Inflamm. res. 55, *Supplement 1* (2006) S28–S29
1023-3830/06/01S28-02
DOI 10.1007/s00011-005-0027-z

Inflammation Research

2. Histaminergic mechanisms in the CNS

Betahistine increases ACh release from the cortex, but not histamine release from the nucleus basalis magnocellularis of freely-moving rats.

G. Cenni, M.B. Passani, P.F. Mannaioni and P. Blandina

Dip. di Farmacologia preclinica e clinica, Universitá di Firenze, Viale G. Pieraccini 6, 50139 Firenze, Italy. Fax : ++39 55 4271280, e-mail : patrizio.blandina@unifi.it

Introduction

Histaminergic perikarya are found exclusively in the tuberomammillary nucleus of the posterior hypothalamus from where they project to all parts of the brain [1]. Histaminergic efferents to the basal forebrain modulate the activity of the nucleus basalis magnocellularis (NBM) neurons [2], which provide cholinergic innervation to the cortex, and play a pivotal role in learning and memory processes [3]. Indeed, intra-NBM administration of H_3 antagonists increased cortical ACh release; this effect was blocked by H_1 antagonists [4]. Likely, blockade of H_3 autoreceptors released endogenous histamine that impacted on postsynaptic H_1 receptors. This modulation seems functionally relevant, as H_3 receptor blockade in the NBM improves place recognition memory [5], and H_1 receptor stimulation ameliorates time-dependent deterioration in memory in a rat object recognition test [6]. Betahistine acts both as a partial histamine H_1 receptor agonist, and as a histamine H_3 receptor antagonist [7] and the current study focuses on the effects of betahistine upon NBM-cortical cholinergic neurons.

Materials and methods

Male Sprague-Dawley rats (200–250 g), were anesthetized and implanted with two microdialysis probes, one in the NBM to measure the output of histamine, and the second in the ipsilateral hemicortex to measure that of ACh. Twenty-four hours after surgery, rats, housed individually, were perfused with Ringer solution (flow rate was 2 µl/min), and fifteen-minute fractions were collected. ACh was determined by HPLC-electrochemical detection [4], and histamine by HPLC-fluorimetric detection [8]. Accurate placement of microdialysis probes was verified histologically. All experiments were done in compliance with the recommendations of the EEC (86/609/CEE) for the care and use of laboratory animals and were approved by the Animal Care Committee of the Universitá di Firenze.

The substances used in this study included betahistine (Grünenthal-Formenti, Italy) and triprolidine (R.B.I., Natick, MA, USA.). All other reagents and solvents were of HPLC grade or the highest grade available (Sigma Chemical Company Ltd., U.K.).

Results and discussion

All experiments were performed between 9.00 am and 2.00 pm. Betahistine, added to the NBM-perfusing medium for 30 min at a concentration of 100 µM, increased ACh spontaneous release from the cortex of freely moving rats by about 200 % (Fig. 1A), but failed to modify significantly histamine spontaneous release from the NBM (Fig. 1B). Spontaneous release levels for both neurotransmitters were restored after withdrawal of betahistine from the NBM perfusion medium. Basal levels of spontaneous release for both ACh and histamine were calculated for each experiment by averaging the mean of the four initially collected 15-min samples. For cortical ACh this was 0.9 ± 0.2 pmol/15 min (N = 5), while NBM histamine was 0.17 ± 0.02 pmol/15 min (N = 7). When 0.5 µM triprolidine, an H_1 receptor antagonist, was given 30 min before and during the administration of betahistine, the increase of cortical ACh was completely antagonized (data not shown, spontaneous release of cortical ACh averaged 1.1 ± 0.3 pmol/15 min, N = 4). Since betahistine increased ACh release without affecting histamine release, its effect may be attributed only to H_1 receptor stimulation, and not to H_3 receptor blockade. Independently of the receptor type involved, cholinergic modulation by betahistine may produce pro-

