Effect of Curcumin on Statin Induced Short Term Memory Loss

Jithendra Chimakurthy[1,2], Talasila EGK Murthy[1]

[1] Dept. of Pharmacology, Bapatla College of Pharmacy, Bapatla, Andhra Pradesh, India
[2] Dept. of Biotechnology, Acharya Nagarjuna University, Nagarjunanagar, Guntur, Andhra Pradesh, India

Conflicting Interest: None Declared

This article has been peer reviewed.

Article Submitted on: 25th August 2011

Article Accepted on: 3rd January 2012

Funding Sources: Bapatla College of Pharmacy, Bapatla, Andhra Pradesh, India

Correspondence to: Jithendra Chimakurthy

Address: Dept. of Pharmacology, Bapatla College of Pharmacy, Bapatla, Guntur Dist., Andhra Pradesh, India-522101

Email: jithu_indra@rediffmail.com

ABSTRACT

BACKGROUND: The present investigation was undertaken to explore the effect of curcumin on rosuvastatin-induced short-term memory loss.

MATERIALS AND METHODS: For our study, we built an experimental model that consisted of a box with a starting point at one end and an ending point at the other end. These two points were separated by three partitions which had interconnecting doors. Control and rosuvastatin-treated rats received different treatments orally; control (vehicle), negative control, 5mg/kg and 10 mg/kg of curcumin and 150mg/kg of piracetam (standard) for 14 days. Rosuvastatin 10mg/kg p.o. was administered to all the four groups except control. At the end of the treatment, rats were placed individually in the apparatus and allowed to explore the pattern of doors. After initial exposure the rats were placed individually and the latency to cross each door was recorded, the reduction in the time taken to cross the 3rd door when compared to the time taken to cross the 1st door is taken as an index of short term memory protection.

RESULTS: Rosuvastatin-treated group (negative control) did not show any decrease in the time taken to cross the 3rd door when compared to the time taken to cross the 1st door. Treatment with curcumin at both 5 and 10mg/kg showed a significant decrease ($p<0.001$) in the time taken to cross the 3rd door when compared to the time taken to cross the 1st door and were comparable with that of piracetam-treated group.

CONCLUSION: Our study shows evidence for the protective effect of curcumin against rovustatin induced short-term memory loss. We suggest further studies be done in order to explore the relationship in humans.

Key Words: Short term memory, Curcumin, Antioxidant, Rosuvastatin

INTRODUCTION

Short-term memory loss in one of the most common types of memory disturbance that occurs with age, central nervous system (CNS) disorders or with certain drugs such as statins [1]. Majority of the CNS disorders are associated with sleep disturbances and have short term memory loss as a common symptom which in turn also affects long-term memory formation [2]. Short-term memory lasts only for a few minutes and is of limited capacity in humans and is far less in laboratory animals [3]. There are two competing theories describing the formation of short-term memory. According to one theory, short-term memory is formed due to adaptation in the median temporal lobe and, therefore, is highly sensitive to disruption since no permanent neural connections are established as observed with long-term memory [4]. According to the

competing theory, sensory input about new information produces new neurons in specific areas of the hippocampus known as the dentate gyrus [5].

Irrespective of the actual mechanism of short-term memory formation, serotonin is present in various structures of the CNS that are reported to play an important role in short term memory [6]. On the other hand, statin therapy is known to be associated with short-term memory loss, probably due to the formation of free radicals [7]. We therefore hypothesized that the drugs that potentiate brain serotonin levels and have antioxidant activities may prevent statin induced short-term memory loss.

Curcumin, an active constituent of *Curcuma longa* (Indian name - Haldi), increases brain serotonin levels in various regions of a rat brain [8] and may have antioxidant acitivity [9]. Henceour's objective was to examine the effect of curcumin on rosuvastatin-induced short-term memory loss [10].

