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ROLE OF ANGIOTENSIN ANTAGONISTS IN MEMORY ENHANCEMENT

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ABSTRACT:

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by a gradual decline in memory associated with shrinkage of brain tissue, with localized loss of neurons mainly in the hippocampus and basal forebrain and also diminished level of central cholinergic neurotransmitter-Acetylcholine. Renin Angiotensin and Aldosterone system plays a major role in progression of many diseases such as hypertension, atherosclerosis, kidney failure etc., Angiotensin IV (Ang IV) is a derivative of the potent vasoconstrictor Angiotensin II (Ang II). Angiotensin receptor blockers mainly blocks AT_1 receptor of Ang II because it has more affinity towards AT_1 receptor. Hence this prevents action of Ang II on AT_1 receptor and enhances the formation Ang IV and it has been proved for its memory enhancing property. In this work memory enhancing activity of Angiotensin Antagonists Losartan, Irbesartan and Valsartan was evaluated using Hebb's William maze (Rectangular maze) and the results shows significant increase in memory ,which is comparable between groups $p<0.01$.The memory enhancing capacity of the drugs were very significant when compared to normal control and negative control ($p<0.001$).

KEYWORDS

Ang II, Ang IV, Losartan, Irbesartan, Valsartan and Acetylcholine.

INTRODUCTION

Alzheimer's disease (AD) refers to dementia that does not have an antecedent cause, such as stroke, brain trauma or alcohol [1]. Dementia is a syndrome of failing memory and other intellectual functions with little or no disturbances in consciousness [2]. Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by a gradual decline in memory[3] associated with a shrinkage of brain tissue, with localized loss of

neurons mainly in the hippocampus and basal forebrain[1] and also diminished level of central cholinergic neurotransmitter-Ach[4,5]. Renin angiotensin and aldosterone system plays a major role in progression of many diseases such as hypertension, atherosclerosis, kidney failure etc., Angiotensin IV is a derivative of the potent vasoconstrictor angiotensin II. Ang II actions are mediated by AT_1 and AT_2 receptors, which are seven transmembrane glycoprotein with 30% sequence similarity [6]. Angiotensin receptor blockers mainly blocks AT_1 receptor of Ang II because Ang II has more affinity towards AT_1 receptor. Hence this prevents action of Ang II on AT_1 receptor and enhances the formation angiotensin IV. Ang IV has been proved for its memory enhancing property[7]. The various types of drugs acts on renin angiotensin and aldosterone system are Angiotensin converting enzyme inhibitor (ACEI), Renin inhibitors and Angiotensin receptor blockers, Except Angiotensin receptor blockers all drugs decrease the synthesis of Ang IV and thus have detrimental effects on learning and memory. So the aim of present study was to evaluate and compare the memory enhancement activity of Angiotensin Antagonists Losartan, Irbesartan and Valsartan by blocking the Ang II receptor and thereby increases the formation of Ang IV.

MATERIALS AND METHODS

Albino Mice of either sex, younger ones (3 months old) and adult ones (16 months old) were used. Animals were procured from the disease free small animal house. They were acclimatized to the laboratory conditions for 5 days. They were kept in poly propylene cages under controlled temperature and humidity. They had free access to food and water and were housed under standard light-dark cycle (12hr each). All the experiments were carried out during day time from 0900 to 1600hr.

Losartan potassium-USP (Simlan Laboratories Ltd., Mumbai), Irbesartan-USP(Hetero Labs Ltd., Andra pradesh) Valsartan – USP (Hetero Labs Ltd., Andra pradesh), Buscopan (scopolamine or Hyoscine 20mg/ml-Cadila Health Care Ltd., Goa), Nootrophil (Piracetam-200mg/ml,UCB India pvt Ltd.,Thane). All the drugs were injected intraperitoneally; volume of injection was made 1ml/100g of body weight of the mouse. All the drugs were dissolved in distilled water, Valsartan alone made suspension with 0.5% CMC. Piracetam is a nootropic drug whereas Scopolamine is an amnestic agent.

Assessment of learning and memory using Hebb's William Maze (Rectangular Maze):The maze consists of completely enclosed rectangular box with an entry and reward chamber appended at opposite ends. The box is partitioned with wooden slats into blind passages leaving just twisting corridor leading from the entry to the reward chamber[8].

