Allergic Bronchospasm and Airway Hyperreactivity in the Guinea Pig

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Received February 10, 1993 Accepted July 1, 1993

ABSTRACT—In passively sensitized guinea pigs, slow infusion of an amount of ovalbumin insufficient to evoke airway obstruction induces hyperreactivity of the airways. A wide range of changed responsivity was observed for different test spasmogens, with leukotriene C₄ > histamine > prostaglandin F₂α > bradykinin > leukotriene E₄ > serotonin > acetylcholine. Injection of ovalbumin as a bolus produced pronounced airway obstruction without hyperreactivity. Airway obstruction due to vascular engorgement (dextran infusion) or edema (histamine infusion) did not result in hyperreactivity. Infusion of PAF induced pronounced airway obstruction together with hyperreactivity, but with a rank order of histamine > leukotriene C₄ > serotonin > bradykinin > leukotriene E₄ > acetylcholine. It can be concluded that allergic airway hyperreactivity in the guinea pig is spasmogen-selective and largely independent of airway obstruction. These observations question the presumption of non-selective hyperreactivity in allergic asthma and cast doubt upon the proposal that airway hyperreactivity is secondary to airway obstruction.

Keywords: Bronchoconstriction, Hyperreactivity (airway), Platelet activating factor, Passive sensitization

Sensitized guinea pigs respond to allergen with acute allergic bronchospasm that may be sufficiently intense to cause obstruction of airflow and death. It might be presumed that hyperreactivity to allergic mediators contributes to allergic bronchospasm; however, allergic hyperreactivity remains poorly defined in the guinea pig, even though this phenomenon is well documented for irritants (1–3), drugs (4–7) and inflammatory mediators (8, 9). Thus, no increased responsivity to acetylcholine or histamine was detected in actively sensitized guinea pigs (10), yet hyperreactivity of the airways to inhaled histamine was reported to follow anaphylactic microshock (11).

Conflicting results may have arisen because of differing sensitization procedures, use of particular test spasmogens, confounding effects of systemic hypotension, anoxia and persisting airway obstruction. The present study has defined conditions which allow reproducible induction of allergic airway hyperreactivity and has investigated the extent to which acute airway obstruction, mast cell activation, smooth muscle spasmogen characteristics and immunoglobulin category determine the intensity of acute airway hyperreactivity in this species.

MATERIALS AND METHODS

Materials

Al(OH)₃ (Merck, Darmstadt, Germany); OA, histamine dihydrochloride and ACh iodide (Fluka, Buchs, Switzerland); 5-HT creatinine sulfate and PGF₂α (Sigma, Buchs, Switzerland); BK (Bachem, Budendorf, Switzerland); PAF (Novabiochem, Laiufelfingen, Switzerland); sodium pentobarbitone and sodium phenobarbitone (Siegfried, Zofingen, Switzerland); gallamine triethiodide (Davis-Geck, New York, NY, USA); dextran (Pharmacia, Dübendorf, Switzerland); and Bordetella pertussis vaccine (IMPF, Bern, Switzerland) were commercial preparations. LTC₄ (purity >95%) and LTE₄ (purity >90%) were synthesized.

Abbreviations used are: Al(OH)₃, aluminum hydroxide; OA, Ovalbumin; ACh, acetylcholine; 5-HT, serotonin; PGF₂α, prostaglandin F₂α; BK, bradykinin; PAF, platelet-activating factor; LTC₄, leukotriene C₄; LTE₄, leukotriene E₄; R₂, airway resistance; Cdyn, dynamic compliance; SR, slope ratio; IgE, immunoglobulin E; IgG, immunoglobulin G.
Animals

Male adult Dunkin Hartley guinea pigs (450–650 g body weight; WIGA, Charles River, Sulzfeld, Germany) were used throughout. Animals, which were housed in groups of 4–6, received food and water ad libitum. All experimental procedures were approved by the "Kantonalen Tierversuchs-Kommission von Basel-Stadt und Basel-Land". Guinea pigs were anesthetized by intraperitoneal injection of sodium phenobarbitone (100 mg/kg) supplemented with sodium pentobarbitone (30 mg/kg) and paralyzed by intramuscular injection of gallamine (10 mg/kg).

