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Airway responsiveness to adenosine 5'monophosphate following inhalation of hypertonic saline

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ABSTRACT: We wished to determine whether the refractory period after hypertonic saline (HS) challenge is due to mast cell mediator depletion. Therefore, the airway responsiveness to adenosine 5' monophosphate (AMP), which induces bronchoconstriction *via* mast cell histamine release, was determined after the inhalation of HS aerosol. Nine asthmatic subjects attended the laboratory on three occasions. On day 1 HS challenge was performed followed one hour later by a second HS challenge. On day 2 an AMP challenge was performed. On day 3 an HS challenge was performed followed one hour later by an AMP challenge. Airway responsiveness (PD_{35} sGaw) to an initial HS challenge ranged from 12 to 315 *l* of aerosol (mean 47 *l*). Airway responsiveness to a second HS challenge ranged from 8 to 800 *l* (mean 102 *l* p=0.035, n=9). Airway responsiveness to AMP increased from 0.44 to 14.0 μmol (mean 2.37 μmol) at baseline to 0.3 to 15.5 (mean 1.3 μmol) (p=0.05) after HS challenge. There was a linear correlation between baseline AMP responsiveness and baseline HS responsiveness (r=0.911, p=0.001). There was no correlation between the degree of refractoriness and the change in AMP responsiveness (r=0.1, p=0.9). Thus airway responsiveness to AMP increased significantly after inhalation of HS aerosol and this increase was independent of refractory behaviour. Our results suggest that the refractory period to HS is not due to mediator depletion.

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Inhalation of hypertonic saline (HS) aerosol elicits bronchoconstriction in many asthmatic subjects [1, 2]. In common with the inhalation of ultrasonically nebulised distilled water [3] and exercise-induced asthma [4], HS induced bronchoconstriction is followed by the development of a refractory period [5]. During the refractory period a second identical HS challenge will elicit substantially less bronchoconstriction. The mechanism of refractory behaviour is not known. It has been suggested that the refractory period is due to mast cell mediator depletion and represents the time necessary to replenish mediator stores following the initial challenge [6].

Adenosine 5'monophosphate (AMP) is a naturally occurring high energy phosphate of adenosine and is cleaved by the cell membrane associated enzyme 5' nucleotidase to form the purine nucleoside adenosine [7]. When inhaled by asthmatic subjects both AMP and adenosine cause a dose related bronchoconstriction [8]. It has been suggested that the mechanism for AMP-induced bronchoconstriction is largely *via* enhanced mast cell degranulation [9] and that the airflow obstruction produced by AMP is almost totally abolished by the pre-administration of an H1 antagonist, terfenadine [10].

We reasoned that if the refractory period to HS represents mast cell mediator depletion, the responsiveness of the airways to a mast cell degranulating agent, such as AMP, would be significantly reduced during the refractory period, but not altered after a similar challenge in non-refractory subjects. We have tested this hypothesis by studying the airway responsiveness to AMP following HS inhalation in 9 asthmatic subjects. We have further studied the airway response to consecutive AMP challenge in these asthmatic subjects.

Methods

Subjects

The demographic data of the nine subjects studied are reported in table 1. Atopy was defined as the presence of a wheal which was 3 mm greater than the diluent control in response to skin prick testing to at least two common aeroallergens (grass, cat, dog, *Dermatophagoides pteronyssinus*). None of the subjects was using cromolyn or theophylline, nor had required oral corticosteroids for at least one month before entry into the study.

Table 1. – Demographic data of subjects studied

Subject	age years	sex	atopic status	treatment
1	43	M	+	S, BDP
2	27	F	+	S
3	25	F	+	S, BDP
4	26	F	-	S, BDP
5	21	M	+	S
6	34	M	+	S, BDP
7	29	M	+	S
8	24	F	+	S, BDP
9	47	F	+	S
Mean	31			

S: inhaled salbutamol, BDP: inhaled beclomethasone dipropionate.

