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Role of Captopril in Reversal of Anterograde and Retrograde Experimental Amnesia

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Abstract: The present study was designed to investigate the effect of captopril (20mg kg^{-1}, i.p.) angiotensin converting enzyme (ACE) inhibitor in learning and memory and on scopolamine (3mg kg^{-1}, i.p), sodium nitrite (75 mg kg^{-1}, i.p.) and BN52021 (15mg kg^{-1}, i.p.) a platelet activating factor (PAF) receptor antagonist, 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 5th day during the retrieval trial. Captopril reduced escape latency time (ELT) and enhanced time spent (TS) in target quadrant (TQ) and significantly reversed scopolamine, sodium nitrite and BN52021 induced attenuation of decrease in ELT and higher TS in TQ during the acquisition and retrieval trials respectively. Findings indicate that captopril reverses anterograde amnesia of scopolamine and sodium nitrite and also reverses retrograde amnesia of sodium nitrite and BN52021. It can be concluded that captopril reverse scopolamine and sodium nitrite induced anterograde amnesia possibly by partial inhibition of angiotensin converting enzyme (ACE) and partially by scavenging reactive oxygen species. Its ameliorative effect on retrograde amnesia of sodium nitrite and BN52021 may be exclusively due to scavenging of free radicals probably by sulphahydral group which is present in its structure.

Key words: Captopril · Scopolamine · Sodium nitrite · BN52021 · Amnesia · Water maze · Mice

INTRODUCTION

Renin-angiotensin system (RAS), enzymes and peptides necessary for the biosynthesis of angiotensins have been recognized within the mammalian central nervous system [1, 2]. RAS and its modulators are involved in neurological disorders related to learning and memory impairment [3-5]. Angiotensin-II (AII) and its receptors are widely distributed in mammalian brain [6, 7]. A-II [8, 9], its fragments i.e. A-IV (3-8) [10-15] and angiotensin converting enzyme (ACE) have been noted to play a critical role in memory [16, 17]. Brain autoradiographic studies have demonstrated high concentration of ACE in the areas involved in memory development [18]. Moreover, enhanced ACE activity is found in several brain regions of patients suffering from Alzheimer's disease [19]. Captopril is a potent inhibitor of ACE responsible for the conversion of angiotensin-I (less active) into angiotensin-II (more active) and prevent hypertension. Antihypertensive agents improve dysfunctions in aged patients by modulating RAS [20]. ACE inhibitors are also reported in the prevention of vascular dementia in the elderly [21]. Captopril and other ACE inhibitors have been demonstrated to improve cognition in various experimental models [22-26] and human clinical trials [27] and slow down the progress of Alzheimer's disease [28]. ACE inhibitors also reported to attenuate age-related decline in spatial learning and memory [29] and modulate the rate or progression of amnesic cognitive impairment [30]. Losartan and valsartan has been documented to facilitate cognitive functions and older memories [24, 31]. On the other side, contradictory findings have been reported. The hippocampal AII [32] and specific receptor antagonists of AII are reported to selectively impair olfactory and spatial learning [33]. The involvement of RAS modulators i.e. captopril, Losartan and PD1232177 in cognition are not confirmed in the study of Shepherd et al. [34]. Cognitive enhancing action of PD123177 detected in the mouse habituation paradigm [35]. Exogenous A-II blocks memory consolidation and endogenous A-II does not participate in the consolidation of long-term memory [36]. Tchekalarova et al. [37] also reported contradictory findings of brain angiotensin II in memory. These reports created a doubt, about the role of brain RAS and its modulators in cognition. Thus, present study was designed to investigate the role of reputed ACE inhibitor, frequently used in hypertension i.e. captopril on experimental amnesia induced by scopolamine, sodium nitrite and BN52021 in mice, using water maze test [38].

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MATERIALS AND METHODS

Animals: Swiss albino mice (28-36g) of either sex procured from Indian Veterinary Research Institute (IVRI) Izatnagar, Bareilly-243022 India, were housed in animal house provided with 12 hours light and dark cycle, free access to water and standard laboratory diet (Kisan feed Ltd. Bombay. India). All the animals were naive to water maze. The experiments were conducted between 10.00 to 17.30 hrs in a semi-sound proof laboratory. The research was conducted as per 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.