Surgical and experimental procedures

Animals were ventilated (8 ml/kg, 1 Hz) with a mixture of air and oxygen (40 : 60, v/v) via a tracheal cannula. Ventilation was monitored at the trachea by a pneumotachograph (Fleisch type 0000; Zabona, Basel, Switzerland) connected to a differential pressure transducer (MP 4514871; Validyne, North Reading, MA, USA). Coincident pressure changes within the thorax were measured via an intrathoracic cannula, using a differential pressure transducer (MP 4524, Validyne), so that the pressure difference between the trachea and thorax could be measured and displayed. To monitor the physiological status of the animal during experimental investigations, the blood pressure and heart rate were recorded from the carotid artery by a pressure transducer (Isotec; Hugo Sachs, Freiburg, Germany); and a cannula was introduced into the right jugular vein to allow intravenous infusion of agents that influence airway reactivity and thorax and heart rate could be measured and displayed. To monitor the physiological status of the animal during experimental investigations, the blood pressure and heart rate were recorded from the carotid artery by a pressure transducer (Isotec; Hugo Sachs, Freiburg, Germany); and a cannula was introduced into the right jugular vein to allow intravenous infusion of agents that influence airway reactivity and into the left jugular vein, for administration of test spasmodens. To achieve a uniform rate of injection, test materials (e.g., spasmogen) were injected intravenously in a volume of 0.2 ml to occupy the dead space in the canula. This was followed by saline (0.5 ml over 30 sec) at a constant rate (1 ml/min) from an infusion pump (Perfusion IV; Bender & Hobein, Zürich, Switzerland). From measurements of air-flow and transpulmonary pressure, both R_l and C_dyn were calculated after each respiratory cycle using a digital electronic pulmonary monitoring system (PMS; Mumed, London, UK) which displayed blood pressure, intrathoracic pressure and airflow and computed R_l and C_dyn in real time for display on a visual display unit (Premium II 486/33; AST, Irvine, CA, USA). Experimental data were stored electronically, and experimental traces or processed data were plotted on a laser jet printer (Laser Jet Series II; Hewlett Packard, Palo Alto, CA, USA).

Dextran (6%, 20 ml) or histamine (3 µg/kg/min, 4 ml) were infused intravenously over 30 min; PAF (600 ng/kg, 6.34 ml) was infused in three successive aliquots (30 ng/kg, 0.32 ml, 10 min; 120 ng/kg, 1.27 ml, 20 min; 450 ng/kg, 4.75 ml, 30 min); OA (32 µg/kg, 3 ml) was infused for 60 min or injected as a bolus (32 µg/kg in 0.2 ml plus saline 0.5 ml) in animals that had been sensitized 1–14 days earlier by intravenous injection of 1.0 ml of serum collected from animals exposed to OA (10 µg) admixed with Al(OH)₃ (10 mg) and injected together with Bordetella pertussis (0.25 ml) 21 and 7 days prior to collection of the blood and separation of the serum. Seven days after intradermal injection of antiserum, PCA reactions (mm diameter) (n=5) were: 15, 12, 6, 0 and 0 when the serum had been heated (56°C for 4 hr) as compared with > 30, > 30, 25, 22 and 20 when the serum was not heated.

Intravenous injection of bolus doses of 5-HT (1.0–3.2 µg/kg), PGF₂α (32–100 µg/kg), ACh (3.2–18 µg/kg), histamine (0.56–1.8 µg/kg), LTC₄ (56–320 ng/kg) or LTE₄ (180–560 ng/kg) at 10-min intervals or BK (0.32–3.2 µg/kg) at 30-min intervals, were used to ascertain the sensitivity of airway smooth muscle. These procedures were repeated 10 min after termination of an intravenous infusion of dextran, histamine or antigen or 20 min after intravenous infusion of PAF.