Study design

All subjects attended the laboratory on three separate occasions (table 2). On the first study day an HS challenge was performed (HS_1). One hour later a second HS challenge was performed (HS_2). On two subsequent days, separated by one week and in random order, the subjects were challenged with AMP (AMP_1) or an initial provocation with HS, followed one hour later by an AMP (AMP_2) challenge. Medication was withheld for 8 hours prior to each visit and for each individual all challenges were performed at the same time of day. The initial dose of HS aerosol given to each individual was identical on each of the two study days. Five subjects subsequently underwent one further study day during which they were challenged with AMP (AMP_A) followed one hour later by a second AMP (AMP_B) challenge. All subjects gave informed consent and the study was approved by the Guy's Hospital Ethical committee.

Table 2. – Diagramatic representation of study design

Day			Airway challenges	
One	=	HS_1	60 mins	HS_2
Two	=	AMP_1		
Three	=	HS	60 mins	AMP_2
Four	=	AMP_A	60 mins	AMP_B

H: Hypertonic Saline; AMP: AMP Challenge. The order of days 2 and 3 was randomised.

Hypertonic saline challenge and measurements of specific airways conductance (sGaw)

HS challenges were performed using a DeVilbiss 65 ultrasonic nebuliser as previously described [11]. The subjects inhaled doubling volumes of HS aerosol commencing at 5 *l* until there was a >35% fall in specific airways conductance (sGaw) or until a maximum cumulative dose of 315 *l* of HS aerosol had been given.

Measurement of sGaw was made in a total body plethysmograph linked to a digital computer [12]. Four to six measurements were recorded at each time point and the mean was calculated. The coefficient of variation of PD_{35} values for two hypertonic saline challenges which were separated by two weeks is 17% in our laboratory [11].

Adenosine 5'monophosphate

Adenosine 5'monophosphate (AMP) challenges were performed using a Hudson nebuliser linked to a breath activated dosimeter. Delivery of air to the nebuliser was regulated to a pressure of 20 lbs per square inch for a duration of 0.6 s from the start of inspiration of each breath. Under these conditions the nebuliser delivers 26 μl of aerosol per 10 actuations [13] with a mass mean aerodynamic diameter of 1.6±3.4 μM. Following baseline measurements of sGaw the subjects inhaled 10 breaths of phosphate buffered saline (PBS) as a control. If the fall in sGaw was less than 10% the patient inhaled two-fold increasing concentrations of AMP diluted in PBS from a starting concentration of 1.25 $mg \cdot ml^{-1}$ (3.6 $\mu mol \cdot ml^{-1}$). SGaw was measured at 2 min after each inhalation of AMP and increasing concentrations were administered until >35% fall in sGaw was achieved or a maximum concentration of 80 $mg \cdot ml^{-1}$ (230 $\mu mol \cdot ml^{-1}$) was given.

Analysis of data

The dose of each agonist required to produce a 35% fall in sGaw (PD_{35}) was determined by linear interpolation from the last two points of the log dose response curve. Two subjects who were studied developed less than 35% fall in sGaw after 315 *l* of nebulised HS aerosol in the second HS challenge; they both developed 15% falls in sGaw with 315 *l* of HS aerosol. The PD_{35} HS_2 values in these subjects were determined by linear extrapolation of the dose response curve to HS. Two subjects developed less than 35% fall with AMP challenges; they developed 30% and 31% falls in sGaw with 230 $\mu mol \cdot ml^{-1}$ AMP. The PD_{35} values were determined by linear extrapolation. The refractory indices of the subjects was calculated as PD_{35} HS_2/PD_{35} HS_1. Paired t–tests of the log transformed data were used to compare PD_{35} values. Correlations were assessed by linear regression analysis of the log transformed data.

