Effect of an inhaled histamine H₃-receptor agonist on airway responses to sodium metabisulphite in asthma

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Histamine H₃-receptor agonists inhibit excitatory neuro-transmission in human and guinea-pig airways. Since neural bronchoconstriction may be important in asthma we have studied the effect of a specific H₃-receptor agonist R- α -methylhistamine (α MeHA) on bronchoconstriction induced by the inhaled irritant sodium metabisulphite (MBS) in six mild asthmatic subjects in a randomised double-blind crossover study. Subjects received either α MeHA, 10 mg (as a chloride salt) or matched placebo (P) and were then challenged with doubling concentrations of MBS (0.3–80 mg ml⁻¹) nebulised from a dosimeter at 5 min intervals with measurement of specific airway conductance (sGaw) and FEV₁ at 2 and 4 min respectively after each inhalation. There was no effect of α MeHA on baseline airway calibre and the log concentrations of MBS required to lower sGaw by 50% (log PC₅₀) and FEV₁ by 20% (log PC₂₀) were not significantly different after α MeHA when compared with placebo, suggesting that selective stimulation of airway H₃-receptors does not inhibit MBS-induced bronchoconstriction.

Keywords histamine H₃-receptor asthma sodium metabisulphite

Introduction

A third histamine receptor (H₃-receptor), identified in rat brain (Arrang *et al.*, 1983), is selectively stimulated by R- α -methylhistamine (α MeHA) and antagonised by thioperamide (Arrang *et al.*, 1987). Histamine controls its own synthesis and release by an auto-feedback mechanism, acting through H₃-receptors present in the central nervous system and lung of rats (Arrang *et al.*, 1987). Stimulation of H₃-receptors with α MeHA modulates cholinergic neurotransmission in guinea-pig and human airways *in vitro* (Ichinose *et al.*, 1989; Ichinose & Barnes, 1989a). Furthermore α MeHA attenuates non-adrenergic non-cholinergic (NANC) bronchoconstriction and neurogenic plasma extravasation in guinea pigs *in vivo* (Ichinose & Barnes, 1989b; Ichinose *et al.*, 1990). Thus H₃-receptors may have a role in the modulation of neurally-mediated bronchoconstrictor responses. Since neurogenic mechanisms may contribute to asthmatic bronchoconstriction (Barnes, 1986), stimulation of H₃-receptors may be beneficial in asthma.

Sodium metabisulphite (MBS), when inhaled, provokes bronchoconstriction in asthmatic subjects, probably by release of sulphur dioxide (Nichol *et al.*, 1989). The underlying mechanism is indirect and may involve sensory nerves as it is inhibited by nedocromil sodium and by anticholinergic agents (Dixon & Ind,

1988). Other effects of MBS inhalation which suggest that it acts as a neural stimulus include cough and pharyngeal irritation.

To evaluate the role of H₃-receptor activation on neurally-mediated bronchoconstriction in asthma, we studied the effects of inhaled α MeHA, a highly selective H₃-receptor agonist on bronchial provocation with MBS in a double-blind placebo controlled study.

Methods

Subjects

Six non-smoking mild atopic asthmatic subjects gave informed consent to participate in the study which was approved by the National Heart and Chest Hospitals Ethics Committee. All were controlled on inhaled β_2 -adrenoceptor agonists alone and had a baseline forced expiratory volume in one second (FEV₁) in excess of 80% of their predicted value (Table 1). None had suffered exacerbation of wheeze nor respiratory infection in the preceding 6 weeks. Inhaled sympathomimetics and caffeinated beverages were withheld for at least 8 h prior to each study day.

Study design

In a balanced randomised double-blind placebo controlled study six subjects with known sensitivity to MBS (Table) attended on two separate occasions 2–7 days apart. Following baseline lung function each inhaled either α MeHA, 10 mg, or placebo by continuous nebulisation for 8 min. Twenty minutes later MBS challenge was performed.

Materials and drug delivery

On each study day solutions of MBS (Sigma, Poole, UK) were made up freshly to produce a range of concentrations in 0.9% saline of 0.3–80 mg ml⁻¹ and administered from a nebuliser attached to a breath-activated dosimeter (Mephar, Brescia, Italy). The nebuliser delivered particles with an aerodynamic mass median diameter of 3.5–4 μ m at an output of 9 μ l per breath. The dosimeter was set to nebulise for 1 s with a pause time of eight seconds at a pressure of 22 psi.

α MeHA chloride 5 mg ml⁻¹ (equivalent to 3.1 mg ml⁻¹ α MeHA base) in distilled water containing sodium bicarbonate, pH 6.7, osmolarity 275 mosmol, Bioproject, Paris, France) or matched placebo (pH 6.8, osmolarity 285 mosmol) were delivered by continuous nebulisation from an Acorn jet nebuliser (Medic-Aid, Pagham, West Sussex, UK) with a calibrated output of 0.25 ml min⁻¹ at a driving pressure of 6 l min⁻¹. The nebuliser delivered an aerosol with a mean aerodynamic diameter of 3.7 μ m (range 2.4–4.5) at this flow rate, measured by a laser particle sizer (Malvern 2600d, Malvern UK).

Bronchial provocation and measurement of pulmonary function

Pulmonary function was measured as specific airway conductance (sGaw) by computerised body plethysmography (Jaeger, Leicester, UK) and FEV₁ with a dry wedge spirometer (Vitalograph, Buckingham, UK). A standard challenge protocol was used. On arrival in the laboratory each subject rested quietly for 15 min prior to five measurements of sGaw at 30 s intervals and three measurements of FEV₁ at 1 min intervals. Fifteen minutes after inhalation of active and placebo treatments repeat measurements (baseline) of sGaw and FEV₁ were recorded. Subjects then inhaled 5 breaths of saline-control by inspiring from functional residual capacity to total lung capacity over 3 s and then breath-holding for 5 s.

