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

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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 AT₁ and AT₂. 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 (AT₁ blocker) (20 mg/kg, i.p.) and PD123177 (AT₂ 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 AT₁ receptor subtype only. These receptors are not involved in retrograde amnesia of sodium nitrite and BN52021. The findings also indicate 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 AT₂ 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 AT₁ and AT₂ 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-
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 AT1 or AT2 sites may exhibit cognitive enhancing effects (38-40). On the other side, the involvement of AT1 and AT2 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 AT2 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 (AT1 and AT2) in cognition. Thus, the present study was designed to investigate the effect of AT1 and AT2 receptor agonists, losartan (AT1 receptor blocker) and PD123177 (AT2 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 cm²) 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

![Graph showing Escape Latency Time (ELT) during learning](image)

**Fig. 1a.** Effect of scopolamine, sodium nitrite and BN52021 on learning. Escape latency time (ELT) was recorded for 4 consecutive days i.e. day 1 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.

![Graph showing Time spent in Quadrants during retrieval](image)

**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](image1.png)

*Fig. 3a. Effect of losartan (angiotensin AT1 receptor blocker) on anterograde amnesia. Escape latency time (ELT) was recorded for 4 consecutive days i.e. day 1 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 day 1 for respective group."

![Fig. 3b](image2.png)

*Fig. 3b. Effect of losartan (AT1 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 (AT2 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 (AT2 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 (AT₁ 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 AT₁ 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 AT₁ receptors in hippocampus.

On the other hand, PD123177 (AT₂ 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 AT₂ 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 AT₁ 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 AT₂ subtype.

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