Results

Airway responsiveness to hypertonic saline

The airways responsiveness to HS challenge is shown in table 3. The geometric mean PD_{35} HS_1 was 47 *l* (range 12 to 315 *l*). The geometric mean PD_{35} HS_2 was 102 *l* (range 8 to 800 *l*). PD_{35} HS_2 was significantly greater than PD_{35} HS_1 (p=0.035, n=9). The refractory indices of the subjects ranged from 0.7 to 6.6 (geometric mean 2.2) (table 3). The baseline sGaw prior to HS_1 and HS_2 are shown in table 4 and did not differ significantly (p=0.9).

The geometric mean PD_{35} for HS prior to AMP challenge (AMP_2) was 49.2 *l* (range 11 to 210 *l*) and was not significantly different (p=0.7) from the PD_{35} HS_1.

Table 3. – The doses of bronchoconstrictor agents which produced a 35% fall in sGaw (PD_{35}) in the first and second hypertonic challenges (HS_1 and HS_2 respectively) and in the first and second AMP challenges (AMP_1 and AMP_2 respectively) for each patient. The refractory index (PD_{35} $HS_2/PD_{35}HS_1$) is also shown.

Subjects	PD_{35} HS_1	PD_{35} HS_2	Refractory Index	PD_{35} AMP_1	PD_{35} AMP_2
	l	*l*		μmol	μmol
1	69	51	0.7	2.50	1.65
2	24	52	2.2	1.60	0.39
3	99	500	5.0	12.00	2.70
4	38	230	6.1	0.95	0.37
5	59	170	2.9	3.00	1.20
6	315	800	2.5	14.00	7.90
7	12	8	0.7	0.44	0.37
8	16	11	0.7	0.53	0.31
9	48	315	6.6	5.00	15.50
Geometric Mean	47	102	2.2	2.37	1.30

Table 4. – Table of baseline sGaw values for subjects prior to each bronchial challenge (sec^{-1} kPa^{-1})

Subjects	HS_1	HS_2	AMP_1	AMP_2
1	1.02	0.96	0.91	0.96
2	1.14	1.04	1.62	1.45
3	1.46	1.39	1.20	1.28
4	1.41	1.64	1.30	1.25
5	1.23	1.00	1.07	1.23
6	1.26	1.45	1.23	1.62
7	1.27	1.35	1.11	1.25
8	1.21	1.04	1.57	1.02
9	1.61	1.58	1.73	1.53
Mean	1.29	1.30	1.28	1.26
SEM±	0.05	0.08	0.08	0.08

Airway responsiveness to AMP

The geometric mean PD_{35} AMP_1 was 2.37 μmol (range 0.44 to 14.0 μmol). There was a linear correlation between baseline AMP responsiveness and baseline HS responsiveness (r=0.91, p=0.001, fig. 1).

Baseline sGaw prior to AMP_1 and AMP_2 challenges are shown in table 4 and were not significantly different (p=0.7). The geometric mean PD_{35} AMP_2 at 60 min following HS_1 challenge was 1.3 μmol (range 0.31 to 15.5 μmol) and was significantly less than the PD_{35} AMP_1 of 2.37 μmol (n=9, p=0.05).

There was no correlation between refractory index and changes in AMP responsiveness ($PD_{35}AMP_2/PD_{35}$ AMP_1) (r=<0.1 p=0.9). The geometric mean PD_{35} of the baseline AMP challenge in subjects who subsequently underwent two serial AMP challenges (AMP_A and AMP_B) was 1.56 μmol (range 0.22 to 14.00 μmol) and the PD_{35} of AMP_B challenge was 1.67 μmol (range 0.36 to 10.3 μmol). These values were not significantly different (p=0.7). Baseline sGaw prior to AMP_A and AMP_B are shown in table 5 and were not significantly different (p=0.5).

The geometric mean PD_{35} of AMP_A was 1.76 μmol (range 0.23 to 13.2 μmol) and was not significantly different from the geometric mean PD_{35} AMP_B (p=0.75, n=5, fig. 2).

