Pharmacodynamic Aspects of Chlorpheniramine-Induced Bronchodilatation

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In 12 asthmatic (A) and ten normal (N) subjects, we measured the effect of inhaled saline solution, acetylcholine, histamine (H), and chlorpheniramine (CP) on specific airway conductance and forced expiratory flows. We found that CP dilated the bronchi in six asthmatic patients and one normal subject by acting on bronchial H₁ receptors. This action is also modulated by the abnormal functions of this receptor-transducer, explaining why CO exerts a tonic effect only in subjects with H hyperresponsiveness. Furthermore, as shown by CO and CP + H responses, bronchial histamine seems to be present primarily in large airways and in relatively small amounts. We also found that bronchial H₂, the abnormal H₁ receptor-transducer, and the bronchial caliber are regulated independently of each other. Consequently, this limits the therapy with H₁ blockers in asthma.

In 1977, a controlled study demonstrated that when given intravenously in relatively high doses, chlorpheniramine (CP), an H₁ blocker with modest in vitro anticholinergic properties, can dilate the bronchi of asthmatic subjects.† With the use of either CP or clemastine, this effect was rapidly confirmed. This indicates that endogenous histamine (H) acting on bronchial H₁ receptors is a modulating agent of resting bronchial tone in chronic asthma. Histamine, acting primarily on bronchial H₁ receptors and to some extent via H₂ receptors as well, may participate in certain types of acute asthma. Finally bronchial responsiveness to H usually potentiates the bronchospastic action of asthmogenic stimuli, both in man and animal.

Considering the emerging clinical importance of endogenous H in asthma and the therapeutic effects in this disease of H₁ blockers, it is important to define the main pharmacodynamic aspects of H₁ blocker-induced bronchodilatation.

The present study had two specific goals. First, we wished to delineate the possible contribution of the cholinergic pathway in H₁ blocker-induced bronchodilatation, an essential but still controversial aspect. Second, should CP exhibit no anticholinergic activity, we planned to correlate the bronchodilator response to this drug with the mechanical tests currently thought to reflect drug receptor interaction at bronchial smooth muscle level, specifically dose-ratio of H (DR-H) after CP, bronchial sensitivity (provocation dose 40 [PD₄₀-H]) and slope of log dose-response curve to H (SLDRC-H).

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Materials and Methods

Pulmonary Function Data

Twelve asthmatic subjects* and ten healthy normal subjects were selected for this study. They had no history of smoking and forced expiratory volume in one second (FEV₁) and specific conductance, expressed per liter of lung volume at which G is measured (Gaw/V̇l) were reproducible within the day and day to day (range/mean of FEV₁ varied at the most 5 and 10 percent and that of Gaw/Vl varied 20 and 30 percent, respectively). In eight subjects, asthma had an allergic component. Seven asthmatic patients treated long-term with inhaled β₂ agonists had their drugs withheld during the 12 hours prior to the experimentation. No subject was taking slow-release theophylline preparations, steroids, or antihistaminic drugs. The subjects with allergic (pollen) asthma were tested outside the offending season.

The physiologic measurements recorded were Gaw/Vl, highest forced expiratory flow (FEF), functional residual capacity (FRC), forced vital capacity (FVC), maximal forced expiratory flow achieved during FVC (FEFmax), forced expiratory flow at 25 and 50 percent of FVC (FEF25% and FEF50%, respectively), and forced expiratory flow between 25 and 75 percent of FVC (FEF25-75%). For Gaw/Vl and FRC a semiautomated constant volume body plethysmograph (Jaeger, Rockford, IL) was used. The FEF values were recorded after body plethysmography measurements with two systems: In experiments dealing with the time course of airway responses to inhaled CP or buffered saline solution, I utilized the volume signal from a wedge spirometer (Med-Science Electronics, St. Louis, MO) as processed by a Tektronix 4054 computer (Chestech, Philadelphia).

