National Journal of Physiology, Pharmacy and Pharmacology

RESEARCH ARTICLE

Scopolamine-induced amnesia model: A possible anticholinergic mechanism with reversibility with statins and nootropic agents

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Received: September 21, 2017; **Accepted:** October 14, 2017

ABSTRACT

Background: High cholesterol turnover is implicated in the pathogenesis of Alzheimer's disease by causing β amyloid plaque deposition and selective degeneration of cholinergic neurons in brain whereas drugs currently used for the treatment of the same are based on mechanisms which are cholesterol independent. **Aims and Objectives:** The aim of the study is to find any cholesterol independent mechanisms such as antioxidant and cholinomimetic action of statins in a reversal of memory deficit in scopolamine-induced amnesia. **Materials and Methods:** Sixty young Swiss albino mice were divided equally into 10 groups, i.e., Group I to Group X. Group I–V and Group VI–X were subjected two exteroceptive behavioral models, i.e., passive avoidance paradigm and Morris water maze, (MWM) respectively. Group I and Group VI served as negative control. Carboxymethyl cellulose (CMC), atorvastatin, simvastatin (test drugs), and piracetam (standard drug), respectively, were given orally to Group II and VII, Group III and VIII, Group IV and IX, and Group V and X for 14 days before inducing amnesia using scopolamine (0.4 mg/kg body weight) injection i.p. **Results:** Step down latency of disease control group treated with CMC was significantly lower than that of the negative control group (42.5 ± 9.07 s vs. 147.5 ± 10.78 s) as well as that of statin and piracetam treated groups. Learning was good among all groups in MWM with a gradual decrease in escape latency from day 1 to day 4 but during memory retrieval test on day 5, CMC treated group performed poorly in comparison to others. There was no significant difference in plasma cholesterol levels among different groups whereas malondialdehyde was significantly lower among groups treated with statins or piracetam. **Conclusion:** Statins reversed the scopolamine-induced amnesia by some cholesterol independent mechanisms.

KEY WORDS: Atorvastatin; Dementia; Memory; Malondialdehyde; Scopolamine; Simvastatin

INTRODUCTION

Alzheimer's disease (AD) is a central nervous system (CNS) degenerative disorder characterized by progressive loss of neurons where the loss of cortical and hippocampal neurons leads to impairment of memory and cognitive ability.[1] A deficiency of intact cholinergic neurons, particularly those extending from subcortical areas like the nucleus of Meynert has been observed with progressive dementia.[2] Like other CNS degenerative disorders, in AD, there is a cholinergic deficiency syndrome in addition to other neurotransmitters like glutamate, 5-HT and neuropeptides with the cortical and hippocampal targets. These areas which receive cholinergic inputs selectively are degenerated. The hallmark of AD is an accumulation of Aβ amyloid plaques and intracellular neurofibrillary tangles consisting of tau protein.[3] At present, treatment consists of augmentation of cholinergic transmission to improve the cognitive functions. Three drugs, namely, donepezil, rivastigmine, and galantamine, all are reversible anticholinesterases and memantine, the NMDA

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DOI: 10.5455/njppp.2018.8.1040114102017	

receptor antagonist, presently used in therapy and at present no disease-modifying drug is available for AD. On the other hand, anticholinergic drug such as scopolamine, produces amnesia, and mimics the symptoms of AD.[4] In the present study experimental AD was produced using scopolamine.

Statins, the HMG Co-A reductase inhibitors have cholesterol-reducing property. In addition, it has been claimed that statins have pleiotropic actions. However, in a recent meta-analysis, it has been shown that statins have also a role in the treatment of AD.[5] In this study, the aim is to delineate the action of statins in experimental dementia models to show whether they improve the cognitive function with simultaneous correlation with their hypocholesterolemic and antioxidant effect.

MATERIALS AND METHODS

Animals

Sixty healthy young (aged about 3 months, weighing 20–25 g) Swiss albino mice of either sex were randomly selected from the animal house of the institute. All the animals were used only once in the experiment. They were acclimatized in the standard laboratory condition and were allowed free access to food and water throughout the period of the experiment. All experiments were carried out in the daytime between 10 h and 16 h. The study was conducted in the Department of Pharmacology, MKCG Medical College, Berhampur, Odisha. Institutional Animal Ethics Committee approved the experimental protocol, and the care of animals was taken as per the guidelines of Committee for the Purpose of Control and Supervision on Experiments of Animals (CPCSEA).

