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Hippocampal asymmetry in angiotensin II modulatory effects on learning and memory in rats

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Learning and memory effects of angiotensin II (Ang II) microinjected unilaterally (left or right) and bilaterally into hippocampal CA1 area on the background of the inhibited hippocampal angiotensin 1 receptors type (AT1) of male Wistar rats were studied. It was found that the combination (losartan 100 μg + Ang II 0.5μg) microinjected bilaterally or into the left CA1 area improved learning and memory in shuttle-box and step through behavioral tests as compared to the respective controls. The effects were more pronounced after injection into the left CA1 area as compared to the right-side. These findings suggest thatAng II infused on the background of the inhibited CA1 hippocampal AT1 receptors ameliorated the cognitive processes. The data show also an asymmetric effect of Ang II on learning and memory processes in the hippocampus. The stronger modulating effect after microinjection of the combination (losartan + Ang II) into the left CA1 hippocampal area suggests a leftward bias in the rat. The results point to a differential distribution of angiotensin II receptors modulating the learning and memory processes in the left and right hippocampal CA1 area.

Key words: angiotensin II, losartan, hippocampus, learning and memory

INTRODUCTION

The brain renin-angiotensin system (RAS) is composed of angiotensinogen, peptidases, angiotensin peptides (angiotensins), and specific receptor proteins. In addition to the most important peptide angiotensin (Ang) II, several biologically active angiotensins (Ang III, Ang IV and Ang-(1–7), are produced through different enzymatic pathways. The bioactive angiotensins of the brain RAS could have variable and sometimes opposite neurobiological activities (Santos et al. 2000, Llorens-Cortes and Mendelsohn 2002, von Bohlen und Halbach 2003 and von Bohlen und Halbach and Albrecht 2006).

An increased activity of brain RAS activity has been related to Alzheimer's dementia and modulation of the stress response (Castrén and Saavedra 1988, Savaskan et al. 2001, Bregonzio et al. 2008).

In accordance with the hypothesis about the involvement of brain RAS in Alzheimer's disease (AD) recent studies have reported improved memory and cognitive processing in animal models and AD patient treated with angiotensin receptor blockers (ARBs) (Tsukuda et al. 2009, Danielyan et al. 2010, Duron and Hanon 2010). Numerous findings support also a central role of AngII/ AT1/AT2 receptor systems in the stress response. Stimulation of brain Ang II activity is associated with enhanced responses to stress and increased anxiety while blockade of brain AT1 receptors or reduction of brain Ang II formation ameliorates the response to stress, anxiety and depression (Saavedra et al. 2011).

The various components of RAS are not restricted to the brain areas involved in the control of cardiovascular functions. They are also expressed in brain regions involved in the processing of cognitive functions, such as the hippocampus (Sirett et al. 1981, Chappell et al. 1989,) and the amygdala (Yang and Raizada 1999, von Bohlen und Halbach et al. 2000, Krizanova et al. 2001). Increasing evidence suggests that the RAS plays a role not only in cardiovascular and body fluid regulation but also in learning and memory. A number of workers have studied the

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involvement of angiotensins and angiotensin receptors in these processes (Armstrong et al. 1996, Belcheva et al. 2000, Kerr et al. 2005, Davis et al. 2006). Evidence concerning the role of the RAS in learning and memory is contradictory, although more studies support the view that angiotensin reduces cognitive function.

There are three recognized angiotensin receptor types: the Ang type 1, type 2 and type 4 receptors (AT1, AT2, and AT4) (de Gasparo et al**.** 2000). Angiotensin II acts through two highly-specific AT1 and AT2 receptors (Culman et al. 2001, Culman et al. 2002, Alexander et al. 2008). In rodents, there are two isoforms of the AT1 receptor (AT1a and AT1b), while in humans a single AT1 receptor type is present. Angiotensin II can be enzymatically cleaved to Ang III and Ang IV. Similar to Ang II, Ang III is a full agonist for the AT1 and AT2 receptors, while Ang IV binds with low affinity to the AT1 and AT2 receptors, but with high affinity and specificity to the AT4 receptor type (Chai et al. 2004, Braszko et al. 2006, Vanderheyden 2009). Unlike the G-protein coupled AT1 and AT2 receptors, the AT4 receptor is an integral membrane spanning protein, which is an insulin-regulated membrane amino peptidase (Albiston et al. 2001). The heptapeptide Ang-(1–7) is another biologically active product of the RAS cascade which can be generated from Ang I or Ang II through different enzymatic pathways. A specific binding site for Ang-(1–7) has been reported (the G-protein coupled receptor Mas) (Santos et al. 2003).

