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Airway responsiveness in wheezy infants: evidence for functional β adrenergic receptors

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ABSTRACT The effect of nebulised salbutamol on the bronchial response to nebulised histamine was studied in five wheezy infants aged 3–12 months. The response to doubling concentrations of up to 8 g/l of histamine was assessed by the change in maximum flow at FRC ($\dot{V}max_{FRC}$), measured by flow-volume curves produced during forced expiration with a pressure jacket. The concentration of histamine required to provoke a 30% fall in $\dot{V}max_{FRC}$ (PC_{30}) was measured. All of the infants responded to low concentrations of histamine during control tests before and after nebulised saline (mean PC_{30} 1·07 and 0·51 g/l). On a separate day there was a similar response to histamine before salbutamol (PC_{30} 0·57 g/l), but after salbutamol the response was completely abolished up to the maximum concentration of histamine in all subjects (PC_{30} > 8 g/l). Thus wheezy infants have highly effective β_2 adrenoceptors in intrathoracic airways.

Wheezing disorders of infancy, although common, are difficult to treat.[1] Physiological studies carried out on wheezy infants have failed to show any useful response to nebulised β adrenergic agents in terms of reduction in the overall respiratory resistance or work of breathing.[2–4] Since, however, in infants more than 50% of total airway resistance is contributed by the upper airways, a change in intrathoracic airway calibre may well be masked in this type of study. In a recent study of airway responsiveness to salbutamol in wheezy infants we used a pressure jacket to produce partial expiratory flow-volume (PEFV) curves. From these curves we determined forced expiratory flow at FRC ($\dot{V}max_{FRC}$) as an index of intrathoracic airway function. In common with others[5–7] we found a significant fall in $\dot{V}max_{FRC}$ after nebulised salbutamol. Although negative, this observation supports the concept that β receptors are present in the infant airway in sufficient density to be recognisable by gross physiological measurements. A possible explanation for this paradoxical response to a "bronchodilator" drug is that a reduction in smooth muscle tone, without a commensurate fall in airway resistance, renders the airways more compliant and therefore less able to support high flow rates.[8]

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Although little information is available pertaining to the human infant airway, β adrenergic receptors have been shown to be present and functional in airway preparations of other infant mammals.[9 10]

We have recently shown that the intrathoracic airways of wheezy infants are capable of an acute and spontaneously reversible response to nebulised histamine.[11] Given an appropriate stimulus therefore, the infant airway can respond acutely, although the site and mechanism of the response is conjectural. In older subjects the bronchial response to histamine can be very effectively blocked by the administration of nebulised β adrenergic drugs.[12] In the present study we measured the degree of protection against histamine induced airway obstruction afforded by nebulised salbutamol as an index of β adrenergic responsiveness. In this way we hoped to determine whether functional β adrenoceptors are present in the human infant airway.

Methods

SUBJECTS

Five recurrently wheezy infants were studied at a mean age of 6·8 months (range 3–12 months). Four of the infants had a first degree family history of asthma, three had a history of eczema, and four had parents who smoked. The history of wheezing ranged from one to eight months and the attacks were intermittent. The interval between attacks varied from 24

hours to eight weeks. The infants were studied when free from respiratory symptoms. Sedation with oral chloral hydrate (100 mg/kg) was given 30 minutes before each test. No infant had received any other medication within 24 hours of a test and none had received bronchodilator treatment.

The studies formed part of an investigation of airway function in wheezy infants, for which approval of the ethics committee had been obtained. A detailed explanation of the procedures was given to parents before consent was requested and obtained in each case. A medically qualified research fellow (AP) was present throughout all the procedures.

The studies took place after some preliminary observations had shown that histamine induced airways obstruction was rapidly reversible, either spontaneously or after nebulised salbutamol, in infants. One author (MS) had previously observed similar studies of cabachol induced airways obstruction performed safely elsewhere (P Gutkowski, personal communication). Because of this preliminary information and because of the graded nature of the histamine challenge, with continuous monitoring of tidal flow and volume, the studies were felt to be without appreciable risk.

