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RESEARCH ARTICLE

Statins: Are they also memory enhancers? A study in relation to their hypocholesterolemic and antioxidant effects in Swiss albino mice

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ABSTRACT

Background: The most common cause of dementia with progressive loss of memory is Alzheimer's disease (AD), a neurodegenerative disorder that occurs due to increased oxidative stress, deposition of amyloid protein, and loss of cholinergic neurons. Statins, by their hypocholesterolemic, antioxidant, and other activities may be helpful in this regard. **Aims and Objectives:** The aim of this study is to examine the relation between memory restoring effect, lipid lowering effect as well as the antioxidant properties of statins in experimental dementia models using Swiss albino mice. **Materials and Methods:** Cognitive ability was tested in randomly selected young Swiss albino mice with two exteroceptive behavioral models, passive avoidance paradigm, and Morris Water Maze (MWM) by assigning 30 animals divided equally into 5 groups for each model. Amnesia was induced by feeding high-fat-diet for 90 days in 4 groups of mice. The 5th group served as control with young mice. Piracetam, atorvastatin, and simvastatin were given, respectively, to 3 of the amnesic groups of each model whereas the 4th group treated with vehicle served as positive control. **Results:** Step-down latency was significantly higher in young mice as well as amnesic mice treated with piracetam, simvastatin, or atorvastatin in comparison to vehicle-treated amnesic mice. Similar result was also seen during retrieval test in MWM, although all the groups performed comparably during acquisition trial. Brain malondialdehyde (MDA) levels were significantly low in all the groups who performed well in either of the exteroceptive behavioral models. Cholesetrol levels in young control and statin-treated groups were significantly low in comparison to piracetam- or vehicle-treated mice. **Conclusions:** Atorvastatin and simvastatin improved the cognitive ability in terms of learning as well as retrieval of learned experience which may be attributed to their hypocholesterolemic and antioxidant properties.

KEY WORDS: Alzheimer's Disease; Atorvastatin; Dementia; Exteroceptive Models; Piracetam; Simvastatin

INTRODUCTION

Memory is the most common cognitive ability which is lost in dementia. Alzheimer's disease (AD), the most common cause of dementia, is a neurodegenerative disorder involving loss of cholinergic, serotonergic, and glutaminergic neurons, characterized by progressive memory deficit, cognitive impairment, and personality changes.[1]

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The pathology in AD is the formation of neuritic plaque containing Aβ amyloid protein. This is derived from a larger transmembrane protein called amyloid precursor protein.[1,2] It appears that cholesterol turnover plays an important role in the deposition and clearance of amyloid peptide in brain.[3-6] Oxygen free radicals produced within the neurons

can cause tissue damage and are also implicated in aging and neurodegenerative process.[7,8]

The most widely used treatments for AD at present are the reversible acetylcholinesterase inhibitors, which aim at prolonging cognitive functions through decreased degradation of acetylcholine at synaptic cleft. The treatment is only symptomatic, without any neuroprotection and provides only modest outcome for the patients.[9,10]

Experimental studies have revealed that cholesterol-fed wild rabbits develop brain pathology similar to that of AD. Transgenic mice fed with cholesterol-rich diet also exhibited increased β-amyloid plaque. Reducing cholesterol can inhibit β-amyloid synthesis both *in vitro* and *in vivo*.[11] Known antioxidants such as vitamin C and E have been shown to possess memory enhancing property.[12,13]

Statins, which act by inhibiting 3-Hydroxy-3-methylglutaryl coenzymeA reductase, the rate-limiting enzyme in cholesterol biosynthesis, are widely prescribed for the treatment of dyslipidemias. Other than lipid lowering effect, there are many pleiotropic effects such as anti-inflammatory, antioxidant activities, and improved endothelial functions which may contribute to the therapeutic effects of statins.[14,15]

In this present study, we made an attempt to use statins in a high-fat-diet (HFD)-induced amnesia model using Swiss albino mice to examine the relation between memory restoring effect, lipid lowering effect as well as the antioxidant properties of statins which may prove beneficial for prevention, progression, and experimental therapeutics of AD.