Ang II exerts its action in the central nervous system *via* AT1, AT2 and AT4 receptor which are differently distributed in the brain regions (Belcheva et al. 2000, de Gasparo et al. 2000). All three receptors may be involved in mediating the effects of Ang II in the brain (Albrecht 2010). While most of the known biochemical and cellular responses to Ang II have been found to be mediated by the AT1 receptor type, the function of the other Ang receptor types has not been clarified yet. Recent data revealed that the brain RAS is involved in the mediation of learning and memory. The role that central Ang receptors occupy in these processes is also not fully understood. Several reports indicate an involvement of Ang II and its receptors in cognitive processes (Georgiev et al. 1988, Kulakowska et al. 1996, Belcheva et al. 2000, Bild et al. 2013). The intracerebroventricularly (icv) applied Ang II has exhibited memory enhancing effects (Georgiev et al. 1988, Kulakowska et al. 1996). The hippocampus is a key brain structure in memory formation. The concentration of Ang II and the expression of its different receptor types are particularly high in the hippocampus (Sirett et al. 1981, von Bohlen und Halbach and Albrecht 1998, Wright and Harding 2008). It has been shown that Ang II regulates synaptic transmission in several brain regions including the hippocampus (Bild et al. 2013). In the hippocampal CA1 area, Ang II directly excites pyramidal neurons (Haas et al. 1980). Moreover, hippocampal Ang II and its metabolites angiotensin IV (AIV) and angiotensin-(1–7) (A1–7) modulate long-term potentiation (LTP) (Wayner et al. 1995, 1997, 2001, Kramar et al. 2001, Hellner et al. 2005), an activity-dependent, plastic process which is considered as a cellular correlate of memory (Martin et al. 2000).

It was also demonstrated that Ang II administered to the hippocampus impaired retention of the single trial step through shock avoidance response by activation of AT1 receptors (Lee et al. 1995). Other studies have provided evidence that Ang II applied to the hippocampal CA1 area blocked memory formation through a mechanism involving the activation of AT2 receptors (Kerr et al. 2005). Additionally, it was stated that there is a possible role of hippocampal angiotensin II receptors in voluntary exercise-induced enhancement of learning and memory in rats (Akhavan et al. 2008). Recently, it has been reported that orally administered losartan (an antagonist of the Ang II type I receptors) suppresses the enhancing effect of voluntary running on cell proliferation in the rat hippocampus (Mukuda and Sugiyama 2007).

Previous studies on the lateralized effects of neuropeptides such as Ang II, vasoactive intestinal peptide and cholecystokinin infused into hippocampal CA1 area (Belcheva et al. 1998, 2000, 2007, Ivanova et al. 2008) and especially the lateralized learning and memory effect of Ang II microinjected into the rat hippocampal CA1 area triggered the interest to examine whether this effect could be attributed to a differential distribution of Ang II receptors in the hippocampus. The aim of the present study was to examine the involvement of angiotensin II type 1 (AT1) receptors in learning and memory processes after unilateral and bilateral topical application of losartan, a specific AT1 receptor antagonist, into hippocampal CA1 area in rats.

METHODS

Subjects

The experiments were carried out on 84 male Wistar rats (200–220 g at the time of surgery). The rats were individually housed in polypropylene boxes with free access to food and water. The animals were maintained in a constant temperature environment (22±2°C) on a 12 h light/dark cycle (lights on at 06:00 AM). The behavioral experiments were carried out between 10:00 AM and 01:00 PM. After the testingprocedure, the rats were returned to their respective home cages.