Data presentation and statistics

Responses to test spasmogens have been expressed as incremental increased resistance (dR_l) and decremental decreased compliance (dC_dyn), being the maximal change less the basal value prior to injection of spasmogen. Airway responsivity to intravenous spasmogens has been estimated as the dose-effect slope for R_l (cmH₂O/l/sec) over a log₁₀ dose-metameter, using RS1 (BBN Software Product Corporation, Cambridge, MA, USA), which estimates the slope by least squares regression and indicates linearity by statistics. For the purpose of comparison, sensitivity has been expressed as an SR (dose-effect slope after treatment/dose-effect slope before treatment). Statistical significance of differences observed have been assessed by Student's t-test.

RESULTS

Airway obstruction following injection of ovalbumin

Animals that had been sensitized by intravenous injection of antiserum 1 day earlier responded to injection of OA (32 µg/kg, i.v.) with acute airway obstruction (dR_l 467.5 ± 90.8 cmH₂O/l/sec, dC_dyn −0.54 ± 0.05 ml/cmH₂O). In animals that had been sensitized 7 days earlier, bolus injection of OA (32 µg/kg, i.v.) produced a similar decrease of dynamic compliance (dC_dyn −0.56 ± 0.06 ml/cmH₂O), yet increased airway resistance (dR_l 161.8 ± 47.0 cmH₂O/l/sec) was significantly (P < 0.05) less than that in animals tested 1 day after sensitization. This marked difference implies that whereas mediator release to cause edema in the lung periphery might be similar in the two...
situations, the release or action of mediators in the large airway was substantially different at the two times. The latency (<10% of maximum RL) and time to maximal response were similar in both groups of animals, but reactions to OA were significantly (P <0.002) slower than subsequent responses to histamine (1.8 μg/kg, i.v.) (Table 1).

### Table 1. The latency to onset (<10% of maximum response) and maximal response (RL) following intravenous injection of OA (32 μg/kg) or histamine (1.8 μg/kg) in naive animals and in animals passively sensitized 1 or 7 days prior to study

<table>
<thead>
<tr>
<th>Sensitization</th>
<th>n</th>
<th>OA (32 μg/kg)</th>
<th>OA</th>
<th>Histamine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>OA</td>
<td>latency</td>
<td>maximum</td>
</tr>
<tr>
<td>Naive</td>
<td>5</td>
<td>INJ</td>
<td>11.5 ± 4.5</td>
<td>N.D.</td>
</tr>
<tr>
<td>1 Day</td>
<td>5</td>
<td>INJ</td>
<td>467.5 ± 90.8***</td>
<td>1.5 ± 0.3</td>
</tr>
<tr>
<td>7 Day</td>
<td>10</td>
<td>INJ</td>
<td>161.8 ± 47.0**</td>
<td>2.0 ± 0.3</td>
</tr>
<tr>
<td>7 Day</td>
<td>10</td>
<td>INF</td>
<td>6.9 ± 3.0</td>
<td>N.D.</td>
</tr>
</tbody>
</table>

N.D., not detectable; INJ, injection as a bolus; INF, infusion over 1 hr. Significant differences: ***(P <0.001), ***(P <0.001) in comparison with naive animals.

Altered responsivity to histamine following infusion of OA

In animals that had been sensitized 7 days earlier, responsivity to histamine (0.56–1.8 μg/kg, i.v.) was determined immediately before and 10 min after the infusion of OA (0–320 μg/kg for one hour). Incremental increased responsivity to histamine was detected when the dose of OA exceeded 10 μg/kg, but responsivity was not significantly increased (P <0.05) for doses less than 32 μg/kg (Fig. 1). Variation of the interval between sensitization and infusion of OA (32 μg/kg) revealed that sensitivity to histamine increased progressively, but was not significantly increased (P <0.05) earlier than 3 days after sensitization (Fig. 2). In animals passively sensitized 1 or 7 days earlier, intravenous injection of the same quantity of OA as a bolus evoked acute bronchospasm, without attendant hyperreactivity to histamine (Table 1).