MATERIALS AND METHODS

Animals

A total of 60 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. HFD-induced amnesia was produced in 48 mice by giving cholesterol-rich diet for 90 days and subsequently during the experiment also.[16] HFD was prepared by adding excess of coconut oil to normal diet so as to provide 42% of total calories form the fat source.[17] The rest of 12 young mice were fed with normal diet and served as control.

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 experiment. All experiments were carried out in the day time between 10 h and 16 h. This study was conducted in the Department of Pharmacology, Maharaja Krishna Chandra Gajapati Medical College, Berhampur, Odisha. Institutional Animals Ethics Committee approved the experimental protocol and care of animals was taken as per the CPCSEA guidelines.

Drugs

Atorvastatin (Systopic Laboratories Ltd.,), simvastatin (USV Ltd.), and piracetam (Pegasus Farmaco India (P) Ltd.) were locally procured from hospital pharmacy. All other chemicals and reagents used were of analytical grade.

Experimental Design

A total of 12 young mice were divided into 2 Groups (Group I and Group VI) and 48 HFD-fed mice were divided into 8 Groups (Group II to Group V and Group VII to Group X) with 6 animals in each group. Passive avoidance paradigm (PAP) and Morris Water Maze were the two exteroceptive behavioral models used in this experiment in a way similar to our earlier experiment on mice with age-induced amnesia.[18,19] Group I to Group V were subjected to PAP and Group VI to Group X were subjected to Morris water maze (MWM).

Atorvastatin, simvastatin, and piracetam were mixed in 1% w/v carboxymethyl cellulose (CMC) and administered to respective groups. Group I, II, VI, and VII were administered 1% w/v CMC (10 ml/kg body weight [b.w]. p.o.) for 14 days. Group I and VI served as negative control (young) and Group II and VII fed with HFD served as disease control (CMC). Group III and VIII were administered piracetam (400 mg/kg b.w, p.o.) for 7 days, Group IV and IX were administered simvastatin (5 mg/kg b.w, p.o.), and Group V and X were administered atorvastatin (5 mg/kg b.w, p.o.) for 14 days before subjecting the animals to any exteroceptive behavioral model. During the acquisition trials (1 day in PAP and 4 days in MWM) and also on the day of memory retention test, 1% CMC, piracetam, simvastatin, and atorvastatin were administered each day to the respective groups 60 min before experiment.

Passive Avoidance Test

The apparatus used for this test comprises 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 the 1st day followed by memory retention test on the second day to note step-down latency (SDL). SDL is 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 V AC current was delivered for 15 s.[13]

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 end of session.[13,20]

Morris Water Maze

The maze comprises 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.[21] Tank was divided into 4 quadrants (Q1, Q2, Q3, and Q4) with the help of 2 threads. There was a hidden platform (white in color with a diameter of 10 cm) 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 animal was released in the water facing toward the wall of the tank and was allowed to escape to the hidden platform and further allowed to remain there for 20 s and the escape latency (ELT) was recorded. ELT is the time taken by the animal from getting released in the water to escape onto 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, and 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.[13]

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 min. 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 1 h 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.

Immediately after the completion of exteroceptive behavioral experiment, the animals were sacrificed and blood was collected for estimation of serum cholesterol by colorimetric method using commercially available kit from Crest Biosystems. The brains were carefully removed, homogenized, and fresh tissue homogenate was used for estimation of MDA 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 of the mean (SEM). Values with $P < 0.05$ were considered statistically significant.

RESULTS

Effect of Drugs on Locomotor Activity

When tested for locomotor activity on rotarod, there was no significant difference in the fall-off time between the different groups (Figure 1).

Effect of Drugs on SDL

The SDL in vehicle (CMC)-treated mice with HFD-induced amnesia (Group II) was significantly lower than that of vehicle-treated young mice (Group I) fed with normal diet (48 ± 2.79 s vs. 131.17 ± 9.4 s). However, the SDL in mice treated with piracetam ($P < 0.01$), atorvastatin ($P < 0.01$), and simvastatin ($P < 0.001$) were found to be significantly higher than that in disease control group (Figure 2).

Effect of Drugs on ELT

ELT as a measure of effective learning was measured during the acquisition trial in MWM (Figure 3). It was found that the day 4 ELTs in all groups subjected to MWM, that is, young- (Group VI), CMC- (Group VII), piracetam- (Group VIII), simvastatin- (Group IX), and atorvastatin (Group X)-treated mice, were significantly lower ($P < 0.001$) than their respective day 1 ELT. There was a gradual decrease in ELT from day 1 to day 4 in all the above groups.

