A possible role for PAF in allergen-induced late responses: modification by a selective antagonist

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ABRAHAM, WILLIAM M., JEFFREY S. STEVENSON, AND REY GARRIDO. A possible role for PAF in allergen-induced late responses: modification by a selective antagonist. J. Appl. Physiol. 66(5): 2351–2357, 1989.—We determined whether platelet-activating factor (PAF) plays a role in allergen-induced airway responses by studying the effects of a selective PAF antagonist WEB-2086 on antigen-induced early and late airway responses in allergic sheep. In seven sheep, inhaled Ascaris suum produced significant early (282%) and late (176%) increases in specific lung resistance (sRL). WEB-2086 (1 mg/kg iv) given 20 min before antigen challenge did not affect the early response, but the peak late increase in sRL was only 37% over baseline (P < 0.05 vs. control). To study the mechanism by which PAF contributes to antigen induced responses, we evaluated the effects of pharmacological probes on PAF-induced bronchoconstriction. Inhaled PAF (dose range 75–700 pg) caused reproducible (r = 0.781, P < 0.05) increases in sRL in eight sheep. The PAF-induced bronchoconstriction was blocked by WEB-2086 (1 mg/kg iv) and by the leukotriene antagonist FPL-55712 (30 mg by aerosol); however, neither the cyclooxygenase blocker indomethacin (2 mg/kg iv) nor the histamine H1-antagonist chlorpheniramine (2 mg/kg iv) blocked the PAF response. WEB 2086, however, did not block bronchoconstriction induced by aerosol leukotriene D4, indicating that PAF acts indirectly through leukotrienes. Finally, we determined whether PAF could induce late airway responses. Inhaled PAF produced an immediate increase in sRL in all seven sheep tested, but late airway responses were observed in only three of the seven sheep. Our observations show that PAF may play a role in allergen-induced late responses in allergic sheep and that a large component of the PAF-induced response is mediated via spasmosgenic leukotrienes. These results support the possibility of sequential mediator activation in vivo.

leukotrienes; asthma; sheep model

PLATELET-ACTIVATING FACTOR (PAF) is a naturally occurring lipid autacoid produced by a variety of inflammatory cells, including but not limited to neutrophils, eosinophils, basophils, mast cells, and macrophages (for review, see Refs. 10 and 30). In addition to its profound systemic vascular effects (21, 27, 35), PAF is also considered a putative mediator of asthma. Inhaled PAF can produce bronchoconstriction (29, 34), prolonged airway hyperresponsiveness (16), and airway inflammation (15), all characteristic of asthma. PAF is a particularly potent chemotactic agent for eosinophils (15, 24), which are considered to be of primary importance in the development of late asthmatic responses (18) and airway hyperresponsiveness (15, 37). These observations strongly suggest a role for PAF in asthma and as such, the logical extension of this would be to determine the effects of selective PAF antagonists on allergen-induced airway responses, especially late asthmatic responses.

WEB-2086, a thienotriazolodiazapine derivative, is a selective PAF antagonist (11, 22, 31). The PAF antagonistic property of WEB-2086 is independent of the central nervous system actions associated with this class of compounds (12). WEB-2086 has been compared with other PAF antagonists including the naturally occurring ginkolides (e.g., BN-52021) in a variety of in vitro and in vivo PAF-dependent assays and was found to be two to ten times more potent than the other agents depending on the assay used (22). This increased potency was maintained in vivo whether the PAF-induced response was platelet dependent (e.g., guinea pig bronchoconstriction) or platelet independent (e.g., rat hypotension) (22). Of particular interest is a recent finding that WEB-2086 inhibited bronchial eosinophil influx 6 h after intravenous administration of both PAF and antigen in guinea pigs (24). Thus the drug may have a potential use in modifying allergen-induced late airway responses that may be mediated in part by eosinophils (18).

The purpose of this study was to determine whether PAF plays a role in allergen-induced early and late airway responses by studying the effect of WEB-2086 on these airway responses in an allergic sheep model (3) and by investigating the mechanism of PAF-induced airway responses in this model. We observed that pretreatment with the PAF antagonist WEB-2086 was capable of blocking antigen-induced late airway responses in allergic sheep and that this effect involved the prevention of PAF-related release of leukotrienes.