Drugs and Solutions: All drug solutions were freshly prepared prior to use. The solutions of Captopril hydrochloride (Torrent Pharma. Ahamadabad, India), Sodium nitrite (s.d. fine chemical Ltd.) and Scopolamine (Merck KgaA, 64271 Darmastadt, Germany) was prepared in distilled water. BN52021 (Gift by Dr. P.Braquet, Institut Henri beaufour, France) in 0.5 M dimethyl sulfoxide (Spectrochem, Pvt. Ltd. Mumbai, India).

Apparatus: Escape latency time (ELT) and time spent (TS) for all animals were measured by employing the water maze test. The test allows the evaluation of spatial memory. Water provides a uniform intramaze environment, thus eliminating any olfactory interference. 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 upto 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 four equal quadrants with the help of two threads fixed at right angle to each other, on the rim of the pool. A platform ($11cm^2$) of 29 cm. height, was placed in the centre of one of these four quadrants i.e. target quadrant (T.Q). 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

Acquisitional Trials: Each mouse was placed in water maze for four consecutive days, with a five minute interval between the trials from the midpoint of peripheral wall of each quadrant with its face towards the wall. Mice were given 120 seconds to locate the hidden platform and allowed to remain on it for 10 sec. Mice unable to locate the hidden platform within 120 sec. were directed by hand to locate the platform and allowed to remain on it for 10sec.and scored as 120 sec. The time taken by the mouse to locate the hidden platform was noted down and was assigned as escape latency time (ELT). Mean of the four escape latency time was calculated for each day. This mean was used as index of acquisition or learning.

Retrieval Trials: On 5^{th} day, platform was removed and time spent (TS) by the animal in each quadrant was noted. The time spent by the mice in target quadrant in search of hidden platform was noticed as an index of retrieval of memory.

Experimental Protocol: Twelve groups of mice (n=10) were employed. All pharmacological agents [Captopril (20mg kg^{-1}), scopolamine (3mg kg^{-1}), sodium nitrite (75mg kg^{-1}) and BN52021] and their vehicles [distilled water (10ml kg^{-1}) and 0.5M DMSO (10ml kg^{-1})] were administered intraperitonially (i.p.), 30 min before the first acquisition trial for 4 consecutive days and 30 min before the retrieval trial on 5^{th} day only. Captopril was administered 5 min after the administration of scopolamine, sodium nitrite and BN52021, respectively.

Statistical Analysis: All the results were statistically interpreted using one-way analysis of variance (ANOVA) followed by Dunnett test. A value of $P<0.05$ was considered statistically significant.

RESULTS

Effect of Normal Saline, Scopolamine, Sodium Nitrite and Bn52021 on Learning and Memory: In control (normal saline treated) group, ELT decreased with consecutive learning trials on day 2, 3, 4 as compared to its means of day 1 (Fig. 1). 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. 2). Anterograde administration of scopolamine and sodium nitrite attenuated the decrease in ELT during the learning trials for 4 consecutive days (Fig. 1). 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

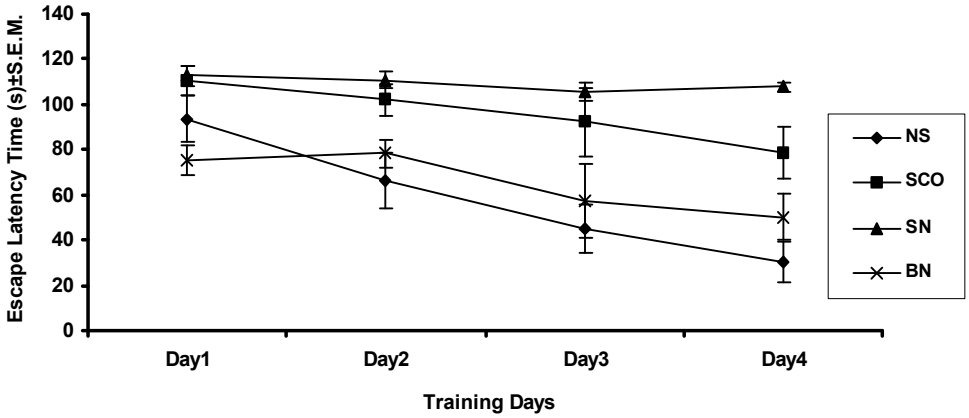

Fig. 1: Effect of normal saline, scopolamine, sodium nitrite and BN52021 on learning
NS represents normal saline (10ml kg^{-1} i.p), SCO represents scopolamine (3mg kg^{-1} i.p.), SN represents sodium nitrite (75mg kg^{-1} i.p.) and BN represents BN52021 (15mg kg^{-1} i.p.) administered 30 min before the acquisition trial conducted from day1 to day 4. Escape latency time (ELT) was recorded for four consecutive days i.e. day1 to day 4. Each value of ELT is a mean value of four consecutive acquisition trials conducted on each day with a gap of 5 min. (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

