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Effect of Telmisartan on Learning and Memory in Albino Rats

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Abstract: Dementia is a syndrome of gradual onset and continuous decline of higher cognitive function. By 2050, more than 115 million people will have dementia. The prevalence of dementia rapidly increases from about 2-3% among those aged 70–75 years to 20–25% among those aged 85 years or more. Etiology of dementia is Alzheimer's disease (AD), vascular dementia, and other neurodegenerative disease. Discovery of complete Renin angiotensin system (RAS) in the brain, and Potential function of Ang II in the etiology of certain neurodegenerative diseases, including Alzheimer's and Parkinson's disease, seizures, and the development of metabolic syndrome and diabetes. Telmisartanpossess partial peroxisome proliferators' activator receptor gamma (PPAR) agonistic activity. PPAR-γ agonists have been reported to effectively attenuate oxidative stress, inflammation and apoptosis in the central nervous system (CNS). Wister albino rats weighing between 150-250 grams were taken for the present study. Rats were divided in five different groups, six animals in each group. The groups were as follows Group A was placebo (1% gum acacia) treated, Group B was treated with telmisartan, Group C was treated with donepezil, and Group D was treated with scopolamine, and Group E telmisartan and scopolamine. Drugs were given for a period of 20 days. The Morris Water Maze Test was carried out from 15th to 20th day. Time taken by the rats to find the hidden platform was defined as "Escape Latency" was recorded. Data were expressed as mean±standard deviation. Statistical difference between the experimental groups was determined by one-way ANOVA. The rate of learning and the extent of memory retention were different in different groups. This may be due to the nature of the drug given to these groups. Telmisartan have markedly improved learning and memory in rats as compared to control. Donepezil caused more improvement when compared to Telmisartan.

Keywords: Dementia, Escape Latency Time, Metabolic syndrome, Morris Water Maze, Renin angiotensin system, Telmisartan.

INTRODUCTION

Dementia is a syndrome of gradual onset and continuous decline of higher cognitive functioning. It is a common disorder in older persons and becomes more prevalent with each decade of life. Approximately 10% of adults 65 years and older and 50% of adults older than 90 years have dementia. It is estimated that, by 2050, more than 115 million people will have dementia [1], this is a progressive neurodegenerative disorder associated with loss of neurons in distinct brain areas.

Dementia rates are growing at alarming proportion in all regions of the world and are related to aging population [2]. Neurologic conditions, including dementia, were estimated by the Global Burden of Disease 2010 Study as the third leading cause of years lived with disability at global level. Selective loss of cholinergic neurons and decrease in cholineacetyltransferase activity was reported to be a characteristic feature of senile dementia of the Alzheimer type [3].

The prevalence of dementia rapidly increases from about 2-3% among those aged 70–75 years to 20–25% among those aged 85 years or more[4]. Several studies showed that the overall prevalence of dementia varies widely among countries, being influenced by cultural and socioeconomic factors [5]. The number of people living with dementia worldwide in 2015 was estimated at 47.47 million, reaching 75.63 million in 2030 and 135.46 million in 2050[6]. The common causes accounting for dementia are Alzheimer's disease (AD), vascular dementia, and other neurodegenerative disease. Other important causes are dementia associated with depression, Parkinsonism and Schizophrenia. Dementia of AD accounts for 50–70% of total dementia cases. Cholinergic neurons in the central nervous

system are degenerated in patient with Alzheimer disease (AD) results into the impairment of memory [7].

Evidences from large clinical trials suggests that blockade of the Renin angiotensin system (RAS) by angiotensin (Ang) II type 1 (AT1) receptor blockers (ARBs) or angiotensin-converting enzyme inhibitors is effective in preventing target organ (such as heart and kidney) damage than other hypertensive agents. The accumulating evidence suggests possible mechanisms by which ARBs prevent brain damage and dementia [8].

A major advance in the field of the renin-angiotensin system (RAS) was the discovery of a complete RAS in the brain, independent from the peripheral system, by Jacques Genest's laboratory in Montreal in 1971. They are also present in structures involved in cognition, behavior, and locomotion [9].

Potential function of Ang II in the etiology of certain neurodegenerative diseases, including Alzheimer's and Parkinson's disease, seizures, and the development of metabolic syndrome and diabetes are evident from many studies [10]. Ang IV is a derivative of Ang II, has been shown to enhance acquisition, consolidation and recall in animal models of learning and memory when administered centrally or peripherally [11].

AT4 binding sites are found in regions associated with cognitive and motor function including neocortex, hippocampus, and cerebellum [12]. According to medical records of more than 5 million patients, people taking ARBs had a 35–40% lower risk of developing Alzheimer disease and similar neurodegenerative disorders [13]. AT4 receptor is mainly associated with learning memory cognitive improvement. AT2 receptor which has vasodilatory property which increases blood flow to areas concerned with memory and cognition. AT2 receptor has vasodilator, anti-inflammatory, anti-oxidant, anti-apoptosis, neural regenerative properties.