Ethical statement

The experiments were performed according to the ''Principles of laboratory animal care'' (NIH publication no. 85-23, revised 1985) and the rules of the Ethics Committee of the Institute of Neurobiology, Bulgarian Academy of Sciences. All efforts were made to minimize animal suffering and reduce the number of animals used in the study.

Surgical procedures

After anesthesia (Calypsol 50 mg/kg ip) the rats were placed in a stereotaxic apparatus (Stoelting, USA). Burr holes were drilled left and right of midline, at the following coordinates relative to bregma: posterior 3.8 mm; lateral 3.0 mm, according to the stereotaxic atlas (Pellegrino and Cushman (1967). Stainless steel guide cannulae (length 7 mm, external diameter 0.559 mm, internal diameter 0.305 mm) were vertically positioned with their tips at a depth of 2.0 mm below the dura. After surgery the animals were allowed 7 days to recover before the behavioral studies. During the recovery period the rats were handled daily.

Losartan (Sigma) and Angiotensin II (Sigma) were dissolved in saline and 0.5 µl of losartan (pH 7.4) and AngII solution (pH 7.4) were microinjected into the CA1 area at a dose of 100 µg for losartan and at a dose of 0.5 µg for Ang II. The drugs and saline were injected through an injection cannula connected by polyethylene tubing with a constant rate microsyringe (Hamilton, Reno, NV, USA) over a period of 1 min which was left in place for additional 30 s. The combination (losartan + Ang II) was applied by separate injections with a 10 min lag (losartan injection preceded the Ang II injection). Five minutes after the Ang II microinjection the rats were placed into the shuttle-box. The combination (losartan + Ang II) was microinjected into left, right and both hippocampal CA1 areas 5 min before the first and second training day. Control animals were microinjected with saline in the same manner. Following the termination of the experiments and immediately prior to sacrifice, the rats were injected with 0.5 µl 2% fast green dye through the injection cannula for verification of cannula placement. Injection sites were then anatomically verified *post-mortem* in 25 mm coronal brain sections cut through the hippocampus by an investigator, blind to the behavioral results. Animals in which cannulae placements were outside of CA1 hippocampal area or not perfectly symmetrical were excluded from the statistical analysis. Thus, 6 of the 42 rats (shuttle-box) and 4 of the 52 (step through) were discarded. The rats with bilaterally implanted guide cannulae were divided into six groups as follows: combination(right side infusion); combination (left side infusion); combination(bilateral infusion); saline (right side infusion); saline (left side infusion) and saline (bilateral infusion).

Two-way active avoidance test (shuttle-box)

The animals were trained for two-way active avoidance in a shuttle-box, according to the method of Burešová and Bureš (1983). The conditioned stimulus was the light of a 20 W bulb; the unconditioned stimulus was an electric non-scrambling shock (20–30 VAC, 0.5 mA, 50 Hz) delivered through the grid floor.

Two training trials in two consecutive days were carried out for the shuttle box task. On the first and second training session, each rat was placed into the experimental chamber and received 50 avoidance trials. The memory (retention) test was given 24 hours after the second training session. Each response of the rat (“avoidance”, “escape” or “inadequate”) was recorded. The primary measure of learning and memory in the active avoidance task is an increase in avoidance responses.

One-way passive avoidance (step through)

In the passive avoidance task the rat must learn to remain in a brightly lit compartment and not enter the preferred dark compartment to avoid a mild foot shock.

One training trial and two retention tests were conducted according to the method of Gozzani and Izquierdo (1976). The training trial was started by placing the rat in the light compartment. Once the rat had entered the dark compartment, a guillotine door was closed and an electrical shock (0.3–0.35 mA for 3 s) was delivered to the animal through the grid floor. Each rat underwent one trial. Retention tests (no shocks) were performed 3 h and 24 h after the acquisition trial. At that time, the animals were returned to the light compartment, and step-through latency was estimated by measuring the time for the rat to move to the dark compartment. A maximum latency of 180 s was used as a criterion for learning.