METHODS

Animals

Inbred adult Wistar rats (*Rattus norvegicus*) (200-250g) of either sex were obtained from the animal house of Bapatla College of Pharmacy (1032/ac/07/CPCSEA), Bapatla, India, and were housed at a constant room temperature (22 ± 1ºC) and 40-50% relative humidity with a 12h/12h light/dark cycle. Standard food pellets (Rayan's Biotech, Hyderabad, India) and water were provided *ad libitum* throughout the experimentation period. Animals were acclimatized to the laboratory conditions 1 week prior to the initiation of the experiments. The experimental protocol was approved by the Institutional Animal Ethics Committee (IAEC/II/1/BCOP/2009), and all experiments were performed between 9.00 a.m. to 11.00 a.m. in accordance with Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) guidelines for the care and use of experimental animals [11].

Drugs and drug administration

Curcumin was obtained from Chemiloids (LailaImpex, Vijayawada, India) and characterized by Proton Nuclear Magnetic Resonance studies. For oral administration, curcumin was dissolved in peanut oil and diluted to the desired concentration (5 and 10mg/kg, p.o.) [8, 12]. Piracetam (150mg/kg) was suspended in 1% CMC (Carboxy methyl cellulose). Rosuvastatin (10mg/kg, p.o.) was suspended in 1% CMC. The peanut oil was used as a control treatment.

Animal groups

Rats were divided into 5 groups (n=6), curcumin and piracetam were administered for 14 days and 60 min prior to evaluation on the last day of treatment. Group 1 served as the control and received peanut oil (0.1 ml/100g, p.o.). Group 2 served as the negative control and did not receive any treatment. Groups 3 and 4 were treated with curcumin at doses of 5 and 10 mg/kg, p.o., respectively. Group 5 was treated with piracetam [13] (150mg/kg p.o.) and served as the standard. All the groups except the control (Group 1) were treated with rosuvastatin 10mg/kg p.o.

Description of animal model (Runway panel)

The Runway panel consists of a wooden box with dimensions 60"x20"x20", with an open roof and three partitions that are placed equidistant. Each partition consists of doors that allow two sided movement of the rats. The doors were placed at the opposite ends of the partitions alternatively as described in Dig-1. A video camera was attached to observe and record the movements of the rats across the doors.

Evaluation procedure

After treatment for 14 days, and 60 min after the last dose, rats were placed individually at the starting point in the first compartment and observed for the time at which they cross the 1st door, the 2nd door and the 3rd door, respectively, using video surveillance. Rats were removed from the apparatus as soon as they crossed the 3rd door. A cutoff time of 10 min was followed (i.e. a maximum of 10 min to cross each door) following which, the rats were returned to their cages.

Statistical analysis

The data obtained from the runway panel apparatus is expressed as mean ± SD (standard deviation), and the comparison of time taken to cross the 2nd and 3rd doors with the 1st door was done using Student's 't' test. The time taken by groups 1, 3, 4 and 5 to cross the doors was compared with group 2 using one-way analysis of variance (ANOVA). Significant effects in the

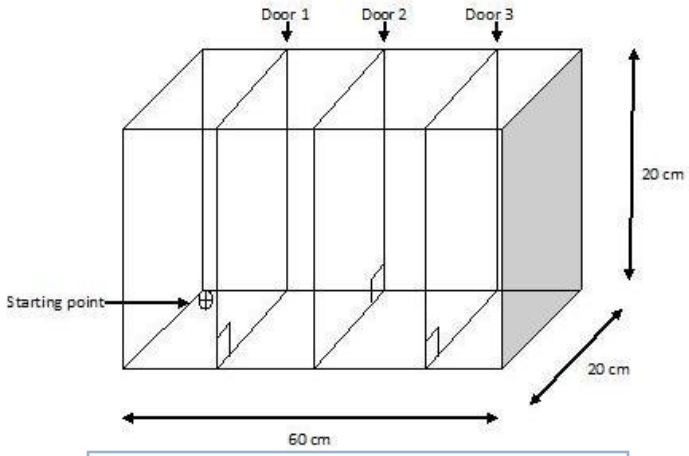

Diagram 1: Diagram describing the apparatus used to study short-term

ANOVA were followed by analyzing inter-group differences using Dunnett's t-test. Values of $p < 0.05$ were considered statistically significant.