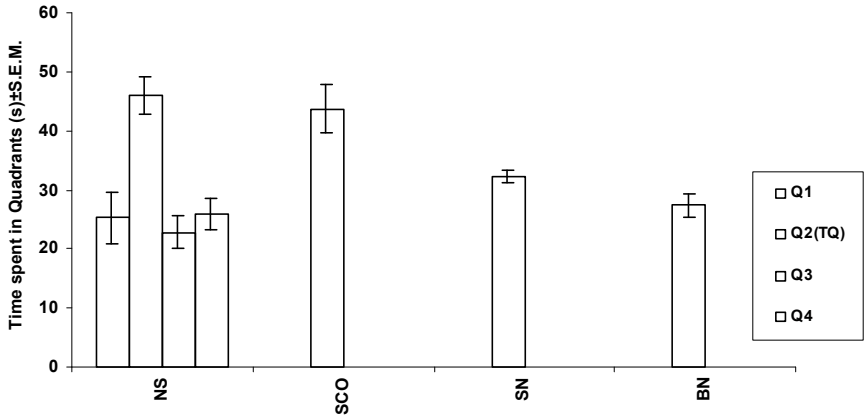

Fig. 2: Effect of normal saline, scopolamine, sodium nitrite and BN52021 on retrieval of learning
NS represents normal saline (10ml kg^{-1} i.p.), SCO represents scopolamine (3mg kg^{-1} i.p.), SN represents sodium nitrite (75mg kg^{-1} i.p.) and BN represents BN52021 (15mg kg^{-1} i.p.) administered 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 white bar represents mean value of time spent in target quadrant in search of missing platform recorded during four consecutive retrieval trials conducted on day 5. a=P<0.05 Vs time spent in other quadrants i.e. Q1, Q3 and Q4 in normal saline treated control group. b=P<0.05 Vs time spent in target quadrant in control group

retrieval trials (Fig. 2). Anterograde administration of PAF antagonist BN52021 did not produce any significant effect on decrease in ELT during the learning trials for 4 consecutive days (Fig. 1). Moreover, retrograde administration of BN52021 significantly decreased the TS in TQ for search of missing platform during the retrieval trials (Fig. 2).

Effect of Captopril (*Per-se*) and on Scopolamine, Sodium Nitrite and BN52021 Induced Amnesia: Anterograde administration (before training) of captopril did not produce any significant effect on ELT during the learning trials for 4 consecutive days (Fig. 3). Moreover, retrograde administration (after training) captopril also did not produce any significant effect on time spent by

