Agents Actions 38, *Special Conference Issue* (1993)

0065-4299/93/04C263-03 $ 1.50 + 0.20/0

Effects of betahistine on locomotor activity and passive avoidance behavior in rats

X. A. Alvarez, A. Franco, L. Fernández-Novoa and R. Cacabelos

Departments of Biomedical Research and Psychogeriatrics, Institute for CNS Disorders, Basic and Clinical Neurosciences Research Center, 15004-A Coruña, Spain

Abstract

Brain histaminergic and cholinergic systems are involved in the neuromodulation of cognitive functions and altered in some neuropsychiatric disorders such as Alzheimer's disease. In this study we have investigated the effects of betahistine dihydrochloride (BH) on locomotor activity (LA) and passive avoidance behavior (PAB) in control and scopolamine(SC)-treated male rats. In an open-field paradigm, BH increased LA at high doses and inhibited SC-induced hyperactivity at moderate ones, without effect on motor habituation. In an electronic maze paradigm, in which animals had to learn to avoid a 1.5 mA electric shock, BH reduced the number of trials required by SC-treated animals to learn to stay in a neutral platform during two consecutive trials. These results seem to indicate that BH influences basal and SC-induced locomotor activity, and attenuates the learning impairment caused by SC.

Introduction

Brain histamine (HA) seems to be involved in several activities of the central nervous system (CNS), including cognitive functions, as well as in the pathogenesis of some neuropsychiatric disorders [1]. Betahistine (BH) is a histaminergic agent that acts as a central and peripheral vasodilator, increasing blood flow in the vertebrobasilar system and improving microcirculation at the chocleovestibular level. Moreover, it has been reported that BH increases cerebral regional blood flow [2] and improves cognitive functions [3] in geriatric patients with cerebrovascular disorders and dementia. In rats, tested in a single-level continuous avoidance task, it was found that BH evoked an increase in avoidance response rates, 1 to 3 hours after injection [4]. Although the mechanism of action of BH is not well understood, several studies seem to indicate that it acts as a partial H1 agonist and H3 antagonist in the CNS [5].

Since the influence of histaminergic agents on behavior remains obscure, in the present study we have evaluated the effects of BH on locomotor activity (LA) and passive avoidance behavior (PAB) in control and scopolamine(SC)-treated rats.

Materials and methods

Male Sprague-Dawley rats (Charles River Spain S.A.) (200–300 g; N = 6–16 rats/group) were used in the following experiments. (1) Study of the dose-response effects of the acute i.p. injection of BH (0, 1, 5, 10 or 25 mg/kg; 5 min before testing) on LA. (2) Effects of the daily i.p. administration of BH (0, 1, 5 and 25 mg/kg/day; 5 min before testing) on

LA. (3) Effects of the daily i.p. administration of BH (10 mg/kg/day), SC (1 mg/kg/day), and SCBH (SC = 1 mg/kg/day + BH = 10 mg/kg/day), 5 min before testing, on LA. (4) Effects of the acute i.p. administration of BH (10 mg/kg), SC (1 mg/kg), and SCBH (SC = 1 mg/kg + BH = 10 mg/kg), 15 min before testing, on PAB.

Behavioral parameters were recorded in the OUCEM-86 (Osaka University Computerized Electronic Maze) as previously described [6]. Locomotor activity was evaluated for 30-min periods after injection in an open-field paradigm, in which animals moved freely on a stainless steel square of 620 × 620 mm. LA is expressed as total inputs (I/O), including movements in the four-footed and two-footed positions, grooming, rearing and jumping activity. In a free-rate paradigm of PAB, animals were tested in consecutive trials of 30 sec each (intertrial interval = 30 sec) and had to learn to stay in a neutral platform (18 × 18 cm) in order to avoid a 1.5 mA electric shock. The test was discontinued when the animals remained in the neutral area for two consecutive assays. The number of trials needed for learning was used as a learning index.

Data were processed by using analysis of variance (ANOVA) and the Scheffé test for *post hoc* comparisons.