METHODS

All protocols used were approved by the Mount Sinai Medical Center Animal Research Committee that is responsible for assuring the humane care and use of experimental animals. A total of 24 adult sheep with a mean weight of 32 kg (range 25–48 kg) were used for these studies. All sheep had previously been shown to develop an early bronchoconstriction after inhalation challenge with A. suum antigen. The sheep that were used to determine the effects of WEB-2086 on antigen-induced late responses and those that were used to determine whether PAF induces late responses had previously been shown to develop both early and late bronchial responses
after inhalation challenge with *A. suum* antigen. The sheep were conscious throughout the procedures.

**Measurement of Airway Mechanics**

These methods have been described in detail previously (3). Briefly, the unsedated sheep were restrained in a cart in the prone position with their heads immobilized. After topical anesthesia of the nasal passages with 2% lidocaine solution, a balloon catheter was advanced through one nostril into the lower esophagus. The animals were then intubated with auffed endotracheal tube through the other nostril using fiberoptic bronchoscopy. (The cuff of the endotracheal tube was inflated only for the measurement of airway mechanics and during aerosol challenge to prevent undue discomfort. This procedure has no effect on airway mechanics.) Pleural pressure was estimated with the esophageal balloon catheter (filled with 1 ml of air), which was positioned 5–10 cm from the gastroesophageal junction. In this position the end-expiratory pleural pressure ranged between −2 and −5 cmH₂O. Once the balloon was placed, it was secured so that it remained in position for the duration of the experiment. Lateral pressure in the trachea was measured with a side-hole catheter advanced through and positioned distal to the tip of the endotracheal tube. Transpulmonary pressure, the difference between tracheal and pleural pressure, was measured with a differential pressure transducer (type DP-45; Validyne, Northridge, CA). Testing of the pressure transducer-catheter system revealed no phase shift between pressure and flow to a frequency of 9 Hz. For the measurement of pulmonary resistance (Rt), the proximal end of the endotracheal tube was connected to a pneumotachograph (Fleisch; Dyna Sciences, Blue Bell, PA). The signals of flow and transpulmonary pressure were recorded on an oscilloscope recorder (model DR-12; Electronics for Medicine, White Plains, NY) linked to a PDP-11 Digital computer (Digital Equipment, Maynard, MA) for on-line calculation of Rt from transpulmonary pressure, respiratory volume (obtained by integration), and flow. Analysis of at least five breaths was used for the determination of Rt. Immediately after the measurement of Rt, thoracic gas volume (Vtg) was measured in a constant volume body plethysmograph to obtain specific lung resistance (sRt = Rt · Vtg) in 1·cmH₂O·l⁻¹·s⁻¹.

**Aerosol Delivery Systems**

Aerosols of *A. suum* extract (82,000 PNU/ml) were generated by using a disposable medical nebulizer (Raindrop; Puritan Bennett), which produced an aerosol with a mass median aerodynamic diameter of 3.2 μm (geometric SD 1.9) as determined by a seven-stage Andersen cascade impactor. The output from the nebulizer was directed into a plastic T piece with one end attached to the endotracheal tube and the other end connected to the inspiratory port of a Harvard respirator. The aerosol was delivered at a tidal volume of 500 ml and a rate of 20 breaths/min for 20 min so that each sheep received 400 breaths of antigen for all challenges.

Aerosols of PAF and other agents used in these studies were also generated with the Raindrop nebulizer system described above. However, to better control the doses of the delivered agents, a dosimeter consisting of a solenoid valve and a source of compressed air (20 psi) was activated at the beginning of the inspiratory cycle of the Harvard respiratory system for 1 s. The aerosols were delivered at a tidal volume of 500 ml and a rate of 20 breaths/min.

