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Evaluation of anxiolytic activity of rousvastatin in male albino mice

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Abstract
Objectives: To assess the anxiolytic activity of ROUSVASTATIN in male albino mice. To compare the anxiolytic activity of ROUSVASTATIN with standard drug as diazepam.
Materials and Methods: The study was conducted in Pharmacology Dept., JJM medical college. Rousvastatin and Diazepam were dissolved in saline. Control group mice were injected with saline. Drugs and saline were injected intraperitoneally.
Results: In elevated plus maze Rousvastatin at dose 30 mg/kg and 50mg/kg increased number of open arm and total arm entries, time spent in open arm and decreased time spent in closed arm.
Conclusion: The results suggest that the significant dose-dependent antianxiety activity of Rousvastatin is similar to the behavioural effects of Diazepam.

Keywords: Anxiolytic activity, Rousvastatin, Diazepam.

Introduction
Anxiety is an emotional state, unpleasant in nature, associated with uneasiness, discomfort and fear about something.(1) Different types of Anxiety disorders includes panic disorder, generalized anxiety disorder, post-traumatic stress disorder, phobias, and separation anxiety disorder.

Prevalence estimates of anxiety disorders are generally higher in developed countries than in developing countries.(2) Women are more prone for anxiety disorder than in men.(3) $42.3 billion was the annual cost of anxiety disorder in US in 1990s, and most of it was due to non-psychiatric medical treatment costs.(4) The primary treatments for anxiety-related disorders include the SSRIs, SNRIs, benzodiazepines, non benzodiazepines and beta adrenergic antagonists. But side effects such as day time sedation and dependence are generally associated with the use of benzodiazepines.(5) There is a need of new anxiolytic drug with lesser side effects and immediate onset of action.

Clinical studies shows direct effects of statins in improvement of endothelial dysfunction, reduction in atherogenesis, Alzheimer's disease, dementia, and anti inflammatory effects which are unrelated to their cholesterol reducing effects.(6,7,8) The aim of this study is to asses the anxiolytic effects of rosuvastatin.

Materials and Methods
This study was conducted at the Department of Pharmacology Animal Experiment Laboratory JJM Medical College, Davanagere, Karnataka, India.

Drugs: Rousvastatin and Diazepam were dissolved in saline. Control group mice were injected with saline intraperitoneally

Animals*:* Twenty four male Albino mice weighing 18-25g (2-2.5months old) were used in this study. All animals were bred in standard laboratory conditions comprising 12-hour light/dark cycle and were allowed to access for food and water freely.

Six mice each were grouped into 4 groups as follows:
group 1: (control group): saline; (i.p route)
group 2: 1 mg/kg Diazepam; (i.p route)
group 3: 30 mg/kg Rousvastatin(i.p route)
group 4: 50 mg/kg Rousvastatin(i.p route)

Experimental procedure: Drugs and/or saline were injected i.p. into the Mice an hour before the experiment. The plus maze test were used to assess the anxiolytic effects of Rousvastatin. It consists of two open arms and two closed arms connected with the central platform. The apparatus is elevated at a height of 25 cms above the ground level. The animals are placed at center of the maze facing towards open arm. Parameters that are recorded are for five minutes. (1) mouse preference towards open or closed arm. (2) Frequency of entries in open arm (3) Average duration of animal in open arm.(9,10)

Statistical Analysis: Within the group comparison was done using analysis of variance with multiple comparison by post hoc Dunnett's *t*-tests. Between the two groups was done by Dunnett's two-sided *t*-tests. Statistical analysis was done using SPSS. $P < 0.05$ level were considered as statistically significant.

Results
Administration of Diazepam has increased the number of open arm and total arm entries, fraction ratio of open/total arm entries, period spent in open arm but reduced period spent in closed arm. Rousvastatin at the dose of 30mg/kg and 50mg/kg has shown similar result by increasing number of open arm and total arm entries, percentage ratio of open/total arm entries, time spent in open arm, analogous results to that of standard drug Diazepam.