Altered responsivity to different spasmogens following infusion of OA

In animals that had been sensitized 7 days earlier, infusion of OA (32 μg/kg/hr) increased the sensitivity to histamine (0.56–1.8 μg/kg), so that the slope (log10 dose-metamer) of the dose-effect relationship increased from 144.0 cmH2O/l/sec to 455.5 cmH2O/l/sec, giving a slope

![Fig. 1. Incremental increased responses (ΔRl) to intravenous injection of histamine (0.56 μg/kg, closed bar; 1.0 μg/kg, open bar; 1.8 μg/kg, hatched bar) following intravenous infusion of increasing doses of OA (μg/kg) over 1 hr (n=6 in each instance). Significant differences: *(P <0.05), ***(P <0.01), ***(P <0.001) in comparison with the corresponding responses following infusion of saline (dose 0).](image1)

![Fig. 2. Incremental increased airway resistance in responses to intravenous injection of histamine (0.56 μg/kg, closed bar; 1.0 μg/kg, open bar; 1.8 μg/kg, hatched bar) following intravenous infusion of OA (32 μg/kg) over 1 hr (n=6 in each instance) at daily intervals after sensitization by intravenous injection of antiserum. Significant differences: *(P <0.05), ***(P <0.01), ***(P <0.001) in comparison with the corresponding responses in naive animals (time 0).](image2)
ratio of 3.16 (n=10). Corresponding experiments with other spasmsgogens revealed a wide range of changed responsivity, with substantially increased responsivity for allergic spasmsgogens such as LTC₄ (SR = 5.48, n=10), PGF₂α (SR=3.11, n=10), BK (SR=2.70, n=10) and LTE₄ (SR = 2.51, n =10), yet little change in responsivity to 5-HT (SR=1.31, n=10) or ACh (SR=1.13, n=10) (Table 2). Compliance changes following infusion of OA (32 pg/kg/hr) were small and inconsistent (Table 3), and dose-related compliance changes to injected spasmsgogens after infusion of OA were only detected using PGF₂α or 5-HT.

**Airway obstruction and airway hyperreactivity**

In anesthetized ventilated guinea pigs, infusion of dextran (40 ml/hr) causes vascular engorgement and hence physical occlusion of the airways. By 30 min, airway resistance and dynamic compliance had changed substantially (Table 3), yet sensitivity to histamine (SR =1.21, n =10) was similar to that observed following infusion of saline (SR =1.50, n=10). Intravenous infusion of histamine (3 μg/kg/min) over 30 min produced edema of the airways with substantial and maintained increased airway resistance and decreased dynamic compliance (Table 3). Nonetheless, airway responsivity to ACh (SR=0.88, n=10) was less than that in animals exposed to an infusion of saline (SR =1.23, n=10). For LTC₄ there was reduced responsivity (SR =0.64, n=10), but this was not as marked as the reduction following the infusion of saline (SR =0.19, n=10).

In clinical asthma, changed responsivity following IgE-mediated reactions has been attributed to the release of allergic mediators; however, of the known allergic mediators, only PAF has been shown to effect sustained airway hyperreactivity in the guinea pig under the test conditions employed. Intravenous infusion of PAF caused increased airway resistance and decreased dynamic compliance (Table 3), with increased responsivity to histamine (SR =2.67, n=10), LTC₄ (SR =2.53, n=10), 5-HT (SR =2.15, n=10) and, to a lesser extent, bradykinin (SR =1.45, n=10) and LTE₄ (SR =1.20, n=10), while responsivity to ACh (SR =0.87, n=10) was diminished (Table 4). No dose-related decremental decrease of dynamic compliance was observed for any of the spasmsgogens tested.

### Table 2. Mean incremental increased Rₓ in response to intravenous injection of airway spasmsgogens at three dose levels, before (Rₓ pre) and after (Rₓ post) intravenous infusion of OA (32 μg/kg) over 1 hr (n = 10 in each instance)

