The combined effects of histamine and methacholine on the maximal degree of airway narrowing in normal humans \textit{in vivo}

P.J. Sterk, M.C. Timmers, E.H. Bel, J.H. Dijkman*

\textbf{ABSTRACT:} In normal subjects \textit{in vivo} the dose-response curve to inhaled nonsensitizing stimuli reaches a plateau at mild degrees of airway narrowing. We investigated whether the limitation of the response is due to non-optimal smooth muscle activation, by administering high doses of histamine and methacholine together. In fifteen normal subjects a complete dose-response curve to methacholine was recorded by a tidal breathing method on three randomized days. On a separate day a complete histamine inhalation test was carried out. Each methacholine test was directly followed by double blind inhalation of the highest dose of either histamine or methacholine, or a dose of saline. The response was measured by flows from partial flow-volume curves ($V_{eq}$), and was expressed in \% fall from baseline. Twelve subjects reached a maximal response plateau to methacholine which was reproducible. The addition of saline or extra methacholine did not change the response from its methacholine plateau value. Histamine caused a small increase in the response on top of the methacholine plateau (\(+9.0\% \text{ fall; } p<0.001\)). However, the response to the combined histamine and methacholine was not significantly larger than the maximal response to histamine alone. We conclude that there is no interaction between histamine and methacholine on the maximal degree of airway narrowing. This suggests that the plateau of the dose-response curve in normal subjects \textit{in vivo} is due to other factors than limited smooth muscle activation.

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Patients with asthma and non-asthmatic subjects differ in airway responsiveness to nonsensitizing chemical or physical stimuli [14]. Airway responsiveness is currently measured by inhalation challenge tests, using e.g. histamine or methacholine and various indices of airway narrowing in a dose-response way [14]. Normal subjects almost invariably reach a reproducible maximal response plateau at relatively mild degrees of airway narrowing, whereas asthmatics usually do not [21, 32, 37]. Asthma is characterized by a leftward shift of the dose-response curve [14] and a continuously rising response with increasing dose, whereby a plateau often cannot be demonstrated [21, 32, 37]. The relatively low response plateau in normal humans and animals [16] does not fit in with predictions based on the considerable contractability of airway smooth muscle \textit{in vitro}, and suggests that severe airway narrowing \textit{in vivo} is normally prevented by a mechanism that might be impaired by asthma [20].

In theory, the determinants of the maximal degree of airway narrowing \textit{in vivo} are smooth muscle strength, the elastic load of the surrounding tissue, local structural characteristics of the airway wall, and the amount of secretions in the airway lumen [24]. Regarding the smooth muscle, limited strength could be due to limited activation. So far, there is no experimental evidence that bronchial smooth muscle activation is attenuated by inhibitory mechanisms in normal humans \textit{in vivo}. The maximal response plateau is unlikely to be due to: 1) the bronchodilation following a deep inspiration [32]; 2) progressive airway narrowing itself or tachyphylaxis induced by cumulative doses of the agonist [32]; 3) neural or humoral inhibitory factors [31]; 4) drug-antagonism or receptor regulation [33]. An alternative explanation of limited airway smooth muscle activation could be the condition that optimal concentrations of the agonists have not been reached at the receptor sites. In the present study, we further investigated the role of smooth muscle activation by testing the hypothesis that the maximal response to one agonist is associated with maximal smooth muscle activation, and cannot be overcome by adding another.

It has been shown that low doses of histamine and muscarinic agonists interact supra-additively on \textit{in vivo} airway narrowing in humans [23] and guinea pigs [34]. We reasoned that if inhalation of high doses of these agonists does not result in optimal concentrations at the receptor sites, there would also be potentiating interaction between the two. Therefore we investigated...
the airway narrowing effect of a high dose of histamine on top of the response plateau to methacholine in normal subjects.

Methods

Subjects

Fifteen non-asthmatic adults (9 men, 6 women; mean age 28.7 yr, range 19-45) volunteered to participate in the study (Table I). They had no current or past history of respiratory disease [35], and their forced expiratory volume in one second (FEV₁) was greater than 80% of that predicted [27]. Five subjects were atopic as indicated by one or more wheal (> 2 mm) and flare responses to prick skin tests with thirteen common allergen extracts (ALK-Soluprick, Copenhagen, Denmark). All subjects were non-smokers or ex-smokers (stopped for at least four weeks). None of the subjects had symptoms of respiratory infection for two weeks prior to the study, and none had been exposed to a relevant allergen for six weeks except for house dust. None of the subjects used medications except for oral contraceptives. All subjects gave informed consent and the project obtained approval from the Ethics Committee of the University Hospital, Leiden.