BASELINE LUNG FUNCTION

When fast asleep, the infant was placed in a whole body plethysmograph incorporating a servo-controlled rebreathing system maintained at 37°C.[13] Baseline measurements of thoracic gas volume and inspiratory airway resistance were then obtained by previously described techniques,[14] and their multiple specific airway resistance (sRaw) was computed as a measure of baseline airway function. The mean reference value for sRaw in infants derived by this method is 3·5 cm H_2O.s.[15]

HISTAMINE CHALLENGE PROCEDURE

The administration of histamine by nebuliser and the measurement of the partial expiratory flow-volume curve as an index of response are described in detail elsewhere.[11 16 17] In brief, PEFV curves were obtained by suddenly inflating a snugly fitting thoracoabdominal jacket at the end of a tidal inspiration, thus causing forced expiration. From the flow signal measured by face mask and screen pneumotachograph and its integral (volume) a PEFV curve is constructed and the maximum flow at a lung volume corresponding to $\dot{V}max_{FRC}$ computed. For each measurement after histamine challenge the mean of three or four values of $\dot{V}max_{FRC}$ was used.

Nebulised histamine and control saline were administered by a Turret nebuliser (Medic-Aid), which was cleaned after each dose. These nebulisers had a measured output of 0·21 ml min^{-1} at an air flow of 6 l min^{-1}. The histamine challenge tests were carried out as follows. Nebulised saline at room temperature was initially administered by directing the output of the nebuliser over the nose and mouth of the sleeping infant for one minute. This was followed by doubling concentrations of histamine phosphate solution administered for one minute periods at five minute intervals, starting at a concentration of 0·25 g/l. A set of PEFV curves was obtained after each dose and the procedure continued until a positive response to histamine was judged to have occurred by a change in the shape of the PEFV curve (more concave) or until a concentration of histamine of 8 g/l had been reached—whichever occurred sooner. Recovery was monitored over the next 30 minutes.

SALBUTAMOL ADMINISTRATION

A pair of histamine challenge tests was carried out on each of two days within one week. On each day, after 30 minutes had been allowed for recovery from the first histamine challenge, a set of PEFV curves was collected and either nebulised salbutamol 2·5 mg in 2·5 ml or saline 2·5 ml were administered by Turret nebuliser, the order being randomised. Fifteen minutes later a further set of PEFV curves was obtained and a full histamine challenge test performed.

Table 1 *Anthropometry and baseline lung function*

Patient No	*Age (m)*	*Length (cm)*	*Control day*		*Salbutamol day*	
			sRaw (cm H_2O.s)*	*$\dot{V}max_{FRC}$ (%)†*	*sRaw (cm H_2O.s)*	*$\dot{V}max_{FRC}$ (%)*
1	8	73	31	58	18	44
2	6	69	10	49	23	57
3	3	62	2·3	50	8·2	32
4	5	61	7·9	84	5·6	82
5	12	71	4·2	50	4·7	95

*Mean reference value for normal infants = 3·5 cm H_2O.s.
†% of reference value for normal infants.[17]
sRaw—specific airway resistance; $\dot{V}max_{FRC}$—maximum expiratory flow at functional residual capacity.

Table 2 *Airway response in terms of maximum flow at functional residual capacity (ml s^{-1}) to saline and salbutamol*

Patient No	Control day			Salbutamol day		
	Baseline (before 1st challenge)	Before saline	After saline (before 2nd challenge)	Baseline (before 1st challenge)	Before salbutamol	After salbutamol (before 2nd challenge)
1	134	155	126	102	88	72
2	107	78	44	124	128	97
3	99	90	98	63	86	87
4	163	127	122	160	158	261
5	114	209	188	213	207	141
Mean	123	132	116	132	133	132
SD	23	47	47	51	46	69

STATISTICAL METHODS

Differences between values following salbutamol and saline administration were compared by the paired *t* test. PC_{30} values were subjected to log transformation before statistical analysis.

Results

Baseline values of sRaw were appreciably raised on only three of the 10 study days, whereas values of $\dot{V}max_{FRC}$ were much lower than reference values on seven study days (table 1).

Both the saline control solution and salbutamol had variable effects on the level of airway obstruction (table 2). There was a tendency for $\dot{V}max_{FRC}$ to decline after saline, although only in one subject (No 2) was the effect considerable. Salbutamol had no net effect, although in one subject (No 4) there was a striking improvement in $\dot{V}max_{FRC}$.

