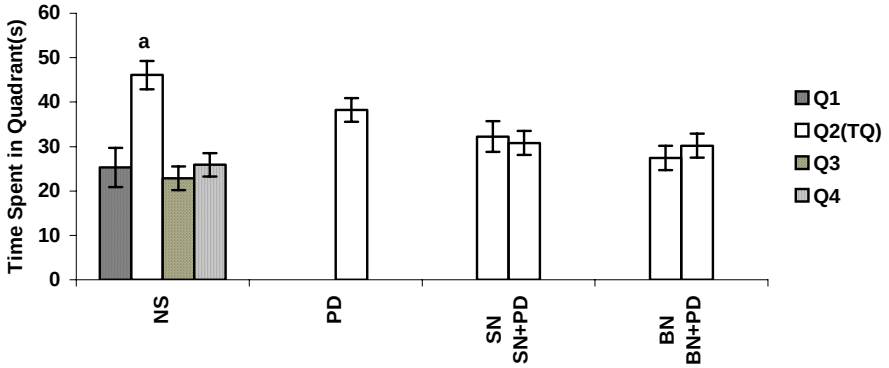

Fig. 4b. Effect of PD123177 (AT_2 receptor blocker) on retrograde amnesia. NS represents normal saline (10 ml/kg i.p.), PD represents PD123177 (20 mg/kg i.p.), SN represents sodium nitrite (75 mg/kg i.p.), SN + PD represents sodium nitrite (75 mg/kg i.p.) + PD123177 (20 mg/kg i.p.), BN represents BN52021 (15 mg/kg i.p.) and BN + PD represents BN52021 (15 mg/kg i.p.) + PD123177 (20 mg/kg i.p.) administered 30 min before retrieval trial conducted on day 5. Q1, Q2 (TQ), Q3 and Q4 represent quadrant one, two (target quadrant), three and four, respectively. Each blank bar represents mean value of TS in TQ in search of missing platform recorded during 4 consecutive retrieval trials conducted on day 5. n=10, a = P<0.05 vs. TS in other quadrants i.e. Q1, Q3 and Q4 in normal saline treated control group.

PD123177 also did not produce any significant effect on sodium nitrite induced attenuation of higher TS in TQ by the mice to search the missing platform during the retrieval trials the 5th day (Fig. 4b). Retrograde administration of PD123177, 5 min after BN52021 administration and 25 min before the retrieval trials, did not produce any significant on BN52021 induced attenuation of higher TS by the mice in TQ to search of missing platform during the retrieval trials (Fig. 4b).

DISCUSSION

The aim of this study was to evaluate the involvement of A-II and its receptors in experimental amnesia. This was assessed by exploring the effect of A-II, losartan and PD123177 in learning and memory and on scopolamine, sodium nitrite, and BN52021 induced amnesia in mice using water maze test. A marked decrease in ELT during ongoing acquisition trials and an increased in TS in the TQ for search of missing platform during the retrieval trial, suggest normal acquisition and retrieval of memory in control or vehicle treated groups. Scopolamine, an anticholinergic, produced only anterograde amnesia (46). Sodium nitrite, a central hypoxic and potent vasodilator, produced both anterograde and retrograde amnesia. Sodium nitrite inhibited synthesis of acetylcholine in brain (47). BN52021, a PAF receptor antagonist produced only retrograde amnesia (48). The cholinergic system (49), hypoxia (36), vasodilatation (50) and PAF (51) are reported to modulate hypertensive conditions by interfering with renin angiotensin system. Moreover, hypertension (52,53) and RAS (54,55) are documented to associated with memory impairment or amnesia. Furthermore, antihypertensives which produce their action through modulation of RAS, angiotensin converting enzyme inhibitors (14,15), A-II blockers are also reported to improve cognitive impairment in dementia (16), Alzheimer's (17-20) and elderly patients (21,22).

The study indicated that A-II did not attenuate acquisition or learning and also did not exhibit any significant effect on scopolamine, sodium nitrite and BN52021 induced amnesia. Losartan (AT_1 blocker) facilitated learning and memory and also significantly reversed anterograde amnesia of scopolamine and sodium nitrite. This contention supported by that losartan documented to facilitate spatial memory in various active and passive tasks by enhancing cholinergic activity (56,57). Recently valsartan another AT_1 receptor blocker has been reported to facilitate cognitive functions (58). It is also reported that losartan and atenolol facilitate immediate and old memory (59). Therefore, it may be possible that the observed effect of losartan to attenuate scopolamine and sodium nitrite induced anterograde amnesia may be due to increase in cholinergic activity by blocking AT_1 receptors in hippocampus. On the other hand, PD123177 (AT_2 blocker) did not produce any significant effect on anterograde amnesia of scopolamine and sodium nitrite. Moreover, losartan and PD123177 did not exhibit any significant effect on retrograde amnesia of sodium nitrite and BN52021. This was supported by previous findings that losartan acted as anti-depressant (60), mood elevator, Anxiolytic (38) and acquisition and retention improving agent (61), whilst AT_2 blocker, PD123177 was inactive (41).