Study design

The subjects attended the lung function laboratory on four study days within two weeks at the same time of the day. On a control day a complete histamine inhalation test was performed in order to document the response plateau to this agonist. On three randomized days a complete methacholine inhalation test was carried out, directly followed by double blind inhalation of the highest dose of either histamine, or methacholine, or a dose of saline (serving as a placebo).

Table I. - Subject characteristics and lung function data

<table>
<thead>
<tr>
<th>Subject number</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Height (cm)</th>
<th>FEV₁ (% pred.)</th>
<th>( V_{40} ) (l/s)</th>
<th>PD₄₀ ( V_{40} ) (μmol)</th>
<th>MV ( V_{40} ) (%)</th>
<th>PD₄₀ ( V_{40} ) (%)</th>
<th>MV ( V_{40} ) (%)</th>
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<tbody>
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<td>1</td>
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<td>188</td>
<td>97</td>
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<td>113.0</td>
<td>44.3§</td>
<td>22.9</td>
<td>65.9§</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>29</td>
<td>162</td>
<td>110</td>
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<td>34.0</td>
<td>84.8§</td>
<td>24.4</td>
<td>78.1§</td>
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<tr>
<td>3</td>
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<td>195</td>
<td>111</td>
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<td>51.8</td>
<td>9.5</td>
<td>58.8</td>
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<td>109</td>
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<td>17.0</td>
<td>59.4</td>
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<tr>
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<td>1.3</td>
<td>93.9</td>
<td>1.0</td>
<td>&gt;100.0§</td>
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</table>

M: male; F: female; FEV₁: forced expiratory volume in 1 s; \( V_{40} \): flow at 40% of control forced vital capacity on the partial flow-volume curve; PD₄₀ \( V_{40} \): provocative dose to cause a 40% fall in \( V_{40} \); MV \( V_{40} \): maximal response by \( V_{40} \) on plateau; *Expressed as the average of the 3 days (geometric mean for PD₄₀ \( V_{40} \)). **Control day. §Largest response without a plateau.
Inhalation tests

Methacholine and histamine (Eur. Pharm. Analytical Grade) were administered and inhaled by a standardized tidal breathing method [14]. Complete dose-response curves were obtained from inhaling doubling concentrations of acetyl-beta-methylcholine chloride (0.03-256 mg·ml⁻¹ in normal saline) or histamine-acid-phosphate (0.03-64 mg·ml⁻¹ in normal phosphate-buffered saline) prepared by the University Hospital Pharmacy. The aerosols were generated by a DeVilbiss 646 nebulizer (DeVilbiss Co., Somerset, PA) with closed vent, 3 ml filling and 0.13 ml·min⁻¹ output. The nebulizer was connected to the central chamber of an inspiratory-expiratory valve box with an expiratory aerosol filter (Pall Ultipor BB50), and was placed straight opposite the mouthpiece. The aerosols were inhaled by tidal breathing for 2 min at 5 min intervals while the nose was clipped. The dose of the drugs was expressed in micromoles delivered to the mouth during tidal breathing, which was calculated by multiplying salt concentration by nebulizer output according to recent recommendations [14]. Even though methacholine produces a small cumulative effect [17], the tidal breathing methods are currently expressed in noncumulative units [14]. The noncumulative nebulized dose of histamine and methacholine therefore ranged from 0.025-54 μmol and 0.04-340 μmol, respectively.

On the three methacholine days, the extra dose of histamine, methacholine or saline was inhaled 5 min after the maximal dose from the methacholine inhalation test. The extra histamine dose consisted of 54 μmol in all subjects, except for subject 15 in whom we used 13.6 μmol because of complaints of discomfort. The extra methacholine dose was a repetition of the maximal dose of 340 μmol in all subjects. Methacholine and histamine solutions were stored in ampules of 3 ml at 4°C, were nebulized at room temperature, and were renewed every four months.

The response was measured by partial expiratory flow-volume (PEFV) curves that were standardized for volume history [38]. The PEFV-curve is one of the most sensitive tests for pharmacologically induced airway narrowing and has been validated in the documentation of the plateau on dose-response curves [32, 38]. The PEFV-curves (three sets for baseline values and one set following each dose) were performed using a dry rolling-seal spirometer (Mijnhardt Volugraph 2000) and a XY-recorder (Gould Bryans 50.000 S). The subject was connected to the spirometer, and a maximal inspiration to total lung capacity (TLC) was carried out 45 s after each dose. Without taking off the mouthpiece, this was followed by another 45 s tidal breathing at lung volumes below 60% of the (largest) control forced vital capacity (FVC), which was marked off from TLC. This 45 s interval is required to restore airway tone to pre-inflation levels after the bronchodilation following the deep breath [25, 38]. Then the PEFV-curve was initiated from the 60% control FVC mark.