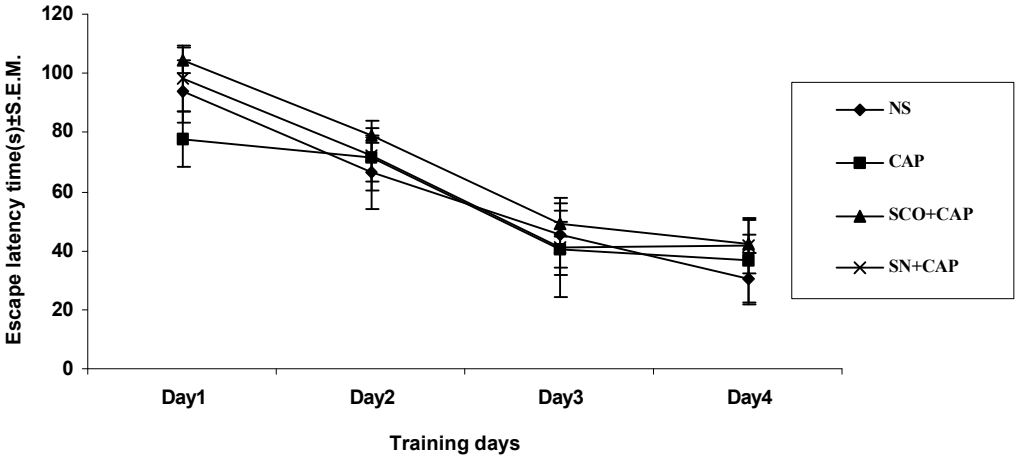

Fig. 3: Effect of captopril (Per-se) and on anterograde amnesia of scopolamine and sodium nitrite
NS represents normal saline (10ml kg^{-1} i.p.), CAP represents captopril (20mg kg^{-1} i.p.), SCO+CAP represents scopolamine (3mg kg^{-1} i.p.) + captopril (20mg kg^{-1} i.p.) and SN+CAP represents sodium nitrite (75mg kg^{-1} i.p.) + captopril (20mg kg^{-1} i.p.) administered 30 min before acquisition trials conducted from day1 to day 4. Escape latency time (ELT) was recorded for four consecutive days i.e. day1 to day 4. Each value of ELT is a mean value of four consecutive acquisition trials conducted on each day with a gap of 5 min. (n=10). a=P<0.05 Vs ELT recorded on day1 for respective group

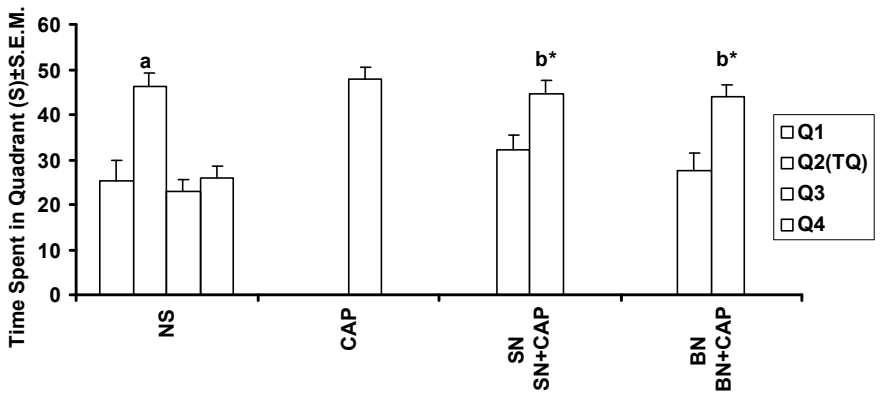

Fig. 4: Effect of captopril (Per-se) and on retrograde amnesia of sodium nitrite and BN52021
NS represents normal saline (10ml kg^{-1} i.p.), CAP represents captopril (20mg kg^{-1} i.p.), SN represents sodium nitrite (75mg kg^{-1} i.p.), SN+CAP represents sodium nitrite (75mg kg^{-1} i.p.) + captopril (20mg kg^{-1} i.p.), BN represents BN52021 (15mg kg^{-1} i.p.) and BN+CAP represents BN52021 (15mg kg^{-1} i.p.) + captopril (20mg kg^{-1} 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 white bar represents mean value of time spent in target quadrant in search of missing platform recorded during four consecutive retrieval trials conducted on day 5. a=P<0.05 Vs time spent in other quadrants i.e. Q1, Q3 and Q4 in normal saline treated control group. b*=P<0.05 Vs time spent in target quadrant in sodium nitrite and BN52021 treated groups, respectively

the mice for searching the missing platform during the retrieval trials (Fig. 4) as compared to control group. Anterograde administration of scopolamine and after 5min of it captopril was administered 25min before the learning trials, significantly reversed scopolamine attenuation of decrease in ELT during the learning trials (Fig. 3). Anterograde administration of sodium nitrite and after 5min of it captopril was administered 25min before the learning trials, significantly overcome, sodium nitrite induced attenuation of decrease in ELT during the

learning trials (Fig. 3). Captopril also significantly overcome, sodium nitrite induced attenuation of higher TS in TQ by the mice to search the missing platform during the retrieval trials on 5th day (Fig. 4). Retrograde administration of BN52021 and after 5min of it captopril was administered 25min before the retrieval trials, significantly overcome, BN52021 induced attenuation of higher TS by the mice in TQ to search of missing platform during the retrieval trials (Fig. 4).