Drugs

Atorvastatin (Systopic Lab., Ltd.), Simvastatin (USV Ltd.), and Piracetam (Pegasus Pharmaco India (P) Ltd.) were locally procured from the hospital pharmacy. All other chemicals and reagents used were of analytical grade.

Experimental Design

Passive avoidance paradigm (PAP) and Morris water maze (MWM) were the two exteroceptive behavioral models used in this experiment. The experiment was conducted in a way similar to our earlier experiment on mice with age-induced and high-fat-diet-induced amnesia.[6,7] Here, in this experiment, scopolamine-induced experimental dementia model was used. All 60 mice were divided into 10 groups (Group I to Group X) with 6 animals in each group. Group I to Group V were subjected to PAP and Group VI to Group X were subjected to MWM.

Groups I, II, VI, and VII were administered 1% w/v carboxymethylcellulose (CMC) per oral at a dose of 10 ml/kg body wt. for 14 days. Atorvastatin, simvastatin, and piracetam were mixed in 1% w/v CMC and administered for 14 days per oral to Groups III, IV, and V, respectively, of PAP model and Groups VIII, IX, and X, respectively, of MWM model. The doses of atorvastatin, simvastatin, and piracetam were 5 mg/kg body weight (b.w.), 5 mg/kg b.w., and 400 mg/kg b.w., respectively. Atorvastatin and simvastatin served as test drug while piracetam and 1% CMC served as standard drug and vehicle, respectively. All the test drugs, standard drug and vehicle were continued during the acquisition trials (1 day in PAP and 4 days in MWM) and also on the day of memory retention test, and were administered each day to the respective groups 60 min before commencement of the experiment.

Dementia was induced in eight groups (Group II to V and Group VII to X) by administering intra-peritoneal injection scopolamine at a dose of 0.4 mg/kg b.w. 30 min before the animals were subjected to any exteroceptive behavioral model.[8] Whereas, for the rest two groups (Group I and Group VI), distilled water was administered intraperitoneally at a dose of 10 ml/kg b.w. 30 min before the animals were subjected to any exteroceptive behavioral model and they served as negative control. Those demented animals which were treated with vehicle (i.e., Group II and Group VII) served as disease control.

Passive Avoidance Test

The apparatus used for this test consisted of a transparent acrylic cage 27 cm × 27 cm × 27 cm with a grid floor (3 mm steel rods set 8 mm apart) inserted in the cage with a wooden platform 10 cm × 7 cm × 1.7 cm in the center of the grid. The box was illuminated with a 15 W bulb. Training was carried out in 2 sessions 1.5 h apart on 1st day followed by memory retention test on the 2nd day to note step down latency (SDL). SDL was the time taken by the mouse to step down from wooden platform on to the grid floor with all its 4 paws.

Day 1, Session 1: Mouse was placed gently on the wooden platform. When the mouse stepped down and placed all the 4 paws on the grid floor, shock with 20 Volt AC current was delivered for 15 s.[9,10]

Day 1, Session 2: It was started 90 min after the 1st session. If the mouse stepped down onto the grid within 60 s, then a second electric shock was given to it. If it did not step down, then it was taken out of the platform and returned to its cage.

Day 2: Retention of the learned experience of day 1 was tested in a similar manner to record SDL. This time no shock was applied. Cutoff time of 300 s was taken as the end of the session.[4,9]

MWM

The maze consisted of a circular tank (150 cm diameter and 45 cm height) filled with water at 25–28°C. Water was made

opaque by addition of small quantity of titanium dioxide.[10] Tank was divided into 4 quadrants (Q1, Q2, Q3, Q4) with the help of 2 threads. There was a hidden platform (white in color with a diameter of 10cm) kept at the center of the 4th quadrant 1 cm below the water level unknown to the animal throughout the training period. Animals were subjected to 4 consecutive trials on each day at 5 min interval for 4 days. The animals were released in the water facing toward the wall of the tank and were allowed to escape to the hidden platform and further allowed to remain there for 20 s, and the escape latency (ELT) was recorded. ELT was the time taken by the animal from getting released into the water to escape on to the platform. If the animal did not locate the platform within the cutoff time of 120 s, then it was guided to the platform and further allowed to remain there for 20 s. The sequence of starting quadrants to which the animal was released during the 4 consecutive trials on each day was as follows:-Day1: Q1 →Q2 →Q3 →Q4. Day2: Q2 →Q3 →Q4 →Q1. Day3: Q3 →Q4 →Q1 →Q2. Day4: Q4 →Q1 →Q2 →Q3.