Measurement of sGaw and FEV₁ were taken at 2 and 4 min respectively after inhalation of saline. Unless a fall in sGaw of >20% or FEV₁ >10% was seen, subjects inhaled 5 breaths of doubling increments of MBS until both a >50% fall in sGaw and a >20% fall in FEV₁ were achieved. Log-dose responses curves were constructed and the provocative concentrations causing a 50% fall in sGaw (log PC₅₀) and a 20% fall in FEV₁ (log PC₂₀) were calculated by linear interpolation. Challenges were performed at the same time on both active and placebo days for each individual.

Analysis of data

The logPC₅₀ (sGaw) and log PC₂₀ (FEV₁) values for MBS following active and placebo treatments and baseline measurements of FEV₁ before and after each treatment were compared using analysis of variance for multiple comparisons.

Results are expressed as mean $\pm$ s.e. mean. Power calculations (1- β) to detect a one doubling dilution difference were made using the sample size and variance on the placebo limb, assuming this as the least acceptable difference.

Results

Neither inhaled α MeHA nor placebo caused any change in airway calibre (Table 1). No side effects were reported by any subject.

Inhalation of α MeHA attenuated MBS-induced bronchoconstriction, as measured by logPC₅₀ sGaw, in four of the six subjects studied (Table 1). However overall log PC₅₀ after MEHA, 0.70 $\pm$ 0.09 was not significantly different than after placebo, 0.52 $\pm$ 0.17 (P = 0.08) (Figure 1). Similarly logPC₂₀ FEV₁ values did not differ between active and placebo treatments (Table 1, Figure 1). The power of this study (1- β) was 48% and 78% using logPC₅₀ sGaw and logPC₂₀ FEV₁ respectively.

Discussion

Inhalation of α MeHA chloride in a dose of 10 mg, failed to inhibit MBS-induced bronchoconstriction. As this is the first study of a nebulised H₃-receptor agonist

Table 1 The results of the study

Subject	Age (years)	Baseline FEV ₁ (% predicted)	FEV ₁ (l)				log PC ₅₀		log PC ₂₀	
			Placebo Pre	Placebo Post	α MeHA Pre	α MeHA Post	Placebo	α MeHA	Placebo	α MeHA
1	34	94	3.96	3.82	3.87	3.71	0.63	0.58	1.25	1.33
2	46	91	3.67	3.58	3.75	3.54	0.38	0.88	0.64	0.89
3	20	106	5.33	5.34	5.27	5.35	0.31	0.83	0.82	1.25
4	41	101	4.42	4.31	4.50	4.45	1.31	0.97	1.34	1.04
5	21	87	4.14	4.20	4.03	4.18	0.24	0.5	0.66	0.59
6	36	84	3.36	3.38	3.28	3.37	0.25	0.39	0.97	0.71
Mean	33	94	4.15	4.11	4.12	4.10	0.52	0.70	0.95	0.97
s.e. mean	4.3	3.5	0.28	0.29	0.28	0.30	0.17	0.09	0.12	0.12

Figure 1 Bronchoconstrictor responses to MBS, as measured by logPC₂₀ (FEV₁, ■) and logPC₅₀ (sGaw, ▲), following placebo and αMEHA.

in human subjects the negative results are difficult to interpret. Either αMEHA is ineffective, the dose used was inadequate or we missed an effect due to inadequate sample size. There are no available data demonstrating a positive effect of αMEHA in asthmatic airways. This agonist is highly selective and would be unlikely to have effects on H₁- or H₂-receptors. This is supported by a lack of a bronchoconstrictor effect of inhaled αMeHA via stimulation of H₁-receptors. We used 10 mg (equivalent to 6.2 mg base) as the highest possible inhaled dose

used in preliminary studies on asthmatic volunteers (Bioprojet Paris). αMEHA is water soluble, highly potent and selective (Arrang *et al.*, 1987) and is therefore likely to remain within the airways to exert receptor effects. We chose six subjects based on previous studies in our laboratory. A type II error cannot be excluded when evaluating the changes in logPC₅₀ sGaw alone but is unlikely as logPC₂₀ FEV₁ is unchanged by αMEHA.

Histamine H₃-receptors modulate cholinergic neurotransmission in guinea-pig trachea (Ichinose *et al.*, 1989) and human bronchi *in vitro* (Ichinose & Barnes, 1989a) and the release of neuropeptides from sensory nerves in guinea pigs (Ichinose *et al.*, 1990). Thus we assessed the effects of an H₃-receptor agonist on neurally-mediated bronchoconstriction in asthmatic subjects. At the dose of αMeHA used in this study no convincing effect on MBS challenge was observed. It is possible that MBS causes bronchoconstriction by mechanisms additional to neural activation (Nichol *et al.*, 1989).

H₃-receptors in lung are poorly localised but may also be present on mast cells (Arrang *et al.*, 1987). Thioperamide, a histamine H₃-receptor antagonist significantly enhances allergen-induced bronchoconstriction in sensitised guinea-pigs (Ichinose & Barnes, 1990). H₃-receptor agonists might be most effective in provocation challenges such as allergen and adenosine 5'-monophosphate which stimulate the release of histamine from airway mast cells.

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