In all H or acetylcholine (ACH) challenge tests, regardless of whether these agonists were preceded by buffered saline or CP, FVC and FEF values were measured with a much faster recording system: with the box door open, flow-volume loops were recorded off the body plethysmograph's pneumotachograph, electronically integrated in the console and displayed on an X-Y plotter. The FVC and FEF values were subsequently hand calculated. Using the first three technically acceptable flow-volume loops, the best values and SD/mean were calculated. Two nebulization systems, one for inhalation of saline solution or CP (lasting up to 30 min) and another for short quantitative nebulization of H or ACH were used. The first system consisted of a DeVilbiss No. 45 nebulizer, flushed with 6 L/min O₂; it delivered a fluid output of 0.22 ml/min and generated an aerosol with a mass median aerodynamic diameter of 3.0 ± 0.8 μ. The second system consisted of a volume ventilator (Monaghan...
chlorpheniramine maleate (Schering, Kenilworth, NJ) was freshly prepared before each inhalation by dissolving the content of 1-ml vials for intravenous usage (10 mg/ml) in sterile, nonbacteriostatic buffered saline solution. Over different time intervals, CP was nebulized in four different concentrations: 1.0, 1.4, 2.0, and 3.3 mg/ml for the 3.3- (CP3), 5.5- (CP5), 11.8- (CP11) and 20.9-mg (CP20) doses, respectively. Each subject was tested at the same time of the day and always after 20 min of rest in the laboratory; the testing was completed in approximately four weeks.

Study Design

In the first series of experiments, Gaw/VL, FVC, and FEV values were recorded in all subjects before and 30, 60, 90 and 150 minutes after single-blind inhalation of buffered saline solution or on a different day, CP20 (Table 1). The asthmatic subjects were challenged a second time with buffered saline solution and 2.9 mg CP and, after the reproducibility of CP response was established, also with CP2, CP3, CP5 and CP11. A 40, 10 or 20 percent increase in Gaw/VL, FEV, or FEV values, respectively, was arbitrarily considered to reflect bronchodilatation.

A second series of experiments carried out in all normal and asthmatic subjects determined the provocation dose 40 (PD40) for H and ACH2 and, using the two points needed to calculate this measurement, SLDRC-H as well.21,22

In the third series of experiments, we measured the change in sensitivity to inhaled H or ACH following the single-blind inhalation of buffered saline solution or CP. The change was expressed as DB, ie, the ratio of PD40-H after CP to PD40-H. All subjects participated in CP20-ACH challenges, whereas for CP + H challenges only 20 of the previously tested subjects were enrolled. (Two asthmatic nonresponders suddenly became unavailable.) In all these 20 subjects, three doses of CP were used on different days, CP3, CP11, and CP20. After CP nebulization, H or ACH were administered again in increasing doses at 15-min intervals, starting 15 min after CP pretreatment with one eighth of the dose needed to produce Δ Gaw/VL immediately greater than 40 percent.23,24 The half-life of CP is much longer (>20 h) than the time needed to reach Δ Gaw/VL > 40 percent after pretreatment with this antagonist. The protocol for CP and H challenge allowed the measurement of DR-H during a known bronchomotor response produced by the H1 blocker while providing an additional check on the reproducibility on the eventual bronchodilator response.10,24

The present study was approved by the Committee on Human Rights in Research of our institution and a signed informed consent was obtained from each individual prior to testing.

Table 1—Study Design

<table>
<thead>
<tr>
<th>Experiment</th>
<th>N</th>
<th>A</th>
<th>Agent Used</th>
<th>Pharmacodynamic Event</th>
</tr>
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<tbody>
<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a</td>
<td>10</td>
<td>S, CP20</td>
<td>CP induced BR (Gaw/VL post-CP)</td>
<td></td>
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<tr>
<td>b</td>
<td>10</td>
<td>S, CP20, CP5, CP11, CP20</td>
<td>CP induced BR (Gaw/VL post-CP)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>10</td>
<td>10</td>
<td>S, H, ACH</td>
<td>Responsiveness to H or ACH (PD40-H or PD40-ACH) Reactivity to H (SLDRC-H)</td>
</tr>
<tr>
<td>III</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a</td>
<td>10</td>
<td>8</td>
<td>S, CP20, CP11, CP20</td>
<td>Protective effect of CP on H responsiveness (DR-H after CP) CP induced BR (Gaw/VL post-CP)</td>
</tr>
<tr>
<td>b</td>
<td>10</td>
<td>10</td>
<td>S, ACH, CP20</td>
<td>Protective effect of CP on ACH responsiveness (DR-AH after CP)</td>
</tr>
</tbody>
</table>

*Abbreviations: N = normal subjects; A = asthmatic subjects; BR = bronchodilatation; S = saline solution; CP = chlorpheniramine (CP2, 3.3 mg CP; CP5, 5.5 mg CP; CP11, 11.8 mg CP; CP20, 20.9 mg CP); H = histamine; ACH, acetylcholine.

