

Effect of nedocromil sodium on platelet-activating factor-induced airway responses

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Platelet-activating factor (PAF) is one of the chemical mediators that may participate in the inflammatory process underlying asthma. It has been shown to produce a prolonged increase in airway responsiveness in several species, including humans. In humans the increase in bronchial reactivity peaks 3 days after inhalation and can last as long as several weeks. PAF may induce this response by recruiting eosinophils into the airways and activating them in the airway walls, with the subsequent release of basic proteins. This process causes eosinophils, which are rich sources of PAF, to release their contents and sets up a self-perpetuating cycle. Nedocromil sodium reduces the increased bronchial responsiveness of asthma and can prevent the development of increased responsiveness after inhaled PAF. The precise mechanism by which this result occurs is not known and requires further investigation. (J ALLERGY CLIN IMMUNOL 1993;92:187-9.)

Platelet-activating factor (PAF) is a lipid mediator, and when inhaled it has many airway effects that mimic the pathology of asthma. Among these effects is the capacity to cause a prolonged increase in airway responsiveness in several species, including humans.^{1, 2}

SOURCE OF PAF IN AIRWAYS

PAF is synthesized from membrane phospholipids by the action of the enzyme phospholipase A₂, which generates the inactive precursor lyso-PAF. Lyso-PAF is acetylated to PAF, a highly active molecule with potent effects on several cells. PAF may be formed by several of the inflammatory cells that have been implicated in asthma, including macrophages, eosinophils, neutrophils, mast cells, platelets, and endothelial cells. Of these cells, eosinophils are the richest cellular source of PAF, and the hypodense eosinophils that are characteristically found in patients with asthma produce more PAF than do cells of normal density.³

Abbreviation used:

PAF: Platelet-activating factor

EFFECTS OF PAF IN AIRWAY FUNCTION

PAF has potent effects on several aspects of airway function; these effects are mediated by specific surface receptors.⁴ When given by inhalation, PAF causes bronchoconstriction, even though it has no direct effect on airway smooth muscle in vitro. This finding suggests that PAF may act by releasing bronchoconstrictor mediators from other cells. In addition, PAF is the most potent known mediator causing microvascular leakage in airways⁵ and also stimulates airway mucous secretion and impairs mucociliary clearance.

Perhaps the most striking property of PAF is its capacity to induce long-lasting increases in bronchial reactivity. This characteristic has been observed in studies involving guinea pigs, rabbits, sheep, dogs, cats, primates, and humans.^{1, 2} In healthy human subjects the inhalation of PAF results in an increase in bronchial responsiveness to methacholine. This enhanced responsiveness is maximal 3 days after inhalation and may last for as many as 4 weeks.⁶ However, the increase in bronchial reactivity is small because PAF's safe

