Editorial

Role of inflammation in the hyperreactivity of the airways in asthma

Although asthma is usually diagnosed because of spontaneous and reversible attacks of bronchoconstriction, its most characteristic feature is the increased bronchial reactivity to a large variety of pharmacological and physical agents, such as histamine, methacholine, leukotrienes, prostaglandins, cold air, and dust. Thus asthmatic subjects develop a greater degree of bronchoconstriction from exposure to these stimuli than do subjects with normal bronchial reactivity. That this feature of asthmatic airways appears to have a fundamental role in the pathophysiology of asthma is supported by the observation that the severity of the disease correlates closely with the degree of hyperreactivity.1

The precise mechanism underlying the hyperreactivity of asthma is unknown. Whether this abnormality is inherent in the intrinsic property of airway smooth muscle or is at the level of its neural control remains unclear. The possibility that airways inflammation could be related to the development and maintenance of the bronchial hyperreactivity of asthma has been the subject of increasing research in recent years. Indeed, inflammation of the airways may create conditions that have themselves been proposed as possible mechanisms of hyperreactivity, such as bronchial oedema, mucosal hyperpermeability, exposure of epithelial sensory nerve endings, and release of inflammatory mediators.2 This article will review (a) the recent experimental data linking the development of airways inflammation to the induction of airways hyperreactivity and (b) the interactions between inflammatory cells and mediators that may be crucial in the pathophysiology of airways hyperreactivity.

Airway inflammation in asthma

The general features of an inflammatory response include vascular dilatation and increased vascular permeability with the formation of an exudate consisting of both plasma proteins and migrating inflammatory cells. Inflammatory reactions that affect mucous membranes such as those of the airways are also characterised by mucus hypersecretion and shedding of the epithelial lining cells into the lumen.3 These features have been described in the airways of subjects dying of acute asthma,4,5 with an inflammatory cell infiltration consisting predominantly of eosinophils and appreciable epithelial cell loss, as shown by the denudation of the airway surface and by clumps of epithelial cells in sputum (Creola bodies). Although no detailed histological information of the airways of individuals with stable asthma is available, bronchoalveolar lavage of these subjects has shown that there are more eosinophils and neutrophils within the airway lumen than in normal subjects.6,7 Biopsies of the airway mucosa of asthmatic patients have confirmed the presence of epithelial cell damage, particularly of the ciliated cell type,8 and of the submucosal infiltration of eosinophils.9 A persistent low grade inflammatory response is therefore present in the airways of those with stable asthma.

Relationship of acute inflammation to airways hyperreactivity

One approach to evaluating the importance of inflammatory changes in asthma has been to examine the effect of inducing acute inflammation of the airways on reactivity of the airways. In several studies the presence of migrating cells such as eosinophils and neutrophils in the airways has been used as the sole index of inflammation, and the temporal relationship of the presence of these cells to the development of airways hyperreactivity has been examined. The effects of a wide range of inflammatory stimuli—for example, the atmospheric pollutant ozone, environmental antigens, and chemicals encountered at work, such as toluene diisocyanate—have been investigated in various species, including man.

Response to ozone

Exposure to ozone results in a transient increase in non-specific airways reactivity in the dog,10 the guinea pig,11 and man.12 In the dog the onset of hyperreactivity is coincident with the presence of neutrophil chemotaxis in the airway wall13 and with the recovery of increased numbers of neutrophils and desquamated epithelial cells in bronchoalveolar lavage fluid.14 Depletion of circulating neutrophils with hydroxyurea inhibits the hyperreactivity,
The mast cell has been proposed as the initiating cell for the release of mediators in vitro. 

The mast cell, for example, is activated by antigen, releasing a variety of mediators including histamine, serotonin, and leukotrienes. These mediators can activate neighboring cells, such as endothelial cells and smooth muscle cells, leading to the production of further mediators.

Inflammation in the airways is characterized by an influx of inflammatory cells, including neutrophils, eosinophils, and macrophages. These cells release pro-inflammatory mediators, such as cytokines and chemokines, which can further recruit and activate other cells.

The primary effector cells in the airways are the mast cells and eosinophils. Mast cells release a variety of mediators, including histamine, leukotrienes, and cytokines, which can activate surrounding cells and contribute to the inflammatory response. Eosinophils, on the other hand, release proteolytic enzymes and cytokines that contribute to tissue damage and remodeling.

Inhalation of allergens or other irritants can activate these cells, leading to the release of mediators and the recruitment of other inflammatory cells. This can result in a cascade of events that leads to airway hyperreactivity and asthma.

The role of eosinophils in asthma is well-documented. Eosinophils are abundant in the airways of patients with asthma and are associated with a more severe disease phenotype. They release a variety of pro-inflammatory mediators, including major basic protein, which has been implicated in airway remodeling and tissue damage.

In conclusion, the mast cell and eosinophil are important in the pathophysiology of asthma. Understanding their role and how to modulate their activity is crucial for developing effective therapies to treat this disease.
achieved through the activation of their low affinity surface IgE receptors by antigen. In addition, the capacity of alveolar macrophages for releasing platelet activating factor provides another mechanism for eosinophil chemotaxis into the airways because platelet activating factor (PAF) aerosolised into the airways of baboons causes eosinophilia in bronchoalveolar lavage fluid.

Epithelial cells
The observation that in tracheal biopsy specimens from dogs exposed to ozone the concentration of migrating neutrophils was higher in the epithelial layer than in the subepithelium suggests that the airway epithelium could be a source of chemotactic factors for neutrophils. In the presence of arachidonic acid canine and human tracheal epithelial cells in vitro generate substantial amounts of 5-lipoxygenase and 15-lipoxygenase metabolites, including leukotriene B4 and 8,15-di-HETE, which are both neutrophil chemotactic agents.