**Agents.** The following agents were used in this study: *A. suum* antigen (Greer Diagnostics, Lenoir, NC) was diluted with buffered saline to a concentration of 82,000 PNU/ml. PAF (Calbiochem, La Jolla, CA) was dissolved in chloroform from which aliquots were taken for each experiment. On the day of the experiment, the chloroform was evaporated under N₂ and the PAF was resuspended in buffered saline containing 2.5 mg/ml ovine albumin (Sigma Chemical, St. Louis, MO). Synthetic leukotriene D₄ (Hyalom, Philadelphia, PA) was diluted with phosphate-buffered saline to a concentration of 50 μg/ml. The histamine H₂ antagonist chlorpheniramine was administered undiluted (2 mg/kg; Schering, Kenilworth, NJ). The prostaglandin synthetase inhibitor indomethacin (2 mg/kg; Merck Sharp & Dohme, West Point, PA) was dissolved in sodium carbonate and diluted in saline to 10 ml. The PAF agonist WEB-2086 (1 mg/kg; Boehringer Ingelheim) was first dissolved in 3 ml 0.1 N HCl, followed by the addition of 2.3 ml of 0.1 N NaOH and then saline to 10 ml. The leukotriene antagonist FPL-55712 (30 mg; Fisons, Loughborough, UK) was dissolved in 3 ml of bacteriostatic water to give a final solution of 1% wt/vol. The doses of chlorpheniramine (7, 26) and FPL-55712 (17) used in this study had previously been shown to be effective in blocking exogenously administered specific agonists or in the case of indomethacin (8), the drug has been shown to inhibit endotoxin-induced generation of cyclooxygenase products.

**Protocols**

**Effects of WEB-2086 on antigen-induced immediate and late responses.** In seven sheep, base-line sRt was measured and then the sheep were given an injection (1 mg/kg iv) of WEB-2086. sRt was remeasured and the sheep were challenged with *A. suum* antigen. sRt was measured immediately after challenge (0–10 min), hourly from 1 to 6 h, and half hourly from 6.5 to 8 h after challenge. On another occasion (≥14 days apart) the sheep were challenged with antigen without drug pre-treatment. The two protocols were randomized. The investigators were not blinded to the protocols.

**Effects of pharmacological agents on PAF-induced bronchoconstriction.** In eight sheep, between 75-700 μg PAF was delivered by aerosol. In each sheep PAF challenge was stopped when sRt had increased by at least 100% over base line and the dose of PAF noted (in one sheep sRt did not increase by 100%). On another occasion at least 1 day later, the dose of PAF determined on day 1 was readministered to the sheep and the change in sRt measured. Once it was determined that the PAF-induced bronchoconstriction was reproducible, the sheep were pretreated with different pharmacological agents on different days to determine their effects on PAF-
induced bronchoconstriction. For these studies intravenous injections of the PAF antagonist WEB-2086 (1 mg/kg, n = 5), the cyclooxygenase inhibitor indomethacin (2 mg/kg, n = 6), or the histamine H1 antagonist chlorpheniramine (2 mg/kg, n = 3), and aerosol administration of the leukotriene antagonist FPL-55712 (1% wt/vol in 3 ml H2O, n = 6) were given 20 min before challenge. Each sheep was then challenged with the dose of PAF that had been determined to give a reproducible bronchoconstriction. For all PAF experiments, the amount of PAF delivered was determined by measuring the volume (ml) of solution nebulized and multiplying this by the starting PAF concentration (µg/ml).

The effect of the PAF antagonist on leukotriene D4-induced bronchoconstriction was also determined. On day 1, each sheep (n = 5) received 100 breaths of 50 µg/ml solution of leukotriene D4, and the change in sRL was measured. At least 1 day later the sheep were given WEB-2086 (1 mg/kg iv) 20 min before the same leukotriene D4 challenge.

PAF-Induced Late Responses

Base-line sRL was measured in seven sheep (with a previous history of antigen-induced late responses) and then the sheep were challenged with PAF aerosol at a dose previously determined to cause an acute bronchoconstriction in these sheep. sRL was measured immediately after challenge, hourly from 1 to 6 h after challenge, and half hourly from 6.5 to 8 h after challenge.