The flow on the PEFV-curve at 40% of the control FVC (again marked off from TLC) was measured (V₄₀₀). The use of TLC as the reference volume was justified in a recent study, showing no change in TLC following maximal methacholine-stimulated airway narrowing [19]. Baseline FEV₁ was measured according to standardization recommendations [27]. Measurements are reported in body temperature and pressure, saturated with water vapour (BTPS).

Data analysis

The response of V₄₀₀ was expressed as the percentage fall from mean baseline value, and was plotted against log nebulized noncumulative dose (in μmol) [14]. The dose-response curves were characterized by their position and maximal response. The position was expressed as the provocative dose that caused a 40% fall in V₄₀₀ (PD₄₀₀V₄₀₀). This was calculated by log linear interpolation between the two adjacent data points. The natural logarithm of the PD₄₀₀V₄₀₀ was used in the analyses. A maximal response plateau was considered if two or more data points of the highest doses fell within a 5% response range. The maximal response was calculated by averaging the points on the plateau for V₄₀₀ (M₄₀₀V₄₀₀), and was expressed in % fall from baseline value. This way of characterizing the plateau has been validated in a previous study [32]. If a dose-response curve did not reach a plateau the maximal response was not calculated and was left out of the analysis. The response of V₄₀₀ to the extra doses of histamine, methacholine or saline, that were given on top of the methacholine plateau, was reported as M₄₀₀V₄₀₀. In the only subject in whom M₄₀₀V₄₀₀ fell to zero 1s⁻¹ (Subject 15) M₄₀₀V₄₀₀ was analysed as being a 100% fall. The differences in variables within and between the study days were examined by two-way analysis of variance and the two-tailed paired t-test [1]. P-values less than 0.05 were considered statistically significant.

Results

Mean values of baseline function data and indices of the inhalation tests are listed in table I. There was no difference between the four days in baseline FEV₁, or V₄₀₀ (p > 0.50). Neither was there a difference between the three randomized days in methacholine PD₄₀₀V₄₀₀ (p > 0.50). Twelve subjects reached a maximal response plateau to methacholine by V₄₀₀ on three days. They showed no difference between the days in M₄₀₀V₄₀₀ (p > 0.50). Among these twelve subjects, only one did not reach a plateau to histamine on the control day (table I).

The extra effect of saline, methacholine or histamine on top of the methacholine plateau was examined by within-day comparison of M₄₀₀V₄₀₀ with M₄₀₀V₄₀₀ in the twelve subjects who reached a plateau on all three methacholine days (fig. 1, table II). An example of the recordings in one subject is illustrated in figure 2. As could be anticipated, saline did not cause a difference
The maximal responses by \( V_{40p} \) in the 12 subjects who reached a plateau to methacholine on 3 days. The response on the plateau (closed triangles) is compared with response after an extra dose of saline (open circles), 340 \( \mu \)mol methacholine (open triangles), or 54 \( \mu \)mol histamine (crosses) on top of the methacholine. In one subject (number 15) the response to extra histamine reached 100% fall (arrow).

**Table II.** Extra airway narrowing after a dose of saline, methacholine, or histamine on top of the methacholine plateau.

<table>
<thead>
<tr>
<th></th>
<th>number of subjects</th>
<th>( M'V_{40p} - M'V_{40p} ) mean±SD (%) fall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>12</td>
<td>-4.1±8.2</td>
</tr>
<tr>
<td>Methacholine</td>
<td>12</td>
<td>0.6±7.1</td>
</tr>
<tr>
<td>Histamine</td>
<td>12</td>
<td>9.0±6.6*</td>
</tr>
</tbody>
</table>

\( M'V_{40p} \): the maximal response on the methacholine plateau for the flow at 40% of the control forced vital capacity on the partial flow-volume curve. \( M'V_{40p} \): the response following an extra dose of saline, methacholine or histamine on top of the methacholine plateau, for the same index. SD: standard deviation. * Significantly different from zero \((p<0.001)\) and effect by histamine significantly different from that by methacholine and saline \((p<0.005)\).

The addition of histamine resulted in a small but significant increase in the degree of airway narrowing on top of the methacholine plateau, the mean difference between \( M'V_{40p} \) and \( M'V_{40p} \) being 9.0% fall, standard deviation \((SD) 6.6 (p<0.001; \) table II).