Mean ELT was derived from each trial. ELT of Day 4 was compared with that of Day 1. On the 5th day retention of memory was tested by doing a probe test in which platform was removed. The quadrant where the platform was originally kept during trial sessions was considered as the target quadrant. The time spent by the animal in the target quadrant (Q4T) was noted and compared.[8,11]

Locomotor Activity

Locomotor activity was measured in all animals using Rotarod before subjecting them to any behavioral model. The speed of Rotarod was set at 20 revolutions per minute. In the initial phase of 180 s, the animals were placed as many times on the rod as they fall from it. In the second phase started 1hour later, the animals were placed on the rod only once, and the duration for which the animal remained on the rod was noted for comparison.[12]

Immediately after the completion of the exteroceptive behavioral experiment, the animals were sacrificed, and blood was collected for estimation of serum cholesterol by colorimetric method using a commercially available kit from Crest Biosystems. The brains were carefully removed, homogenized and fresh tissue homogenate were used for estimation of malondialdehyde in the brain tissue.

Statistical Analysis

Data were analyzed using one-way ANOVA followed by *post hoc* Tukey's test with the help of Microsoft Excel 2007 and GraphPad Prism software version 5.0. Results were given as mean ± standard error mean. Values with $P < 0.05$ were considered statistically significant.

RESULTS

Effect of Drugs on Locomotor Activity

Before subjecting the animals to any amnesia model, they were tested in rotarod for intact locomotor function. It was found that there was no significant different difference in the fall off time in rotarod among different amnesia models and control groups as shown in Figure 1. This indicates there is no effect of drugs as well as a vehicle on locomotor activity of mice.

Effect of Step-down Latency

In scopolamine-induced amnesia [Figure 2] the SDL of mice treated with CMC (42.5 ± 9.07 s) was significantly lower than that of mice injected with distilled water without scopolamine (147.5 ± 10.78 s). However, the SDL in mice treated with piracetam (169.50 ± 20.86 s), atorvastatin (166.50 ± 16.27 s), or simvastatin (206.50 ± 30.88 s) before scopolamine-induced amnesia were significantly higher than the SDL in mice treated with CMC (166.84 ± 6.43) with $P < 0.001$.

Effect on ELT

In scopolamine-induced amnesia [Figure 3] the day 4 ELTs in respective groups treated with distilled water,

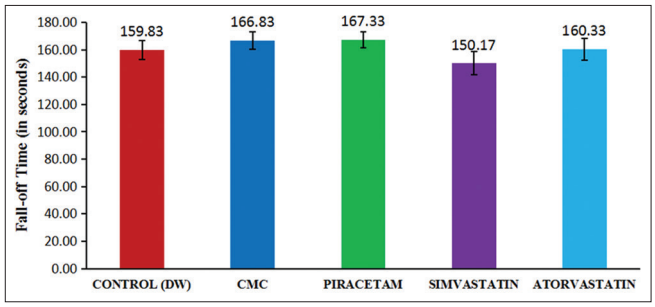

Figure 1: Effect of drugs on fall-off time in scopolamine-induced amnesia in rotarod. (*n*=6 in each group). Values were expressed in mean ± standard error mean, the differences were not statistically significant between the different groups