<table>
<thead>
<tr>
<th>Spasmsgogen</th>
<th>Rₓ pre low</th>
<th>Rₓ pre middle</th>
<th>Rₓ pre high</th>
<th>Rₓ post low</th>
<th>Rₓ post middle</th>
<th>Rₓ post high</th>
<th>Slope ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>LTC₄</td>
<td>5.7±0.6</td>
<td>14.1±4.7</td>
<td>74.9±40.2</td>
<td>101.2±26.0</td>
<td>324.4±78.1</td>
<td>479.1±73.1</td>
<td>5.48</td>
</tr>
<tr>
<td>Histamine</td>
<td>8.7±1.5</td>
<td>25.6±5.0</td>
<td>81.6±16.1</td>
<td>50.8±10.4</td>
<td>118.0±22.6</td>
<td>281.5±45.8</td>
<td>3.16</td>
</tr>
<tr>
<td>PGF₂α</td>
<td>15.4±2.7</td>
<td>45.8±12.7</td>
<td>107.1±46.5</td>
<td>28.8±5.2</td>
<td>89.7±28.1</td>
<td>312.1±120.0</td>
<td>3.11</td>
</tr>
<tr>
<td>Bradykinin</td>
<td>19.4±4.5</td>
<td>71.6±14.0</td>
<td>160.4±40.7</td>
<td>106.3±28.8</td>
<td>213.2±45.0</td>
<td>487.1±83.7</td>
<td>2.70</td>
</tr>
<tr>
<td>LTE₄</td>
<td>5.1±0.8</td>
<td>13.3±2.8</td>
<td>95.0±28.1</td>
<td>25.8±8.1</td>
<td>111.5±32.2</td>
<td>250.7±46.2</td>
<td>2.51</td>
</tr>
<tr>
<td>5-HT</td>
<td>9.6±1.7</td>
<td>39.2±10.1</td>
<td>234.8±58.7</td>
<td>20.9±5.7</td>
<td>108.8±31.4</td>
<td>315.3±67.6</td>
<td>1.31</td>
</tr>
<tr>
<td>Acetylcholine</td>
<td>13.2±5.0</td>
<td>47.3±12.5</td>
<td>178.2±28.0</td>
<td>38.3±9.7</td>
<td>89.1±21.9</td>
<td>224.5±41.1</td>
<td>1.13</td>
</tr>
</tbody>
</table>

Doses of LTC₄ (100, 180, and 320 ng/kg), histamine (0.56, 1.0, and 1.8 μg/kg), PGF₂α (32, 56, and 100 μg/kg), bradykinin (0.32, 1.0, and 3.2 μg/kg), LTE₄ (180, 320, and 560 ng/kg), 5-HT (1.0, 1.8, and 3.2 μg/kg), and acetylcholine (5.6, 10.0, and 18.0 μg/kg) were used.

### Table 3. Effects of treatments on basal Rₓ and Cₓ dyn

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rₓ pre</th>
<th>Rₓ post</th>
<th>Rₓ difference</th>
<th>Cₓ dyn pre</th>
<th>Cₓ dyn post</th>
<th>Cₓ dyn difference</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>91.1±1.7</td>
<td>93.6±1.8</td>
<td>2.5±1.1</td>
<td>0.93±0.02</td>
<td>0.88±0.02</td>
<td>-0.05±0.01</td>
<td>80</td>
</tr>
<tr>
<td>Dextran</td>
<td>86.2±2.7</td>
<td>129.4±4.8</td>
<td>43.2±3.6***</td>
<td>0.87±0.03</td>
<td>0.41±0.02</td>
<td>-0.46±0.03***</td>
<td>20</td>
</tr>
<tr>
<td>Histamine</td>
<td>86.7±3.6</td>
<td>159.1±7.9</td>
<td>72.4±7.6***</td>
<td>0.84±0.04</td>
<td>0.52±0.03</td>
<td>-0.32±0.03***</td>
<td>20</td>
</tr>
<tr>
<td>Antigen infusion</td>
<td>94.6±2.0</td>
<td>102.8±2.8</td>
<td>8.1±2.2*</td>
<td>0.97±0.03</td>
<td>0.96±0.03</td>
<td>-0.01±0.03</td>
<td>80</td>
</tr>
<tr>
<td>PAF</td>
<td>97.2±2.6</td>
<td>120.7±3.9</td>
<td>23.7±3.2***</td>
<td>0.87±0.03</td>
<td>0.60±0.02</td>
<td>-0.27±0.02***</td>
<td>60</td>
</tr>
</tbody>
</table>