On the basis of results it can be concluded that brain renin angiotensin system involved in learning and memory. Moreover, anterograde amnesia of scopolamine and sodium nitrite may be associated only with AT_1 receptor subtype. These receptors have no involvement in retrograde amnesia of sodium nitrite and BN52021. However, the brain areas involved in learning and memory are little bit insensitive to exogenous A-II and PD123177 or have very less density of angiotensin receptor particularly AT_2 subtype.

ACKNOWLEDGMENT

The author expresses his heartfelt thanks to Dr. Shobhna Singh, Head, Department of Pharmacy, M.J.P. Rohilkhand University, Bareilly-243006, (U.P), India and Dr. Ranjit Singh, Prof. & Head, School of Pharmaceutical Sciences, Shobhit University, NH-58, Modipuram, Meerut-250 110, (U.P.)

India, for their technical support.

REFERENCES

1. Izquierdo I, Medina JH. Neurotransmitter mechanisms in memory consolidation. Drugs of Today. 1992;28:421-429.
2. Markowitsch HJ. Diencephalic amnesia: a reorientation towards tracts. Brain Res Rev. 1988;13:351-370.
3. Squire LR, Clark RE, Knowlton BJ. Retrograde amnesia. Hippocampus. 2001;11:50-55.
4. Millan MA, Kiss A, Aguilera G. Developmental changes in brain angiotensin-II receptors in the rat. Peptides. 1991;12:723-737.
5. Sirett NE, Bray JJ, Hubbard JI. Localization of immunoreactive angiotensin-II in the hippocampus and striatum of rat brain. Brain Res. 1981;217:405-411.
6. Tsutsumi K, Saavedra JM. Characterization and development of angiotensin-II receptor subtypes (AT_1 and AT_2) in rat brain. Am J Physiol Regul Integr Comp Physiol. 1991;26:R209-R216.
7. Wright JW, Yamamoto BJ, Harding JW. Angiotensin receptors subtype mediated physiologies and behaviours: new discoveries and clinical targets. Prog Neurobiol. 2008;84:157-181.
8. Wright JW, Harding JW. Angiotensins in brain functions. In: Lim R, editor. Handbook of neurochemistry and molecular neurobiology: neuroactive proteins and peptides. New York: Springer Science Publications; 2006. p. 627-653.
9. Fisher-Ferraro C, Mahmod VE, Goldstein DJ, Finkielmen S. Angiotensin and renin in the rat dog brain. J Exp Med. 1971;133:353-561.
10. Ganten D, Minnich JE, Granger P, Hayduk K, Brecht HM, Barbeau A, et al. Angiotensin forming enzyme in brain tissue. Science. 1971;173:64-65.
11. Hacioglu G, Agar A, Ozkaya G, Yargicoglu P, Gumuslu S. The effect of different hypertension models on active avoidance learning. Brain Cogn. 2003;52:216-222.
12. Halbach OV. The rennin-angiotensin system in the mammalian central nervous system. Curr Protein Peptide Sci. 2005;6:355-371.
13. Kehoe PG, Wilcock GK. Is inhibition of the renin-angiotensin system a new treatment option for Alzheimer's disease. Lancet Neurol. 2007;6:373-378.
14. Rozzini L, Chilovi BV, Vertoletti E, Conti M, DelRio L, Trabucchi M, et al. Angiotensin converting enzyme inhibitors modulate rate of progression of amnestic mild cognitive impairment. Int J Geriatr Psychiatry. 2006;21:550-555.