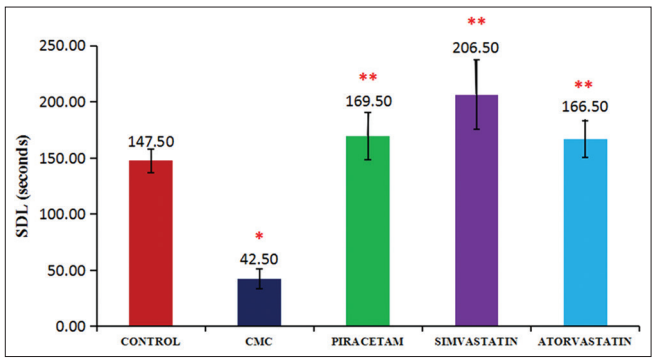

Figure 2: Effect of drugs on step down latency in passive avoidance paradigm. (n = 6 in each group). Values were expressed in mean ± standard error mean, *denotes $P < 0.001$ compared to control, **denotes $P < 0.001$ compared to carboxymethylcellulose treated group

CMC, piracetam, simvastatin, and atorvastatin were 29.00 ± 1.93 s, 60.17 ± 7.38 s, 40.93 ± 5.01 s, 43.46 ± 7.66 s, and 29.17 ± 4.66 s, respectively, and were significantly lower than respective day 1 ELTs (i.e., 117.38 ± 1.05 s, 116.88 ± 2.66 s, 115.83 ± 4.17 s, 103.96 ± 5.77 s, and 91.83 ± 11.10 s, respectively). There were also gradual decreases in ELT durations from day 1 through day 2, day 3, and day 4 in all groups except in CMC treated group where there was a slight increase in day 4 ELT in comparison to day 3 ELT but was found not to be statistically significant.

Effect on day 5 Q4T

When tested for memory retention on day 5 it was revealed that in scopolamine-induced amnesia the day 5 Q4T of mice treated with CMC (25.67 ± 2.01 s) was significantly lower than that of young mice treated with distilled water without scopolamine (37.67 ± 0.99 s). However, the day 5 Q4T in mice treated with piracetam (36.83 ± 1.62 s), atorvastatin (37.17 ± 0.95), and simvastatin (38.5 ± 0.62) was significantly higher than that of disease control group [Figure 4].

Effect on Brain Malondialdehyde (MDA) and Plasma Cholesterol Levels

The effect of drugs on brain MDA and plasma cholesterol levels in those mice subjected to PAP was shown in Table 1. It was observed that the MDA level of mice treated with CMC in disease control group (381.20 ± 7.31 nmol/g) was significantly higher than that of the negative control group (308.04 ± 15 nmol/g) treated with distilled water. However, the MDA level in mice pre-treated with piracetam (333.89 ± 6.78 nmol/g) or simvastatin (330.54 ± 8.61 nmol/g) before scopolamine-induced amnesia was significantly lower than that of CMC treated group. Whereas, no significant difference was observed in atorvastatin-treated group as compared to CMC treated group. However, atorvastatin decreased the MDA level (346.15 ± 4.8 nmol/g) in comparison to CMC treated group.

Result of the blood samples sent for estimation of plasma cholesterol level revealed that there was no significant difference in plasma cholesterol level between negative control and disease control group. The drugs such as piracetam, simvastatin, and atorvastatin also had got no statistically significant action on plasma cholesterol in the respective groups.

DISCUSSION

We selected Swiss albino mice for this study as the rodents (rats / mice) were standardized experimental animal for behavioral study. These animals are small in size, so feeding, handling and drug administration were relatively easy. They could withstand longer duration of experimentation and relatively resistant to infection.[12] It was well recognized that inhibition of cholinergic neurotransmission plays an important role in dementia.[4] Neurochemical analysis of AD has revealed that there is a marked reduction of acetylcholine content of cortical and hippocampal regions of human brain. Centrally acting anticholinergic such as scopolamine

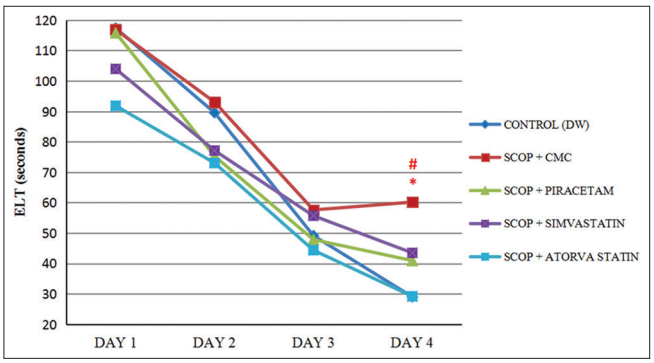

Figure 3: Effect of drugs on escape latency (ELT) during acquisition trial in Morris water maze (*n*=6 in each group). Values expressed in mean ± standard error mean, *denotes $P < 0.001$ compared to day 1 ELT in case of piracetam, simvastatin, and atorvastatin-treated and control (DW) groups

