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ANTIDEPRESSANT ACTIVITY OF STATINS IN ALBINO MICE AN EXPERIMENTAL STUDY

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ABSTRACT

Objective: To evaluate the antidepressant activity of statins in mice.

Methods: Sixty adult Swiss albino mice weighing 25-30 grams were selected. Thirty were allocated to forced swim test and thirty to tail suspension test models. In each model there were 5 groups. The control group received vehicle (10 ml/kg, p.o), the standard, Imipramine (10 mg/kg, p.o) and the three test groups received atorvastatin, simvastatin and rosuvastatin respectively, 1hour prior to the acute study. In chronic study the drugs were given orally once a day for 10 days and the last dose was given 1hour before the experiment. Duration of immobility was noted in forced swim test and tail suspension test. Statistical analysis was performed using Mean +/- SEM. ANOVA followed by Dunnett's test. $P<0.05$ was considered statistically significant.

Results: Statins produced significant antidepressant effect at all the doses, as indicated by reduction in the duration of immobility compared to the standard. The antidepressant effect was higher with atorvastatin when compared to simvastatin and rosuvastatin.

Conclusion: Statins has shown significant antidepressant activity greater than imipramine in mice.

Keywords: Forced swim test, Tail suspension test, statins, Depression

INTRODUCTION

Depression is a chronic illness that affects people of all ages. Although there are many effective antidepressants available today, the current armamentarium of therapy is often inadequate, with unsatisfactory results in about one-third of all subjects treated. This provides impetus in the search of newer and more effective antidepressants [1].

Statins are effective and commonly prescribed drugs for hypercholesterolemia. They have received considerable attention in recent times due to their beneficial effects on multiple physiological systems. After realization of pleiotropic effects of statins [2], they are being prescribed to patients suffering from cardiovascular disorders like hypertension and ischemic heart disease, irrespective of the lipid profile. Atorvastatin is the most commonly prescribed statins in the world [3]. Cholesterol reduction using statins improves memory in some cases but not others. Controversy exists over use of statins to alleviate memory problems in Alzheimer's disease (AD) [4]. Correlations of cholesterol and cognitive function are mixed and association studies find that some genetic polymorphisms are related to cognitive function but others are not [5].

Recently, some concerns are raised regarding effects of atorvastatin (and all statins) on memory and psychomotor functions.

Hypercholesterolemia is thus suggested to partly mediate age-related brain changes**.** Possible link between cholesterol and depression has been

suggested in both Clinical and preclinical studies. The recently proposed entity of 'vascular depression' provides indirect support for hypercholesterolemia as a risk factor in the path physiology of depression. Hence this study was undertaken to find out its role in animal models of depression.

MATERIALS AND METHODS

The experimental protocol was approved by the Institutional Animal Ethics Committee (IAEC) of Chettinad Hospitals and Research Institute, Chettinad University, Chennai, India.

Animals

Adult male Swiss albino mice weighing 25-35 gm from our breeding stock were used in this study. The animals were housed at 24±2^{o} C with 12:12 h light and dark cycle. They had free access to food and water. The animals were acclimatized for a period of 7 days before the study. The animals were used according to the CPCSEA guidelines for the use and care of experimental animals.

Drugs and chemicals

The standard antidepressant drug imipramine, statins drugs like atrovastatin, simvastatin and rosuvastatin was obtained from our institutional pharmacy

Experimental design

On the day of the experiment, the animals were divided randomly into control and experimental groups (n=6). Group 1 received the vehicle, normal saline (10ml/kg) and served as the control group, group 2 received the standard drug imipramine (10mg/kg), groups 3 , 4 and 5 the test drug (statin drugs like atrovastatin, simvastatin, rosuvastatin .) in doses of 10mg, 30mg 20mg/kg per oral respectively. Drugs/vehicle was administered to the animals 60 minutes prior to the evaluation in acute study, for chronic study, a new set of animals were used. They were grouped as in acute study and were administered the drug/vehicle orally once daily for a period of 10 days. Behavioral evaluation was carried out 60 minutes post drug/vehicle administration on the 10th day [6]. The antidepressant activity of the test drug was evaluated using the experimental models of depression TST and FST:

Tail suspension test (TST): The method described by *Steru, et. al.* was used in our study [7]. The animals were hung by the tail on a plastic string 75 cm above the surface with the help of an adhesive tape. The duration of immobility was observed for a period of 8 minutes, last 6 minutes of the observation were taken for calculation. Mice were considered immobile only when they hung passively and were completely motionless.

