ABSTRACT

The effect of BR-16A (Mentat) on aluminium-induced cognitive deficits and cognition in aged rats was studied in a one-trial step-through passive avoidance task. Aluminium chloride (1000 mg/kg/day) was administered to Wistar rats for 40 days to produce significant cognitive deficits \( p<0.05 \). Aluminium-treated rats received BR-16A (Mentat) \( 100 \) mg/kg/day) for 20 days starting day 21. In a second experiment, aged Wistar rats (12 months) received BR-16A (Mentat) \( 100 \) mg/kg/day) or vehicle for 20 days. BR-16A (Mentat) significantly prolonged the shortened latency of step-through induced by aluminium administration \( [300 \ (214.17-300) \ vs \ 60.5 \ (16-213) ; \ p<0.05] \). It also significantly improved retention of learning in aged rats \( [300 \ (120.80-300) \ vs \ 37 \ (27.5-189.5) ; \ p<0.01] \). These results suggest that BR-16A (Mentat) improves learning and memory in aluminium-treated and aged rats.

Keywords: BR-16A (Mentat); aluminium; cognitive deficits; passive avoidance task; aged rats

INTRODUCTION

BR-16A (Mentat) is a herbal medication derived from Ayurveda and claimed to enhance cognition and to ameliorate various forms of brain deficits\(^1\). It contains over 20 different ingredients of which the following are suggested to improve memory functions: Jal-brahmi (Bacopa monnieri), Mandookaparni (Centella asiatica), Ashwagandha (Withania somnifera), Shankapushpi (Evolvulus alsinoides), Jatamansi (Nardostachys jatamansi), Vacha (Acorus calamus), Malkangni (Celastrus paniculatus) and Sonth (Zingiber officinale)\(^2\). Previous experimental studies in rodents have shown that BR-16A (Mentat) improves memory and learning. It has been shown to improve acquisition and retention of learning in mice\(^3\) and attenuate the amnesic effects of scopolamine\(^4\) and electro-convulsive shock (ECS)\(^5\).

The present study was undertaken to confirm the nootropic effects of BR-16A (Mentat) in two animal models i.e., (1) aluminium-induced cognitive deficits in rats and (2) aged rats. Aluminium has for long been implicated in clinical conditions like senile and presenile dementia of the Alzheimer type, Guam Parkinsonism - dementia complex, Guam amyotrophic lateral sclerosis and dialysis encephalopathy\(^6\). It has been shown to produce cognitive deficits in rodents, which can be utilized as models for the above conditions\(^7,8\). Similarly aged rats utilized in this study are a more appropriate model for age-related mental decline seen in humans\(^9\).
MATERIALS AND METHODS

Animals: Adult wistar rats of either sex (120 - 170 gms; 6 months) and aged wistar rats of either sex (>220 gms; 12 months) were utilized. The animals were housed two per cage under standard light/dark cycle with food and water provided ad libitum. The experiments were performed between 900 and 1400 hrs.

Drugs: BR-16A (Mentat; The Himalaya Drug Co., Bangalore) in a freshly prepared aqueous suspension (100 mg/ml/kg) was administered using an intragastric tube. Aluminium chloride (AlCl$_3$.6H$_2$O; Sarabhai Chemicals Ltd.) dissolved in distilled water (1000 mg/10ml/kg) was administered orally once daily. The animals consumed 4.14 mmol. aluminium/kg/day for 40 days.

Procedure: The rats were weighed before and at the end of the period of drug administration. The spontaneous motor activity (SMA) of the animal was recorded for 30 minutes using the Columbus activity meter. The rota-rod performance of animals was assessed in 5 trials on a Ugo-Basile rota-rod treadmill as described by Dunham and Miya$^{10}$.

Passive avoidance paradigm: A one-trial step-through passive avoidance task was carried out as previously described$^{11}$. The apparatus consisted of two compartments, an illuminated compartment (27 x 30 x 21 cm) and a dark compartment (10 x 30 x 21 cm) having a grid floor through which shock could be delivered. These compartments were separated by a guillotine door. On completion of the treatment schedule each rat was placed in the illuminated compartment and 10 sec. later the door was raised and the latency to enter (LTE) the dark compartment was noted and upon entry, the door was closed and a footshock administered (100 V for 2 sec.). Twenty-four hours after the acquisition trial the rat was again placed in the illuminated chamber and the response LTE was again noted upto a maximum of 300 sec. (Retention trial). The difference between LTE in the acquisition and retention trial was noted. For those animals that did not enter the dark compartment for 300 sec., score was taken as 300.

Experiment 1: Rats were administered aluminium chloride (1000 mg/kg/day) once daily using an intragastric tube for a period of 40 days. From day 21 of aluminium treatment, BR-16A (Mentat) (100 mg/kg/day) was also administered once daily. Control groups received equal volume of vehicle (distilled water). At the end of the treatment schedule, the rats were subjected to passive avoidance paradigm.

Experiment 2: Aged rats received either BR-16A (Mentat) (100 mg/kg/day) or vehicle (distilled water) once daily for a period of 20 days to be followed by passive avoidance task.

Statistical analysis: The results are expressed as Mean ± SEM and Median ± interquartile range. $p<0.05$ was taken as significant. Data was analysed using Student's t-test (unpaired) for weight and SMA, Chi-square test with Yates' correction for rota-rod-test and Wilcoxon rank sum test for latencies.
RESULTS
The locomotor activity, rota-rod performance and latencies of various groups are presented in Table 1. There were no significant differences between test and control groups with regard to weight, SMA and rota-rod performance. Administration of AlCl₃, BR-16A (Mentat) or both did not significantly alter these parameters. SMA score was lesser in aged rats compared to the young adult rats.