15. Jenkins TA, Chai SY. Effect of chronic angiotensin converting enzyme inhibition on spatial memory and anxiety like behaviours in rats. Neurobiol Learn Mem. 2007;87:218-224.
16. Poon IO. Effects of antihypertensive drugstreatment on the risk of dementia and cognitive impairment. Pharmacotherapy. 2008;28:366-375.
17. Gard PR. Angiotensin as a target for the treatment of Alzheimer's disease, anxiety and depression. Expert Opin Ther Targets. 2004;8:7-14.
18. Hemming MI, Selkoe DJ. Amyloid beta-protein is degrade by cellular angiotensin converting enzyme and elevated by an ACE inhibitor. J Biol Chem. 2005;289:3744-3750.
19. Oba R, Igarashi A, Kamata M, Nagata K, Takano S, Nakagawa H. The N-terminal active centre of human angiotensin-converting enzyme degrades Alzheimer's amyloid beta-peptide. Eur J Neurosci. 2005;21:733-740.
20. Hajjar IM, Keown M, Frost B. Antihypertensive agents for aging patients who are at risk for cognitive dysfunction. Curr Hypertens Rep. 2008;7:466-473.
21. Wyss JM, Kadish I, vanGroen T. Age related declinein spatial learning and memory: attention by captopril. Clin Exp Hypertens. 2003;25:455-474.
22. Hanes DS, Weir MR. Usefulness of ARBs and ACE inhibitors in the prevention of vascular dementia in the elderly. Am J Geriatr Cardiol. 2007;16:175-182.
23. Das UN. Can memory be improved? A discussion on the role of RAS, GABA, acetylcholine, NO, insulin, TNF-alpha, and long chain polyunsaturated fatty acids in memory formation and consolidation. Brain Dev. 2003;25:251-261.
24. Wright JW, Stubley LA, Pederson ES, Kramar EA, Hanesworth M, Harding JW. Contributions of the brain angiotensi-IV-AT_4 receptor subtype system to spatial learning. J Neurosci. 1999;19:3952-3961.
25. Pederson ES, Krishnan R, Harding JW, Wright JW. A role for the angiotensin AT_4 receptor subtype in overcoming scopolamine-induced spatial memory deficits. Regul Pept. 2001;102:147-156.
26. Kramar EA, Armstong DL, Ileda S, Wayner MJ, Harding JW, Wright JW. The effects of angiotensin-IV analogs on long-term potentiation within the CA1 region of the hippocampus *in vitro*. Brain Res. 2001;897:114-121.
27. Wayner MJ, Armstrong DL, Phelix CF, Wright JW, Harding, JW. Angiotensin-IV enhances LTP in rat dentate gyrus *in vivo*. Peptides. 2001;22:1403-1414.
28. Lee J, Chai SY, Mendellsohn FA, Morris MJ, Allen AM. Potentiation of cholinergic transmission in the rat hippocampus by angiotensin-IV and LVV-hemorphin-7. Neuropharmacol. 2001;40:618-623.
29. Lee J, Albiston AL, Allen AM, Mendelsohn FA, Ping SE, Barrett GL, et al. Effect of i.c.v. injection of AT_4 receptor ligands, NLE1-angiotensin-IV and LVV-hemorphin 7, on spatial learning in rats. Neuroscience. 2004;124:341-349.
30. Braszko JJ, Kulakowska A, Karwowska-Polecka W. CGP 42112A antagonism of the angiotensin II and angiotensin II (3-7) facilitation of recall in rats. Pharmacol Res. 1998;38:461-468.
31. Belcheva I, Ternianov A, Georgiev V. Lateralized learning and memory effects of angiotensin II microinjected into the rat CA1 hippocampal area. Peptides. 2000;21:407-411.
32. Denny JB, Polan-Curtain J, Wayner MJ, Armstrong DL. Angiotensin-II blocks hippocampal long-term