The combination (losartan+Ang II) or saline was microinjected uni- and bilaterally 5 min prior to the training trial only and was not injected before the retention test (on the 3rd h and 24th h after the training trial).

Statistical analysis

Separate two-factor analysis of variance (ANOVA) was used to analyze the data obtained for the number of avoidances for learning (first and second training day) and memory test (24 h after second training day) between subject factors: drug (two levels: combination and saline) and side of injection (three levels: left, right and bilateral). Findings from the ANOVAwere *post-hoc* analyzed by Student-Newman-Keuls test. Analysis of the passive avoidance data was performed using $\chi 2$ tests.

RESULTS

Shuttle box test

On the first training day two-way ANOVA demonstrated significant effects of the number of avoidances for the factors drug (combination: losartan+Ang II) ($F_{1,35}$=30.593; $P\leq0.001$) and side of injection ($F_{2,35}$=5.742; $P\leq0.01$). There was also significant interaction between side ofinjection and drug ($F_{2,30}$=13.374, $P\leq0.01$). *Post-hoc* SNK comparisons showed that the combination significantly increased the number of avoidances when it was infused into the left CA1 area ($P\leq0.001$) and into both CA1 areas ($P\leq0.001$) as compared to the respective controls, while right-side microinjections showed no significant difference compared to the controls. Microinjections of the combination into the left CA1 area produced a significant increase in the number of avoidances as compared to the right-side injections ($P\leq0.001$) (Fig. 1).

On the second training day ANOVA showed significant effects of the factors drug ($F_{1,35}$=21.73; $P\leq0.001$) and side of injection ($F_{2,35}$=3.302; $P\leq0.05$) as well as a significant interaction between them ($F_{2,\ 35}$=13.028, $P\leq0.001$). SNK comparisons indicated that the effect of the combination was significantly greater when it was injected into the left ($P\leq0.001$) and into both ($P\leq0.001$) CA1 areas as compared to the controls. The effect after microinjection into the right CA1 area was similar to the controls (Fig. 2). *Post-hoc* test showed also a significant increase in avoidance responses when the combination was infused into the left-side as compared with the right-side effects ($P\leq0.001$) (Fig. 2).

At the retention test, significant effects of the factors drug ($F_{1,35}$=38.244; $P\leq0.001$), side ($F_{2,35}$=24.244; $P\leq0.001$) and a significant interaction between drug X side ($F_{2,35}$=7.025; $P\leq0.01$) was observed. *Post-hoc* comparisons demonstrated that the combination exerted a memory-improving effect when it was infused into the left ($P\leq0.001$) and both ($P\leq0.001$) CA1 areas as compared to the respective saline microinjected rats. The microinjections into the left CA1 hippocampal area had a significantly greater effect as compared to the right CA1area ($P\leq0.001$) (Fig. 3).

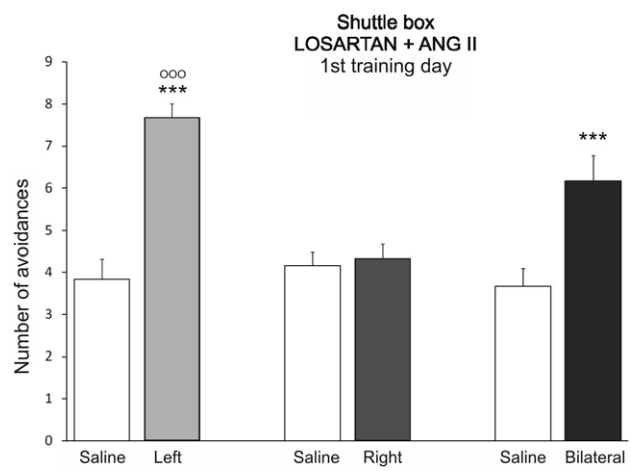

Fig. 1. Effects of combination (losartan 100 μg + Ang II 0.5 μg) microinjected bilaterally or unilaterally (left or right) into the hippocampal CA1 area on the learning: first training day (shuttle box). Asterisks depict comparisons of the number of avoidances, following injections of the combination vs respective saline injections into CA1 areas, ***$P\leq0.001$ Circles depict comparisons of the number of avoidances, following left side vs. right side injections, $^{ooo}P\leq0.001$. n=6. Means (±SEM) are presented.

