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Effects of Atorvastatin on Spatial Learning and Motor Behavior Against Neurotoxicity Induced in Wistar Rats

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ABSTRACT
Lipid lowering drugs like statins were shown to have protective effects on memory deterioration. The aim of the present study is to screen atorvastatin for spatial memory against aluminium induced neurotoxicity. The study included thirty male wistar rats, randomized, acclimatized under standard housing conditions. The ethics approval was obtained from institutional animal ethics committee. The drug dosing was done as per study plan and the effects were evaluated using behavioural parameters like Morris maze test, elevated plus maze test and rotarod test following standard methods. The atorvastatin showed significant improvement in Morris maze behavior (P=0.0002) and elevated plus maze behavior (P=0.0007). The results of this reveal the protective effects of atorvastatin on neurobehavioral activities against aluminium chloride toxicity.

INTRODUCTION

Statins or cholesterol-lowering drugs against development of memory deterioration in AD are being ever more reported from epidemiological studies and from model systems[1,2]. The agents have been shown to be neuroprotective and restore memory loss caused by traumatic brain injury in animal models. In a study conducted by Lu D et al, atorvastatin promoted the restoration of spatial memory function in an experimental model of traumatic brain injury[3]. The role of these agents on cognitive parameters has not been assessed in models of dementia, although studies are available which show their modulatory effects on the biochemical parameters involved in the pathogenesis of dementia in Alzheimer's disease (AD). Aluminium chloride induced neurotoxicity was shown to cause dementia which is of Alzheimer's type[4,5]. The aim of the present study is to screen atorvastatin in Aluminium induced neurotoxicity using behavioural tests.

MATERIALS AND METHODS

Thirty adult male Wistar rats (150-200gm, 6months) were used in the study. All the animals were housed under standard laboratory conditions of ambient temperature of 25+2°C, with relative humidity of 65+5% and a 12-hour dark/light cycle. All the animals were fed with standard rodent pellet and tap water ad libitum. The Institutional Animal Ethical Committee has approved the study design. All the animals were acclimatized for one week following randomization and grouping. They were treated with aluminium chloride for 30 days after acclimatization and were given specific treatments according to their groups (each group containing 10 animals) for the last 15days (i.e.16th to 30th day) of aluminium chloride treatment is described in (Table 1).

AlCl3, Aluminium Chloride. I.P, Intra Peritoneal: Atorvastatin was procured from Ind swift, Ltd. (Mumbai). Aluminium chloride was procured from Avantor Performance Materials India Ltd. (Gurgaon). Aluminium induced neurotoxicity in the brain was developed to determine drug activity. Aluminium chloride will be dissolved in distilled water to prepare 35 a solution of concentration 10mg/ml. Al administered once daily by intra peritoneal injections of AlCl3 (10mgAl/kgbodyweight) for 30 days[6].

Behavioural Parameters

Morris Water Maze Test: Morris water maze test was performed following previous method. Training in the maze was given for 5 days with one session of four trials each day to all rats in the study. The platform remained in the same place during all the training sessions. Training was followed immediately by test Session. The procedure during all subsequent test sessions was identical to the training. Escape latency, the time duration between the animal placed in water and escape to platform was recorded and evaluated[7].

Elevated plus Maze Test: Elevated plus maze test was done as described in previous studies[8]. The elevated plus-maze test was used to evaluate spatial, long term memory, following the procedure described. Each mouse was placed at the end of an open arm. Transfer latency, the time taken by the mouse to move in to one of the enclosed arms, was recorded on the 1st day. An arm entry is defined as the entry of all the four feet of the animal into closed arm. If the animal did not enter an enclosed arm within 90s, it was gently pushed into one enclosed arm, and the Transfer latency was assigned as 90s. The mouse was allowed to explore the maze for 20s and was then returned to its home cage.

Rotarod Test: The muscle strength and coordination is evaluated. Rats were placed on the metallic rod (2cm) in diameter rotating at a rate of 20 revolutions per minute. Circular section divided the linear space of the rod in to 4 lengths so that 4 rats could be initially screened for their ability to maintain themselves on the rotating rod for more than 3 minutes. If the animal after treatment cannot remain on the rod for 3 successive trials of 3 minutes each, the test was considered positive i.e. motor inco-ordination was produced by the test compound. Rotarod performance was evaluated as fall-off time in seconds from the rotating rod (20rpm/min) with in a period of 3min[9].