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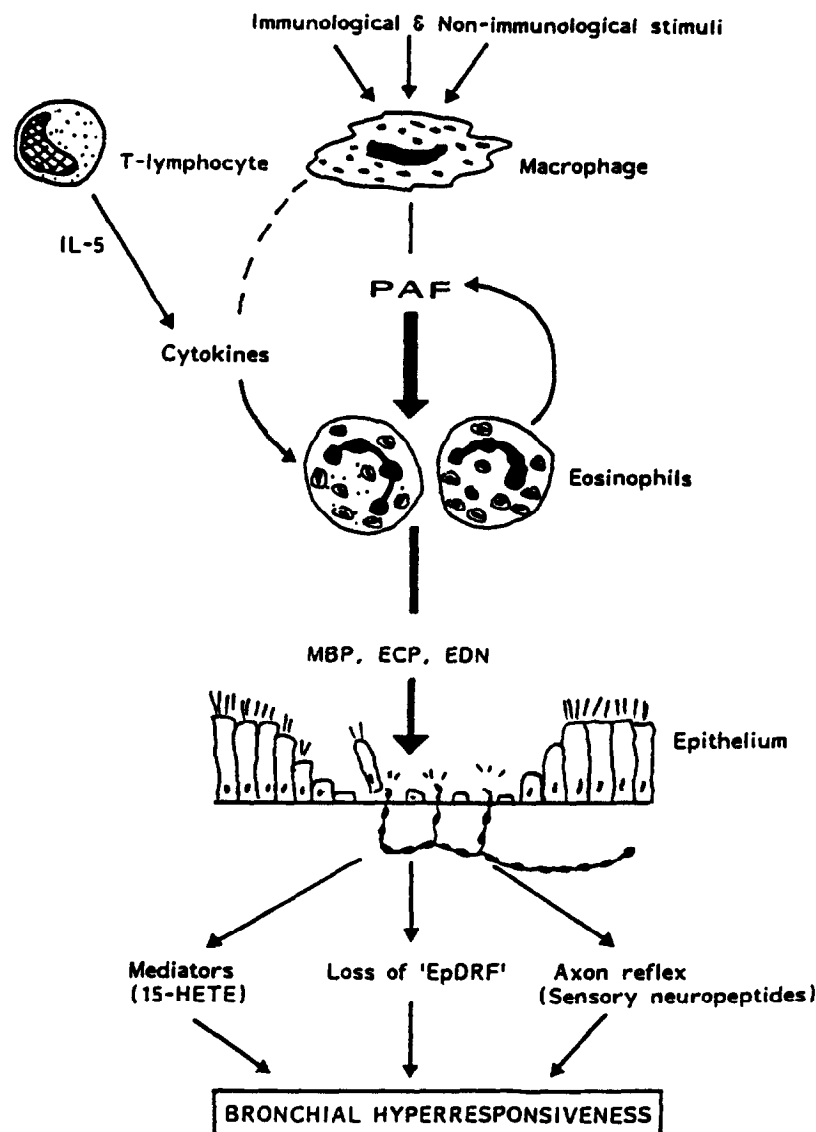


FIG. 1. Proposed mechanism for the increase in bronchial hyperresponsiveness after platelet-activating factor.

dosage range is limited, and a single inhalation of PAF cannot be expected to mimic the chronic release that may occur in patients with asthma. PAF-induced changes in airway reactivity are more difficult to observe in patients with asthma, probably because of the greater variability in their airway function.⁷

INTERACTION WITH EOSINOPHILS

The mechanisms by which PAF increased bronchial reactivity are not yet known. However, it is possible that the increased reactivity may be linked to the interaction between PAF and the eosinophils. PAF induces the selective accumulation of eosinophils in tissues and stimulates the

adhesion of eosinophils to endothelial cells.⁸ Thus studies have shown that PAF causes a selective influx of eosinophils within several hours after its injection into the skin of atopic subjects, mimicking the cellular influx of the late response to allergen.⁹ Similarly, when instilled into the lungs of primates, PAF results in a selective accumulation of eosinophils that may persist for 2 weeks.¹⁰ Because PAF is rapidly inactivated in the airways, such a long-lasting effect must result from a subsequent cascade of events.

PAF is a potent activator of eosinophils and triggers their degranulation.^{11, 12} The release of basic proteins from eosinophils may result in disruption of the bronchial epithelium, which is

characteristic of asthmatic airways.¹³ Indeed, PAF-activated eosinophils have been shown to cause airway epithelial shedding.¹⁴ Thus PAF may induce bronchial hyperresponsiveness by recruiting eosinophils into the airways and activating them in the airway wall with the subsequent release of basic proteins—a process that leads to epithelial shedding (Fig. 1). PAF-induced eosinophil activation may also result in further release of PAF. This result in turn attracts more eosinophils in a self-perpetuating cycle that may culminate in progressive epithelial shedding. The end result of such a cycle would be bronchial hyperresponsiveness caused by the loss of endogenous relaxant substance or by the exposure of sensory nerves.

EFFECT OF NEDOCROMIL SODIUM

Nedocromil sodium reduces the increased bronchial responsiveness of asthma and might therefore be expected to prevent the development of increased responsiveness after inhaled PAF. In a preliminary study in four subjects, nedocromil sodium (given in a dose of 4 mg four times a day for 2 days before challenge), but not placebo, was shown to prevent the increase in bronchial responsiveness to inhaled methacholine after PAF inhalation. In this study neither the active drug nor the placebo had any effect on the immediate bronchoconstrictor response to inhaled PAF.¹⁵ In a more recent study, inhaled nedocromil significantly attenuated the immediate airway narrowing in response to PAF in healthy subjects, which suggests that nedocromil may inhibit the release of inflammatory mediators.¹⁶ Indeed, inhaled PAF causes airway narrowing that is markedly reduced by a potent sulfidopeptide leukotriene antagonist, which suggests that nedocromil may inhibit the release of leukotrienes from cells in the airway.¹⁷

