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RESEARCH ARTICLE

COMPARISION OF EFFECTS OF CARVEDILOL AND PROPRANOLOL ON LEARNING AND MEMORY IN RATS

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Abstract

Alzheimer's disease is one of the commonest neurodegenerative disorders encountered worldwide. Rise in oxygen free radical levels is considered to be the main reason for the signs and symptoms of Alzheimer's disease. Carvedilol, due to its antioxidant property, has been shown to have neuroprotective action. The objective of this study was to investigate the effect of Carvedilol against scopolamine induced cognitive impairment and compare its effect with that of propranolol. Wistar rats (150-200 g) were divided into 6 groups (n=6 each). Control group and scopolamine only group received equivolume of water for 15days. Each of the four drug treated groups received either Carvedilol 5mg/kg or Propranolol 25mg/kg for 15 days. . Scopolamine 0.5 mg/kg was administered i.p. 5 min before the learning trial in two of the groups of rats treated with carvedilol and propranolol and to the scopolamine control group of rats. Passive avoidance test using two compartment model was used to test learning and memory in the animals. Amongst the scopolamine treated groups, time taken to enter the dark compartment was higher in both the propranolol group (79 ± 5 secs) as well as the carvedilol group (142.33 ±7.5 secs) as compared to the control group (33.98 ± 4 secs). Time spent in dark compartment was much lesser in Carvedilol group (38.83 ± 2.24 secs) and Propranolol group (75.83 ± 6.30 secs) as compared to control group (121.83 ± 10.87 secs). All the differences in time were statistically significant. Therefore, in conclusion carvedilol seems to have a positive effect on learning and memory in scopolamine induced amnesia in rats.

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INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disease that leads to devastating problems like dementia, unusual behavior, personality changes and can sometime cause death.[1] Increasing experimental and clinical evidence support the hypothesis that oxygen free radicals play an important role in initiation and progression of Alzheimer's disease.[2] Oxygen free radicals are produced in the brain during brain insults. These increases in free radical production are believed to cause damage to the cellular elements such as lipids, proteins and nucleic acids by oxidative stress.[3] For a number of biochemical, physiological and anatomical reasons, the brain is more vulnerable to oxygen free radicals as compared to other organs of the body. Scopolamine, a muscarinic cholinergic receptor antagonist, which interferes with acetylcholine transmission in the central nervous system, could be used to induce impairment of learning and memory, in experimental animals.[4] This scopolamine induced amnesia has been used to screen drugs with potential

therapeutic value in dementia.[5] The mechanism of memory impairment by scopolamine is by altering the oxidative stress in the brain.[6]

Carvedilol is a non-selective beta blocker, with moderate lipid solubility, is used for treating congestive cardiac failure and hypertension. It has other multiple actions like alpha-1 blocking, vasodilation, inhibition of apoptosis, anti-inflammatory, mitochondrial protective non-competitive inhibition of NMDA receptor and antioxidant actions.[7] It has been shown to exert neuroprotective effects in several models of transient focal stroke.[8] And this effect has been attributed to its antioxidant and free radical scavenger property.[7] The antioxidant activity has been related to its carbazole moiety and it is approximately 10 fold more potent as an antioxidant than vitamin E.[9] Carvedilol has been shown to exert neuroprotective effect in colchicine induced cognitive impairment and oxidative damage in rats.[9] Based on this background, the present study was done to investigate the effect of Carvedilol against scopolamine induced cognitive impairment and compare its effect with that of propranolol.

MATERIALS AND METHODS

Animals:

Male Albino rats of Wistar strain (36 in number) weighing 150-200 g were used. The rats were maintained under standard laboratory conditions in Central animal house. The animal s were provided with stand ard rat feed and water ad libitum. They were maintained under alternating 12hr light- dark cycle. The protocol was approved by institutional animal ethics committee and was carried out in accordance with the Indian National Science Academy Guidelines for the use and care of animals.

Drugs and experimental design

Animals were randomized into 6 groups containing 6 rats each. Control group and scopolamine only group received equivolume of water for 15days. Each of the four drug treated groups received either Carvedilol or Propranolol .The drugs were dissolved in sterile water and administered orally at a dose of 5mg/kg and 25mg/kg respectively for 15 days. Scopolamine 0.5 mg/kg was administered i.p. 5 min before the learning trial in two of the groups of rats treated with carvedilol and propranolol and to the scopolamine control group of rats.

Behavioral assesment

Passive avoidance test (two compartment model) [10]:

The test apparatus consists of two compartments. First is an illuminated square box (50cm x 50cm) with a grid floor (3 mm stainless steel rods set 8 mm apart) and wooden walls of 35cm height. The illumination was provided by a 100W bulb placed 150 cm above a corner of the compartment. The second is a dark compartment (15x15cm) connected to the first compartment by an opening (6cm x 6cm) in the center of one of the walls. This compartment is provided with an electrifying grid floor which can be connected to a shock source. The connection between the two compartments can be closed with a sliding door made of transparent plexiglas.