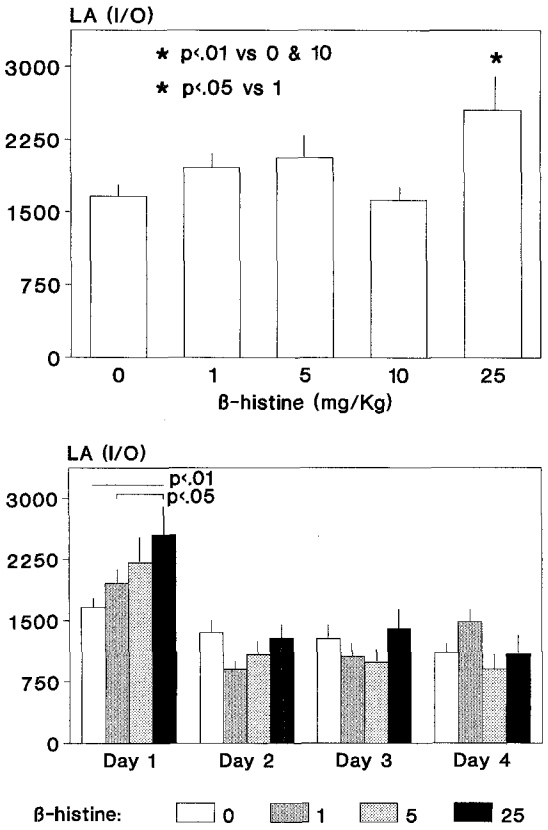

Figure 1
Acute (top panel) and daily (bottom panel) dose-dependent effects of betahistine on locomotor activity (LA). Animals received i.p. injections of 0.9% saline (C) and BH (1, 5, 10 or 25 mg/kg) five min before testing. Results X±S.E.M.

Results

Animals tested in an open-field paradigm after acute i.p. injections of BH showed a dose-dependent increase in LA ($F = 4.32$; $p < 0.005$) (Fig. 1). When compared to controls (0), BH-induced LA increase reached significant values for the 25 mg/kg dose (C = 1661.9 ± 426.7 I/O; BH-25 = 2555.8 ± 826.6 I/O, $p < 0.01$), with no significant effects at doses of 1, 5 and 10 mg/kg. However, the 4-days treatment with BH (0, 1, 5 and 25 mg/kg/day) did not significantly modify the mean LA levels ($F = 1.01$; $p < 0.4$) (Fig. 1). Furthermore, BH-treated animals showed a motor habituation (decrease of LA levels in consecutive days) similar to that of controls (Fig. 1).

The i.p. injection of BH (10 mg/kg) inhibited the increase of LA induced by SC (1 mg/kg) in novel conditions (day 1) (Fig. 2). Animals treated with SCBH showed lower mean LA levels ($p < 0.05$) than controls or SC-treated rats for the 4-days period, but the daily treatment with BH, SC, or SCBH did not modify motor habituation (Fig. 2). In a free-rate PAB paradigm, BH (10 mg/kg) significantly ($p < 0.05$) reduced the number of trials required by SC-treated animals to learn to stay in the neutral area during two consecutive trials (Fig. 2).

Discussion

According to our results, BH induces hyperkinesis at high doses, while at low and moderate doses does not alter LA records in novel conditions (day 1). This initial effect of BH was not obvious when i.p. BH injections were given on consecutive days,