RESULTS

The latency to reach the goal from the start point was taken as an index of short-term memory loss. Group 2 rats treated with rosuvastatin alone showed a marked increase in the latency to cross the 2nd (6%) and 3rd door (29%) after crossing the 1st door as compared to the control group. This is consistent with previous findings that rosuvastatin use is associated with short-term loss. Rats which were given curcumin at 5mg/kg in addition to rosuvastatin, showed a significant decrease in the time taken to cross the 2nd and 3rd door ($p<0.01$, 64%), ($p<0.001$, 81%), respectively. Whereas, curcumin at 10mg/kg had shown a significant decrease in the time taken to cross the 2nd ($p<0.001$, 80%) and 3rd door ($p<0.001$, 92%) when compared with that of the time taken to cross the 2nd and 3rd door of the rosuvastatin-treated group and is parallel to the effect of the piracetam-treated group, i.e. 82% and 90% for the 2nd and 3rd door respectively. Table.1. Fig.1.

DISCUSSION

In this study, we have confirmed that rosuvastatin use associated with impaired short-term memory as an increase in the time taken to cross the subsequent doors after crossing the 1st door was observed, which was against the results obtained with control rats, i.e., a decrease in the time taken to cross the subsequent doors after crossing the 1st door implicating induction of memory loss about the presence of doors by rosuvastatin, and that curcumin use can ameliorate short-term memory loss in rosuvastatin-treated rats. We have further shown that the memory-preserving effect of curcumin is similar in magnitude to what is obtained with a known memory-enhancing agent, piracetam. The proposed mechanisms underlying the loss of short-term memory by rosuvastatin include an increase in nitric oxide, which produces 3-((+/-)-2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid (CPP) [14]**.** Increased nitric oxide prevents new memory formation and erases existing memory by modifying hippocampal synaptic transmissions [15]. Further, nitric oxide synthase (NOS) is highly reactive in nature [7] and may result in hippocampal synaptic destruction. In addition, statins adversely affect tau proteins, which are synthesized by brain cells to maintain structure. Also, serotonin depletion has been reported to impair short-term memory [16].

Moreover, statins disrupt the enzymatic pathway involved in the production of cholesterol by glial cells (the supporting cells of nervous system). Cholesterol is seen in high concentrations in the myelin sheaths which insulate neurons and facilitate nerve conduction and synapse formation, which are affected with statin use. This in turn affects nerve plasticity which plays a key role in the formation of new memory. Apart from this disruption of the enzymatic pathway, statins also reduce the production of coenzyme Q 10 (Co Q10) to half of its normal level [18].

GROUPS/TREATMENT		TIME TAKEN TO CROSS DIFFERENT DOORS (SEC)		
		1ST DOOR	2ND DOOR	3RD DOOR
I	CONTROL	263.5 ± 42.7^{BNS}	43 ± 17$^{A\#B\#}$	25.5 ± 6$^{A\#B\#}$
II	ROSUVASTATIN ALONE	188.7 ± 25.1	201.3 ± 33.7^{ANS}	253 ± 45.5^{ANS}
III	ROSUVASTATIN + CURCUMIN 5	237.2 ± 76.8^{BNS}	106.7 ± 15.2^{A**B**}	71.5 ± 16.4$^{A\#B\#}$
IV	ROSUVASTATIN + CURCUMIN 10	229.5 ± 69.3^{BNS}	56.7 ± 11.6$^{A\#B\#}$	29 ± 4.4$^{A\#B\#}$
V	ROSUVASTATIN + PIRACETAM	255.5 ± 56.3^{BNS}	53 ± 9.9$^{A\#B\#}$	28.17 ± 7.4$^{A\#B\#}$

Table-1: Data represents the mean ± SD of time taken to cross different doors. a=comparison of time taken to cross 2nd and 3rd doors with 1st door using student's 't' test, b= Group I, III, IV and V, were compared with group II using one way ANOVA followed by Dunnett's test. *P<0.05; *P<0.05; **P<0.01; #P<0.001; ns-non significant.