By between-day comparison, the additional effect induced by histamine appeared to be larger than that by methacholine or saline \((p<0.005; \) table II). However, the response to methacholine plus histamine was not significantly larger than the response to the same dose of histamine alone, as derived from the

fix. 2. Example of the methacholine dose-response curves by \( V_{40p} \) (closed triangles) in subject 5 on 3 study days. An extra dose of saline (continuous line, open circle), 340 \( \mu \)mol methacholine (dashed line, open triangle), or 54 \( \mu \)mol histamine (dotted line, cross) was administered on top of the methacholine plateau.

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fix. 3. The maximal responses by \( V_{40p} \) obtained after the addition of 54 \( \mu \)mol histamine on top of the methacholine plateau (crosses) compared with those to 54 \( \mu \)mol histamine alone derived from the histamine challenge test on the control day (circles) in 11 subjects.

**Discussion**

The results demonstrate that the maximum attainable degree of airway narrowing in vivo obtained by methacholine can only be increased to a small extent by adding a high dose of histamine. There does not seem to be an interaction between these two agonists on the maximal degree of airway narrowing, because the maximal response to the combined histamine and methacholine was not significantly larger than that to the histamine alone. These findings suggest that the plateau on the dose-response curve in normal humans
in vivo cannot be explained by limited airway smooth muscle activation.

This study confirms that the plateau is a reproducible feature of the dose-response curve to inhaled histamine or methacholine in normal subjects [21, 32, 37]. We designed three methacholine inhalation tests for the following reasons. The saline day allowed us to investigate the stability of methacholine induced maximal airway narrowing with time. The unchanged response after saline inhalation at 5 min following the highest methacholine dose confirmed that the action of methacholine was sufficiently prolonged [6] to interpret any interaction with histamine. By repeating the highest dose of methacholine on another day, we examined the effect of an extra dose of the same agonist on the degree of maximal airway narrowing. As expected the extra methacholine did not alter the response from its plateau value.

The effect of administering two combined agonists on the maximal degree of airway narrowing was assessed from the experiments where histamine was given on top of the plateau to methacholine. There was a small, far less than additive effect of extra histamine on maximal degree of methacholine-induced airway narrowing. However, the response to the combined stimuli was not different from that to the same dose of histamine alone. This would imply that histamine is a slightly stronger stimulus than methacholine at maximal degrees of airway narrowing, without interaction between both drugs. These findings are seemingly in contrast with our previous observations that the plateau to histamine is not higher than that to methacholine [33]. In our opinion, there are two reasons for this discrepancy. Firstly, there was an increasing trend in the maximal attainable response going from methacholine alone, to histamine alone, to methacholine plus histamine, in which only the difference between the first and the latter reaches statistical significance. Secondly, in the comparison between the maximal responses to histamine and methacholine, we previously [33] and presently observed some exceptions with a higher plateau to histamine (e.g. subjects 6 and 7, table I). It therefore appears that at least in some individuals histamine can be a slightly stronger stimulus than methacholine. In this respect histamine resembles leukotriene D₄, a mediator that has recently been shown to induce a higher maximal response of airway narrowing than methacholine in normal subjects in vivo [4]. These differences in maximal response are of interest regarding the mode of action of the drugs.

Clearly, there are differences in pharmacodynamic properties between histamine and methacholine. Histamine acts through H₁, and possibly H₂ receptors on smooth muscle [13, 36], plus, primarily at low doses, a vagovagal reflex component [9, 29] that seems to be of minor importance in inhalation challenge tests in man [26]. In addition, there is evidence for a local, neurally mediated action of histamine in the airways [29]. Methacholine stimulates muscarinic receptors on smooth muscle and possibly on autonomic ganglia [13, 22]. In theory, the small additive effect of histamine on top of maximal airway narrowing to methacholine can be explained by partially non-overlapping sites of action of both drugs, or by greater effects of histamine on processes other than muscle contraction, such as swelling of the airway wall [36]. Both possibilities might be involved in vivo, since histamine leads preferentially to peripheral airway narrowing [7] and induces more mucosal oedema [3] as compared to muscarinic agonists. It cannot be excluded that these mechanisms would also lead to a greater sensitivity in vivo (leftward shift of the dose-response curve) to histamine as compared to methacholine [24]. Although it has been shown that the sensitivity to both agonists is equal [17], even when comparing equimolar doses [33], a relatively greater sensitivity to histamine was reported in a population of smokers [11]. The PD₄₀Vₑₒ values in the present study are also indicative of a relatively greater sensitivity to histamine as compared to methacholine (table I). However, our study design does not allow statistical analysis of these data, because it concerns repeated methacholine tests and a single histamine experiment.