Results

Baseline Values and Variability of Pulmonary Function Tests

As shown in Tables 2 and 3, except for asthmatic subjects (patients 8 and 10), resting Gaw/VL was within normal limits.28 In asthmatic responders and nonresponders, %FEV1/FVC averaged 75.4 ± 7.1 and 69.9 ± 11.3, respectively; expressed as percent of predicted,27,28 FEFmax was 81.6 ± 25.1 and 75.1 ± 21, FEF50 was 48.8 ± 20.9 and 42.5 ± 11.8, and FEF25-75 was 64.2 ± 25.4 and 53.7 ± 29.3 (for all tests 0.1>p>0.05).

The within-day variability of Gaw/VL, FVC and FEV values averaged 15.8 percent for Gaw/VL, 3.3 percent for FVC, 3.2 percent for FEV1, 7.4 percent for FEFmax, 4.8 percent for FEF25-75, and 4.1 percent for FEF50%. Thus the “physiologically significant” changes considered arbitrarily to indicate the presence of bronchodilatation were approximately three times the size of the average coefficient of variation of the test used.

Effect of CP on Resting Bronchial Tone

Six out of 12 asthmatic subjects and one out of ten normal subjects (henceforth called responders) showed reproducible and physiologically significant airway responses to CP20. One of these seven responders
### Table 2—Airway Responses to Histamine and Chlorpheniramine in Asthmatic Subjects*

<table>
<thead>
<tr>
<th>Subject</th>
<th>R/NR</th>
<th>Gaw/Vl (μg) Delivered and DR</th>
<th>% Gaw/Vl.</th>
<th>After</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>R</td>
<td>3.73</td>
<td>7.50</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>R</td>
<td>0.89</td>
<td>140.4</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>R</td>
<td>0.34</td>
<td>80.2</td>
<td></td>
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<tr>
<td>4</td>
<td>R</td>
<td>0.26</td>
<td>2.5</td>
<td></td>
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<tr>
<td>5</td>
<td>R</td>
<td>0.58</td>
<td>17.0</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>R</td>
<td>0.31</td>
<td>57.4</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>R</td>
<td>0.34</td>
<td>24.5</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>NR</td>
<td>0.11</td>
<td>5.2</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>NR</td>
<td>0.11</td>
<td>5.2</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>NR</td>
<td>0.05</td>
<td>4.8</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>NR</td>
<td>0.34</td>
<td>80.2</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>0.31</td>
<td>15.3</td>
<td></td>
</tr>
</tbody>
</table>

*Abbreviations: R = responder; NR = non-responder; Gaw/Vl = specific conductance expressed per liter of lung volume at which G is measured; O = open test; S = pretreatment with saline solution; PD<sub>H</sub> = provocative dose 40 for histamine (H); DR = dose range; CP<sub>H</sub> = pretreatment with 5.5-mg dose of chlorpheniramine (CP); CP<sub>2H</sub> = pretreatment with 11.5-mg dose of CP, CP<sub>1H</sub> = 20-mg dose of CP; SLDRC-H = slope of log dose-response curve to histamine. NR = subjects with an open test as well as S + H and CP<sub>1H</sub> + H challenge; NR<sub>5</sub> = subjects with an open H test only. CI = confidence interval.

### Table 3—Airway Responses to Histamine and Chlorpheniramine in Normal Subjects*

<table>
<thead>
<tr>
<th>Subject</th>
<th>R/NR</th>
<th>Gaw/Vl (μg) Delivered and DR</th>
<th>% Gaw/Vl.</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>NR</td>
<td>0.28</td>
<td>718.1</td>
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<tr>
<td>10</td>
<td>NR</td>
<td>0.21</td>
<td>600</td>
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<tr>
<td>12</td>
<td>NR</td>
<td>0.20</td>
<td>686.6</td>
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</tr>
<tr>
<td>14</td>
<td>NR</td>
<td>0.20</td>
<td>686.6</td>
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</tr>
<tr>
<td>16</td>
<td>NR</td>
<td>0.40</td>
<td>825.4</td>
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<tr>
<td>17</td>
<td>NR</td>
<td>0.45</td>
<td>305.4</td>
<td></td>
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<tr>
<td>18</td>
<td>NR</td>
<td>0.20</td>
<td>768.5</td>
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</tr>
<tr>
<td>19</td>
<td>NR</td>
<td>0.10</td>
<td>425.5</td>
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</tr>
<tr>
<td>20</td>
<td>NR</td>
<td>0.30</td>
<td>385.8</td>
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</tr>
<tr>
<td>Mean</td>
<td></td>
<td>0.34</td>
<td>55.6</td>
<td></td>
</tr>
</tbody>
</table>