Procedure

The experiment was performed according to the method described by Bures J *et al* [11] and Narayanan SN *et al* [12] with modifications.

It was performed in three stages.

A) Exploration: The animals were placed in the center of the large compartment facing towards the light and away from the entrance into the small compartment. The sliding door was kept open and the rats were allowed to explore the apparatus for 3 minutes. The rats were then returned to their cage.

B) Learning: On the next day, the rat was placed in the large illuminated box. The time taken for the rat to enter the small compartment and time spent in both compartments were measured using a stopwatch. After 3 minutes, the sliding door between the two compartments was closed and an unavoidable foot shock (50 Hz, 1.5mA, 1s) was given. The ceiling was opened and the rat was returned to the home cage.

C) Retention testing: Retention was tested after 24 hrs. The time taken by rat and time spent in the small compartment was measured with a stop watch. After 3 minutes, animal was returned to the home cage. The animals not entering the dark compartment, received latency time of 180 seconds. Increase in the latency time was considered as an index of improvement of memory.

Statistical analysis:

The results are expressed as mean ± SD. The results were analyzed using one-way analysis of variance (ANOVA), followed by Post hoc test, using SPSS 16. A p value of <0.05 was considered statistically significant.

RESULTS AND DISCUSSION:

During learning period, the time taken to enter the dark compartment was statistically insignificant in propranolol and carvedilol groups as compared to control, while during retention both propranolol and carvedilol groups showed significant delay in the entry time, as shown in table 1. Similar results were obtained in the time spent in the dark compartment with significantly less time spent by both propranolol and carvedilol groups during retention testing (table 2)

Table 1: COMPARISION OF LATENCY TIME TO ENTER DARK COMPARTMENT DURING LEARNING AND RETENTION PERIOD

Group	Latency time to enter dark compartment during learning (in secs)	Latency time to enter dark compartment during retention (in secs)
Control	7.70 ± 1.35	16.16 ± 3.50
Propranalol	11.26 ± 2.02	110.09 ± 8.89*
Carvedilol	7.68 ± 0.51	147.83 ± 9.45*

*p< 0.05 according to one way ANOVA

Table 2: COMPARISION OF TIME SPENT IN DARK COMPARTMENT DURING LEARNING AND RETENTION PERIOD

Group	Time spent in dark compartment during learning (in secs)	Time spent in dark compartment during retention (in secs)
Control	111.13 ± 10.58	116.67 ± 10.84
Propranalol	119.00 ± 8.24	48.5 ± 4.00*
Carvedilol	137.33 ± 6.00	21.83 ± 1.5*

*p< 0.05 according to one way ANOVA

Amongst the scopolamine treated groups, time taken to enter the dark compartment was higher in both the propranolol as well as the carvedilol treated groups. However, it was significantly higher in the carvedilol treated group as compared to propranolol group. The total time spent in the dark compartment was statistically lower in both the propranolol as well as the carvedilol treated groups as demonstrated in table 3.

TABLE 3: COMPARISION OF LATENCY TIME AND TIME SPENT IN DARK COMPARTMENT AMONG THE SCOPOLAMINE TREATED GROUPS DURING RETENTION TIME

Group	Latency time to enter dark compartment during retention (in secs)	Time spent in dark compartment during retention (in secs)
Control (Scopolamine)	33.98 +/- 4.00	121.83 +/- 10.87
Propranolol + Scopolamine	79.00 +/- 5.00*	75.83 +/- 6.30*
Carvedilol + Scopolamine	142.33 +/- 7.5*	38.83 +/- 2.24*

*p< 0.05 according to one way ANOVA

The latency time to enter the dark compartment and time spent in the dark compartment were taken as parameters to assess learning and memory in rats. The principle behind the study is that if the drug has positive effect on learning and memory, then the rat takes more time to enter the dark compartment during retention testing. Administration of scopolamine (3mg/kg) i.p. 5 min before the retention testing induces amnesia.[13]

The study showed that chronic administration of carvedilol significantly improved the learning and memory in rats as indicated by increase in latency time to enter dark compartment and decrease in overall time spent in the compartment during the retention testing as compared to control.

Amongst the scopolamine treated groups, both carvedilol as well as propranolol showed increase in time taken to enter the dark compartment as compared to scopolamine group, which suggests an improvement in learning. However, the increase was statistically significant in carvedilol treated group .This shows that carvedilol provides better protection against scopolamine induced disruption of memory as compared to propranolol. Previous research has shown scopolamine to cause memory impairment by increasing brain 3, 4-Methylenedioxyamphetamine (MDA) levels and

reducing glutathione (GSH) levels after scopolamine injection,[3] thereby increasing oxidative stress. The beneficial effect of carvedilol, as demonstrated in this study, could be attributed to the anti-oxidant property of the drug.
Increased levels of oxidative stress in the brain caused by scopolamine administration, is similar to the clinical situation of AD. [14] The overall production of oxygen free radicals and peroxidation activity in the brain of AD patient is also significantly increased.[15] This may lead to the consumption of detoxifying endogenous anti-oxidants such as GSH. [3] In AD, the compensatory increase in anti-oxidant enzymes does not occur because of the degenerative process.[16] Thus, it is possible that the above proposed anti-oxidant action of carvedilol might contribute to its ability to interfere with AD-type cognitive deterioration.
Few studies have reported that beta blockers could affect the delayed memory in patients with cognitive impairment, while few others have shown that beta blockers didn't have any such negative effect on memory.[17] In our study propranolol or carvedilol did not adversely affect the cognitive impairment.