Effect of Drugs on Q4T

The effect of drugs on Q4T on the 5th day served as a measure of retrieval of memory (Figure 4). It showed that the Q4T in mice with HFD-induced amnesia treated with CMC was significantly lower than that of young mice ($P < 0.001$). However, the Q4Ts in piracetam-, atorvastatin-, and simvastatin-treated mice were significantly higher ($P < 0.001$) than that of disease control group treated with CMC.

Effect of Drugs on Brain MDA Level

In the present experiment, the MDA level in brain tissue of mice subjected to PAP was measured and expressed as nmol/gram of brain tissue. MDA level among mice with HFD-induced amnesia treated with CMC was significantly higher

($P < 0.01$) than that of among young mice treated with CMC. However, the MDA level in groups pre-treated with piracetam, atorvastatin, or simvastatin were significantly lower ($P < 0.001$) than the MDA level in CMC-treated group (Figure 5).

Effect of Drugs on Plasma Cholesterol Level

The effect of drugs on plasma cholesterol levels in those mice subjected to PAP has been shown in Figure 6. It was found that the plasma cholesterol level in mice with HFD-induced amnesia treated with CMC or piracetam was significantly higher than that young mice ($P < 0.001$). However, the plasma cholesterol levels in HFD-fed mice treated with atorvastatin and simvastatin were significantly lower than that of disease control group as well as those treated with piracetam ($P < 0.001$). The memory enhancer drug piracetam did not decrease in plasma cholesterol level significantly in comparison to disease control group.

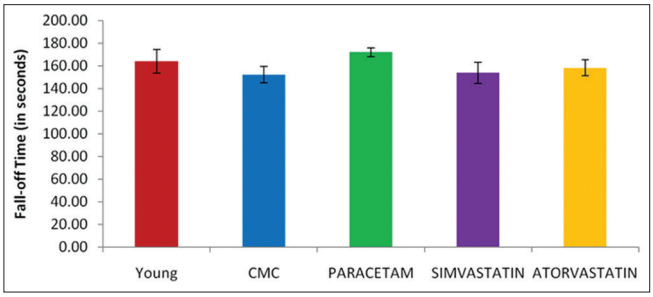

Figure 1: Effect of drugs on fall-off time from rotarod in mice with high-fat-diet-induced amnesia ($n = 6$ in each group). Values are expressed in mean ± SEM. The differences are not statistically significant between the different groups

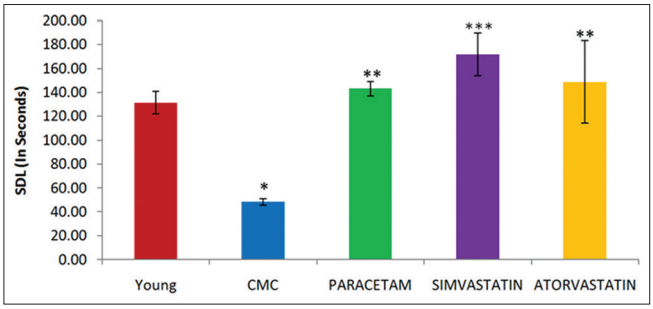

Figure 2: Effect of drugs on step-down latency in high-fat-diet-induced amnesia of mice in PAP ($n = 6$ in each group). Values are expressed in mean ± SEM. *Denotes $P < 0.05$ as compared to young control group; ** and ***denotes $P < 0.01$ and $P < 0.001$, respectively, as compared to CMC-treated group

Figure 3: Effect of drugs on escape latency (ELT) in Morris water maze during acquisition trial in high-fat-diet-induced amnesia ($n = 6$ in each group). Values are expressed in mean ± SEM. *Denotes $P < 0.001$ as compared to day 1 ELT in all 5 groups