What are the implications of the present findings for our understanding of the mechanisms which limit maximal airway narrowing to a mild degree in normal subjects? By combining two pharmacodynamically different agonists, each in a dose that produces a maximal effect on its own, we were not able to induce a substantial increase in the response beyond the plateau obtained by histamine alone. It can be argued that the plateau is caused by relatively low agonist concentrations at the receptor sites due to limited accessibility of the agonists to the airway wall. This could occur e.g. by mucus hypersecretion at high doses which has been shown to blunt the response to aerosolized stimuli in dogs [18]. If only relatively low concentrations of histamine and methacholine can be reached locally, one would expect potentiating interaction between the two drugs based on the supra-additive effects of submaximal doses of histamine and muscarinic agonists on in vivo airway narrowing [23, 34]. This potentiation may arise from geometrical interaction by the physical relationship between airway calibre and resistance [5, 34], or may be due to direct pharmacological interaction at the level of the cholinergic nerve terminals and smooth muscle [30].

The present observation of a lack of interaction between both drugs at maximal degrees of airway narrowing is supported by in vitro experiments [34], and supplies indirect evidence that maximal doses indeed have been achieved at the receptor sites.

What are the alternative hypotheses in order to explain that normals, in contrast to asthmatics, are being protected against severe airways obstruction? There are at least three possibilities. Firstly, postjunctional subsensitivity at the level of the smooth muscle may play a role [12]. Initial studies, showing no correlation between the characteristics of in vitro and
in vivo dose-response curves [2], did not support this hypothesis. Moreover, it has recently been shown that the maximal contractility of small airway smooth muscle in vivo is unrelated to the maximal degree of airway narrowing in vivo in non-asthmatics [8]. However, the few in vitro data of patients with asthma do seem to indicate that posijunctional sensitivity changes can be involved [28]. Secondly, normals may be protected by their relatively small amount of smooth muscle. However, it is not clear yet whether or not airway smooth muscle hyperplasia [15] is a requirement for high maximum responses in vivo. And thirdly, there is experimental evidence that the viscous and elastic loads on muscle shortening by airway cartilage [24] and lung elastic recoil pressure [10] are of importance in preventing severe airway narrowing in normals. Loss of structural support by local oedema or hyperaemia in and around the airways may then be responsible for the high maximal response in asthma [24]. By using the results of the present study we cannot differentiate between these alternative explanations of limited maximal narrowing in vivo. The potentially protective mechanisms need further investigation, because any abnormalities may be relevant in the cause of asthma.

In conclusion, we have not been able to demonstrate interaction between two pharmacodynamically different stimuli on the maximal degree of airway narrowing in normal human subjects. This favours the hypothesis that the plateau on the dose-response curve in vivo is due to other factors than limited smooth muscle activation.

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References


RÉSUMÉ: Chez le sujet normal in vivo la courbe dose-réponse à l’inhalation de stimuli non sensibilisants atteint un plateau à un degré modéré de rétrécissement des voies aériennes. Nous nous sommes demandés si cette limitation pouvait être la conséquence d’une activation suboptimale du muscle lisse, en administrant ensemble des doses élevées d’histamine et de méthacholine. Chez quinze sujets normaux des courbes dose-réponse à la méthacholine ont été enregistrées à trois jours reprises. Une courbe utilisant la méthode en respiration courante dose-réponse à l’histamine était de même enregistrée un jour différent. Chaque test à la méthacholine était suivi, en double issu, par l’inhalation soit de solution physiologique soit de la dose la plus élevée de méthacholine ou d’histamine. La réponse était évaluée en mesurant sur des courbes débit-volume partielles $V_{40}$ et était exprimée en % de chute par rapport à la valeur initiale. Chez douze sujets le plateau pour la méthacholine était atteint de façon reproductible. L’addition de solution physiologique ou de méthacholine n’a pas modifié le plateau, l’histamine par contre a entraîné une faible réponse complémentaire (+9% de chute, p < 0.001). Cependant la réponse à l’administration combinée d’histamine et de méthacholine n’est pas supérieure à la réponse maximale observée avec l’histamine seule. Nous concluons que l’histamine et la méthacholine n’interagissent pas pour fixer le degré maximum de rétrécissement des voies aériennes. Ceci suggère que le plateau observé in vivo chez le sujet normal est dû à des facteurs autres qu’une limitation de l’activation du muscle lisse.