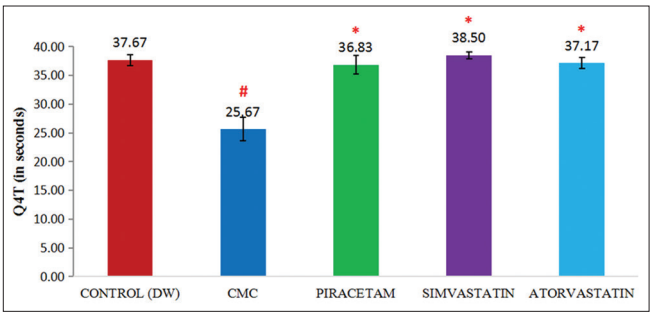

Figure 4: Effect of drugs on Q4T on the 5th day in Morris water maze (n = 6 in each group). Values expressed in mean ± standard error mean, #denotes $P < 0.001$ as compared to control (DW), *denotes $P < 0.001$ as compared to carboxymethylcellulose treated group

Table 1: Effect of drugs on brain MDA and plasma cholesterol levels

Parameters	Control (DW) 10 ml/kg i.p.	1% w/v CMC 10 ml/kg p.o	Piracetam 400 mg/kg p.o.	Simvastatin 5 mg/kg p.o.	Atorvastatin 5 mg/kg p.o.	*F*	*P*
Brain MDA level	308.04±15.0	381.20[a]±7.31	333.89[b]±6.78	330.54[b]±8.61	346.15[b]±4.80	8.551	<0.001
Plasma cholesterol level	84.33±1.56	89.33±0.61	84.00±2.00	84.00±1.55	88.67±0.95	3.575	<0.05

n=6 in each group. Values expressed in mean±SEM, [a]denotes $P<0.001$ as compared to control (DW), [b]denotes $P<0.01$ as compared to CMC treated group. SEM: Standard error mean, MDA: Malondialdehyde, CMC: Carboxymethylcellulose

impairs learning and memory of rats and human beings.[13] Scopolamine was used as amnesia-inducing agent as it was the agent known to produce short-term amnesia in humans as well as in animals. In our experiment, it led to increased SDL time, Q4T time and brain MDA in disease control groups and significantly decreased in atorvastatin, simvastatin, and piracetam treated groups.

The disease control group treated with CMC showed a significant decrease in SDL in comparison to the only distilled water treated group. The effect on SDL with piracetam, simvastatin, and atorvastatin was significantly increased in comparison to disease control group. The effect of statins was found to be similar to that of piracetam. This study result is corroborated with that of Milind Parle *et al*.[11] This effect of statins might be due to their antioxidant properties as there was an increased MDA level in amnesia induced group. In scopolamine-induced amnesia, the Day 4 ELT in all groups including controls and test showed a significant decrease in respect to their day 1 ELTs. Hence, this result showed the normal acquisition of memory in all the study groups. The Day 5 Q4T was significantly lesser in disease control (CMC treated) than that of normal control (DW treated) not received scopolamine whereas it was significantly more in all drug-treated groups in comparison to disease control. This result is similar to earlier report.[11] The study showed a significant increase in tissue MDA level in brain of disease control group in comparison to that of normal control.[14] The standard drug piracetam and test drugs such as simvastatin and atorvastatin significantly decreased the tissue MDA level in comparison to disease control group.[15] As MDA is an important marker of oxidative stress and suppressed significantly by statins (simvastatin and atorvastatin), it proved their antioxidant property. This result correlated with the fact that antioxidant property of statins might be responsible for their antiamnesic effect.[16] A protective effect against dementia by use of statin was observed in the meta-analysis of THIN database and in a prospective study on elderly African American cohort.[5,17] This action might be related to their vascular action. Hence, statins by virtue of their cholesterol-lowering property and antioxidant property protect both the neuronal and vascular activities of the brain. In our earlier study on dementia using high-fat diet, the statins also protected against learning impairment and memory loss.[7] Some similar but reversible changes in altering the memory, cognition and learning were caused by the use of scopolamine, a known anticholinergic drug in our present experimental study model of AD. Further, Naringenin, a flavanone found in citrus fruits was found to have reversed the scopolamine-induced amnesia attributed to its antioxidant and anticholinesterase activity.[18] In our experiment, it was proved that in all interoceptive models used, statins such as simvastatin and atorvastatin reversed the memory deficit. In our earlier experiments with age-induced amnesia model as well as in high-fat-diet-induced amnesia model, there was a definite increase in total cholesterol and MDA level. As the statins (simvastatin and atorvastatin) significantly reversed the memory deficit along with cholesterol-lowering and antioxidant action, the memory-enhancing effect may be due to both hypocholesterolemic and antioxidant effect.[11] But in scopolamine-induced amnesia, there was no significant change in plasma cholesterol in comparison to distilled water treated group, but there is an increase in MDA level in brain.[4] Statins exhibit no significant effect on total plasma cholesterol due to lack of its action on normal cholesterol level. The standard drug piracetam also produced no action of plasma cholesterol level, but all of them decreased the brain MDA level. Hence, its antiamnesic effect of statins may be due to cholesterol independent mechanisms such as antioxidant and anticholinesterase action.[18-20]