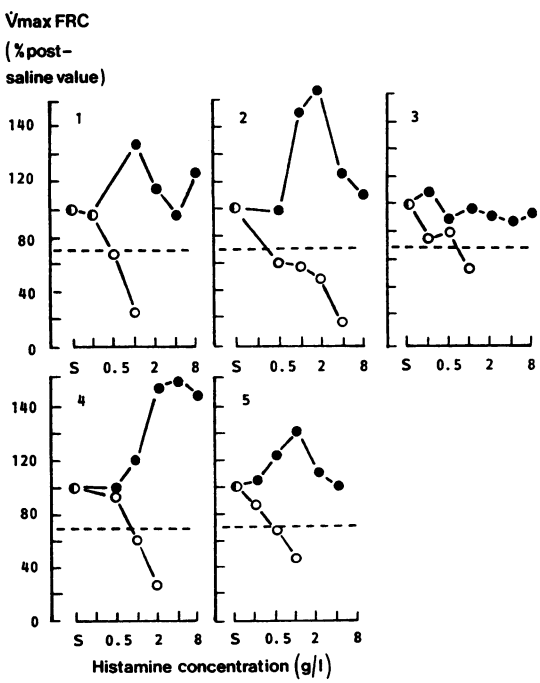
All five subjects responded to histamine (table 3). There was a clear response before and after the control saline inhalation, and before the salbutamol was given. In association with the response to histamine on the saline control day there was a significant decline in tidal volume (from 55 to 46 ml; $p < 0.025$) and an increase in breathing frequency (from 33 to 42/min; $p < 0.02$).

Salbutamol completely abolished the response to nebulised histamine at all concentrations up to 8 g/l^{-1} (table 3, figure). This response was highly significant. After salbutamol there was no significant change in

Table 3 *Histamine responsiveness (PC_{30} g/l) before and after saline and salbutamol*

Patient No	Control day		Salbutamol day	
	Before saline	After saline	Before salbutamol	After salbutamol
1	1·6	2·0	0·49	> 8
2	0·53	0·33	0·38	> 8
3	0·23	0·33	0·78	> 8
4	2·8*	0·95	0·85	> 8
5	2·2*	0·17	0·48	> 8
Mean†	1·03	0·51	0·57	> 8
Confidence interval	(0·40, 2·6)	(0·21, 1·23)	(0·42, 0·77)	

*On their first control histamine challenge, patients 4 and 5 had a rise in $\dot{V}max_{FRC}$ after the lowest concentration of histamine; using maximum values of $\dot{V}max_{FRC}$ as baseline gives PC_{30} values of 1·9 and 0·45 g/l respectively.
†After log transformation.
PC_{30}—concentration of histamine required to provoke a 30% fall in maximum expiratory flow at functional residual capacity ($\dot{V}max_{FRC}$).



Individual response curves on the salbutamol study day. Changes in maximum flow at functional residual capacity ($\dot{V}max_{FRC}$) (in relation to the baseline value at the start of each test) are given at each concentration of histamine (log scale) before salbutamol (open circles) and 20 minutes after salbutamol (closed circles).

tidal volume (57 and 57 ml) or breathing frequency (33 and 35 breaths/min) during histamine challenge.

After salbutamol there was a striking increase in $\dot{V}_{maxFRC}$ during histamine challenge in four of the five subjects, especially at the lowest concentrations of histamine (figure). This effect occurred whether or not there had been a decline (subject 2) or an improvement (subject 4) in $\dot{V}_{maxFRC}$ after salbutamol alone (table 2).

The lack of response to histamine after salbutamol could not be explained by altered baseline airway calibre (table 2) nor by altered pattern of breathing. The mean breathing frequency and tidal volume were similar before each pair of histamine challenge tests on the control and salbutamol test days.

Discussion

We have shown that the selective β_2 adrenergic agent salbutamol has a large effect on the airway response to histamine of wheezy infants, responsiveness to nebulised histamine being reduced at least 16 fold. Since salbutamol is not known to have any appreciable pharmacological effect other than on the β_2 receptor, we conclude that the airways of wheezy infants do possess functional β_2 adrenergic receptors. The fact that in this and in a previous study[5] we found, as have many others before us[2-4] that baseline lung function did not improve after bronchodilators suggests that there may be a difference between the mechanisms causing chronic airway narrowing in wheezy infants and the mechanism of the acute response to an irritant trigger, represented in this study by the histamine challenge. Before we suggest reasons for this discrepancy some technical points need consideration.