Telmisartan an ARB with ability to cross blood brain barrier and effectively block AT1 receptor. It also possesses partial peroxisome proliferator's activator receptor gamma (PPAR) agnostic activity. PPAR-γ agonists have been reported to effectively attenuate oxidative stress, inflammation and apoptosis in the central nervous system (CNS), thus reducing neuronal damage [14]. Based on the above evidence and information plan of this research work was made.

MATERIALS AND METHODS

The experiment was carried out in the Department of Pharmacology (RIMS, Ranchi) a tertiary care center after taking approval of the Institutional Animal Ethics Committee (IAEC).

Healthy Male Wister albino rats weighing between 150-250 grams were taken for the present study. They are most standardized of all experimental animals. They are particularly suitable for testing of psycho-pharmacological study because they can be trained properly for various types of performances including development of conditioned reflex.

These rats were divided in five different groups, six animals in each group. The groups were as follows Group A was placebo (1% gum acacia) treated, Group B was treated with telmisartan 0.3 mg/Kg, Group C was treated with donepezil 0.07mg/Kg, Group D was treated with scopolamine 1mg/kg, and group E telmisartan and scopolamine in the above mentioned dose. The doses of drugs were determined on the basis of surface area of rats [15].

All the rats were given respective drugs according to the group allocated for a period of 20 days. The Morris Water Maze Test was carried out from 15th to 20th day. During this period the rats were trained to learn the task in first four days (i.e. to find out the hidden platform). The training days were designated as "day 1, 2, 3, 4". A gap of 48hrs was given before performing the memory retention test. This time gap simulates normal forgetting, which occurs due to lack of rehearsal of learned task. Then on 20th day, rats were tested for retention of the learned task using Morris Water Maze. The memory test day was designated as "day 6".

Procedure

Rats were placed in the water at a designated starting location and the time taken by the rats to find the hidden platform was defined as "Escape Latency". Each rat was tested for two trials/day with an inter-trial period of two minutes during which it was placed in its home cage. The rats were trained to navigate through the submerged platform. They were given a maximum time of 120 seconds (cut-off time) to find the hidden platform and were allowed to stay on it for 30 seconds to get oriented to the external cues. The platform was kept in the same position during the training days. Rats those failed to locate the platform within 120 sec were put on platform only in the first session. Average of the two Escape latency times to reach the platform was calculated for each rat.

All the data were expressed as mean±standard deviation. Statistical difference between the experimental groups were determined by one-way ANOVA, and differences were considered to be statistically significant if $P < 0.005$. Tukey's HSD test was used for post-hoc analysis of significant overall differences between the groups. All the computation was done by using statistical software IBM SPSS Statistics 20.

RESULTS

Table-1: Table 1 shows escape latency time of rats to find the hidden platform by rats in morris water maze

	GROUP A (CONTROL)	GROUP B (TELMISARTAN)	GROUP C (DONEPEZIL)	GROUP D (SCOPOLAMINE)	GROUP E (TELMISARTAN & SCOPOLAMINE)
	MEAN ESCAPE LATENCY TIME				
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD
Day 1	76.50±4.92	78.33±6.94	74.55±4.48	81.72±13.14	80.30±13.07
Day 2	49.98±5.17	47.69±6.07	43.80±5.00	77.22±15.89	63.60±18.96
Day 3	36.33±5.13	31.30±7.76	28.75±5.41	74.51±13.34	49.55±6.69
Day 4	26.51±1.78	22.10±3.93	19.13±5.14	73.05±13.39	36.38±3.44
Day 6	18.48±4.2	11.34±1.77	9.25±1.00	70.68±6.90	30.46±3.61

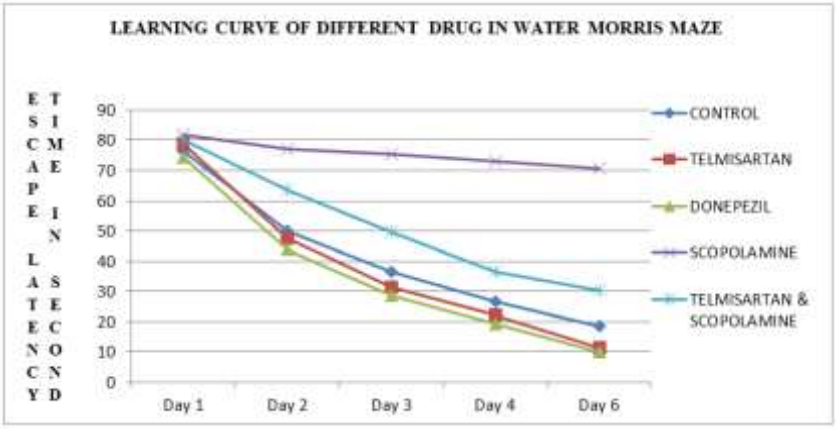

Fig-1: Figure 1 shows learning curve due to different drugs in rats in morris water maze

DISCUSSION

Control (group A) rats showed a normal learning behaviour, which is evident from a continuous decrease in Escape latency time for the finding hidden platform in Morris Water Maze Test. There was delayed learning in this group which was measured by an increased in escape latency time. Scopolamine impaired the learning and memory processing activities in rodents.