Experimental Protocol: Adult mice and young mice were randomly divided into 10 groups each, each group consist of five animals. First 10 groups consist of adult mice and next 10 groups consist of young mice. The treatment protocols were same for both the animals.

Group I: 0.5% CMC was injected intraperitoneally for 8 days (vehicle control).

Group II: Scopolamine (0.4mg/kg) was injected intraperitoneally on 8th day.

Group III: Piracetam (400mg/kg) was injected intraperitoneally for 8 days (positive control).

Group IV: Losartan potassium (20mg/kg) was injected intraperitoneally for 8 days.

Group V: Irbesartan (20mg/kg) was injected intraperitoneally for 8 days.

Group VI: Valsartan (20mg/kg) was injected intraperitoneally for 8 days.

Group VII: Piracetam (400mg/kg) was injected intraperitoneally for 8 days. After 60 min of last injection, Scopolamine (0.4mg/kg) was injected.

Group VIII: Losartan potassium (20mg/kg) was injected intraperitoneally for 8 days. After 60 min of last injection, Scopolamine (0.4mg/kg) was injected.

Group IX: Irbesartan (20mg/kg) was injected intraperitoneally for 8 days. After 60 min of last injection, Scopolamine (0.4mg/kg) was injected.

Group X: Valsartan (20mg/kg) was injected intraperitoneally for 8 days. After 60 min of last injection, Scopolamine (0.4mg/kg) was injected.

Transfer latency was noted at 45 min after the injection on the 8th day and after 24 h (i.e.) on the 9th day in all the treated animals.

On the first day i.e. on the 8th day all the mice were familiarized with Hebb's William Maze for a period of 10 min. This is known as training session. On 2nd day i.e. on 9th day the mouse was placed in the entry chamber and the timer was activated as soon as the mouse leaves the entry chamber. The time taken for the mouse to reach the reward chamber was taken as the transfer latency. For each animals four readings were taken, the average is taken as learning score (transfer latency) for that animal. Lower scores of assessment indicate efficient learning while higher score indicate poor learning in animals. During learning assessment, the animals were exposed to food and water only after 1 hour of maze exposure.

Table-1.

Memory Enhancement Activity of Angiotensin Antagonists (In Adult mice):

Groups	Treatment And Dose	Transfer Latency (In Sec)	
		On 8th Day	On 9th Day
Group I	0.5% CMC (10 ml/Kg i.p).	64±0.32	52±2.5
Group II	Scopolamine (0.4mg/kg)	76±1.28	84±3.17
Group III	Piracetam (400 mg/Kg i.p).	35±2.8*	30±2.9*
Group IV	Losartan potassium (20 mg/Kg i.p).	35±2.2*	31±2.1*
Group V	Irbesartan (20 mg/Kg i.p).	32±0.6*	29±0.32*
Group VI	Valsartan (20 mg/Kg i.p).	43±0.95*	38±4.84*
Group VII	Piracetam(400mg/kg)+Scopolamine(0.4mg /kg)	67±9.9	62±14.3
Group VIII	Losartan(20mg/kg)+ Scopolamine(0.4 mg/kg)	80±2.6	79±4.3
Group IX	Irbesartan(20mg/kg)+ Scopolamine(0.4 mg /kg)	52±0.84	43±4.61
Group X	Valsartan(20mg/kg)+ Scopolamine(0.4 mg/kg)	75±0.87	65±1.1

*Using ANOVA p value is significant (p<0.01). Using dunnet's t test *p<0.001 vs Normal control , n=5.*
Using student's t test all groups showed significant result p<0.001 vs negative control (scopolamine)

***Table*-2.**

Memory Enhancement Activity of Angiotensin Antagonists (In young mice):