The histamine challenge test that we have described[11] is modified from a well standardised technique for older subjects. By using flow-volume curves the response to histamine can be localised to intrathoracic airways. This is important since nebulised drugs administered to sleeping infants must be preferentially deposited in the nasal passages, and they may have their major physiological effect there. Indeed, some of the intrathoracic effects of histamine may be indirectly mediated by neural reflexes originating in the nose.[18] Only if this were the complete explanation for the intrathoracic effect of histamine, which is unlikely, could the blocking effect of salbutamol be explained by a local effect in the nose.

The design of the studies represents a compromise imposed by the need to complete a set of observations within a single period of sleep (up to 2–3 hours). This allowed only a 30 minute recovery period after the first histamine challenge test and a 15 minute period after nebulisation of the bronchodilator. Recovery following the first histamine test was incomplete in some infants (table 2), and this may explain the fact that reproducibility of histamine responsiveness was poorer than in older children.[19] A 15 minute period after administration is normally sufficient time for nebulised bronchodilator drugs to achieve their maximum protective effect against histamine challenge in older subjects, after which the beneficial effect wears off rapidly.[12] The very striking effect of salbutamol on histamine response in our infants cannot easily be explained by the design of the study.

The mode of action of histamine is not clear. It may have direct or indirect effects (by nasal or lower airway reflexes) on airway smooth muscle.[20] At higher concentrations nebulised histamine has additional direct or indirect vascular and inflammatory effects on the airway mucosa, leading to oedema.[21] It thus mimics some of the pathogenetic mechanisms in acute asthma. Provided, however, that the effects of nebulised histamine are mainly intrathoracic, the precise mode of action is immaterial to the present study.

Although there is no information in human infants, autoradiographic studies with labelled receptor specific ligands have shown the presence and distribution of β receptors in young mammals[22] and in adult human lungs.[23] There is a predominantly peripheral distribution, with receptors concentrated in the mucosa as well as on airway smooth muscle.[23] The beneficial effect of salbutamol might accord with a predominantly mucosal effect for histamine.

Although in older subjects increased bronchial responsiveness to histamine cannot be directly equated with clinical asthma, much has been learned about airway pathophysiology, clinical management, and the clinical epidemiology of asthma by the study of bronchial responsiveness. There are clearly great differences between wheezy infants and asthmatic children, the most obvious being the difference in the response to β adrenergic agents. The fact that histamine responsiveness is common to the two groups, however, suggests that the differences may be in quantity, and not in quality. The evidence from this study suggests that, while reversible airways obstruction may occur in wheezy infants, it does so against a background of airway narrowing unresponsive to bronchodilators. This "fixed" obstruction may be inflammatory or secretory in nature. In such circumstances airway smooth muscle tone may be helping to "splint" the airways. A reduction in such tone would then cause impairment of airway function, especially during forced expiration.[5 8]

The improvement in maximum flows that was seen with low concentrations of histamine after nebulised salbutamol (figure) has not previously been reported. Histamine seems to be exerting two effects on the airway, one of which is to cause airway obstruction and

a fall in $\dot{V}max_{FRC}$, and this is blocked by salbutamol. The other is to improve maximum expiratory flows, and this is not blocked by salbutamol. In theory, the latter effect could be brought about by a small decline in airway compliance, perhaps by an increase in airway smooth muscle "tone" or a minor vascular effect. We have no evidence for this, although we have noted in infants[11] and older asthmatic children (N M Wilson and M Silverman, unpublished observations) that very low concentrations of nebulised histamine often produce a transient improvement in expiratory flows. Alternatively, increased elastic lung recoil or an increase in the level of FRC could explain the apparent improvement in airway function, though both seem unlikely as there was no change in breathing pattern (tidal volume or frequency of breathing). Because of their complexity, we were not able to make repeated measurements of TGV and Raw during the studies.

The results of this study provide strong evidence for the presence of effective functional β_2 receptors in the infant airway, in sufficient quantity to protect against a non-specific challenge. Their density and distribution cannot be determined from a study such as this and will require the use of autoradiographic techniques. Evidence on the role of adrenergic agents in the treatment of infantile asthma remains equivocal. The importance of the present study is not in its immediate clinical application but in the approach that it provides to the study of airway function in wheezy infants. It is hoped that by techniques similar to those described here the pathogenesis and natural history of wheezing disorders in infancy can be studied safely.

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