Statistical Analysis

A Friedman's analysis of variance followed by a post hoc comparison was used to determine when antigen challenge resulted in significant increases in sRL over base line within each trial (i.e., control and treated). The Wilcoxon paired analysis was used to compare immediate increases and peak late increases in sRL between the control and WEB-treated trials (14). A least-squares linear regression analysis was used to compare the reproducibility of the two control PAF challenges. Paired t analysis was used to evaluate the effects of different pharmacological agents on PAF-induced bronchoconstriction and the effects of WEB-2086 on leukotriene D4-induced bronchoconstriction. The Friedman's test was also used to identify significant increases in sRL (over base line) after PAF inhalation in the studies designed to determine if PAF caused late responses. Between group comparisons (i.e., responders and nonresponders) were made with an unpaired t test. For all tests significance was accepted when P < 0.05 using a two-tailed analysis. Values reported in the text are mean ± SD.

RESULTS

Effect of the PAF Antagonist on Antigen-Induced Responses

When the sheep were untreated, antigen challenge resulted in an immediate 282 ± 116% increase in mean sRL (P < 0.05) from a base-line value of 0.9 ± 0.3 l·cmH2O·l⁻¹·s. Mean sRL was still significantly elevated over base line 1 h after challenge, but returned to values not significantly different from base line between 2 and 5 h after challenge. At 6 h after challenge mean sRL again increased significantly over base line and remained so through 8 h after challenge (Fig. 1). Pretreatment with WEB-2086 had no significant effect on base-line sRL and did not block the early response to antigen, but blocked the late response. Immediately after challenge mean sRL increased 200 ± 157% (P < 0.05) from a base-line value of 1.0 ± 0.3 l·cmH2O·l⁻¹·s. At 1 h postchallenge sRL was not different from the base-line values and remained at these values throughout the 8-h study. Individual changes in the control and treated trials for the early and peak late responses showed that WEB-2086 had variable effects on the early antigen-induced response, but the drug was consistent in reducing the peak late response in all animals (Table 1).

Mechanism of PAF-Induced Bronchoconstriction

Airway challenges with the same dose of PAF aerosol produced reproducible increases in sRL (Table 2, Fig. 2). For these studies, base-line sRL was not different between the two study days (Table 2). The PAF-induced bronchoconstriction was significantly inhibited by pretreating the animals with the PAF antagonist WEB-2086 and the sulfidopeptide leukotriene antagonist FPL-55712. Neither the cyclooxygenase inhibitor indometha-
TABLE 1. Effect of WEB-2086 pretreatment on antigen-induced early and late airway responses in allergic sheep

<table>
<thead>
<tr>
<th>Animal No.</th>
<th>Early Response</th>
<th>Late Response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Treated</td>
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<tr>
<td>8</td>
<td>187</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>321</td>
<td>280</td>
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<td>315</td>
<td>161</td>
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<tr>
<td>492</td>
<td>176</td>
<td>85</td>
</tr>
</tbody>
</table>

Mean±SD 282±116 200±157 176±64 37±32

Values are means ± SD for percent change of specific lung resistance from baseline. * P < 0.05 vs. control.

TABLE 2. Effects of pharmacological agents on PAF-induced bronchoconstriction

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>sRl, 1 x cmH2O.l-1.s</th>
<th>Post-PAF, %</th>
<th>PAF Delivered, μg</th>
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<tr>
<td></td>
<td></td>
<td>Base line</td>
<td>Postdrug</td>
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<tr>
<td>Reproducibility</td>
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<td>0.9±0.1</td>
<td>1.1±0.1</td>
<td>153±65</td>
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<tr>
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<tr>
<td>Test 2</td>
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<td>1.1±0.1</td>
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<td>WEB-2086</td>
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<td>0.9±0.1</td>
<td>1.1±0.1</td>
<td>151±23</td>
</tr>
<tr>
<td>FPL-55712</td>
<td>6</td>
<td>0.9±0.1</td>
<td>1.1±0.1</td>
<td>119±45</td>
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<tr>
<td>Indomethacin</td>
<td>3</td>
<td>0.9±0.1</td>
<td>1.2±0.3</td>
<td>160±30</td>
</tr>
<tr>
<td>Chlorpheniramine</td>
<td>3</td>
<td>0.9±0.1</td>
<td>1.2±0.3</td>
<td>186±53</td>
</tr>
</tbody>
</table>

Values are means ± SD; n, no. of sheep tested. Post-PAF, PAF-induced increase in sRl, over base-line or postdrug values; PAF delivered, amount of PAF nebulized.