Table 1: The number of entries (open and total) of mice in EPM (*n*=6)

Group	Mean+ SEM		
	Number of entries in open arm	Total entries	Percentage ration of open/total arm sentry
Control	5.83+0.54	28.00+0.63	20.70+1.51
Diazepam	33.83+0.54*	47.16+0.54*	71.74+0.93*
Rousvastatin30mg/kg	25.01+0.37*	41.16+0.48*	60.74+0.89*
Rousvastatin50mg/kg	29.17+0.75*	44.33+0.96*	65.77+0.49*

*p<0.001when compared to control

Table 2: The time spent by mice on EPM in open and closed arms (*n*=6)

Group	Mean±SEM	
	Timespent in open arm in seconds	Time spent in closed arm in seconds
Control	4.33±0.62	265.67±0.63
Diazepam	132.330±.96*	167.67±0.96*
Rousvastatin30mg/kg	93.0±0.86*	207.0±0.86*
Rousvastatin50mg/kg	118.67±0.80*	181.33±0.80*

*p<0.001when compared to control

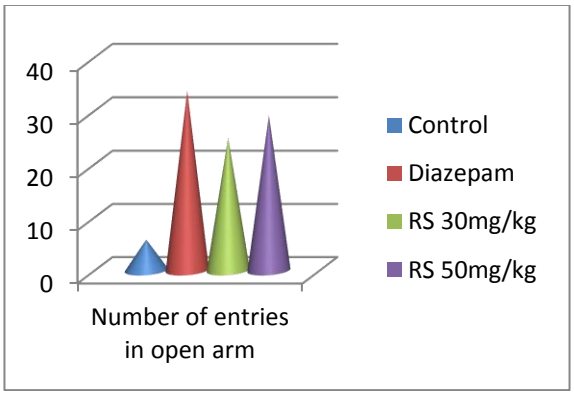

Fig. 1: Effect of Rousvastatin(RS) shows antianxiety effect in open arm entries

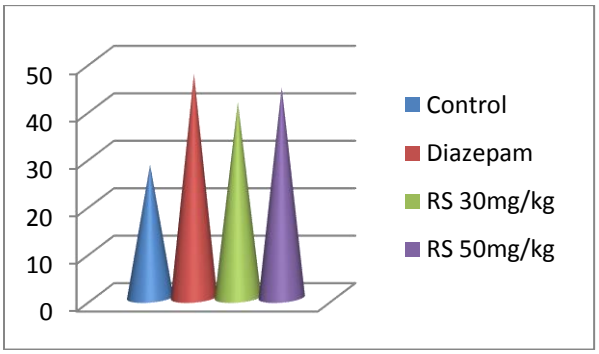

Fig. 2: Effect of Rousvastatin shows antianxiety effect in total entries

Discussion

The elevated plus maze model works on the basis that, inhibition of normal behaviour will occur in the presence of brightly lit, unfamiliar, unprotective environment. It is one of the most widely used and easy animal anxiety model. Hence it was chosen to investigate the anxiolytic activity of Rousvastatin. Site of action of drugs is gamma-aminobutyric acid receptor complex. Standard drug Diazepam increased the number of entries in open arm and the total time spent in the open arms, hence confirming its anxiolytic effects.[11,12]

In this study Rousvastatin at the doses 30,50 mg/kg increases the number of entries in open arm incomparison to control and significantly decreased the number of entries in closed arm compared to that of control.

Diazepam showed decreased fear and increase in exploratory behaviour. The BZDs are comparatively safe and most commonly used anxiolytic agents. Site of action is BZD-GABA receptors; the role of GABA in anxiety is well established. The behavioural changes by Rousvastatin was comparable to that produced by diazepam and suggestive of anxiolytic effect of the statins. The results of our study is consistent with earlier studies. However, several human studies have shown contrary results demonstrating that there were no association between statins and anxiety and depression. The contrary outcomes may mainly result from their different methodology and followup.

Conclusion

The results suggest that the behavioural dis-inhibitory effects of Rousvastatin is similar to the behavioural effects of Diazepam

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