DISCUSSION

The aim of this study was to investigate the role of captopril 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 accusation trials and on increased in TS in the target quadrant for search of missing platform during the retrieval trial, noted in the present study, suggest normal acquisition and retrieval of memory.

Scopolamine is reported to be muscarinic cholinergic receptor blocker [39]. The hippocampus is innervated with cholinergic neurons and possesses muscarinic cholinergic receptors [40]. Therefore, it may be postulated that scopolamine induced anterograde amnesia may be due to its anticholinergic effect on hippocampus. Captopril significantly reverse anterograde amnesia of scopolamine. The present results supported by the previous observations that the captopril elevates mood [16] and cognition in human [27] and animals [22-25]. Elevated ACE activities have been noted in several brain regions of the patients suffering from Alzheimer's disease [19]. An another active ACE-inhibitor enalapril also reported to enhanced memory consolidation [25]. This was further supported by previous findings that RAS modulators, Losartan and Volsartan are reported to facilitate spatial memory in various active and passive tasks by enhancing cholinergic activity [22, 24, 31, 41] and also improve cognition [10, 25]. Antioxidants i.e. rutin, bioflavonoids and *Bacopa monniera* are reported to inhibit scopolamine induced amnesia [42-44] due to its modulatory effect on cholinergic system [45]. Activation of brain cholinergic system has been reported in hypertensive state [46]. Thus it may be possible to suggest that the noted property of captopril to attenuate scopolamine induced amnesia may be mediated through cholinergic system and which might be somewhere related to RAS and oxidative stress.

Sodium nitrite ($NaNO_2$) has reported to produced anterograde and retrograde amnesia [43] by damaging hippocampus and neocortex respectively. The hippocampus is responsible for anterograde memory or acquisition of information [47] and neocortex is the site for retrograde memory or retrieval of information [48]. The hippocampus is innervated with cholinergic neurons and possesses muscarinic cholinergic receptors [40]. $NaNO_2$ induced methemoglobinemia may be responsible to produce cerebral hypoxia [49] that initiate generation of free radicals and may damage hippocampus. $NaNO_2$ also reported to produce severe vasodilatation [50], which is documented to enhance the formation and release of angiotensin [51]. The activation of brain renin-angiotensin system is reported to impair learning and memory [52]. Hypertensive patients are also reported to suffer from amnesia [3, 53]. Moreover, activation of brain cholinergic system has been reported in hypertensive state [46]. In the present study captopril significantly reverse anterograde and retrograde amnesia of sodium nitrite. It is postulated that captopril has attenuated $NaNO_2$ induced anterograde amnesia partially by inhibiting ACE and partially by scavenging reactive oxygen species. Its ameliorative effect on retrograde amnesia may be exclusively due to scavenging of free radicals by sulphahydral group present in its structure. Captopril and others are reported to facilitate cognitive functions [24] in hypertensive patients. Therefore, the observed effect of captopril to attenuate $NaNO_2$ induced amnesia may be due to inhibition of ACE and consequent decrease in the formation of angiotensin. RAS modulators by activating cholinergic system are reported to improve sodium nitrite induced anterograde amnesia only not retrograde amnesia. The present contention is further supported by that antioxidant reversed sodium nitrite induced anterograde and retrograde amnesia [42, 43] by preventing the damage of both hippocampus as well as neocortex.

BN52021 is a platelet activating factor (PAF) receptor blocker, reported to produce retrograde amnesia [54]. BN52021 enhanced oxidative stress by facilitates degradation of PAF and consequently induced retrograde amnesia. The oxidative stress is demonstrated to produce neuronal cell damage [55]. Captopril significantly reverse BN52021 induced retrograde amnesia; possibly due to sulphahydral group present in its structure [56] that prevents oxidative stress induced neuronal cell death. The present contention is further supported by that antioxidant like rutin and bacosides elevate glutamate mediated release of PAF [57, 58] and attenuated BN52021 induced retrograde amnesia [43].

CONCLUSION

On the basis of present results it can be concluded that Captopril reverse scopolamine and sodium nitrite induced anterograde amnesia due to partially by inhibiting ACE and partially by scavenging oxygen species. Its ameliorative effect on retrograde amnesia of sodium nitrite and BN52021 may be exclusively due to scavenging of free radicals probably by sulphahydral group present in its structure, atleast in mice species.

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