

BR-16A – Restricts Development of Electroconvulsive Shock-induced Retrograde Amnesia

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ABSTRACT

Forty nine adult male Sprague Dawley rats were selected for rapid learning in a T-maze to study the effects of BR-16A, a herbal preparation on ECS-induced retrograde amnesia. Half the rats received 200 mg/kg BR-16A and the other half received vehicle alone. The rats were trained to run into the enclosed chamber of either the left or the right arm on a T-maze; a food pellet served as a reward in the correct arm. Satisfactory learning was defined as 9 correct arm entries over 10 consecutive trials on the maze. On the 5th day, the rats in both the groups were randomised to receive true or sham ECS. The post-ECS data revealed that the number of trials to satisfactory learning and the number of trials with wrong arm entries were large in the ECS-vehicle group, which suggests that BR-16A prevented the development of amnesia. Cholinergic facilitation may be involved, as evidenced by the reversal of scopolamine-induced amnesia and it may also influence opioid neurotransmission. Since ECT-induced retrograde amnesia is a particularly distressing adverse consequence of the treatment, it is hoped that BR-16A will offer a viable solution to the problem of memory deficits following ECT.

Key Words: Electroconvulsive therapy, electroconvulsive shock, amnesia, learning, BR-16A, rats.

INTRODUCTION

Methods employed to limit electroconvulsive therapy (ECT) induced cognitive morbidity include modifications in ECT technique and co-administration of putative anti-amnestics drugs. (Andrade 1990; Nobler and Sackeim 1993). Recent reports suggest that a herbal medication, BR-16A may reduce memory deficits induced by electroconvulsive shocks (ECS). BR-16A (Mentat; The Himalaya Drug Company, Bangalore, India) is a herbal preparation formulated with over 20 ingredients in defined proportions these are suggested to complement each other in meditation of benefit. A review of BR-16A is available elsewhere (Andrade *et al.*, 1994a; Joseph *et al.*, 1994). The available literature suggests that BR-16A facilitates learning in rats, and that it attenuates certain memory deficits induced by ECS. The present study was undertaken to assess the efficacy of BR-16A in protection against ECS-induced retrograde amnesia.

MATERIALS AND METHODS

Adult male Sprague Dawley rats (180-200; n=49), preselected for rapid learning in a T-maze, were housed four per cage. The rats were allowed 24 hour free access to tap water, but fed *ad*

libitum on standard laboratory diet for just 1 hour each day, at approximately 3.30 PM, after the day's work with the animals was complete.

Half the rats received 200 mg/kg of BR-16A in a freshly prepared 200 mg/ml aqueous suspension; the other half received vehicle alone in the same volume. BR-16A/vehicle was orally administered by slow syringing through a smooth-tipped, wide-bore needle inserted far back in the oral cavity. Administration was once daily from the beginning to the end of the study.

The rats were trained to run into the enclosed chamber of either the left or the right arm of a T-maze; a food pellet served as a reward in the correct arm. Arm assignment was random and was retained unchanged for each rat to the end of the study; the number of left- and right-arm rats was equal in the BR-16A and vehicle groups.

Satisfactory learning was defined as nine correct arm entries over 10 consecutive trials on the maze. On each of four consecutive days, the rats were trained to the criterion for satisfactory learning. Two learning measures were recorded; the number of trials to satisfactory learning and the number of trials with wrong arm entries (Bures *et al.*, 1976). T-maze training was conducted between 10 AM to 3 PM.

On the fifth day, rats in the BR-16A and vehicle groups were randomised to receive true or sham ECS. True ECS was administered through saline-soaked earclip electrodes using the Electrocon MK II 50 Hz sinusoidal wave ECT device (Associated Electronics Engineering, Bangalore, India). The stimulus settings were 130 volts x 0.5 sec. Sham ECS involved identical handling without passage of current. True/sham ECS were administered at approximately 10 AM and again at approximately 3 PM on the same day.

The motor seizure duration (in the true ECS groups) and the subsequent spontaneous righting time were recorded by an experienced observer using a stopwatch. The motor seizure was defined to extend from the commencement of passage of current to the commencement of asymmetrical/asynchronous limb activity or the cessation of movement, whichever occurred earlier. Righting time was defined as extending from the termination of the motor seizure to the spontaneous righting to an erect posture upon all four limbs.

On the day after ECS, the rats were reassessed on the T-maze until satisfactory learning was attained. Learning measures, reflecting efficiency of recall of pre-ECS learning, were recorded as before. ECS was expected to impair recall, and the effect of BR-16A vs. vehicle on this ECS-induced retrograde amnesia was proposed to be compared.

All assessments were conducted by raters blind to the treatment status of the rats.