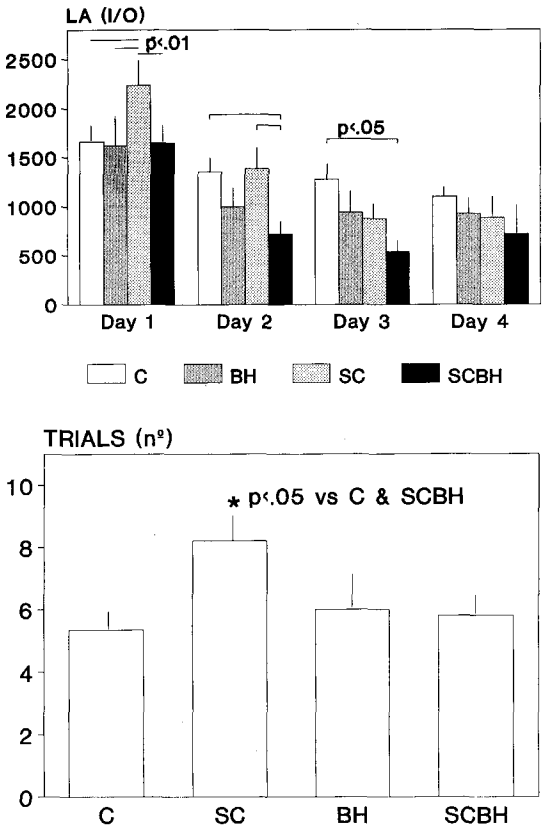

Figure 2
Effects of the daily i.p. administration of betahistine (BH), scopolamine (SC) and scopolamine plus betahistine (SCBH) on LA (top panel). Bottom panel represents the effects of BH, SC and SCBH in PAB, evaluated in a free rate paradigm. Animals received acute i.p. injections of SC (1 mg/kg), BH (10 mg/kg), or SCBH (SC = 1 mg/kg + BH = 10 mg/kg) 5 and 15 min before testing LA and PAB, respectively. Results: X±S.E.M.

suggesting an adaptation to repeated BH administrations. We have previously found that L-histidine [6], which increases the hypothalamic HA content, elicited hyperkinesis, while alpha-fluoromethylhistidine [7], which reduces by 60–80% the levels of hypothalamic HA, reduced LA. All these data together suggest that BH might influence LA by increasing endogenous HA, via H3 receptors, and/or acting directly at the H1 receptor sites as an agonist. However, the involvement of peripheral mechanisms in this process cannot be ruled out. Our results also indicate that BH (10 mg/kg) blocks the hyperactivity induced by SC in novel conditions, and attenuates the impairment of learning in SC-treated animals. Recent data showed that HA improves memory in old rats, an effect blocked by the H1 antagonist pyrilamine, and was effective in treating the amnesia caused by hippocampal lesions [8]. The present results, together with data indicating that atropine blocks the positive effects of HA on water consumption in deprived rats [4], suggest that an interaction between histaminergic and cholinergic systems might be involved in some behavioral processes. However, this functional association is not yet clear.

In conclusion, the present results seem to indicate that BH influences locomotor activity and blocks the SC-induced effects on psychomotor and learning parameters, suggesting the involvement of neuronal HA as well as the interaction of brain histaminergic and cholinergic systems in these behavioral actions.

Acknowledgements

This study was supported in part by F.I.S. (91/0651), Duphar España S.A., Ramón Areces Foundation and EUROESPES Foundation.

References

[1] R. Cacabelos, *Histaminergic system: Neuroendocrine function of brain histamine*. Meth. Find. Exp. Clin. Pharmacol. *12*, 341–376 (1990).

[2] J. S. Meyer, N. T. Mathew, A. Hartmann et al., *Orally administered betahistine and regional cerebral blood flow in cerebrovascular disease*. J. Clin. Pharmacol. *14*, 280–289 (1974).

[3] J. Pathy, G. Menon, A. Reynolds and R. Van Strik, *Betahistine hydrochloride (Serc) in cerebrovascular disease: a placebo-controlled study*. Age Ageing *6*, 179–184 (1977).

[4] M. C. Gerald and R. P. Maickel, *Studies on the possible role of brain histamine in behavior*. Br. J. Pharmacol. *44*, 462–671 (1972).

[5] J. M. Arrang, M. Garbarg, T. T. Quach, M. D. T. Tuong, E. Yeramia and J. C. Schwartz, *Actions of betahistine at histamine receptors in the brain*. Eur. J. Pharmacol. *111*, 73–84 (1985).

[6] H. Niigawa, K. Nakamura, S. Hariguchi, T. Nishimura and R. Cacabelos, *Effects of chronic administration of L-histidine on behavior and learning. A computerized analysis with OUCEM-86 system*. Anu. Psiquiat. *1*, 287–298 (1990).

[7] R. Cacabelos and X. A. Alvarez, *Histidine decarboxylase inhibition induced by alpha-fluoromethylhistidine provokes learning-related hypokinetic activity*. Agents and Actions *33*, 131–134 (1991).

[8] K. Tasaka and C. Kamei, *Effect of histamine on memory impairment ensuing from a long interruption of training or from hippocampal lesion in rats*. Abstracts book of the XXI annual meeting of the European Histamine Research Society (Torremolinos-Málaga, Spain), p. 114 (1992).