The mechanisms by which nedocromil sodium inhibits the increased airway responsiveness induced by PAF are not clear. Nedocromil sodium might prevent the PAF-induced infiltration of inflammatory cells into the airway. On the other hand, it might prevent PAF from activating eosinophils in the airway. As a third alternative, nedocromil sodium might act at the level of the airway epithelium to prevent epithelial damage or sensory nerve activation. These possibilities are testable in animal models and may shed light on the mode of action of nedocromil sodium in clinical asthma.

REFERENCES

1. Barnes PJ, Chung KF, Page CP. Platelet-activating factor as a mediator of allergic disease. *J ALLERGY CLIN IMMUNOL* 1988;81:919-34.
2. Barnes PJ, Chung KF, Page CP. Platelet-activating factor and human disease. In: Barnes PJ, Page CP, Henson PM, eds. PAF and human disease. Oxford: Blackwell, 1989; 158-78.
3. Lee TC, Lenihan DJ, Malone B, Roddy LL, Wasserman SI. Increased biosynthesis of platelet-activating factor in activated human eosinophils. *J Biol Chem* 1984;259:5526-30.
4. Dent G, Ukena D, Barnes PJ. PAF receptors. In: Barnes PJ, Page CP, Henson PM, eds. PAF and human disease. Oxford: Blackwell, 1989;58-81.
5. Evans TW, Chung K, Rogers DF, Barnes PJ. Effect of platelet-activating factor on airway vascular permeability: possible mechanisms. *J Appl Physiol* 1987;63:479-84.
6. Cuss FM, Dixon CSM, Barnes PJ. Effects of inhaled platelet activating factor on pulmonary function and bronchial responsiveness in man. *Lancet* 1986;2:189-92.
7. Chung KF, Barnes PJ. Effects of platelet activating factor on airway calibre, airway responsiveness and circulating cells in asthmatic subjects. *Thorax* 1989;44:108-15.
8. Kimani G, Tonneson MG, Henson PG. Stimulation of eosinophil adherence to human vascular endothelial cells in vitro by platelet activating factor. *J Immunol* 1988;140: 3161-6.
9. Henocq E, Vargaftig BB. Skin eosinophilia in atopic patients. *J ALLERGY CLIN IMMUNOL* 1988;81:691-5.
10. Denjean A, Arnoux B, Benveniste J. Long-lasting effect of intratracheal administration of PAF-acether in baboons [Abstract]. *Am Rev Respir Dis* 1988;137:283.
11. Kroegel C, Yukawa T, Dent G, Chanez P, Chung KF, Barnes PJ. Platelet activating factor induces eosinophil peroxidase release from purified human eosinophils. *Immunology* 1988;64:559-62.
12. Kroegel C, Yukawa T, Dent G, Venge P, Chung KF, Barnes PJ. Stimulation of degranulation from human eosinophils by platelet activating factor. *J Immunol* 1989; 142:3518-26.
13. Gleich GJ, Flavahan NA, Fujisawa T, Vanhoutte PM. The eosinophil as a mediator of damage to respiratory epithelium: a model for bronchial hyperreactivity. *J ALLERGY CLIN IMMUNOL* 1988;81:776-81.
14. Yukawa T, Read RC, Kroegel C, et al. The effects of activated eosinophils and neutrophils on guinea pig airway epithelium in vitro. *Am J Respir Cell Mol Biol* 1990;2: 341-4.
15. Di Maria GU, Bellofiore S, Ciancio N, Ruggieri F, Missetta A. Nedocromil sodium prevents the increase in airway responsiveness to methacholine induced by platelet activating factor (PAF). *Am Rev Respir Dis* 1989;139: A109.
16. Hayes JP, Chung KF, Barnes PJ. Nedocromil sodium attenuates platelet activating factor induced bronchoconstriction in normal subjects. *Eur Respir J* 1992;5:1173-96.
17. Kidney JC, Ridge S, Chung KF, Barnes PJ. Inhibition of PAF-induced bronchoconstriction by the oral leukotriene antagonist ICI 204-219 in normal subjects. *Am Rev Respir Dis* 1993;147:215-7.