Significantly different from saline treatment: *P<0.05, ***P<0.001.
Table 4. Mean incremental increased $R_i$ in response to intravenous injection of airway spasmogens at three dose levels, before ($R_i$ pre) and after ($R_i$ post) intravenous infusion of PAF (600 ng/kg) over 1 hr ($n = 10$ in each instance)

<table>
<thead>
<tr>
<th>Spasmogen</th>
<th>$R_i$ pre</th>
<th></th>
<th>$R_i$ post</th>
<th></th>
<th>Slope ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>low</td>
<td>middle</td>
<td>high</td>
<td>low</td>
<td>middle</td>
</tr>
<tr>
<td>Histamine</td>
<td>24.1 ± 8.1</td>
<td>47.2 ± 14.5</td>
<td>167.2 ± 47.3</td>
<td>84.1 ± 26.4</td>
<td>173.1 ± 29.7</td>
</tr>
<tr>
<td>LTC₄</td>
<td>5.3 ± 1.0</td>
<td>9.4 ± 2.4</td>
<td>57.7 ± 21.7</td>
<td>24.7 ± 9.5</td>
<td>61.1 ± 28.7</td>
</tr>
<tr>
<td>5-HT</td>
<td>11.6 ± 2.7</td>
<td>73.9 ± 20.0</td>
<td>331.5 ± 56.0</td>
<td>55.7 ± 14.3</td>
<td>224.2 ± 66.8</td>
</tr>
<tr>
<td>Bradykinin</td>
<td>18.4 ± 4.0</td>
<td>102.4 ± 16.0</td>
<td>279.0 ± 49.6</td>
<td>75.9 ± 23.8</td>
<td>273.1 ± 63.8</td>
</tr>
<tr>
<td>LTE₄</td>
<td>7.9 ± 1.6</td>
<td>18.4 ± 2.7</td>
<td>164.9 ± 29.3</td>
<td>9.8 ± 1.3</td>
<td>20.6 ± 6.6</td>
</tr>
<tr>
<td>Acetylcholine</td>
<td>93.6 ± 37.4</td>
<td>299.0 ± 86.7</td>
<td>736.0 ± 169.6</td>
<td>72.7 ± 15.7</td>
<td>219.1 ± 45.0</td>
</tr>
</tbody>
</table>

Doses of histamine (0.56, 1.0, and 1.8 µg/kg), LTC₄ (100, 180, and 320 ng/kg), 5-HT (1.0, 1.8, and 3.2 µg/kg), bradykinin (0.32, 1.0, and 3.2 µg/kg), LTE₄ (180, 320, and 560 ng/kg), and acetylcholine (5.6, 10.0, and 18.0 µg/kg) were used.

IgE and allergic hyperreactivity

The method used for generation of antiserum in this study has been reported to evoke IgE formation in this species (12). To ascertain whether IgE-mediated responses contributed to acute allergic bronchospasm or allergic hyperreactivity, serum was heated for 4 hr at 56°C, prior to intravenous injection. Animals that received heated serum 7 days before injection of OA (32 µg/kg/hr) had significantly (P<0.05) smaller responses to histamine (1.8 µg/kg) than had been observed in animals receiving unheated serum (Fig. 3).

DISCUSSION

The present study has confirmed that acute allergic bronchospasm in the guinea pig is not necessarily associated with airway hyperreactivity (10) and that minimal allergic reactions are associated with expression of airway hyperreactivity (11). The inability of acute allergic bronchospasm to lead to expression of airway hyperreactivity cannot be attributed to suppression of airway responses by endogenous hormones (such as adrenaline or glucocorticosteroids), since there was no impairment of responsivity to histamine in these animals; moreover, comparable acute airway obstruction following infusion of PAF was accompanied by unequivocal airway hyperreactivity. It follows that neither sensitization per se nor activation of mast cells to produce acute allergic bronchospasm provide a basis for airway hyperreactivity in this species.