Table I

Effects of combination (losartan 100 μg + Ang II 0.5 μg) microinjected bilaterally or unilaterally (left or right) into the hippocampal CA1 area in retention tests (step through) (n=8)

	Retention test					
	3 h			24 h		
Groups	Latent time X±SEM	% rats	Criteria for learning	Latent time X±SEM	% rats	Criteria for learning
Left – Saline	151.3±13.0	50	(4/8)	158.8±10.2	50	(4/8)
Left – Combination	175.9±2.7^{*o}	75	(6/8)	178.5±1.5^{**oo}	88	(7/8)
Right – Saline	146.5±13.2	50	(4/8)	148.7±12.1	50	(4/8)
Right – Combination	152.9±14.4	50	(4/8)	152.6±11.7	50	(4/8)
Bilateral – Saline	149.5±13.4	50	(4/8)	149.1±13.4	50	(4/8)
Bilateral – Combination	172.6±3.7*	63	(5/8)	176.1±2.6**	63	(5/8)

$^{*}P\leq0.05$; $^{**}P\leq0.01$ significance vs. respectively saline treated rats; $^{o}P\leq0.05$;$^{oo}P\leq0.01$ left- side vs. right-side

Step-through test

Left-side and bilateral microinjections significantly improved the performance in the step-through avoidance task as compared to the saline-treated controls. Left-side infusion of the combination into the CA1 area significantly prolonged the latent time in the retention tests on the 3rd h ($P\leq0.05$) and 24th h ($P\leq 0.05$) and increased the percentage of rats reaching the learning criteria as compared to the respective saline-treated rats (Table I). The combination infused bilaterally significantly increased the latent time on the 3rd h ($P\leq0.05$) and 24th h ($P\leq0.05$) and the percentage of rats that reached the learning criteria (Table I).There was no significant effect of the combination into the right CA1 area on learning criteria (Table I). Comparing the effect of the unilateral injections (left-side vs. right-side) the results show that the left-side injections increased significantly the latent time on the 3rd h ($P\leq0.05$) and 24th h ($P\leq0.05$) and the learning criteria on the 3rd h and 24th h (Table I).

DISCUSSION

The present results showed that microinjections of Ang II on the background of inhibited AT1 receptors into the left or both hippocampal CA1 areas significantly improved learning and memory examined using the passive and active avoidance tests. The effect was more pronounced after the microinjection into the left hippocampal CA1 area thus suggesting a dependence on the side of injection. In the shuttle box test the combination (losartan+Ang II) infused into the left or both CA1 areas significantly increased the number of avoidances during the training sessions (learning) and at the retention test (memory), while the microinjection into the right CA1 area did not show a significant effect. In the step through test the administration of the combination (losartan+Ang II) into the left or both CA1 areas increased the latent time on the 3rd and 24th h tests compared to respective saline-treated controls. The latent time on the 3rd h and 24th h was significantly prolonged upon administration into the left-side as compared to the right-side treated rats. The left-side microinjection significantly increased the percentage of rats that reached the learning criteria on the 3rd h and 24th h as compared to the right-side saline-treated rats.

Much contradictory data about the involvement of Ang II and its receptors (AT1, AT2 and AT4) in cognitive processes is found in the literature. It has been shown that icv administration of Ang II enhances aversive memory in rodents (Baranowska et al. 1983, Braszko and Wisniewski 1988, Braszko et al. 1988a, Georgiev et al. 1988, Georgiev 1990, Braszko 2002). The administration of Ang II into the dorsal neostriatum decreased the retention in the step-down shock avoidance test (Morgan and Routtenberg 1977), while

retrieval in the passive avoidance task was increased after icv administration of Ang II (Braszko et al. 1988a,b, Braszko 2002, von Bohlen und Halbach and Albrecht 2006).