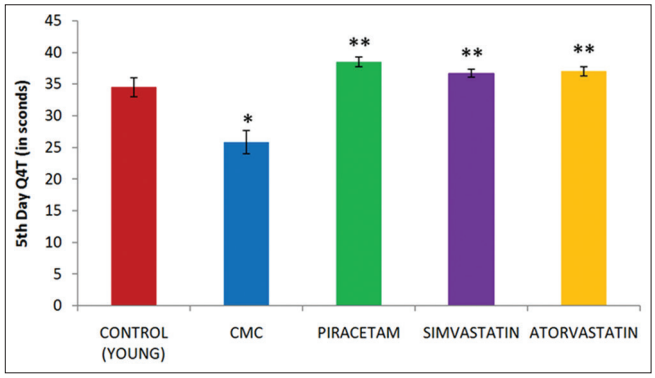

Figure 4: Effect of drugs on the 5th day Q4T in high-fat-diet-induced amnesia ($n = 6$ in each group). Values are expressed in mean ±SEM. *Denotes $P < 0.001$ as compared to day 5 Q4T young control group; ** $P < 0.001$ as compared to day 5 Q4T of CMC-treated group

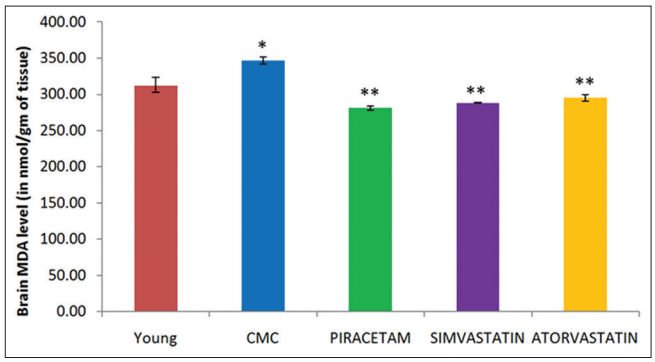

Figure 5: Effect of drugs on brain MDA levels in high-fat-diet-induced amnesia ($n = 6$ in each group). Values are expressed in mean ± SEM. *Denotes $P < 0.01$ as compared to young control group; **$P < 0.001$ as compared to CMC-treated group

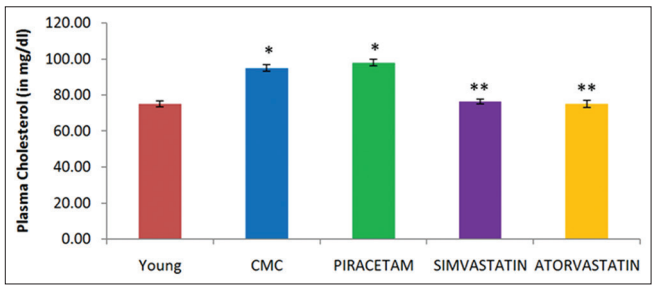

Figure 6: Effect of drugs on plasma cholesterol in high-fat-diet-induced amnesia ($n = 6$ in each group). Values are expressed in mean ± SEM. *Denotes $P < 0.001$ as compared to young control group; **$P < 0.001$ as compared to CMC- and piracetam-treated group

DISCUSSION

The present study was conducted to explore the effect of lipophilic statins such as simvastatin and atorvastatin on memory with HFD-induced amnesia. Piracetam, a known memory enhancer, acts by facilitating choline uptake, acetylcholine turnover, and cholinergic transmission.[20,21] Scopolamine-induced amnesia which represents the main clinical symptom of AD is well reversed by piracetam in both rodents and humans.[13]

Free radical injuries due to reactive oxygen species are also implicated in the process of aging and are among the factors responsible for the development of AD. Ascorbic acid which has known antioxidant property has shown promising result in experimental models of amnesia.[13] *Emblica officinalis*, a rich source of vitamin C, also improved the memory in aged animals and in scopolamine-induced amnesia.[22]

It was also reported that in AD there had been an increase in serum cholesterol level. Reversal of memory deficit by giving statins was observed in experimental models of dementia but was not corroborated with corresponding antioxidant level in brain tissue.[16] Protective effect against dementia was observed in a population-based cohort study to assess the effect of statins on a range of health outcomes using The Health Improvement Network (THIN) database.[23] Statins are also claimed to posses many other effects in addition to its primary hypocholesterolemic effects such as improved endothelial function, reduced vascular inflammation, increased neovascularization of ischemic tissue, and increased circulating endothelial progenitor cells.[15] The present study, like others also established the relation of the antiamnesic effect of statins with hypocholesterolemic as well as antioxidant properties.[14,23]

We used two exteroceptive behavioral models in, that is, PAP and MWM to test the cognitive ability in Swiss albino mice. Responses of animals in both the models required normal musculoskeletal functions as well as proper motor coordination.[24] Therefore, before experimenting, they were subjected to rotarod test to rule out any musculoskeletal deficiency and motor incoodination. It was found that there was no significant difference in fall-off time among the different study groups. This indicated that differences in performances, if any, during the behavioral tests were not due to any musculoskeletal malfunction.

