ABSTRACT
BR-16A is a herbal (non-allopathic) medication used in India to enhance cognition in this study. Wistar rats (n=24) received either BR-16A (200 mg/kg/day) or vehicle alone for 3 weeks. Over 4 consecutive days during the third week, the rats were tested for learning in the Hebb Williams complex maze. BR-16A treated rats showed significant learning while controls did not. It is concluded that BR-16A facilitates learning. The literature on human and basic science research on BR-16A is briefly reviewed with special reference to its potential applications in psychiatry.

INTRODUCTION
BR-16A (Mentat: The Himalaya Drug Company) is a herbal medication derived from Ayurveda, a system of healing in India’s NCH culture and traditional medicine. It contains over 20 different ingredients the exact formulation differing between pediatric and adult presentations of the composite. Important ingredients of BR-16A suggested to improve memory functions include the following: Brahmi (Bacopa monnieri) Mandokaparni (Centella asiatica), Ashwagandha (Withania somnifera), (Evolvulus alsinoides), Jatamansi (Nardostachys jatamansi), Vach (Acorus calamus), Malkangni (Celastrus paniculatus) and Sonth (Zingiber officianle).

Other ingredients of BR-16A claimed to be nerve tonics, include Tagar (Valeriana wallachii), Bagam (Prunus amygdalus), Salap (Orchis mascula), Lavang (Syzygium aromaticum) and Pearl (Mukta pishti). The remaining ingredients are putative general tonics and vitalisers (Iyengar 1981, The Himalaya Drug Company 1991; Satyavati 1993; Andrade et al., 1994a).

Each ingredient is a plant extract, which contains a variety of psychotropic and other compounds. The formulation of BR-16A is in accordance with Ayurvedic principles – different components of the formulation mutually complement each other’s properties. BR-16A is claimed in Ayurveda to enhance cognition and to ameliorate various forms of deficits in organic brain states.

The present study, using an animal model of learning, sought to assess whether BR-16A indeed enhances cognition.
METHODS

Adult, male, Sprague Dawley rats, weighing 180-200 g at intake, were housed 4 per cage with free access to tap water and standard laboratory diet and were kept in a 12-hour light dark cycle (lights on at 6 am.) room during the period of the study.

In each cage, the rats were randomised two by two to receive either BR-16A in a freshly prepared aqueous suspension (200 mg/ml) or water alone. Administration was effected using an intragastric tube, in a volume of 1 ml/kg once a day (circa 3 p.m.) for 3 weeks.

During the first 2 weeks, 24 rats received BR-16A or vehicle alone. On the first day of the third week, all rats were familiarised with the Hebb Williams complex animal maze (Techno Electronics, Lucknow, India). From the second to the fifth day (circa 9 p.m.), the rats received 5 consecutive trials of training per day in the maze.

The maze comprises a completely enclosed hexagonal box with an entry and a reward chamber appended at opposite ends. The box is partitioned with wooden slots into blind passages, leaving just one, twisting corridor leading from the entry to the reward chamber. In each trial, the rat is placed in the entry chamber, a timer is activated immediately the rat leaves the chamber. A pressure-sensitive plate detects the entry of the rat into the reward chamber, and the timer is immediately deactivated.

The five-trial total of the times taken by the rat to reach the reward (food pellet) chamber was taken as its learning score for the day. Since animals showing more efficient learning reach the reward chamber faster, higher scores indicate poorer learning (Rao et al., 1991)

To ensure adequate motivation during learning assessments in the third week the animals were exposed to (ad lib) food for just one hour a day after the maze exposure for the day was completed. The learning assessments were conducted under a single zero-watt dim red bulb so as to minimally disturb the rats nocturnal cycle.

The Mauchley test revealed no significant violation of sphericity (W=0.59, Chi square df 5=11.0, NS) and Box’s multivariate test for homogeneity of dispersion revealed no significant violation of homogeneity of variances (M=16.37, F df 10, 2313=1.31, NS; chi square df 10=13.1, NS). These tests justified the application of the repeated measures ANOVA, the results of which follow.

A one way repeated measures ANOVA revealed a significant effect for time in the BR-16A group (F 3.33=17.63, p<0.001) indicating significant attenuation of learning scores across time. There was, however, no significant effect for time in the vehicle group (F 3.39=0.26, N.S.)

A two way repeated measures ANOVA revealed a significant main effect for groups (F 1.22=43.12 p<0.001), indicating that, overall, learning scores were significantly smaller in
the BR-16A as compared with the vehicle group. The group x time interaction was also significant \((F_{3,66}=4.88, p<0.004)\) indicating that the BR-16A group showed a faster attenuation of scores across time.

**DISCUSSION**

There is presently much interest in India in the investigation of traditional systems of medicine; scientists hope to identify herbal ingredients with potential allopathic applications; much as reserpine was isolated over half a century ago from the roof of *Rauwolfia serpentina*.