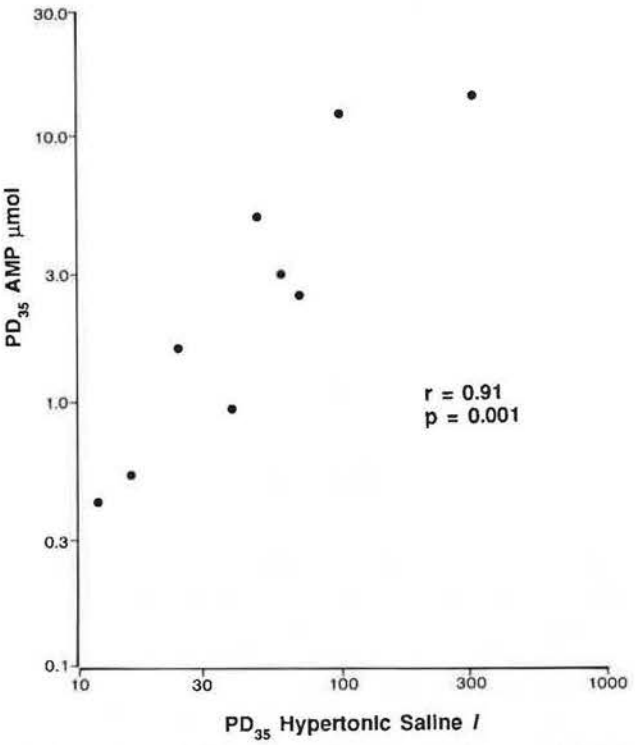

Fig. 1. – The correlation between airways responsiveness to inhaled AMP (PD_{35} AMP; μmol) and airways responsiveness to inhaled hypertonic saline aerosol (PD_{35} HS; *l*)

Table 5. – Baseline sGaw of sequential AMP challenges AMP_A and AMP_B (sec^{-1} kPa^{-1})

Subject	AMP_A	AMP_B
4	1.64	1.90
5	1.07	1.20
6	1.08	1.15
7	1.17	1.08
8	1.15	1.05
Mean	1.22	1.28
SEM±	0.11	0.16

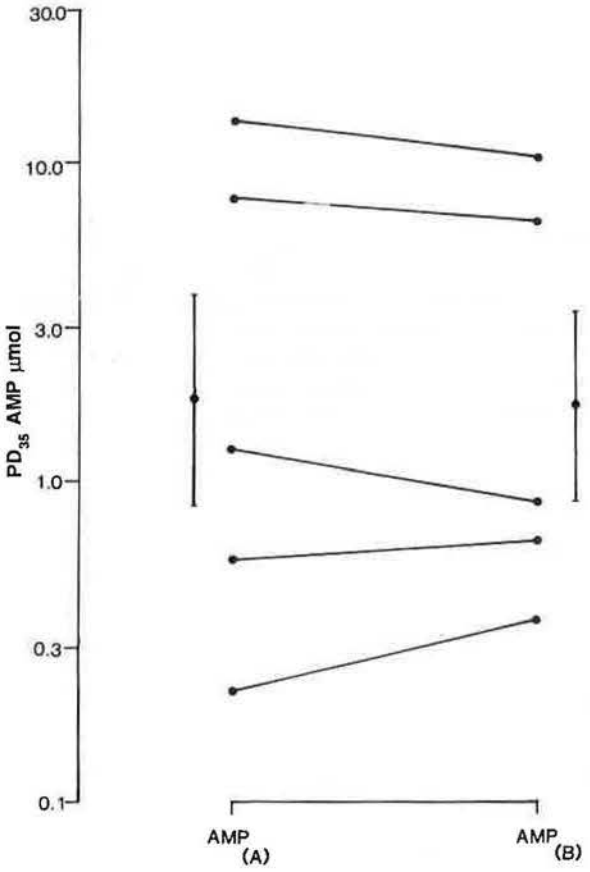

Fig. 2. – PD_{35} of sequential AMP challenges, AMP_A and AMP_B.