*Abbreviations: N = normal subject; A = asthmatic subject; p(t) = value of Student’s t test; 95% CI MW = 95% confidence interval in medians difference (Mann-Whitney [MW] test); p(MW) = p-value of test; R = responder; NR = non-responder; Gaw/Vl = specific conductance expressed per liter of lung volume at which G is measured; O = open test; S = pretreatment with saline solution; PD<sub>H</sub> = provocative dose 40 for histamine (H); DR = dose range; CP<sub>H</sub> = pretreatment with 5.5-mg dose of chlorpheniramine (CP); CP<sub>2H</sub> = pretreatment with 11.5-mg dose of CP, CP<sub>1H</sub> = 20-mg dose of CP; SLDRC-H = slope of log dose-response curve to histamine. NR = subjects with an open test as well as S + H and CP<sub>1H</sub> + H challenge; NR<sub>5</sub> = subjects with an open H test only. CI = confidence interval.

### Chlorpheniramine-induced Bronchodilatation (Valentin Popa)

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- Chlorpheniramine-induced Bronchodilatation (Valentin Popa)
(subject 4) also reacted to a lower dose (CP11). Three types of bronchodilating responses were noted: an isolated increase in Gaw/VL in five subjects (patients 1, 2, 5, and 6, Table 2 and subject 13, Table 3), an isolated increase in flow at low lung volume (FEF25-75% and FEF50) in one subject (subject 3, Table 2), and a mixed conductance and flow response (FEV1, FEF50%, FEF25-75%) in another subject (subject 4, Table 2). In responders, statistical analysis of pooled data showed that the peak changes in Gaw/VL produced by CP were higher (p<0.01) than those produced by saline solution or any other CP concentrations (Tables 2 and 3) and occurred at 30, 60, 90, and 120 min (data not shown). Peak Gaw/VL in responders, invariably present at 30 or 60 min, also differed (p<0.01) from Gaw/VL changes produced by CP in nonresponders (Tables 2 and 3). The changes in FEV1 and FEF values produced by CP were, with the exceptions noted previously, within the range of variability of the corresponding test.

Asthmatic responders were not different from asthmatic nonresponders with respect to age (average values, 24 vs 29 years). Subjects with allergic asthma were found in both groups, but those with intrinsic asthma were nonresponders. Asthmatic responders tended to display higher resting Gaw/VL, FEV1 (Table 2) and FEF values (see group data mentioned before) than the nonresponders, but the differences were not significant (p>0.05).

Single-blind challenge with CP or saline solution failed to alter PDACH significantly (p>0.05) in both asthmatic and normal responders or nonresponders (Fig 1).

**Correlation between CP-Induced Bronchodilation and Other Mechanical Measurements of H1 Receptor-Operated Pathway**

As shown in Table 2, no statistically significant differences existed between the average PDACH of asthmatic responders and asthmatic nonresponders (54.04±46.94 vs 47.25±76.1 μg H, respectively (p>0.05). However, the pooled PDACH values for asthmatic (49.25±81.1 μg) and normal (282.4±557.67 μg) subjects were significantly different (p<0.01). They were within the range of the threshold doses previously reported in these groups by means of quantitative nebulization and an identical11,12 or a comparable endpoint, −FEV1>10 percent.10 As indicated in Table 3, the normal subject who had bronchodilatation following CP had the lowest PDACH of the normal group (60 μg); he remained normal for two years after these PDACH experiments.

The changes in FEV1 corresponding to a 40 percent decrease in Gaw/VL (PDACH) were comparable in H and ACH challenge tests and were “physiologically significant.” They were roughly three times higher than the coefficient of variation of this measurement: 9.1, 9.9, 8.9, 10.3 and 9.5 percent for straight H, S + H, C3 + H, C11 + H and C90 + ACH, respectively. The corresponding changes in FEV50 were 16, 15.5, 15, 16.5 and 17.2 percent while those in FEF25-75% were 16.5, 15.6, 14.8, 15.4, 16.9 and 17.0 percent. No relationship could be observed between PDACH and resting Gaw/VL, SLDRC-H and magnitude of CP-induced bronchodilatation (Tables 2 and 3, Fig 2; [p>0.05]).