RESULTS

The mean \pm standard deviation (M \pm SD) seizure duration and righting time for the 2 ECS in each of the true ECS groups are presented in Table 1. Two-way repeated measure analyses of variance (ANOVAs) were conducted separately for the seizure duration and the righting time data. In both analyses there was no significant main effect either for drug status (BR-16A vs. vehicle) or occasion (ECS 1 vs. ECS 2) nor was there a significant drug \times occasion interaction.

	Seizure duration		Righting time	
	1	2	1	2
ECS-BR-16A (n=12)	17.42 \pm 1.56	17.25 \pm 1.48	117.92 \pm 24.16	116.25 \pm 11.31
ECS-vehicle (n=12)	16.58 \pm 1.24	16.58 \pm 0.90	103.75 \pm 19.08	116.25 \pm 11.31

The M \pm SD number of trials to satisfactory learning over the 4 (pre-ECS) training days and the single (post-ECS) reassessment day are presented in Table 2. A three-way repeated measures ANOVA (with Huynh Feldt epsilon correction of degrees of freedom for significant departure from sphericity) was conducted on the pre-ECS data of Table 2 with drug (BR-16A vs. vehicle) and ECS (true vs. sham ECS) status between subjects factors and day of assessment as the within-subjects factor. There was a significant main effect for day of assessment (F 2, 106=26.32, p <0.001). The remaining main effects and interactions were nonsignificant.

	Pre-ECS				Post-ECS
	Day 1	Day 2	Day 3	Day 4	Day 1
ECS-BR-16A (n=12)	10.00 \pm 0.74	9.25 \pm 0.45	9.33 \pm 0.49	9.00 \pm 0.00	9.58 \pm 0.90
ECS-vehicle (n=12)	10.83 \pm 1.75	9.58 \pm 0.51	9.50 \pm 1.00	9.08 \pm 0.29	22.25 \pm 3.91
Sham ECS-BR-16A (n=13)	10.46 \pm 0.97	9.46 \pm 0.88	9.31 \pm 0.48	9.15 \pm 0.38	9.46 \pm 0.52
Sham ECS-vehicle (n=13)	10.17 \pm 1.19	9.50 \pm 0.52	9.33 \pm 0.65	9.25 \pm 0.45	9.33 \pm 0.49

The post-ECS data of Table 2 were analysed using a two-way ANOVA with drug status and ECS status as the two factors, and with day 4 pre-ECS scores as a covariate. There was a significant drug \times ECS interaction (F 1, 44=132.38, p <0.001).

Analysis of the wrong arm entry data yielded results similar to those presented for Table 2; these data are therefore not presented.

DISCUSSION

The post-ECS data revealed that the number of trials to satisfactory learning and the number of trials with wrong arm entries were large in the ECS-vehicle group, but were smaller and similar in the remaining three groups. This demonstrates ECS-induced retrograde amnesia in

the ECS-induced retrograde amnesia in the ECS-vehicle group, and suggests that BR-16A prevented the development of amnesia in the ECS- BR-16A group. This result was statistically significant, as is evident from the significant ECS x drug interactions in the analysis of the post-ECS data. Since the groups of rats were comparable in seizure indices and pre-ECS learning performances, these variables are unlikely to have influenced the findings.

BR-16A has been found to attenuate ECS-induced anterograde amnesia in the complex maze and in the T-maze (Andrade *et al.*, 1994a; Joseph *et al.*, 1994). Using an avoidance paradigm, Kulkarni and Verma (1992a) demonstrated that BR-16A attenuates ECS-induced retrograde amnesia as well.

The mechanism of action of BR-16A is presently uncertain. Cholinergic facilitation may be involved, as evidenced by the reversal of scopolamine-induced amnesia (Verma and Kulkarni, 1991). BR-16A may also influence opioid neurotransmission: Kulkarni and Verma (1992b) found that BR-16A prevents the development of tolerance to and dependence on morphine in mice. BR-16A was also found to enhance dopamine postsynaptic receptor functioning without affecting dopamine autoreceptors or alpha-2 adrenergic receptors (Andrade *et al.*, 1994b).

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 root of *Rauwolfia serpentina*. It is hoped that clinical trials of BR-16A in patients with various states of cognitive dysfunction will live up to the expectations generated by preclinical trials.

It is acknowledged that the ECS schedule employed in this experiment is not representative of clinical practice. The purpose here was to ensure that (retrograde) amnesia resulted from the ECS; the use of a clinically representative ECS schedule could have led to time-dependent, ECS-unrelated amnesia in all groups of rats. It is assumed that the mechanism by which two ECS given on the same day produce retrograde amnesia does not differ substantially from the mechanism by which schedules of conventional in human ECT produce the amnesia. Since ECT-induced retrograde amnesia (e.g., the development of autobiographical memory deficits) is a particularly distressing adverse consequence of the treatment, it is hoped that BR-16A will offer a viable solution to the problem of memory deficits following ECT. A note of caution is, however, sounded that it is sometimes hard to replicate in clinical contexts the positive results obtained in animal studies.

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