Discussion

We have studied AMP responsiveness in a group of asthmatic subjects who demonstrated a wide range of refractory indices following HS challenge. AMP responsiveness was assessed by constructing cumulative dose response curves and by obtaining the PD_{35} value by linear interpolation. Specific airways conductance (sGaw) was used as a measurement of large airways calibre [14]. Using this method we have previously demonstrated that airways responsiveness to hyperosmolar saline challenge is highly reproducible [11].

We have demonstrated that during the refractory period after HS provocation there was an increase in the airways responsiveness to inhaled AMP. The use of regular inhaled beclomethasone was not related to the changes in AMP responsiveness. If refractory behaviour was due to mediator depletion then a reduction in AMP responsiveness would be expected. Prior bronchoprovocation with AMP, which produced a similar degree of bronchospasm as HS, did not significantly alter subsequent airways responsiveness to AMP. Since there was no attenuation of the airways responsiveness to AMP in asthmatic subjects after 2 consecutive AMP challenges, the results suggest that the degree of mast cell degranulation produced by consecutive AMP challenges was inadequate to deplete the mast cells of preformed mediators. Since the magnitude of the decreases in sGaw elicited by AMP and HS were similar, it is also unlikely that the degree of mast cell degranulation resulting from HS provocation would have depleted mediator stores. Thus, the development of a refractory period after HS challenge probably occurs independently of depletion of preformed mediators. These results do not exclude the possibility that HS may produce a stimulus-specific desensitisation of mast cells.

The assumption in this study is that HS and AMP act *via* mast cell degranulation and it is important to review the evidence for this concept. Both AMP and HS induce bronchoconstriction partly *via* the release of the preformed mast cell mediator histamine [9, 15]. *In vitro* adenosine enhances the release of histamine from rat serosal mast cells challenged with the calcium ionophore A23187 [16]. Human mast cells isolated from lung tissue and peripheral blood basophils also respond to adenosine with enhanced histamine release [17, 18]. *In vivo* the airflow obstruction elicited by inhalation of AMP is virtually abolished by pretreatment with an H_1 receptor antagonist [9, 10] and is only partially attenuated by pretreatment with flurbiprofen [19]. This suggests that cyclooxygenase products have a lesser role to play than histamine in AMP induced bronchoconstriction. Although it has also been suggested that adenosine-induced bronchoconstriction could be mediated by an irritant effect of the nucleoside or by stimulating vagal afferent nerve endings [20], pretreatment with the inhaled muscarinic cholinergic antagonist ipratropium bromide does not inhibit adenosine induced bronchoconstriction in man [21]. This suggests that bronchoconstriction induced by adenosine is not mediated by stimulation of cholinergic reflexes. This may be species-specific since PAUWELS *et al.* [22] have demonstrated in the rat that atropine will inhibit intravenous adenosine-induced bronchoconstriction. Nevertheless the efficacy of anti-histamine drugs in attenuating AMP-induced bronchoconstriction suggests a primary role for mediator release in adenosine-induced bronchoconstriction. In asthmatic subjects airways responsiveness to inhaled AMP correlates with that to inhaled histamine [8].

Histamine is also released from human basophils when they are exposed *in vitro* to hyperosmolar buffers [23]. Local hyperosmolar challenge to isolated airway segments and nasal airways results in histamine release [24, 25].

Furthermore, bronchospasm induced by inhalation of HS is accompanied by the release of the mast cell associated mediator, high molecular weight neutrophil chemotactic activity, into the peripheral circulation [26]. The finding that the specific H_1 antagonist terfenadine attenuates HS induced bronchospasm [15] supports the view that histamine is also responsible in part for the bronchoconstriction produced by a hyperosmolar stimulus to the bronchial mucosa. Thus the evidence which supports the role of mast cell in the mechanism(s) of HS- and AMP-induced bronchoconstriction is compelling. We cannot exclude the unlikely possibility that HS and AMP are activating different mast cells.