The DR-H after CP was different from that after saline solution (p<0.01) and varied with the dose of CP presence of CP-induced bronchodilatation and subject group (Tables 2 and 3). The DR-H produced by the two lowest nonbronchodilating doses of CP (5.5 and 11.8 mg) were significantly different between themselves (Tables 2 and 3, p<0.05). Compared with the nonresponders (normal and asthmatic subjects), the responders (six asthmatic and one normal subject)
tended to display a higher DR-H after either one of these nonbronchodilating doses of CP. This tendency reached a significant level when DR-H after 11.8 mg CP was analyzed by the Mann-Whitney test (Table 3).

After pretreatment with 20.9 mg CP, DR-H was significantly higher in the six asthmatic and one normal responders than in the normal or normal and asthmatic nonresponders (p<0.03, by all statistical tests; Table 2). In either group of subjects, responders or nonresponders, DR-H after 20.9 mg CP was significantly higher than DR-H after 5.5 and 11.8 mg (p<0.05 by all statistical tests).

The fact that DR-H after a nonbronchodilating dose of CP was only marginally higher in responders than in nonresponders contrasts with the difference in PD40-H between these groups. This difference is striking when responders (mostly asthmatic subjects) are compared with normal nonresponders (p<0.05 by all statistical tests; Table 2) but persists when asthmatic nonresponders also are included in the nonresponder group. The difference in PD40-H between all responders and all nonresponders is significant by t tests (Student's or Steel-Torrie's); the probability value obtained by the Mann-Whitney test was only slightly higher than 5 percent (6 to 10 percent).

In the entire group of subjects in whom DR-H after CP was measured (ie, normal and asthmatic subjects, responders as well as nonresponders), PD40-H and DR-H after CP5 of CP11 were inversely related. This relationship persisted when PD40-H was related to DR-H after 20.9 mg CP in the pooled group of all nonresponders, normal or asthmatic subjects (Table 3). Multiple regression analysis revealed no additional interrelationship between the tests measured in this

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**Figure 2.** Scatter diagram of the peak Gav/Vt response to 20.9 μg inhaled CP and PD40-H in normal and asthmatic subjects. There is no correlation (p>0.05) between CP-induced bronchodilation measured as Gav/Vt post-CP and bronchial processing of H measured as PD40-H.

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**Figure 3.** The steepness and plateauing of dose-related responses to histamine (left panel) and insulin (right panel). The right panel, showing the pattern of dose-related responses to insulin when the postreceptor mechanism is normal vs hyporesponsive is the mirror image of the left panel showing the airway responses to H in normoresponsive vs hyperresponsive individuals.
study (i.e., resting Gaw/VT, PD_{A0}-H, SLDRC-H, DR-H and Gaw/VT after CP) [Tables 2 and 3]). The minimum and maximum %Gaw/VT recorded in this study for PD_{A0}-H (and SLDRC-H) calculation were 23 and 60, respectively. Thus, as the lowest %Gaw/VT was higher than 20 percent, two- and three-point log-dose responses to H were expected to have the same slope (4, 20, 24). With the exceptions noted before, Student’s t test, the robust t test and the Mann-Whitney test gave concordant results. Replacing PD_{A0} by log PD_{A0} did not change the statistical outcome.

**DISCUSSION**

**CP-Induced Bronchodilatation as an H_{1}-Receptor Mediated Event**

In responders, a reproducible, physiologically convincing and placebo-controlled airway response to CP inhalation suggests drug-induced bronchodilatation rather than a random change in airway caliper.

The anticholinergic (Fig 1), antiserotoninic and antilocal anesthetic properties of CP had probably a trivial, if any, role^{30,31} in this bronchodilatation. Consequently, this effect seems to be produced by the competition between the drug and bronchial H. Differences in the magnitude of bronchodilatation, patient population, intrinsic variability of physiologic measurements, and route of administration, rather than the selection of a physiologic test (Gaw/VT vs FEV\_1^{4,10}) may explain why H\_1 blockers administered intravenously can occasionally decrease bronchial sensitivity to ACH.\_4^{10}

**The H Signal: Abnormal Processing in the Bronchial Muscle of Asthmatic Subjects**

This conclusion is based on three lines of evidence: (1) The well known H hyperresponsiveness in asthma\_3^{31} (Tables 2 and 3). (2) The lack of relationship between PD_{A0}-H and SLDRC-H.\_4^{22} (Tables 2 and 3). (3) The borderline, almost flat, relationship between bronchial responsiveness to agonist (PD_{A0}-H) and the antihistaminic effect (DR-H) of nonbronchodilating doses of CP.