Belcheva and coauthors (2000) have found that Ang II facilitated learning and memory, especially when microinjected into the left CA1 hippocampal area, thus suggesting a differential distribution of Ang receptors (AT1 and/or AT4) in the brain hemispheres. The present data is in accordance with this finding and expanded it. The study is the first to provide information on the positive learning and memory effects of Ang II microinjected on the background of inhibited AT1 receptors into the left but not into the right hippocampal CA1 area. The results suggest that the right and left CA1 hippocampal areas have different roles in learning and memory processes in rats, with the role of the left CA1 hippocampal area being more significant. The differential behavioral effects of Ang II microinjected into the left or the right CA1 imply a different distribution of Ang receptors in these hippocampal areas (Rowe et al. 1991, Wright and Harding 1995, Belcheva et al. 2000, Bild and Ciobica 2013).

Angiotensin II interacts with AT1 and AT2 receptors, which are expressed in the rat hippocampus (Reagan et al. 1994). The effects of brain Ang II depend mainly on AT1 receptor stimulation. It is generally assumed that the AT2 receptor counteracts the action of the AT1 receptor (de Gasparo et al. 2000).

Regarding synaptic plasticity, Ang II blocks long-term potentiation (LTP) in the hippocampus (Denny et al. 1991, Armstrong et al. 1996) and amygdala (von Bohlen und Halbach and Albrecht 1998). Activation of AT1 receptors by Ang II has also been found to inhibit both synaptic LTP (Wayner et al. 1993) and long-term depression (Tchekalarova and Albrecht 2007). It has been also demonstrated that hippocampal angiotensin II receptors are involved in voluntary exercise-induced enhancement of learning and memory in rat (Akhavan et al. 2008). There are reports that Ang II reduces N-methyl-D-aspartate (NMDA) receptor signaling through AT2 (Ang II type 2) receptor-mediated mechanisms (Schelman et al. 1997, Jing et al. 2004, Schelman et al. 2004). The Ang II applied to the hippocampal CA1area has been shown to block memory formation through a mechanism involving activation of AT2 receptors (Kerr et al. 2005).

Controversial data have been reported concerning the effects of Ang II receptor antagonists, losartan and PD-123177 (selective for the AT1 and AT2 receptor, respectively). No effects of either compound has been found in two different models of working memory in

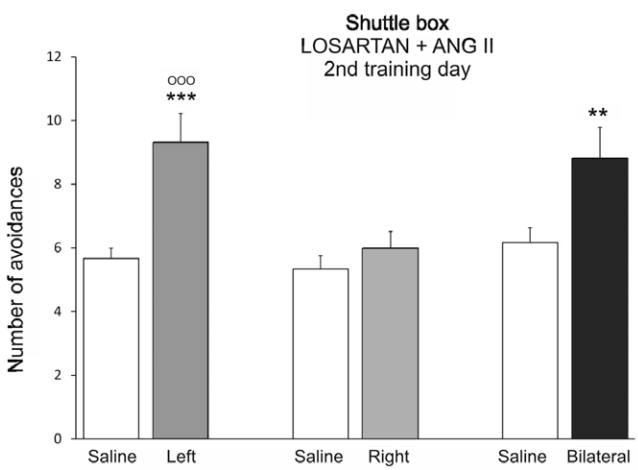

Fig. 2. Effects of combination (losartan 100 μg + Ang II 0.5 μg) microinjected bilaterally or unilaterally (left or right) into the hippocampal CA1 area on the learning: second training day (shuttle box). Asterisks depict comparisons of the number of avoidances, following injections of the combination vs. respective saline injections into CA1 areas,**$P\leq0.01$; ***$P\leq0.001$. Circles depict comparisons of the number of avoidances, following left side vs. right side injections, $^{ooo}P\leq0.01$. n=6. Means (±SEM) are presented.