Our results with consecutive AMP challenges are in contrast to those of DAXUN *et al.* [27] who demonstrated that in atopic non-asthmatic subjects, AMP challenges at one hourly intervals will induce a reduction of AMP responsiveness. The differences between these two studies may be due to the fact that the doses of AMP used in DAXUN's study were 5-fold greater than those used in the present study and/or the fact that one study used non-asthmatic subjects whereas the other study involved asthmatic individuals.

Our data suggests that either the airway responsiveness to released mediators may be increased after the osmotic challenge or that the release of histamine from the airway mast cells may be enhanced following an initial HS challenge. In support of the initial hypothesis we have previously demonstrated that a prior HS challenge will enhance the airways responsiveness to methacholine. In support of the latter hypothesis BELCHER *et al.* [26] have previously demonstrated that the release of high molecular weight neutrophil chemotactic activity is significantly greater after the second HS challenge than following the initial provocation. Our present results with AMP are also consistent with this view, suggesting that the enhancement of AMP responsiveness is at the mast cell level.

In conclusion we have demonstrated that the airways responsiveness to inhaled AMP correlates closely with the responsiveness to inhaled HS. Furthermore the refractory period after HS challenge is characterised by an increase in airways responsiveness to AMP. Consecutive AMP challenges elicited no attenuation of the AMP response. These results suggest that the mechanism of refractory behaviour to HS is not due to airway mast cell depletion of preformed mediators.

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Réactivité des voies aériennes au 5'monophosphate d'adénosine à l'inhalation de solution saline hypertonique. S.P. O'Hickey, P.J. Rees, T.H. Lee.

RÉSUMÉ: Nous avons cherché à déterminer si la période réfractaire après provocation à la solution saline hypertonique est due à une déplétion des médiateurs des mastocytes. Dans ce but, la réactivité des voies aériennes à l'adénosine 5' monophosphate (AMP), qui induit une bronchoconstriction par libération d' histamine mastocytaire, a été déterminée après inhalation d'un aérosol de solution saline hypertonique. Neuf sujets asthmatiques ont fréquenté le laboratoire à trois reprises. Au jour 1, la provocation par solution saline hypertonique a été réalisée, suivie une heure après d'une seconde provocation du même type. Au jour 2, une provocation à l'AMP a été réalisée. Au jour 3, une provocation à la solution saline hypertonique a été pratiquée, suivie une heure plus tard d'une provocation par l'AMP. La réactivité des voies aériennes (PD_{35} sGaw) à la provocation initiale à la solution saline s'étendait de 12 à 315 litres d'aérosol (moyenne 47 litres). La réactivité à une seconde provocation par solution saline va de 8 à 800 litres (moyenne 102 litres, $p = 0.035$, $n = 9$). La réactivité des voies aériennes à l'AMP a augmenté de 0.44 à 14.0 µmol (moyenne 2.37 µmol) à l'état basal, jusqu'à 0.3 à 15.5 (moyenne 1.3 µmol, $p = 0.05$) après provocation par solution saline. Il y avait une corrélation linéaire entre la réactivité de base à l'AMP et la réactivité de base à la solution saline ($r = 0.911$, $p = 0.001$). Il n'y avait pas de corrélation entre le degré de caractère réfractaire et les modifications de la réponse à l'AMP ($r = 0.1$, $p = 0.9$). En conclusion, la réactivité des voies aériennes à l'AMP augmente de façon significative après inhalation d'un aérosol de solution saline hypertonique, et cette augmentation est indépendante du comportement réfractaire. Nos résultats suggèrent que la période réfractaire à la solution saline hypertonique n'est pas due à une déplétion des médiateurs.

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