For normal receptors, the molar ratio between the concentration of agonist producing a standard response and the concentration of competitive antagonist blunting this response is constant.\_1^{19,22} In this study, the ratio of PD_{A0}-H to DR-H after nonbronchodilating doses of CP was 1:10 to 1:100 in normal subjects (Table 2). This is similar to that observed in vivo for organs that in asthmatics are normoresponsive to H, i.e., skin.\_3^{23} In contrast with normal subjects, the asthmatic subjects had a ratio of 1:10 to 1:100 (Table 3). Thus, in asthmatics the increase in bronchial smooth muscle sensitivity to agonist (H) is associated with practically no change in the sensitivity to competitive antagonist (CP). Allowing for the lack of direct biochemical proof for this abnormality, I think that the abnormality is real and not factitious: the subjects had reproducible H responses; CP did not affect the airway caliber; the ratio PD_{A0}-H/DR-H was comparable after two nonbronchodilating doses of this antagonist C\_2 and C\_11, and was not influenced by another test of drug-receptor interaction, SLDRC-H. The abnormal function of bronchial H\_1 receptor-transducer accounts for some important aspects of H\_1 blocker-induced bronchodilatation and offers a new explanation for H hyperresponsiveness in asthma.

In vivo CP-induced bronchodilation may not represent the unmitigated result of the interaction between CP and H. Obviously, CP-induced bronchodilation implies the presence of bronchial H, as was previously noted in the “Discussion” of this article, but data suggest an additional modulatory effect of the H\_1 receptor. This complicates the relationship between bronchial H and H\_1 blocker-induced bronchodilation. For instance, the hyperresponsiveness of H\_1 receptor-transducer may explain why asthmatic rather than normal subjects respond to drugs blocking the action of bronchial H on bronchial muscle. The low DR-H in asthma, inappropriately low for the level of PD_{A0}-H justifies the empiric observation that high doses of H\_1 blockers are needed in asthma for bronchodilation or antiallergic effects.\_1^{2,11} Unless very potent agents are given orally,\_1 other high doses require intravenous or inhalation routes.\_1^{4,5,6,7,12,13} Another test of drug-receptor interaction, SLDRC-H, is apparently irrelevant to H\_1 blocker-induced bronchodilation, since the competitive action of different CP doses is not influenced by the steepness of these slopes. Similar to the bronchial response produced by other agents, the resting airway caliper can modulate the magnitude of airway responses to CP in responders, i.e., in subjects with a tonic concentration of bronchial H. However, bronchial caliper cannot separate responders from nonresponders (1, 2, 6, and 7 vs 10 and 12; [Table 2]) because the nonresponders may be a mixed group; some may have a low concentration of bronchial H while others may display a low degree of H responsiveness.

The type of abnormal function of bronchial H\_1 receptor-transducer system observed in asthma suggests that in this disease the latter, not the former, component is hyperresponsive. In the absence of direct experimental measurements of the H\_1 receptor-transducer function and pharmacologic modelling one has to contend with a working hypothesis. I suspect that in mild forms of asthma the postreceptor (transducer) rather than the H\_1 receptor fragment is hyperactive; additionally in advanced forms of disease, the receptor itself may become abnormal, in terms of number or affinity for H or both. The arguments are consistent with our current understanding of drug...
receptor interaction: (1) An increase in the number of H₁ receptors or their affinity for H in asthma should make SLDRC-H steeper in patients with this disease than in normal subjects. This happens, however, only in advanced asthma. (2) A pre-H₁ receptor hyperresponsiveness via cholinergic reflexes is highly unlikely. (3) A postreceptor hyperresponsiveness with (initially) a normal receptor number or affinity for H or both can account for the pharmacologic abnormalities found in asthma: (a) hyperresponsiveness to agonist; (b) normal graded responses to H (as shown by SLDRC-H) or CP + H (as shown by an almost normal rate of increase in DR-H from CP₃ to CP₁₁ and, in nonresponders, CP₆₀ as well); (c) inappropriately high doses of CP needed to overcome the effect of H on hypersensitive postreceptor regulatory proteins (ie, inappropriately high DR-H after single nonbronchodilating doses of CP); (d) the elevation of the normal plateau of H bronchoconstriction response. Note that a figure from an article by Woolcock et al²⁵ (left panel, Fig 3) is the mirror image of the early plateauing and flattening of dose-related responses to insulin in the case of diabetes mellitus associated with postreceptor hypersensitivity (right panel, Fig 3). If for H bronchoconstriction the latter type of response is considered to represent normality, the hyperresponsiveness of the postreceptor mechanism in asthma would lead to the elevation and eventual desparation of the response plateau. This model also accounts for the increase in the SLDRC-H steepness with the increase in the severity of asthma. Such a concept could explain better the diffuse hyperresponsiveness to constrictor agents in asthma than a discrete, simultaneous involvement of all the bronchial smooth muscle receptors. Actually a postreceptor mechanism recently has been postulated in the cholinergic hyperresponsiveness of asthmatics and the correlation of H and ACH responses.²²