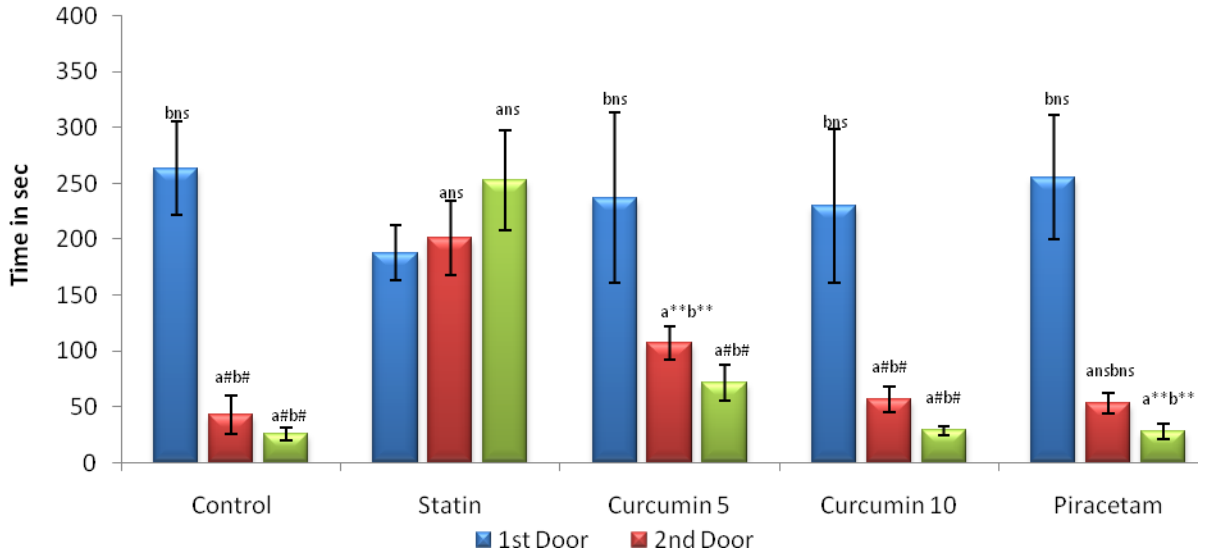

Figure 1: Figure represents the Mean ± SD of time taken to cross different doors. a=comparison of time taken to cross 2nd and 3rd doors with that of time taken to cross 1st door using student's 't' test, b= Group I, 3, 4 and 5 were compared with group 2 using one way ANOVA followed by Dunnett's test. **P<0.01; #P<0.001; ns - nonsignificant.

Since the brain, apart from the heart, liver and kidney, is the organ that consumes energy extensively, suppression of Co Q10 also underlies the cognitive dysfunction affecting neurological sequences of memory formation [19].

Curcumin, which increases monoamine levels, such as dopamine and serotonin, and has antioxidant properties, may protect against statin-induced memory loss [9]. The antioxidant effect of curcumin includes reduced depolymerization and aggregation of tau protein in the brain [17]. Curcumin's ability to potentially increase antioxidant activity and brain monoamine levels could be the mechanism responsible for preventing short-term memory loss.

The present study has provided evidence of the protective action of curcumin against short-term memory loss induced with rosuvastatin. The observations can be further substantiated by performing similar studies using other animal models and exploring the underlying biochemical changes to report the possible mechanism involved in the protective effect of curcumin.

CONCLUSION

The influence of curcumin on a novel animal model was studied in the present investigation. Curcumin had shown to be effective in protecting against statin-induced short-term memory loss.

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