Group	Treatment And Dose	Transfer Latency(In Sec)	
		On 8th Day	On 9th Day
Group I	0.5% CMC (10 ml/Kg i.p).	76±1.45	63±1.83
Group II	Scopolamine (0.4mg/kg)	90±1.91	92±10.3
Group III	Piracetam (400 mg/Kg i.p).	49±0.77*	40±1.83*
Group IV	Losartan potassium (20 mg/Kg i.p).	56±1.1*	43±1.83*
Group V	Irbesartan (20 mg/Kg i.p).	46±0.55*	37±0.97*
Group VI	Valsartan (20 mg/Kg i.p).	51±0.39*	40±3.85*
Group VII	Piracetam(400mg/kg)+ Scopolamine(0.4 mg /kg)	77±3.5	72±3.7
Group VIII	Losartan(20mg/kg)+ Scopolamine(0.4 mg/kg)	82±2.5	80±1.39
Group IX	Irbesartan(20mg/kg)+ Scopolamine(0.4 mg /kg)	81±0.86	67±1.56
Group X	Valsartan(20mg/kg)+ Scopolamine(0.4 mg/kg)	66±2.24	61±0.6

*Using ANOVA p value is significant (p<0.01). Using dunnet's t test *p<0.001 vs Normal control, n=5. Using student's t test all groups showed significant result p<0.001 vs negative control (scopolamine)*

STATISTICS

The values given for transfer latency were mean ± SEM; p values are calculated using students' t' test, dunnets 't' test and ANOVA.

RESULT

The memory enhancing activity of Angiotensin antagonists Losartan, Irbesartan and Valsartan were evaluated using rectangular maze. Adult and young mice showed higher transfer latency on 8th day compared to 9th day in all treatment groups except scopolamine treated group which was given in the Table 1 and 2 respectively. This indicates memory enhancing capacity of the drugs of angiotensin antagonists. Piracetam 400mg/kg treated for successive 8 days acts as positive control, possessed significant decrease in transfer latency when compared to normal and negative using dunnets ' t' test and students 't'-test. ANOVA shows p<0.01, hence the differences between groups were comparable. Losartan, Irbesartan and Valsartan shows p<0.001 when compared to vehicle control and negative control. On combination with scopolamine it decreases the transfer latency in all groups than that of negative control, but the results were not more significant.

DISCUSSION

The present work was undertaken to study the effect of angiotensin antagonists on learning and memory in young and adult mice for their establishment in Alzheimer's disease. Effect of angiotensin antagonists Losartan, Irbesartan and Valsartan were evaluated using the interoceptive model of learning and memory shows significant result. From the above results decrease in transfer latency indicates increase in memory. Administration of drugs is a complementary approach, in some cases enabling more specific targeting of neuronal anatomy or biochemical functions that are suspected to underlie formation of memory. In this experiment scopolamine was

used as an amnestic agent, Scopolamine induced impairment of memory is due to cholinergic deficits in certain brain areas and appears to be unrelated to oxygen free radical.[9,10]

Piracetam 400mg/kg, Angiotensin antagonists Losartan, Irbesartan and Valsartan (20mg/kg) injected for successive 8 days to young mice and adult mice improved learning and memory significantly ($p<0.001$) when compared to vehicle and negative control. They also reverse scopolamine induced amnesia but they were not more significant.

Elevated brain Ang II may interfere with Acetylcholine (Ach) release that in turn interferes with cognitive function[11].It also interfere with potassium mediated release of Ach from rat entorhinal cortex slices[12].This effect of Ang II could be blocked by sartans.

Antagonists of the angiotensin type, AT_1 receptor (angiotensin antagonists) selectively prevents the vasoconstrictor action of Ang II and enhance the formation of Ang IV. Ang IV was found to recall of a passive avoidance response and enhance memory. Except Ang II receptor antagonist, renin inhibitors and ACE inhibitors found to decrease the synthesis of Ang II and in turn decreasing the synthesis of Ang IV [13]. So the mechanism of memory enhancement activity of angiotensin antagonists may be due to blocking Ang II receptor, thus potassium mediated release of Ach might be enhanced and facilitation of formation of Ang IV (or) Ang IV like compound and its ligand that acts on the AT_4 receptor subtype to improve performance.

Hence our finding suggested that if we use angiotensin antagonists in hypertensive patients associated with memory deficit, it will prevent the patient to consume more than one drugs for separate ailments and also these drugs may prevents the hypertensive patients to become memory deficit.

CONCLUSION

Our present study revealed that Angiotensin Antagonists Losartan, Irbesartan and Valsartan enhances memory when tested using rectangular maze, however further studies has to be conducted to study the receptor action of the drugs responsible for memory.

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