PAP is based on negative reinforcement and used as a standard method to examine the long-term memory by recording SDL.[18] In this present study, it was observed that with administration of atorvastatin, simvastatin, or piracetam to the respective groups, there was a significantly increased SDL time as compared to that of disease control group which received only CMC. This indicated better retention of memory with simvastatin and atorvastatin which was comparable with the memory enhancer drug piracetam. The earlier study showed similar results like our study.[16]

MWM is a common method to assess the spatial learning and memory of rodents. The technique of using escape from water to motivate learning is the basis of this model. ELT of day 4 when compared with that of day 1 served as index of learning and acquisition. Q4T is the time spent in target quadrant to search the hidden platform, served as index for retrieval of memory.[25] In our study, there was a gradual and definite decreasing trend in ELT starting from day 1 through day 2, day 3 up to day 4 in all mice. When the day 4 ELTs in all the drug-treated groups as well as in the vehicle-treated groups were compared with their corresponding day 1 values, the differences were significant. This denoted the normal pattern in acquisition of memory in all the groups of animals.[26] During the retrieval test on day 5, the Q4T decreased significantly in disease control group in comparison to young control and all drug-treated groups. This implies that the HFD-induced amnesic mice were unable to retrieve from memory, the exact location of hidden platform and therefore spent less time in target quadrant. Our study showed results consistent with earlier study reports.[16,19,27]

MDA is a degradation product generated in the tissue as a result of lipid peroxidation. It reacts with thiobarbituric acid and produces coloured product that absorbs light at 532 nm. Level of this thiobarbituric acid reacting substance can be estimated using spectrophotometry. During the biochemical estimation, it was observed that brain tissue MDA level in disease control group was significantly higher than that of the young control group. Piracetam, simvastatin, and atorvastatin produced significant decrease in brain MDA levels and hence decreased oxidative stress in treated mice in comparison to that of disease control group while the effects produced by statins are not significantly different from piracetam-treated group. This finding proved the earlier hypothesis by Parle and Dhingra, 2003, that the antiamnesic effect of statins may be due to their antioxidant properties.[13]

The HFD-induced amnesic mice treated with vehicle CMC only showed significant rise in plasma cholesterol level in comparison to that of normal control comprising young mice. This increase in plasma cholesterol level in HFD-induced amnesia corroborated with other study results that elevated serum cholesterol level could be an important risk factor for AD.[4-6] Atorvastatin and simvastatin in 5 mg/kg b.w. dose significantly decreased the plasma cholesterol level whereas piracetam did not show any significant change in plasma cholesterol level. Piracetam probably produces its antiamnesic effect by other mechanism such as stimulating cholinergic transmission which is not the case with statins. Hence, in addition to the antioxidant property, hypocholesterolemic effect of statins can also be implicated for the antiamnesic effect.[28] The present study was conducted in laboratory animals. Further long-term studies should be conducted for

promoting its clinical use in prevention and treatment of dementia.[22,29,30]

CONCLUSION

This study was conducted to evaluate the antiamnesic property of statins (simvastatin and atorvastatin) and corroborate with their hypocholesterolemic and antioxidant property. HFD for a prolonged period impaired the learning and memory of Swiss albino mice. This effect was successfully reversed by administration of piracetam or by the statins before new learning. It was also found in this study that memory enhancing property of statins was in agreement with decrease in plasma cholesterol as well as brain MDA levels. There is a possible association of hypocholesterolemic and antioxidant properties with the learning and memory. As piracetam also enhanced the learning and memory along with decrease in MDA but without lowering plasma cholesterol level, it seems some cholesterol-independent mechanisms such as antioxidant and anticholinesterase activities might be operating.

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