BR-16A was addressed as a candidate drug in this study; the term ‘drug’ is used for convenience, for BR-16A, as indicated earlier, is actually a combination of substances.

Rats pretreated with BR-16A were found to show significant learning while control rats failed to learn within the same time span. There is some support in literature for the beneficial effect of BR-16A on cognition.

In normal volunteers, BR-16A was found to improve memory parameters and decrease anxiety parameter after 12 weeks of administration in the dose of 350 mg twice daily (Agrawal *et al.*, 1990a and b).

Verma and Kulkarni (1991) studied mice in elevated plus maze. Transfer latency the timer by the animal to leave the open arm and enter the closed arm, was used as a measure of learning. Pre-treatment with BR-16A (50-100 mg/kg) was found to produce a dose-dependant reversal of scopolamine-induced prolongation of the transfer latency.

Kulkarni and Verma (1992a) studied mice using an avoidance paradigm. The apparatus consisted of a grid through which an electrical shock could be delivered with an elevated shock-free zone in the centre of the grid. Latency to reach the shock-free zone was recorded, as also the number of descents onto the grid over a period of 15 minutes. These two variable operationalized the efficiency of recall of the electric shock offered by the grid during training. In separate experiments, scopolamine, single ECS and 6 once-daily ECS were found to induce amnesia as evidenced by increases in latency and increases in the number of descents. Pretreatment with BR-16A (50 to 500 mg/kg) was found to result in dose-dependant attenuations of these indices of amnesia.

Andrade *et al.*, (1994a) used a reward-oriented paradigm to study the baseline learning behaviour of rats in a T-maze and in a complex maze. Number of trials to satisfactory learning and number of wrong arm entries were recorded as the learning variable in the T-maze experiment while time taken by the animal to reach the reward chamber was recorded as the learning variable in the complex maze experiment. After establishing baselines, rats were treated with BR-16A (200 mg/kg/day) or vehicle for 3 weeks. During the second week of treatment, all rats received 6 once daily ECS. Learning assessments were resumed during the third week of treatment were compared with baseline scores in both experiments. BR-16A
(200 mg/kg/day) was observed to attenuate ECS-induced (anterograde amnestic) learning deficits.

Joseph et al., (1994) treated rats with BR-16A for 3 weeks. During the second week, all rats received six once-daily electroconvulsive shocks (ECS). During the third week, the rats were assessed for ECS-induced anterograde amnesia using a complex maze. BR-16A treated rats exhibited significantly less anterograde amnesia than controls.

Andrade et al., (1995) administered two ECS in a single day to rats pretreated with BR-16A. The rats were then assessed in a T-maze for efficiency of recall of a task-learnt pre-ECS. BR-16A-treated rats showed less ECS-induced memory impairment (retrograde amnesia) than controls.

Faruqi et al., (1995) studied rats in a complex maze before and after the administration of two once-daily ECS. BR-16A was administered all through the study. Rats receiving BR-16A were found to exhibit less amnesia than controls for material learnt pre-ECS and were also found to exhibit less impairment of new learning post ECS.

What do these results suggest? BR-16A seems to improve cognitive parameters in both animal and human experiments. In animal experiments furthermore, BR-16A exerts a protective effect against ECS-induced anterograde and retrograde amnesia.

The mechanism of action of BR-16A is unclear Cholinergic facilitation may be involved, as the drug reverses scopolamine-induced memory deficits (Verma and Kulkarni 1991; Kulkarni and Verma 1992a) BR-16A may also influence opioid neurotransmission; Kulkarni and Verma (1992b) found the drug to prevent the development of tolerance and dependence to morphine in mice. Preliminary work indicates no effects on adrenergic or dopaminergic autoreceptors, but an enhancement of dopamine postsynaptic receptor function (Andrade et al., 1994b).

BR-16A has a high therapeutic index with no mortality observed in mice even at a dose of 1600 mg/kg; compare this with the recommended human dose of 15-30 mg/kg/day. The drug does not influence the course or outcome of pregnancy, nor does it produce teratogenic effects in Wistar rats even at 2000 mg/kg/day for 20 days. In humans chronic use of BR-16A does not produce impairments in cardiophysiological hematological and biochemical indices (Himalaya Drug Company, 1991). Several years of experience with the drug post-marketing have not resulted in the record of any adverse effects of note (The Himalaya Drug Company, data on file).

Systematic testing of BR-16A in allopathic contexts is presently under way. There is hope that BR-16A may be of utility in the attenuation of the cognitive deficits induced by electroconvulsive therapy (Andrade, 1990 and 1995); a study testing this is currently being
conducted. There is also scope for the investigation of the utility of BR-16A in organic brain states characterised by cognitive deficits (Andrade, 1993).

REFERENCES