Forced Swim Test (FST): The method described by *Porsolt, et. al.* was used in our study [8], Each animal was placed individually in a 5 litre glass beakers, filled with water up to a height of 15 cm and were observed for duration of 6 minutes, last 4 minutes of the observation were taken for calculation The mouse was considered immobile when it floated motionless or made only those moments necessary to keep its head above the water surface. The water was changed after each test.

STATISTICAL ANALYSIS:

The mean±S.E.M. values were calculated for each group. The data were analyzed using one-way ANOVA followed by Dunnet's multiple comparison test. $P< 0.05$ was considered to be statistically significant.

RESULTS

Tail suspension test (TST): Results are given in table-1. A significant ($P<0.01$) decrease in the duration of immobility was seen with the standard drug imipramine and test drug (statin) in all the tested doses as compared to the control (group 1) in acute study but in chronic study the dose of 10mg/kg produced a greater decrease in the duration of immobility as compared to the standard drug imipramine.

Forced swim test (FST): Results are given in table-2. A significant decrease in the duration of immobility was seen with the standard drug imipramine and all tested doses of statins as compared to the control (group 1). In acute study, test drug (statin) in a dose of 10mg/kg is more efficacious than imipramine in reducing the duration of immobility. However in chronic study, statin both the doses tested (100 and 200mg/kg) was more efficacious than imipramine.

DISCUSSION

The present studies establish statin (atrovastatin, simvastatin rosuvastatin) have antidepressant activity in laboratory animals like rats. As evidence by force swim test and tail suspension method. Alteration in cholesterol and phospholipids of brain cell membranes may influence membrane fluidity, consequently affecting various catecholamine neurotransmitter systems, including 5HTand noradrenaline [9]. Preclinical studies have demonstrated that low cholesterol levels may lead to decreased 5-HT function in the brain through reduced numbers and/or function of postsynaptic 5-HT receptors [10]. In contrast, mechanisms by which cholesterol depletion may favourably affect the 5-HTsystem have also been proposed. These include an inverse correlation between platelet 5-HTconcentrations and serum cholesterol levels in patients with hyperlipidemia or renal disease; an association between cholesterol lowering treatment and normalization of initially lowintraplatelet5-HT; and a directly adverse impact of elevated cholesterol levels on 5-HTtransporteror receptor function [11, 12, 13,14].

CONCLUSION

The results of the present study have shown that statins have antidepressant activity better than Imipramine and we believe that statins has the potential to be used as an adjuvant in the treatment of depression. Further studies may help to elucidate the possible mechanisms of action of statins.

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Table 1: Effect of Statins on immobility time in the Forced Swim Test (FST) using mice

Group (Drug Treatment)	Duration of Immobility (in seconds)	
	Acute Study	**Chronic Study**
Group 1 (Normal saline 10ml/kg)	120.83 ±7.19	128.17 ± 15.02
Group 2 (Imipramine 10mg/kg)	88.16 ± 9.02	82.16 ± 12.15
Group 3 (Atorvastatin10mg/kg)	53.16 ± 6.40***	49.50 ± 6.80 ***
Group 4 (Simvastatin 10mg/kg)	62.83 ± 12.51***	64.33± 7.84
Group 5 (Rosuvastatin 10mg/kg)	70.00 ± 6.66**	68.66 ± 12.73

Values represented mean ± S.E.M. (n=6), **P<0.05, ***P<0.001 vs. STD (group 2).

Table 2: Effect of Statins on immobility time in the Tail Suspension Test (TST) using mice

Group (Drug Treatment)	Duration of Immobility in (sec)	
	Acute Study	**Chronic Study**
Group 1(Normal saline 10ml/kg)	230.33 ± 9.11	209.5 ± 13.54
Group 2(Imipramine 10mg/kg)	167.00 ± 7.21	153.5 ± 12.35
Group 3 (Atorvastatin10mg/kg)	124.17 ± 12.46***	113.0 ± 7.87***
Group 4 (Simvastatin 10mg/kg)	147.17 ± 14.68**	138.17 ± 29.96**
Group 5 (Rosuvastatin 10mg/kg)	151.33 ± 5.98	143.67 ± 8.57

Values represented mean ± S.E.M. (n=6), **P<0.05, ***P<0.001 vs. STD (group 2).