Neurodegenerative disorder like AD is characterized by deposition of Aβ amyloid neuritic plaques in the brain which has causal relation with high cholesterol turnover.[1] Loss of cholinergic, glutaminergic and serotonergic neurons due to oxidative stress are also implicated in dementia. Vascular dementia, the second most common form of dementia occurs mostly due to causes such as hyperlipidemia, hypertension, and diseases causing endothelial dysfunction.[21] Treatments directed at dementia had been mostly anticholinesterases such as rivastigmine, donepezil, galantamine with or without N-methyl-d-aspartate (NMDA) antagonist, and memantine and there is a modest outcome which is least likely to be detected in routine clinical encounters. Anticholinesterases improve cholinergic synaptic transmission without interfering the progressive cholinergic neuron damage. Memantine decreases neuronal excitotoxicity to protect the neurons but neither effective in improvement of endothelial dysfunction nor in preventing deposition of amyloid Aβ protein. None of these drugs have antioxidant property to neutralize the oxidative stress of neurons and are not protective in the AD.[21] Statins, the HMG CoA reductase inhibitors, on the other hand, possess many therapeutic properties having relevance in the treatment of dementia. Important ones are hypolipidemic, antioxidant effect, and improvement of endothelial function. Bestowed with these properties statins could prevent hypercholesterolemia and consequent amyloid deposition in brain, prevent atherosclerosis, and improve an endothelial function that was helpful in preventing vascular dementia, and also reduce oxidative stress to impart neuroprotection.[22] Results of experiments in aged animals (Swiss albino mice) and in those with high-fat diet-induced dementia were consistent with these. In addition, improvement of cholinergic neurotransmission as imparted by anticholinesterases appears to be an additional modality through which statins may be helpful in the treatment of dementia. The present study has a few limitations like extrapolation of animal data to that of humans and study of mood and behavior is difficult in experimental animals. The role of scopolamine as a CNS depressant and model for the AD has its own limitations though known to affect memory and cognition.

CONCLUSION

It might be concluded from the study of ours and that of others that AD could be induced by scopolamine and tested experimentally because the disease has a multifactorial origin. Therefore, the approaches to treatment would be with many therapeutic agents such as (1) anticholinesterases (rivastigmine, donepezil, and galantamine), (2) antioxidants (simvastatin and atorvastatin), (3) nootropics (piracetam), and (4) NMDA receptor antagonists (Memantine).

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How to cite this article: Mishra MR, Sahoo N, Pradhan SC. Scopolamine-induced amnesia model: A possible anticholinergic mechanism with reversibility with statins and nootropic agents. Natl J Physiol Pharm Pharmacol 2018;8(3):420-425.

Source of Support: Nil, **Conflict of Interest:** None declared.