Correspondence to: P. Blandina

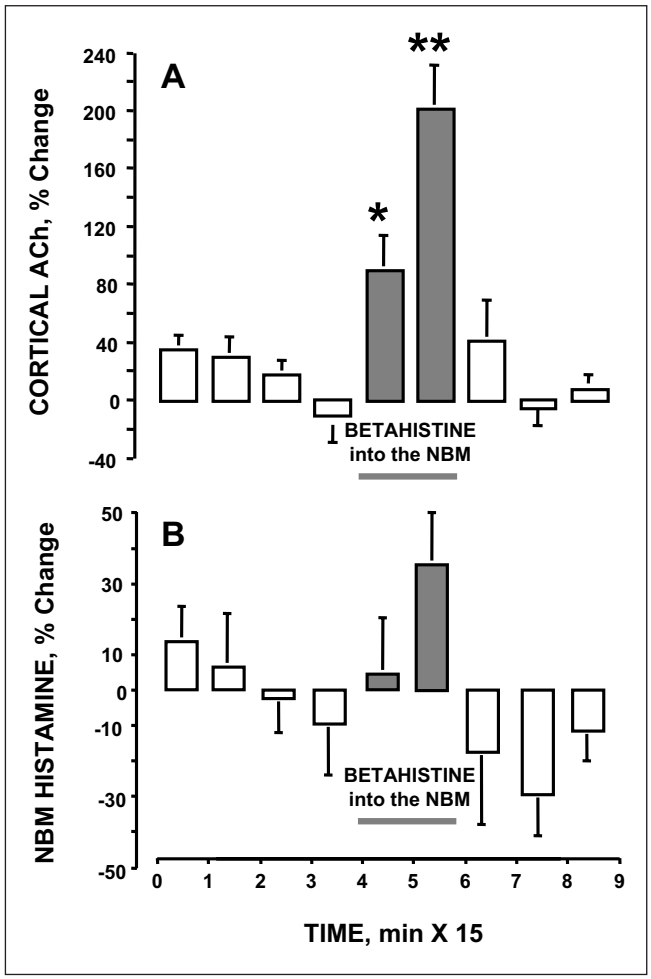

Fig. 1. Effects of intra-NBM administration of betahistine on cortical ACh release (A), and NBM histamine release (B) in freely moving rats. Twenty-four hours after surgery, ACh or histamine were measured in fractions collected every 15 min beginning 60 min after the onset of the perfusion. Betahistine was dissolved into the perfusion medium and infused into the NBM through the dialysis probe for 30 min at the time indicated. Basal spontaneous release was obtained by averaging ACh or histamine content in the four 15-minute samples collected before the onset of the drug treatment. Both ACh and histamine releases were expressed as a percentage of their respective spontaneous release value. The spontaneous release of cortical ACh averaged 0.9 ± 0.2 pmol/15 min, that of NBM histamine 0.17 ± 0.02 pmol/15 min. Bars show the period of betahistine application. Shown are means ±SEM of 5 (ACh) and 7 (histamine) experiments. *($p < 0.05$), **($p < 0.01$), vs last sample before drug administration (ANOVA and Bonferroni's test).

cognitive effects. The report that H_1 receptor stimulation improved performance in the rat object recognition test [6] supports this contention.

Acknowledgements. This research was supported by FIRB (RBAU017SWS).

References

[1] Haas H, Panula P. The role of histamine and the tuberomamillary nucleus in the nervous system. Nat Rev Neurosci 2003; 4: 121–30.
[2] Passani MB, Lin J-S, Hancock A, Crochet S, Blandina P. The histamine H3 receptor as a novel therapeutic target for cognitive and sleep disorders. Trends Pharmacol Sci 2004; 28: 618–25.
[3] Pepeu G, Giovannini MG. Changes in acetylcholine extracellular levels during cognitive processes. Learn Mem 2004; 11: 21–7.
[4] Cecchi M, Passani MB, Bacciottini L, Mannaioni PF, Blandina P. Cortical Acetylcholine release elicited by stimulation of histamine H1 receptors in the nucleus basalis magnocellularis: a dual probe microdialysis study in the freely moving rat. Eur J Neurosci 2001; 13: 68–78.
[5] Orsetti M, Ferretti C, Gamalero R, Ghi P. Histamine H3-receptor blockade in the rat nucleus basalis magnocellularis improves place recognition memory. Psychopharmacology 2002; 159: 133–7.
[6] Malmberg-Aiello P, Ipponi A, Blandina P, Bartolini L, Schunack W. Pro-cognitive effect of a selective H1 receptor agonist, 2-(3-trifluoromethylphenyl)histamine, in the rat object recognition test. Inflamm Res 2003; 52: S33–S34.
[7] Timmerman H. Histamine agonists and antagonists. Acta Oto-Laryngol 1991; Suppl 479: 5–11.
[8] Cenni G, Cangioli I, Yamatodani A, Passani MB, Mannaioni PF, D. Felice AM, Blandina P. Thioperamide-elicited increase of histamine release from basolateral amygdala of freely moving rats and its therapeutic implications. Inflamm Res 2004; 53: S53–S54.