CONCLUSION:

Beta blockers like carvedilol and propranolol improve learning and memory in scopolamine induced amnesia models in rats which simulate AD in humans. However, further studies, measuring the oxidants and anti- oxidants levels in the brain, are needed before conclusively proving the efficacy of beta blockers like carvedilol for treatment and prophylaxis of AD in humans.

REFERENCES:

1. Jewart RD, Green J, Lu C, Cellar J, Tune LE. Cognitive, Behavioral, and Physiological Changes in Alzheimer Disease Patients as a Function of Incontinence Medications. Am J Geriatr Psychiatry. 2005:13;324-8.

2. M. Sano, C. Ernesto, R. G. Thomas, Klauber MR, Schafer K, Grundman M, et al. A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. N Engl J Med. 1997:336;1216-22.

3. El-Sherbiny DA, Khalifa AE, Attia AS, Eldenshary EES. Hypericum perforatum extract demonstrates antioxidant properties against elevated rat brain oxidative status induced by amnestic dose of scopolamine. Pharmacol Biochem Behav. 2003:76;525-33..

4. Misane I, Ogren SO. Selective 5-HT (1A) antagonists WAY 100635 and NAD-299 attenuate the impairment of passive avoidance caused by scopolamine in the rat. Neuropsychopharmacology 2003;28:253– 64.

5. Mishima K, Tsukikawa H, Miura I, Inada K, Abe K, Matsumoto Y, et al. Ameliorative effect of NC-1900, a new AVP(4 – 9) analog, through vasopressin V(1A) receptor on scopolamine-induced impairments of spatial memory in the eight-arm radial maze. Neuropharmacology 2003;44:541–52.

6. Fan Y, Hu J, Li J, Yang Z, Xin X, Wang J, et al. Effect of acidic oligosaccharide sugar chain on scopolamine-induced memory impairment in rats and its related mechanisms. Neurosci Lett. 2005:374;222-6.

7. Kumar A, Prakash A, Dogra S. Neuroprotective effect of carvedilol against aluminium induced toxicity: possible behavioral and biochemical alterations in rats. Pharmacological Reports 2011:63; 915-23.

8. Savitz SI, Erhardt JA, Anthony JV, Gupta G, Li X, Barone FC. The novel -blocker, carvedilol, provides neuroprotection in transient focal stroke. J Cereb Blood Flow Metab 2000:20;1197–204.

9. Kumar A, Dogra S. Neuroprotective effect of carvedilol, an adrenergic antagonist against colchicine induced cognitive impairment and oxidative damage in rat. Pharmacol Biochem Behav 2009:92;25–31.

10. Stuchlik A, Petrasek T, Vales K. A dose-response study of the effects of pre-test administration of beta-adrenergic receptor antagonist propranolol on the learning of active place avoidance, a spatial cognition task, in rats. Behav Brain Res. 2009:200;144-9.

11. Bures J, Buresova O, Huston JP. Techniques and basic experiments for the study of brain and behavior. 2nd ed., New York; Elsevier Science Publishers: 1983. p.148.

12. Narayanan SN, Kumar RS, Potu BK, Nayak S, Bhat PG, Mailankot M. Effect of radio-frequency electromagnetic radiations (RF-EMR) on passive avoidance behaviour and hippocampal morphology in Wistar rats. Ups J Med Sci. 2010:115;91–6.

13. Kanwal A, Mehla J, Kuncha M, Naidu VGM, Gupta YK, Sistla R. Anti-Amnesic Activity of Vitex Negundo in Scopolamine Induced Amnesia in Rats. Pharmacology & Pharmacy 2010:1;1-8

14. Balazs L, Leon M. Evidence of an oxidative challenge in the Alzheimer's brain. Neurochem Res 1994;19:1131–7.

15. Marcus DL, Thomas C, Rodriguez C, Simberkoff K, Tsai JS, Strafaci JA, et al. Increased peroxidation and reduced antioxidant enzyme activity in Alzheimer's disease. Exp Neurol 1998;150:40– 4.

16. Kish SJ, Morito CL, Hornykiewicz O. Brain glutathione peroxidase in neurodegenerative disorders. Neurochem Pathol 1986;4:23– 8.

17. Saber AJ, Cain DP. Combined beta-adrenergic and cholinergic antagonism produces behavioral and cognitive impairments in the water maze: implications for Alzheimer disease and pharmacotherapy with beta-adrenergic antagonists. Neuropsychopharmacology. 2003; 28:1247– 56.