Fig. 2. Reproducibility of PAF-induced bronchoconstriction in allergic sheep. Delivered PAF dose for test 1 was 509±163 and test 2 was 550±177 (SD) μg. sRl, specific lung resistance.

The PAF antagonist WEB-2086 did not have an inhibitory effect on leukotriene D4-induced bronchoconstriction. Without WEB-2086 pretreatment, aerosol challenge with leukotriene D4 produced a mean 440±101% increase in sRl over base line. When the sheep were treated with WEB-2086 mean sRl increased 898±344% over base line. The increase in the constrictor response in the drug-treated animals was greater (P < 0.05) than that observed when the sheep were untreated.

PAF-Induced Late Responses

Inhaled PAF (158±88 μg) produced both immediate and late responses in three of seven sheep tested (Fig. 4). In the three responders, sRl increased to 192±40% immediately after challenge from a base-line value of 0.9 l cmH2O l-1.s. sRl returned to base-line values by 1 h and remained so until 6 h after challenge when sRl again increased significantly. sRl remained elevated throughout the 8-h measurement. In the remaining four sheep, inhaled PAF (163 ± 63 μg) caused an immediate bronchoconstriction (sRl increased 109±73% from a base-line value of 1.0 ± 0.2 l cmH2O l-1.s). This immediate response was lower (P < 0.05) than that observed in the responders. After the initial response no other significant...
changes in sRl. were observed throughout the 8-h time course.

DISCUSSION

The results of this study indicate that the PAF antagonist WEB-2086 can block antigen-induced late responses in allergic sheep, possibly by interfering with the generation of sulfidopeptide leukotrienes.

PAF is a proinflammatory agent that has received much attention because of its ability to induce a variety of airway effects associated with the pathophysiology of asthma. These PAF-induced effects are thought to be receptor mediated because they can be blocked by specific receptor antagonists (10). WEB-2086 is such an antagonist and demonstrates typical PAF-antagonist effects in a number of model systems (11, 22, 31). The drug is reported not to have antihistaminic or antileukotriene activity in classic pharmacological models.

Our findings that WEB-2086 blocks antigen-induced late responses in the sheep are in agreement with the findings that other PAF-antagonists, BN-52021 (100 mg/kg orally) (28) and L-659,989 (1 mg/kg iv) (33), block antigen-induced late responses in rabbits. Another PAF antagonist BN-52063 has been shown to reduce acute antigen-induced bronchoconstriction and partially alleviate the airway hyperresponsiveness to acetylcholine that follows 6 h after antigen provocation in patients (20).

Studies in humans (18), rabbits (28), and sheep (6) have suggested that the eosinophil may be an important effector cell in the development of late responses. Based on these observations it may be relevant to the present study that WEB-2086 (as well as another PAF antagonist BN-52021) administered intravenously blocked PAF and antigen-induced airway eosinophilia in guinea pigs (24) and BN-52021 blocked allergen-induced eosinophil influx in rabbits (28). Whether or not WEB-2086 prevented eosinophil influx in the present study cannot be answered because airway inflammation was not measured. However, it is possible that the anti-inflammatory effects of WEB-2086 contributed to its beneficial action in the present studies.

We have previously demonstrated the importance of 5-lipoxygenase products in the development of late responses in the allergic sheep model based on the ability of several structurally different leukotriene antagonists to prevent the occurrence of late responses and the observation that leukotriene D₄ could induce late responses in this model (1, 2). On the basis of these studies it was somewhat difficult to understand the mechanism by which the PAF-antagonist worked in the sheep. Our observation that FPL-55712 also prevented PAF-induced bronchoconstriction, but that WEB-2086 did not block leukotriene D₄-induced bronchoconstriction provided the connection, in that it suggested that PAF may work as a bronchoconstrictor via the generation of leukotrienes. PAF has been shown to stimulate leukotriene production in cat pulmonary tissue (23) and rat lungs (36). PAF has also been shown to stimulate leukotriene B₄ production in human neutrophils and eosinophils (25). Additionally, FPL-55712 has been reported to prevent PAF-induced increases in airway responsiveness to histamine in guinea pigs (9). Thus the concept that PAF-induced effects could be mediated by leukotrienes is not a new concept, but our findings that the bronchoconstrictor actions of inhaled PAF may be mediated via leukotrienes is the first description in the sheep model.

