BR-16A does not interfere with Alpha-2 Noradrenergic and Dopamine postsynaptic receptor functioning

Chittaranjan Andrade, MD,
Associate Professor, Department of Psychopharmacology, NIMHANS, Bangalore
Jennifer George, MD, Lecturer, and
Thangam Joseph, MD, Professor and Head,
Department of Pharmacology, St. John’s Medical College, Bangalore, India.

SUMMARY
BR-16A is a herbal preparation with several putative psychotropic effects. Recent work has suggested that it facilitates certain aspects of cognition and that it ameliorates ECT-induced amnesia in animal models. The present study sought to assess whether it affects noradrenergic and dopaminergic functioning in the central nervous system. Adult male Sprague-Dawley rats received BR-16A (200 mg/kg) or vehicle for one month. The animals were subsequently challenged with clonidine (100 µg/kg, I.P.), apomorphine (2 mg/kg, I.P.), or saline in a factorial design, and motility of the animals was immediately thereafter assessed using a small open field. BR-16A neither attenuated clonidine-induced alpha-2 noradrenergic receptor-mediated hypomotility nor accentuated apomorphine-induced dopamine postsynaptic receptor-mediated hypermotility, suggesting that it does not interfere with alpha-2 noradrenergic and dopamine postsynaptic receptor functioning.

INTRODUCTION
BR-16A (Mentat: The Himalaya Drug Company) is a herbal preparation derived from India’s rich culture in traditional medicine. BR-16A contains Jal-brahmi (Bacopa monnieri), Mandookaparni (Centella asiatica), Ashwagandha (Withania somnifera), Shankapushpi (Evolvulus alsinoides), Jatamansi (Nardostachys jatamansi), Vach (Acormus calamus), all of which are claimed to improve memory functions; other ingredients include Tagar (Valeriana wallachii), Badam (Prunus amygdalus), Salap (Orchis mascula), Lavang (Syzygium aromaticum) and Pearl (Mukta pishti), which are claimed to be nerve tonics; all other ingredients are putative general tonics and vitalizers (The Himalaya Drug Co., 1991; Satyavati, 1993).

Recent research has found BR-16A to improve several cognitive – particularly memory – functions. Agrawal et al. (1990a & b) reported that BR-16A improves memory parameters and decreases anxiety parameters in normal volunteers. Verma and Kulkarni (1991) observed that BR-16A reduces scopolamine-induced delay in transfer latency in rats tested in an elevated plus maze. Kulkarni and Verma (1992a) found that BR-16A attenuates acute and chronic ECT-induced retrograde amnesia in rats tested with a passive avoidance paradigm. Joseph et al. (1993) and Andrade et al., (1993) found BR-16A to protect against the development of ECT-induced anterograde amnesia in rats tested in a complex maze and in a ‘T’ maze using a reward oriented paradigm.

Considering these various central nervous system effects of BR-16A, it seemed reasonable to expect that this preparation influences neuroceptor functioning. The present study therefore
addressed the possible effects of BR-16A on alpha-2 noradrenergic and dopamine postsynaptic receptor functioning in the rat brain using chemical neuroreceptor agonists challenges in vivo.

MATERIAL AND METHODS
Adult, male, Sprague-Dawley rats, housed four per cage with free access to tap water and standard laboratory diet, received either BR-16A (The Himalaya Drug Company) in a dose of 200 mg/ml/kg or vehicle (distilled water) alone once daily for one month. To ensure accurate dosing, intragastric administration of BR-16A/vehicle was adopted.

The animals were then parenterally challenged with clonidine (Sigma Chemicals; 100 µg/ml/kg, i.p.), apomorphine (Sigma Chemicals, 2 mg/ml/kg, i.p.) or saline (1 ml/kg, i.p.) in a factorial design with BR-16A/vehicle as one factor and neuroreceptor challenge/saline as the other factor.

In the administered dose, clonidine is an alpha-2 adrenoceptor agonist, which induces hypomotility while apomorphine is a dopamine postsynaptic receptor agonist, which induces hypermotility (Andrade et al., 1990; Andrade & Pradhan, 1991).

In effect, therefore, there were two factorial design experiments: one with clonidine for alpha-2 adrenoceptor effects, and the other with apomorphine for dopamine postsynaptic receptor effects. In each of the two experiments there were 4 groups: BR-16A + Neuroreceptor agonist, BR-16A + saline, vehicle + neuroreceptor agonist and vehicle + saline. Vehicle-treated rats served as controls to the BR-16A-treated group. Saline-injected rats served as internal controls to the neuroreceptor agonist-challenged animals; the internal controls were necessary to control for perturbations induced by BR-16A in non-adrenergic/dopaminergic neurotransmitter systems.

Immediately after the injection, the animal was placed in a glass cylinder measuring 22 cm in internal diameter and 45 cm in height. Three minutes were allowed for the animal to adapt to the stress of being handled, and to the new environment. Motility of the animal was then recorded as number of quadrants (marked off on the floor of the cylinder) crossed by the animal during a 3 minute period. The procedure followed is the one described for the small open field (Van Ree & De Wied, 1988). Monitoring was conducted between 10 am and 2 pm only (to control for diurnal variations in motility) in a disturbance free environment, by an experienced rater who was blind to the experimental status of the rats. Data were analyzed using Two Way Analysis of Variance.

RESULTS
M ± SD motility scores of BR-16A and vehicle treated rats injected with clonidine or with apomorphine are presented in Tables 1 and 2 respectively. The main effect for BR-16A/vehicle X receptor challenge interaction were not significant in both clonidine and apomorphine experiments. The main effects for clonidine (F 1, 36 = 375.23, p<0.0001) and apomorphine (F 1,40 = 290.69, p<0.0001) were however both significant, testifying to the known effects of these drugs on motility.
DISCUSSION

The absence of a significant main effect for BR-16A/vehicle indicates that BR-16A exerts no effect on animal motility independent of the neurotransmitter systems challenged. The absence of a significant BR-16A/vehicle x receptor challenge interaction indicates that BR-16A exerts no effect on motility specific to the neurotransmitter system challenged.

Expressed otherwise, BR-16A does not alter alpha-2 adrenoreceptor and dopamine postsynaptic receptor functioning. Since these neurotransmitters are sensitive to neurotransmitter systems, it seems likely that BR-16A has neither adrenergic nor dopaminergic effects.

These findings eliminate two possible mechanisms of action of BR-16A. These findings also suggest that BR-16A will not interfere with functioning in these two neurotransmitter systems, occasioning adverse effects mediated by these receptors much as is observed with psychotropic drugs such as neuroleptics and tricyclic antidepressants. Scope exists for the investigation of cholinergic and opioid peptidergic effects of BR-16A, as evidenced by the preliminary work of Kulkarni and Verma (1992 a & b).

REFERENCES