Statistical Analysis: The statistical analysis was done using SPSS v16.0 software. All results data was represented as mean±SD. Difference between groups was calculated with one-way ANOVA followed by Post Hoc Scheffe's test. $p \leq 0.05$ was considered to be statistically significant.

RESULTS AND DISCUSSION

Effect of Atorvastatin on Morris water maze activity: The escape latency was evaluated in Morris maze test. There was no significant (P = 0.54) difference in escape latency time on day 1, while the day 15 test showed significant increase (P = 0.0001) in escape latency of group B,C rats in comparison to group A. Group C rats showed significant (P = 0.0002) improvement in comparison to group B rats on day 30 test.

This test has been included to evaluate the effect of Al salt on learning and memory and to screen atorvastatin. In various experiments Morris water maze has been successfully used for evaluation of anti-dementia and anti-amnesic drugs. The conditioning processes have been considered to be the basic element of learning[10]. Atorvastatin treatment in group C rats attenuated the toxic effects

of aluminium chloride and enhanced Morris maze behaviour (Fig. 1).

Effect of atorvastatin in elevated plus maze activity: The transfer latency on day 1 elevated plus maze activity was comparable between group B rats and group C rats, but significantly (P=0.0001) increased in group B rats compared to group A rats. The evaluation on day 30 revealed significant (P=0.0007) improvement in maze behavior of group C rats in comparison to group B rats (Fig. 2).

Effect of Atorvastatin on Motor Behaviour Activity: The aluminium chloride toxicity couldn't affect the motor behaviour significantly (P = 0.17) during the initial 15 days, later there was significant decrease (P = 0.004) in motor behavior in rotarod performance on 30th day. Though this is statistically significant, only about 20% decrease in motor behaviour was observed and couldn't impact the motor behavior in normal environment.

Fig. 1: Effect of atorvastatin on escape latency of Morris maze test

Various studies have been done evaluating the Aluminium induced neurobehavioral effects and morphological changes in the rat brain[5,11]. Animals loaded with aluminium develop both symptoms and brain lesions that are similar to those found in AD. The performance of the control group animals (Al treatment for 30 days) *et al*. the three-neurobehavioral paradigms was significantly lower than the normal control group A (normal saline treatment for 30 days). The decline in cognitive function was assessed at 15 days and 30 days of treatment. There was a constant decline in memory of Al treated animals. There is increasing data from epidemiological studies and from model systems indicating that cholesterol-lowering drugs may have an impact on the development of memory deterioration in AD[1,2]. The agents have been shown to be neuroprotective and restore memory loss caused by traumatic brain injury in animal models. In a study conducted by Lu *et al*, atorvastatin promoted the restoration of spatial memory function in an experimental model of traumatic brain injury[3]. The role of these agents on cognitive parameters has not been assessed in models of dementia; although studies are available which show their modulatory effects on the biochemical parameters involved in the pathogenesis of dementia in AD. In our study we are able to find significant advantage in neurobehavioral parameters of animals treated with atorvastatin as assessed in various tasks. As compared to the other treatment groups the performance of animals in the behavioral tasks did not deteriorate with the treatment. The findings of our study suggest that atorvastatin showed improvement in memory and significant statistically. Another study reported that, atorvastatin therapy may be of benefit in the

Fig. 2: Effect of atorvatatin on transfer latency of elevated plus maze

Fig. 3: Effect of atorvastatin on latency of fall in rotarod test

treatment of mild-to-moderately affected AD patients, but the level of benefit produced may depends on earlier treatments with other drugs[12]. There have been indirect findings in some studies on surrogate end points. They demonstrated in an animal study that Atorvastatin prevents AßO induced synapto toxicity

Table 1: Study plan for screening insulin against aluminium toxicity.

Group	Description	Treatment	Number of Animals
Group A	Normal Control	normal saline i.p. for 30days	10
Group B	Disease Control	AlCl3 (10mg Al / kg body weight) for 30 days, i.p	10
Group C	Atorvastatin Treated	AlCl3 (10mg Al / kg body weight) for 30 days, i.p + Atorvastatin, 15mg/kg/d, i.p during 16th to 30th day	10

and memory dysfunction through P38 MAPK-dependent pathway[13]. Similarly the findings of other study, in context of atrial fibrillation patients had inferred that improvement in neurocognitive functions correlate with reduced inflammatory burden in atrial fibrillation patients treated with intensive cholesterol lowering therapy[14].

CONCLUSION

The reduction of toxicity neurobehavior induced by aluminium chloride reveals the protective effects of atorvastatin which may be considered for further evaluation studies including biochemical and histological markers.

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