**Distribution of Endogenous H Along Bronchial Tree and Its Role in Resting Bronchial Tone and Airway Caliber**

Endogenous bronchial H seems to be preferentially located in the large bronchi, since in responders, CP₆₀ usually leads to ΔGaw/VL > 40 percent without associated FEF (five of seven subjects, Tables 2 and 3). This does not reflect the gradient of H₁ receptors as measured by bronchial responsiveness to exogenous H; in the same subjects, exogenous H produces a convincing ΔFEF for a lower ΔGaw/VL (ie, - 40 percent). Such a longitudinal gradient of bronchial H may not be seen universally in mild asthma because subject 3 (Table 2) exhibits an isolated small airway response while other subjects, possibly with more severe asthma, respond with both large and small airway bronchodilation (subject 4, Table 2). From a practical standpoint this means that although Gaw/VL and FEF have been used interchangeably or in parallel to document H₁ blocker-induced bronchodilation, the former test is more sensitive than the latter.

Bronchial H apparently, because of its low concentration, plays a mild and inconsistent role in bronchial tone at rest. Indeed, the antihistaminic effect of two nonbronchodilator doses of CP (CP₅₀ and CP₁₀₀) was similar in responders and nonresponders despite their different reaction to a higher CP dose (CP₂₀₀). Stated differently, this means that small doses of CP are capable of blunting the effect of exogenous H, but larger doses of this antagonist are needed to compete with endogenous H and thereby dilate the bronchi. Thus, for H₁ blocker-induced bronchodilatation the small concentration of bronchial H compounds the negative influence exerted by the function of H₁ receptor-transducer, namely the influence of H responsiveness and DR-H. This small concentration of bronchial H shows a substantial interindividual variability since asthmatic subjects with similar function of the H₁ receptor-transducer may not necessarily respond to CP₂₀₀ (Fig 2).

The bronchial responses mediated via muscarinic and H₁ receptor-transducers appear to be interrelated-at postreceptor level?-²² while ACH and H are equipotent in equimolar doses both in vitro and in vivo.²² However, the bronchial concentration of the former is much larger than that of the latter because unlike CP, atropine has a similar bronchodilating effect in both normal and asthmatic subjects and its antimuscarinic effect is invariably associated with bronchodilatation.²²

The asthmatic responders and nonresponders had similar PD₆₀-H SLDRC-H and DR-H after nonbronchodilating doses of CP and resting Gaw/VL, despite widely different responses to straight CP. Consequently, the function of bronchial receptor-transducer, the resting airway caliber and the low concentration of bronchial H appear to be regulated independently of each other. This may explain, to a large extent, why no respiratory physiologic, pharmacologic or demographic measurement can predict a bronchodilator response to CP. That a single mediator may not fully control the resting airway caliber and the function of its bronchial receptor, let alone the function of other receptors—as previously theorized—²¹ reduces considerably the effectiveness of competitive antagonist treatment in asthma.

The major limitations of the study are the nonepidemiologic methods applied in the selection of subjects and the fact that the pharmacologic tests have not been complemented by appropriate biochemical measurements of bronchial H and function of H₁ receptor-transducer. At the present time, these logistic and technical limitations are difficult if not impossible
to overcome in humans. They do confer, however, hypothetical character to the pharmacologic explanations of the data.

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