<table>
<thead>
<tr>
<th>Group</th>
<th>Weight (gms)</th>
<th>Locomotor activity (score)</th>
<th>Rota-rod (%)</th>
<th>Initial latency (sec.)</th>
<th>Retention latency (sec.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Adult Rats</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vehicle</td>
<td>149.67 ± 10.64</td>
<td>187.83 ± 43.22</td>
<td>83.33</td>
<td>28 (23-36.5)</td>
<td>291.5 (190-300)</td>
</tr>
<tr>
<td>AlCl₃</td>
<td>148.22 ± 7.5</td>
<td>214.33 ± 52.23</td>
<td>77.78</td>
<td>25 (12-34)</td>
<td>61.0a (34-217.7)</td>
</tr>
<tr>
<td>AlCl₃ + Vehicle</td>
<td>141.16 ± 10.06</td>
<td>186.33 ± 28.03</td>
<td>88.88</td>
<td>26 (20.5-34.5)</td>
<td>60.5 (16-213)</td>
</tr>
<tr>
<td>AlCl₃ + BR-16A (Mentat)</td>
<td>133.71 ± 10.60</td>
<td>178.50 ± 60.69</td>
<td>85.71</td>
<td>26 (12.5-32)</td>
<td>300.0b (214-300)</td>
</tr>
<tr>
<td>B. Aged rats</td>
<td></td>
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<td></td>
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<tr>
<td>Vehicle</td>
<td>240.83 ± 8.40</td>
<td>134.16 ± 40.08</td>
<td>100.00</td>
<td>49.5 (24-68)</td>
<td>37.0 (27.5-189.5)</td>
</tr>
<tr>
<td>BR-16A (Mentat)</td>
<td>248.57 ± 11.6</td>
<td>120.57 ± 16.83</td>
<td>100.00</td>
<td>39 (23.41-87.03)</td>
<td>300.0c (120.8-300)</td>
</tr>
</tbody>
</table>

Latencies are expressed as Median ± 25th to 75th percentiles (interquartile range)
Weight and activity score are expressed as Mean ± SEM
a p<0.05; b p<0.01 and c p<0.01 compared to respective vehicle groups. (n=6-9 per group)

There was no significant difference in the initial latencies to enter (LTE) between the test and control groups. However, the initial latencies in the aged groups were more, than in the young adult rats. On testing for the retention latency, AlCl₃-treated rats showed significantly reduced latency compared to vehicle treated group [61(34 - 217.7) vs 291.5 (190 - 300); p<0.05]. On treating AlCl₃-treated rats with BR-16A (Mentat) there was a significant improvement in their latencies to enter [300(214.17 - 300) vs 60.5 (16 - 213); p<0.05]. This shows that BR-16A (Mentat) was able to reverse the cognitive deficit produced by aluminium. In the second experiment, BR-16A (Mentat) significantly improved learning and memory in aged rats.
rats, as shown by improvement in retention latency [300(120.8 - 300) vs 37 (27.5 - 189.5); \( p<0.01 \)]. Similar results were obtained on comparing the LTE difference (Figure 1).

**DISCUSSION**
In the present study, BR-16A (Mentat), a compound herbal preparation was found to improve cognition in two rat models of cognitive deficits. BR-16A (Mentat) prevented the cognitive deficits produced by subchronic aluminium administration. It also improved the learning and memory in aged rats on subchronic administration. Similar results have been described with this dose of BR-16A (Mentat) in previous studies using other animal models. Pretreatment with BR-16A (Mentat) (50-100 mg/kg) was found to produce a dose-dependent reversal of scopolamine-induced prolongation of transfer latency in an elevated-plus maze\(^4\). In another study using an avoidance paradigm, BR-16A (Mentat) was found to produce dose-dependent attenuations of the amnesia produced by scopolamine, single and multiple electroconvulsive shocks\(^3\). Three weeks administration of BR-16A (Mentat) attenuated ECS-induced learning deficits in a T-maze test\(^5\). Yet another study reported that BR-16A (Mentat) (100 mg/kg) reversed the cognitive deficits induced by under-nutrition, environmental deprivation and hypoxia in rats\(^2\). However, the animal models utilized in the present study are in pathophysiological terms more akin to human conditions of intended use of nootropic agents.

The passive avoidance paradigm is widely utilised for testing learning and memory in rats and mice\(^9\). In this study the test and control groups were balanced for weight, spontaneous motor activity, motor endurance and motivational factors which could confound the results.

Aluminium is linked to a number of human conditions with cognitive deficits including SDAT and produces cognitive deficits in rodents\(^6-8\). It produces lipid peroxidation\(^12\), neurofibrillary degeneration\(^8\) and alteration in brain cyclic nucleotide\(^6\), choline levels\(^6\) leading to cognitive deficits. The results of this study show that BR-16A (Mentat) prevents the cognitive deficits produced by aluminium.

The use of aged rats provides a more appropriate model for study of age-related mental decline and senile dementia seen in humans\(^9\). In this study, 20 days administration of BR-16A (Mentat), significantly improved learning and memory in aged rats.

In conclusion, the cognitive enhancing properties of BR-16A (Mentat) shown in this study warrant the study of its mechanism of action and also controlled clinical trials to establish its place in therapy of cognitive disorders.

**ACKNOWLEDGEMENT**
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**REFERENCES**