potentiation. Brain Res. 1991;567:321-324.
33. Landfield PW, Deadwyler SA. Long-term potentiation: From biophysics to behaviour. New York: Alan R, Liss, Inc; 1988. p. 548.
34. Lynch G, Kessler M, Arai A, Larson J. The nature and causes of the hippocampal long-term potentiation. In: Storm-Mathisen J, Zimmer J, Ottersen OP, editors. Understandings of brain through the hippocampus. New York: Elsevier; 1990;83:233-250.
35. Traub RD, Miles R. Neuronal network of hippocampus. Cambridge: Cambridge University Press; 1991. p. 281.
36. Wright JW, Kramar EA, Meighan SE, Harding JW. Extracellular matrix molecules, long-term potentiation, memory consolidation and the brain angiotensin system. Peptides. 2002;23:221-246.
37. Massicotte G, Baudry M. Triggers and substrates of hippocampal synaptic plasticity. Neurosci Biobehav Rev. 1991;15:415-423.
38. Barnes NM, Costall B, Kelly ME, Murphy DA, Naylor RJ. Anxiolytic action of DuP 753, a non-peptide angiotensin II receptor antagonist. Neuroreport. 1990;1:20-21.
39. Barnes NM, Costall B, Kelly ME, Murphy DA, Naylor RJ. Cognitive enhancing action of PD123177 detected in the mouse habituation paradigm. Neuroreport. 1991;2:351-353.
40. Barnes NM, Costall B, Kelly ME, Murphy DA, Naylor RJ. Cognitive enhancing actions of DuP 753 detected in mouse habituation paradigm. Neuroreport. 1990;2:239-342.
41. Shepherd J, Bill DJ, Dourish CT, Grewal S, McLenachan A. Effects of the selective angiotensin II receptor antagonists losartan and PD123177 in animal models of anxiety and memory. Psychopharmacology. 1996;126:206-218.
42. Kerr DS, Bevilaqua LR, Bonini IS, Rossato IL, Kohler CA, Medina IH, et al. Angiotensin II blocks memory consolidation through an AT_2 receptor-dependent mechanism. Psychopharmacology. 2005;179:529-535.
43. Raghavendra V, Chopra K, Kulkarni SK. Brain renin angiotensin system (RAS) in stress induced analgesia and impaired retention. Peptides. 1999;20:335-342.
44. Tchekalarova J, Pechlivanova D, Kambourova T, Matsoukas J, Georgiev V. The effects of sarmesin, an angiotensin II analogue on seizure susceptibility, memory retention and nociception. Regul Pept. 2003;111:191-197.
45. Morris R. Developments of a water maze procedure for studying spatial learning in the rat. J Neurosci Meth. 1984;11:47-60.
46. Izquierdo I. Mechanism of action of scopolamine as an amnesic. TIPS. 1989;10:175-177.
47. Gibson BW. Exploiting proteomics in the discovery of drugs that target oxidative damage. Science. 2004;304:176-177.
48. Saraf MK, Kishore K, Thomas KM, Sharma A, Singh M. Role of platelet activating factor in triazolobenzodiazepines induced retrograde amnesia. Behav Brain Res. 2003;142:31-40.
49. Buccafusco JJ, Spector S. Role of central cholinergic neurons in experimental hypertension. J Cardiovasc Pharmacol. 1980;2:347-355.
50. Nickerson M. Vasodialation drugs. In: Goodman LS, Gilman A, editors. The pharmacological basis of therapeutics, New York: Macmillan; 1975. p. 727-743.
51. Vargaftig BB, Lefort J, Chignard M, Benveiste J. Platelet activating factor induce a platelet dependent bronchoconstriction unrelated to the formation of prostaglandin derivatives. Eur J Pharmacol. 1980;65:185-192.
52. Lichter I, Richardson PJ, Wyke MA. Differential effects of atenolol and enalapril on memory during treatment for essential hypertension. Br J Clin Pharmacol. 1986;21:641-645.
53. Starr JM, Whalley LJ, Deary IJ. The effects of antihypertensive treatment on cognitive function: results from the HOPE study. J Am Geriatr Soc. 1996;44:411-415.
54. Morgan JM, Routtenberg A. Angiotensin injected into the neostriatum after learning disrupts retention performance. Science. 1977;196:87-89.
55. Lee EH, Ma YL, Wayner MJ, Armstrong DL. Impaired retention by angiotensin-II mediated by the AT_1 receptor. Peptides. 1995;16:1069-1071.
56. Raghavendra V, Chopra K, Kulkarni SK. Involvement of cholinergic system in losartan induced facilitation of spatial and short-term working memory. Neuropeptides. 1998;32:417-421.
57. Raghavendra V, Chopra K, Kulkarni SK. Comparative studies on the memory enhancing actions of captopril and losartan in mice using inhibitory shock avoidance paradigm. Neuropeptides. 2001;35:65-69.
58. Fogari R, Mugellini A, Zoppi A, Marasi G, Pasotti C, Poletti L, Rinaldi A, Preti P. Effects of valsartan compared with enalapril on blood pressure and cognitive function in elderly patients with essential hypertension. Euro J Clin Pharmacol. 2004;59:863-868.
59. Fogari R, Mugellini A, Zoppi A, Derosa G, Pasotti C, Fogari E, et al. Influence of losartan and atenolol on memory function in very elderly hypertensive patients. J Hum Hypertens. 2003;17:781-785.
60. Martin P. Effects of Losartan and angiotensin II antagonist, alone and in combination with antidepressant drugs (ADS) in animal model of depression. FASEB J. 1994;8:2187.
61. Ramanathan M, Srinivasan J, Jayadev S, Kumaran D, Haja Nazeer Ahamed KF, Suresh B. Effect of losartan and enalapril on congnitive deficit caused by goldblatt induced hypertension. Indian J Exp Bio. 2005;43:241-246.