Interpretation of the results of the inhaled PAF study depended on two factors, the specificity of the pharmacological agents used and the reproducibility of the inhaled PAF challenge. Our previous studies with each of these agents indicate that they are effective and have specificity of drug action at the doses and routes of administration used. Indomethacin has been shown to inhibit endotoxin-induced production of thromboxane, and 6-ketoprostaglandin₁₇,₆₇,₆₉,₆₁₀ (8), chlorpheniramine, has been shown to inhibit bronchoconstriction induced by aerosol histamine (7, 26), as well as the histaminic component of antigen-induced bronchoconstriction (4). FPL-55712 has been shown to inhibit exogenously administered leukotriene D₄ (17).

Figure 2 shows that the bronchoconstriction to inhaled PAF is reproducible. The inhibition of this PAF-induced bronchoconstriction achieved with WEB-2086 and FPL-55712 are well outside the range of variability obtained in the reproducibility tests. Indomethacin caused a slight but nonsignificant reduction of PAF-induced bronchoconstriction suggesting that if prostanoids play a role in the bronchoconstrictor response to inhaled PAF in allergic sheep it is only a minor one (see below). Our findings with indomethacin are similar to those previously reported in humans (34) and in baboons (19). However, our observation that chlorpheniramine has no effect on PAF-induced bronchoconstriction is not in agreement with the findings of Smith and co-workers (34). Those investigators found that oral chlorpheniramine (8 mg) significantly increased the dose of PAF necessary to cause a 35% fall in specific airway conductance in human subjects. Except for species variability, we have no explanation for these different results.

It could be misleading to extrapolate the results from the studies of the various pharmacological agents on PAF-induced bronchoconstriction to the effects of PAF released after inhalation of antigen because the sites of PAF release are not known. Although inhaled PAF appears to produce bronchoconstriction indirectly through sulfidopeptide leukotrienes in sheep, parenterally administered PAF causes bronchoconstriction through platelet-dependent mechanisms in rabbits and guinea pigs (for review, see Refs. 10 and 30). It is not clear, however, which platelet metabolites are responsible for the bronchoconstriction in these models (10, 30, 35). Platelets and their metabolites may not play as large a role in airway responses to PAF in sheep compared with rabbits and guinea pigs, because PAF injection in platelet-deprived sheep results in significant bronchoconstriction in spite of reductions in cyclooxygenase products (13).

Thus it appears that at the doses of antigen and PAF used in the present experiments, the airway effects of PAF are probably not dependent on platelet-derived cyclooxygenase products.

Because our findings suggested that PAF-induces leu-
late responses in allergic sheep. These findings are consistent with reports of PAF-induced late responses in rabbits (8). PAF, however, has not been found to produce late responses in asthmatic subjects (32), but in contrast to the present studies it is not known if the asthmatic patients tested also developed late responses to antigen.

The variability in the production of late responses by PAF may have resulted from differences in the amount of PAF-induced leukotriene release or differences in the sensitivity to the leukotrienes released among the sheep. The three sheep that developed late responses had significantly higher PAF-induced acute responses than did the nonresponders. In this context it is interesting that two sheep from the responder group and two sheep from the nonresponder group, in a previous study, had been challenged with leukotriene D4 (~50 μg). In the two responders, leukotriene D4 produced an increase in rRL of 601 ± 119% (SD), whereas in the two nonresponders, the leukotriene D4-induced increase in rRL was 311 ± 108% (P < 0.05). Thus differences in PAF-induced leukotriene release or sensitivity to the leukotrienes released might have contributed to the ability of PAF to produce late responses.

In summary, our findings show that a selective PAF-antagonist WEB-2086 can inhibit allergen-induced late responses in allergic sheep and that a large component of the PAF-induced response is mediated by sulfidopeptide leukotrienes. This suggests that some mediators may provoke a cascade-like release of other mediators that ultimately are responsible for the end organ responses observed. Therefore, in the context of these experiments, preventing or changing this sequence of events may be important in regulating the severity and duration of bronchial obstruction.

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