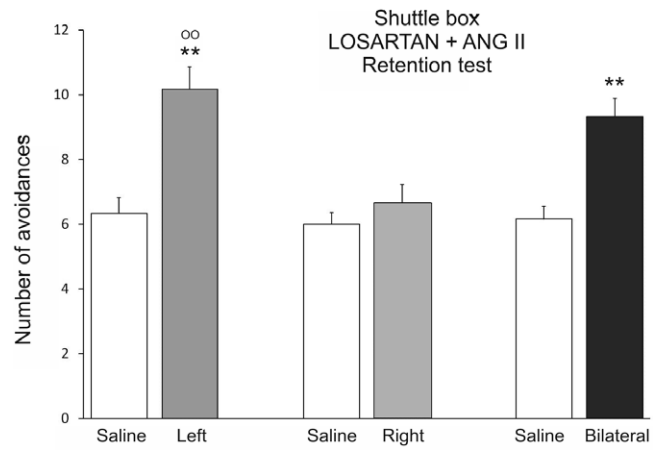

Fig. 3. Effects of combination (losartan 100 μg + Ang II 0.5 μg) microinjected bilaterally or unilaterally (left or right) into the hippocampal CA1 area on the retention test: 24 hours after second training day (shuttle box). Asterisks depict comparisons of the number of avoidances, following injections of the combination vs. respective saline injections into CA1 areas, **$P\leq0.01$. Circles depict comparisons of the number of avoidances, following left side vs. right side injections, $^{oo}P\leq0.01$. n=6. Means (± SEM) are presented.

rats (Shepherd et al. 1996). Other studies have shown that low doses of the above mentioned Ang II receptor antagonists improved scopolamine-impaired performance in a light/dark box habituation task (Chalas and Conway 1996). Recent studies revealed that the administration of AT1 receptor blocker, telmisartan, decreased hypertension-induced learning and memory deficits in a water maze task (Sharma and Singh 2012) while in another study telmisartan ameliorated memory deficits in type 1 diabetic mice (Du et al. 2014). In a shuttle-box avoidance task, the AT1 blocker, olmesartan, diminished the cognitive alterations observed for the human renin and human angiotensinogen gene chimeric transgenic mice, together with an increase of the cerebral blood flow (Inaba et al. 2009). An opposite effect was observed in a study where the inhibition of AT1 receptor by losartan improved learning and memory (Gard 2002, 2008). It was also reported that the administration of AT2 receptor agonist improved the cognitive deficit observed in a specific type 2 diabetes mellitus model in mice (Mogi et al. 2012).

The data showed that upon pretreatment with losartan (AT1 receptor antagonist) Ang II injected bilaterally or into the left CA1 hippocampal area improved learning and memory of rats tested in two different avoidance tasks as compared to the controls. Taking into consideration the learning and memory facilitating effect of Ang II (shuttle box) especially into the left CA1 hippocampal area (previously reported from Belcheva and colleagues (2000) an assumption about the involvement of hippocampal angiotensin receptors in learning and memory processes could be made**.** The learning and memory effect of combination (losartan+Ang II) might not be associated with involvement only of AT1 receptors.

Since the effect of Ang II administered alone is comparable with the one of the Ang II applied on the background of the inhibited AT1 receptors, we suggest that some other receptors might be involved in mediating these effects. Blockade of the AT1 receptor allows stimulation of the AT2 receptor, and additionally increases the bioavailability of Ang II for an enzymatic conversion to Ang IV (Guimond and Gallo-Payet 2012). Several studies have confirmed that stimulation of the AT2 receptor activates multiple signaling pathways which are linked to beneficial effects on neuronal functions (including excitability, differentiation, and regeneration (Guimond and Gallo-Payet 2012). Data accumulated that the therapeutic effects of angiotensin receptor blockers (ARBs), which are widely used in patients of hypertension may reflect not only the inhibition of the AT1 receptor but also an activation of the AT2 receptor (Gallo-Payet et al. 2011). For example, it was revealed that the stroke protective effects of ARBs were exerted not only by the selective blockade of the central AT1 receptors but also to the stimulation of the unoccupied AT2 receptors by Ang II (Chrysant 2007). In another study it was reported that AT2 receptor stimulation could be involved in the beneficial effects of ARBs on cardio vascular remodeling (Wu et al. 2002). Besides, the extensive research on the role of AT2 receptors in cognitive processes provided evidence about their positive effect on cognitive processes (Jing et al. 2012, Mogi et al. 2012).