SECONDARY EFFECTOR CELLS
Eosinophils and neutrophils
The recruitment of the eosinophil in preference to the neutrophil to the human asthmatic airway when the chemotactic agents released by primary effector cells are active for both cell types remains to be explained. The infiltrating eosinophil can generate mediators that play a part in enhancing airways reactivity. Eosinophil cationic protein and major basic protein, both major components of eosinophilic granules, are cytotoxic to the respiratory epithelium and could therefore account for the denudation of the epithelium seen in asthma. Because airway epithelium elaborates a smooth muscle relaxant factor that remains to be identified, epithelial denudation may underlie the exaggerated response of the muscle to bronchoconstrictor substances. Eosinophils have the capacity to generate sulphidopeptide leukotrienes, notably leukotriene C4, and also the potent inflammatory mediator PAF. Although both mediators are potent bronchoconstrictors, only PAF has been reported to induce a transient increase in airways reactivity in several species, including the guinea pig, the dog, and man. Interestingly, PAF production is possibly enhanced through the interaction between the alveolar macrophage and the eosinophil, as more eosinophils are recruited through the generation of PAF by both cell types.

Although the neutrophil is less conspicuous than the eosinophil in the airway wall of asthmatic subjects, it is an extremely potent cell, capable of generating prostaglandins and thromboxane, leukotriene B4, and PAF; not surprisingly, it has been implicated in ozone induced and antigen induced hyperreactivity in dogs and rabbits respectively. Supernatants from phagocytosing neutrophils in vitro may induce hyperreactivity when nebulised into the airways of rabbits but the responsible mediator has yet to be identified.

Platelets
A role for the platelet has also been suggested because platelet depletion prevented PAF induced airways hyperreactivity in guinea pigs, implying that this effect of PAF is mediated through the recruitment of platelets to the airways. After antigen inhalation challenge of asthmatic subjects platelets have been recovered in lavage fluid, and are activated in the circulation. The mechanism by which platelets may affect airway function remains to be elucidated, but the close apposition of these cells to airway smooth muscle in guinea pigs challenged with PAF suggests that they may have a direct effect, perhaps through the release of mediators. Platelets can also be primarily activated through an IgE dependent mechanism.

MEDIATORS OF AIRWAYS HYPERREACTIVITY
The role of several mediators released during airway inflammation has already been mentioned. While some of these mediators, such as PAF, may induce airways hyperreactivity through the activation of intermediary cells, others—for example, the cyclo-oxygenase product prostaglandin F2a—may act directly. Cyclo-oxygenase metabolites have been implicated in ozone induced hyperreactivity in dogs because it is blocked by indomethacin. This effect, however, is species dependent: in the guinea pig indomethacin had no effect but inhibition of the lipoxygenase pathway of arachidonic acid metabolism was effective. The role of cyclo-oxygenase and lipoxygenase products in the induction of hyperreactivity in man remains to be elucidated but the late phase bronchoconstrictor response after antigen challenge is known to be inhibited by indomethacin. Direct potentiation of airway smooth muscle contraction in vitro by inflammatory mediators, such as 5-HETE and leukotrienes C4 and D4, has been reported. Whether these effects are at the level of membrane binding or are due to changes in calcium fluxes remains to be determined. It seems unlikely that increases in the affinity of receptors or in their numbers explain hyperreactivity since this characteristic property of asthmatic airways occurs in response to a wide range of bronchoconstrictor agents in vivo. Because airway smooth muscle responsiveness in vitro of a group of subjects with wide ranging activities in vivo are similar, it has been suggested that airways hyperreactivity may not result from an intrinsic abnormality of airway smooth muscle. These results, however, were obtained from patients with...
chronic obstructive airways disease but not from asthmatic patients.

Inflammatory mediators may also influence reactivity through neural mechanisms. Augmented release of acetylcholine from postganglionic nerve endings by serotonin66 or thromboxane A269 has been suggested, but the failure of anticholinergic drugs to inhibit antigen induced hyperreactivity in man does not support this mechanism.70 Local axon reflexes may be sensitised after epithelial damage and local release of inflammatory mediators such as bradykinin, with the liberation of neuropeptides such as substance P; this could enhance the effect of other bronchoconstrictor substances.71 Finally, because several putative mediators in asthma can increase vascular permeability in the airways, the resulting oedema of the airway wall may theoretically contribute to the enhancement of airways reactivity through geometric factors.73

Conclusion

The interaction of inflammatory cells and mediators with airway smooth muscle and its neural control may form the basis for the exaggerated airway responses in asthma. The initial clinical and animal studies have been mainly descriptive, but they strongly suggest a role for inflammatory cells in altering airways reactivity. In vitro studies of these cells and of the mediators they generate have indicated several mechanisms by which airways hyperreactivity could occur. The initiating stimulus may determine the action of specific effector cells and cellular activation pathways in this process. Future research should be devoted to examination of the direct effect of inflammatory cells in the airways by experimental techniques already available. The mechanisms by which inflammation in the airways is maintained once it is initiated remain unclear; possibly the persistence of airways hyperreactivity in asthma results from a defect in the switching off of the inflammatory process. Further understanding of the basis for the airways hyperreactivity in asthma will depend on an interdisciplinary approach using the methods of physiology, pharmacology, biochemistry, and cell biology.

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References

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