Sensitization over several days and slow infusion of OA consistently induced increased responsivity to histamine. Slow infusions of OA, 1 day after sensitization, did not lead to changed responsivity to histamine, even though such animals exhibited more intense reactions to injection of OA as a bolus than did animals tested 7 days after sensitization. These observations imply that the process of passive sensitization is accompanied by a parallel event which modifies the response to antigen in sensitized cells. Processes such as receptor cross-talk between IgG and IgE molecules during interaction with antigen which might account for this phenomenon have yet to be investigated. Whatever mechanism accounts for this prolonged latency, it is not peculiar to IgE.

It is widely accepted that non-selective airway hyperreactivity might be expected when airways narrow (13, 14). In the present study, substantial airway obstruction has been effected by vessel engorgement following intravenous infusion of dextran and by edema due to intra-
venous infusion of histamine. In neither instance was noteworthy increased responsivity of the airways detected. The implied lack of association between airway responsivity and airway obstruction was strongly reinforced by investigation of the allergic reaction. Thus, injection of antigen as a bolus evoked airway obstruction without changed responsivity to histamine, whereas injection of the same dose of antigen by slow infusion increased responsivity to histamine in the absence of airway obstruction, albeit only when recipient animals had been sensitized several days earlier.

An alternative test of the concept that airway obstruction determines airway hyperreactivity was to investigate the presumption that hyperreactivity of the airways is non-selective. By extending the range of test spasmogens, it was evident that manifestation of hyperreactivity was determined by the test spasmogen. For allergic hyperreactivity, these differences were not slight; and in comparison with the infusion of saline, exposure to antigen yielded changes of responsivity that ranged between less than 10% and more than 2500%. The rank order of spasmogen responsivity following an allergic reaction may provide a more stringent criterion (15) for identification of autacoids as mediators of allergic hyperreactivity. For instance, the present study revealed that infusion of PAF led to hyporeactivity if acetylcholine was the test spasmogen and showed that in comparison with antigen, there was less intense airway hyperreactivity to all other test spasmogens, with the exception of serotonin. Hence, the rank order of spasmogen sensitivity after infusion of PAF was distinct from that observed following an allergic reaction.

It can be concluded that in the anesthetized ventilated guinea pig, increased responsivity to airway spasmogens is a selective process. Heterogeneity of airway hyperreactivity cannot be a direct consequence of airway obstruction, being evident in animals that show profound airway obstruction (as following infusion of PAF) and in animals that exhibited no overt airway obstruction (as following an infusion of antigen). In these circumstances, it is possible that vagal reflexes contributed to increased responsivity of the airways, since airway hyperreactivity due to infusion of (±)isoproterenol (5), ozone (2), antigen (16), immune complex deposition or infusion of neuropeptides (J. Morley et al., unpublished observations) are pre-empted or diminished by bilateral vagal section. No subcellular mechanism has been defined to account for increased airway responsivity in the guinea pig; however, intracellular recording from bronchial neurons has revealed membrane depolarization and enhanced excitability of these cells following exposure to antigen (17), a phenomenon which could account for the differential increased responsivity of airway smooth muscles to spasmogens.

This study has demonstrated that expression of an acute allergic reaction was insufficient to account for airway hyperreactivity in the guinea pig, which is consistent with the clinical finding that suppression of acute manifestations of the allergic response is not necessarily accompanied by diminished hyperreactivity (18, 19) and the lack of clinical efficacy of compounds selected as antiasthma drugs by reference to acute allergic reactions (20). Observation of changed responsivity to inhaled spasmogens following inhalation of allergen is a widely used technique for studying the airway hyperreactivity in clinical asthma. Heterogeneity of airway hyperreactivity in this situation is not yet established, but seems likely since substantial (20- to 30-fold) and protracted (2-4 weeks) increased responsivity to bradykinin cannot be accommodated with the coincidental slight (2- to 3-fold) and transient (1-2 days) changed responsivity to methacholine that follows inhalation of allergen (21). Hence, use of histamine or methacholine sensitivity could be misleading when surveying sensitivity of the airways or sensitivity of airway hyperreactivity to therapeutic agents (22, 23). It is to be hoped that these animal studies will prompt a definition of the pattern of airway reactivity to different spasmogens in allergic asthma, since such observations may allow identification of a pivotal mediator of this phenomenon.

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