Brain angiotensin II can be enzymatically cleaved to Ang III (which activates AT1 and AT2 type of receptors) and to Ang IV, which binds to the AT4 receptor (Chai et al. 2004, Vanderheyden 2009). The hippocampus has a high density of AT4 receptors, which could be implicated in the enhanced cognitive functioning in the presence of exogenous Ang II (von Bohlen und Halbach and Albrecht 1998, Wright and Harding 1995, 2011, Albrecht 2010). Therefore, conversion of Ang II to Ang IV and the activation of the hippocampal AT4 receptors is also likely to contribute for the observed memory enhancing effect.

In recent years evidence has accumulated that activation of AT4 receptors is involved in the expression of Ang II related learning and memory effects. Numerous studies indicate that Ang IV and Ang IV analogues can facilitate learning, memory consolidation and long-term potentiation (Wright et al. 1993, 1999, Kramar et al. 2001, Albiston et al. 2004).

Studies have demonstrated that upon icv infusion of Ang IV facilitates memory retention and retrieval in rats in passive avoidance paradigms (Braszko et al. 1988b, Wright et al. 1993). In addition, in two different rat models of memory deficits the AT4 receptor agonists reversed the performance deficits observed in the Morris water maze task (Pederson et al. 1998, Wright et al. 1999). Central administration Ang IV dose-dependently enhanced learning and memory performance in a novel object recognition task (Paris et al. 2013) and enhanced LTP in hippocampal CA1 neurons (Wayner et al. 2001, Davis et al. 2006).

The mechanisms by which Ang IV enhances cognitive performance are still a subject of investigation. The distribution of AT4 receptors which are associated with cholinergic neurons, motor and sensory nuclei in the brain suggests that Ang IV may modulate central motor and sensory activities, as well as memory (Vauquelin et al. 2002, Albiston et al. 2004, De Bundel et al. 2008, Wright et al. 2008). The stimulation of AT4 receptors has been shown to potentiate depolarization-induced release of acetylcholine from hippocampal slices (Lee et al. 2001). The memory-improving effects of Ang IV are not only dependent on the cholinergic system (Wilson et al. 2009), but also on the functional integrity of dopamine receptors (Braszko 2009).

Angiotensin-(1–7) is another metabolite Ang II degradation in the brain. It activates Mas receptor (encoded by Mas proto-oncogene). Highest concentrations of Mas receptors have been identified in the dentate gyrus of the hippocampus and piriform cortex (Freund et al. 2012). Ang (1–7) has been shown to facilitate hippocampal long-term potentiation (Hellner et al. 2005) suggesting its importance in learning and memory.

Finally, it should be considered that the facilitation of active and passive avoidance behavior induced by Ang II might be related to a stimulation of brain dopaminergic, gamma-aminobutyric acid (GABA) and cholinergic (Ach) neurotransmission (Wisniewski and Braszko 1984, Yonkov et al. 1986, 1987, 1989, Georgiev et al. 1988, Yonkov and Georgiev 1990).

CONCLUSION

This study demonstrates that Ang II infused on the background of inhibited AT1 receptors in the hippocampal CA1 area produced a lateralized learning and memory enhancing effect as showed in active (shuttle box) and passive (step through) avoidance tasks. The infusion of the combination (losartan+Ang II) into the left CA1 but not into the right CA1 area enhanced learning and memory. This finding suggests a differential distribution of Ang receptors (most likely AT4) which might be involved in the mediation of the cognitive processes and a/or a possible interaction of Ang II with other brain neurotransmitter systems (dopamine, Ach, GABA). Further studies using specific angiotensin receptor ligands are needed to define the role of the different types of angiotensin receptors in learning and memory processes.

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