Telmisartan treated animals (group B) showed an improvement in learning of task in Morris Water Maze Test which is evident by decrease in mean escape latency time from day 1 to day 6 (Table 1). There was a significant improvement in learning of task on day 4 ($p < 0.05$) and it became highly significant on day 6 ($p < 0.01$) when compared to group A.

T. Kishi *et al.*[16] showed that low dose of Telmisartan protects against cognitive decline via up-regulation of brain-derived neurotrophic factor (BDNF) and its receptor tropomyosin-related kinase B (TrkB)) in the hippocampus of stroke-prone spontaneously hypertensive rats (SHRSPs), partly because of Peroxisome Proliferator Activated Receptor gamma (PPAR- γ) activation which is independent of blood pressure-lowering effect. Telmisartan improves memory impairment and reduces neural apoptosis in hippocampus via a PPAR-gamma-dependent anti-apoptotic mechanism in rats with repeated cerebral ischemia.

PPAR- γ isoform is expressed in monocytes and macrophages, where it suppress the expression of the pro-inflammatory cytokines i.e. IL-1β, TNF α, IL-6 and other neurotoxic product elaborated by β- amyloid stimulated microglial cells and monocytes[17].

Angiotensin II induces cerebrovascular remodeling, which promotes vascular inflammation and oxidative stress and results in impairment of regulation of cerebral blood flow. Experimental studies have shown that endogenous Ang II, which is released in response to AT1 receptor blockade, interacts with AT2 receptors, which may lead to memory-enhancing effects possibly through the modulation of dopaminergic and noradrenergic transmission. Blockade of Ang II at AT1 receptor level may also result in increased synthesis of Ang IV that selectively binds to AT4 receptors; activation of AT4 receptors is involved in memory acquisition and recall, perhaps by modulating neurotransmitter release and/or by remodeling the cholinergic and glutaminergic pathways in the hippocampus. Ang IV causes LTP and acetylcholine release in the hippocampus. AT4 receptors are densely located in neocortex, hippocampus, amygdala and basal nucleus of myernet, which is consistent with central location of cognitive processing [18]. Singh *et al*. [19]

demonstrated that telmisartan can attenuate streptozotocin induced experimental dementia of Alzheimer's disease type.

Jawaid *et al*.[20] in his study found that ARBs exhibit anti-oxidant action as evident from his study where ARB Telmisartan reduced lipid peroxidation product malondialdehyde (MDA), and tumor necrosis factor alpha (TNF-α) and elevated antioxidant, i.e. glutathione (GSH). Antioxidant action of ARBs is due to blockade of AT-II binding to AT1 receptors which activates NADPH oxidase.

Donepezil (group C) which was used as a reference drug showed improvement in learning of task which is evident from decrease in escape latency time from day 1 to day 6. Compared to Control (group A), Donepezil treated rats showed improvement in learning of task in Morris Water Maze Test which were statistically significant on day 3 (p value-0.032), and became highly significant on day 4 (0.008) and day 6.

Previous studies have shown that neuroprotective effects of Donepezil might be mediated by upregulation of nicotinic acetylcholine receptor (nAChR) and activation of the (nAChR/PI3K) phosphatidylinositol 3-kinase pathway. Activation of this pathway activates intracellular anti-apoptotic secondary messenger systems that protect neurons against death [21].

Debasree Deb *et al*.[22] states that antioxidant mechanism is involved in ameliorating dementia by their inhibition on acetylcholinesterase activity within the hippocampus. According to medical records of more than 5 million patients, people taking ARBs had a 35–40% lower risk of developing Alzheimer disease and similar neurodegenerative disorders [23]. Improvement of cerebral microcirculation by ARBs prevents neuronal damage. Therefore, blockade of the RAS by ARBs could prevent dementia due to metabolic syndromes.

The data obtained from this research work indicates that there is a decrease in mean Escape Latency Time in all groups. This is due to the learning and memory process in rats due to repetition of the task in all groups. The rate of learning and the extent of memory retention were different in different groups. This may be due to the nature of the drug given to these groups.

There is need of more sensitive and specific study for accurate determination of the above mentioned effects due to limitation of this research work i.e. A short duration study, long term studies are required for better and precise result and adopting the methods for observing the changes in the brain by Chemical methods like micro dialysis of acetylcholine release at synapses, CT scan, and functional MRI, might be helpful in such type of study.

CONCLUSION

The findings of this study reveals significant improvement in learning and memory in scopolamine induced dementia in albino rats given pretreatment with drug telmisartan. Donepezil was found superior to telmisartan. The beneficial effect on memory observed may be due to antioxidant, cholinergic effect and by modulation of RAS on the central nervous system. A worthwhile extension of the current study could be conducted to assess whether these findings are replicable in other models of learning and memory.

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