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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 wall[13] 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,

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implying that the neutrophil is an important effector cell in the response.[15] Hydroxyurea may, however, have had effects on other cells apart from neutrophils. In man exposure to a lower concentration of ozone results in a more modest increase in reactivity to methacholine, an effect that is also associated with an influx of neutrophils in bronchoalveolar lavage fluid.[16]

Subsequent studies in the guinea pig have highlighted the species differences that exist in the response to the same stimulus, ozone. Neutrophil infiltration into the airways is absent during the phase of increased reactivity but occurs during the remission of hyperreactivity.[17] A similar sequence of events was seen when guinea pigs were exposed to cigarette smoke[18]; the hyperreactivity induced by this agent occurred during the phase of fluid and protein extravasation, associated with an increase in airways permeability, possibly resulting from disruption of epithelial tight junctions.[19] The resulting increase in the exposure of epithelial sensory nerve fibres to inhaled substances could be a mechanism for hyperreactivity, as was first suggested for the exaggerated bronchomotor response resulting from upper respiratory tract infections.[20] Guinea pigs exposed to ozone are, however, hyperreactive to inhaled as well as intravenous methacholine,[11] and asthmatic patients with sustained hyperreactivity have normal respiratory mucosal permeability.[21] In contrast to these studies of ozone and cigarette smoke, the hyperreactivity induced by toluene diisocyanate in the guinea pig coincides with the peak of neutrophil influx in the airway wall,[22] suggesting not only species differences but also stimulus specificity with regard to the temporal sequence of hyperreactivity and the components of the inflammatory response.

RESPONSE TO ANTIGEN

Of greater relevance to asthma is the effect of responses mediated by immunoglobulin E (IgE) in sensitised subjects. A single inhalation of antigen in individuals with atopic asthma results in an early and late phase bronchonconstrictor response, and in a prolonged increase in airways reactivity that is associated with exacerbation of asthmatic symptoms[23]; while avoidance of antigen over a period of two to three months improves asthma and results in a decrease in airways reactivity.[24] The capacity of antigen for causing an inflammatory response in the skin of atopic subjects with an infiltration of mononuclear cells, neutrophils, and eosinophils has been well documented.[25] In the ragweed sensitised dog and rabbit the development of airways hyperreactivity is temporally associated with an increased number of neutrophils in bronchoalveolar lavage fluid.[26 27] Only antigen challenged dogs with neutrophilia in the bronchoalveolar lavage fluid developed airways hyperreactivity.[26] By contrast, in the asthmatic subjects bronchoalveolar lavage fluid obtained during the late phase response to antigen has showed an increase in eosinophils and in the concentration of eosinophilic cationic protein, the latter reflecting eosinophil degranulation,[28] although there were no significant changes in numbers of neutrophils recovered. These asthmatic subjects with antigen induced late phase responses would have shown increases in reactivity,[29] and therefore eosinophils may play a part in the pathophysiology of airways hyperreactivity in asthma.

Putative role of inflammatory cells and mediators in airways hyperreactivity

The foregoing studies support the notion that inflammatory stimuli delivered to the airways activate cells within the airways ("primary effector cells") to release mediators that are chemotactic for cells derived from the circulation ("secondary effector cells"). The precise role of these cells and of their interactions remains to be defined, but these cells and their mediators are potential modulators of airways reactivity.

PRIMARY EFFECTOR CELLS

Mast cells

The mast cell has been proposed as the initiator of inflammatory responses to both allergic and non-allergic stimuli in the airways.[30] Although mast cells are abundant in lung tissue, they form a relatively small proportion of the cells recovered from the lumen of the airways of normal and asthmatic subjects.[7 31] It has been suggested that activation and degranulation of these relatively few intraluminal mast cells leads to increased mucosal permeability, with subsequent activation of tissue mast cells.[32] The mast cell releases a wide array of inflammatory mediators that may mimic some of the features of asthma, including smooth muscle contraction and mucus secretion.[30] It also generates chemotactic factors for neutrophils and eosinophils, such as hydroxyeicosatetranoeic acid (HETE) and leukotriene B4.[30 33] The fact that 15-HETE generated from eosinophils[34] and airway epithelial cells[35] and major basic protein released from eosinophils can activate mediator release from mast cells[36 37] is an illustration of the highly complex and interdependent roles of the different cell types present in inflamed airways.

Alveolar macrophages

Alveolar macrophages are in greater abundance within the airway lumen than are mast cells, and they also possess the capacity to generate chemotactic factors for eosinophils and neutrophils.[38 39] This may be

achieved through the activation of their low affinity surface IgE receptors by antigen.[40] In addition, the capacity of alveolar macrophages for releasing platelet activating factor[41] 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.[42]

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.[13] In the presence of arachidonic acid canine and human tracheal epithelial cells in vitro generate substantial amounts of 5-lipoxygenase[43] and 15-lipoxygenase metabolites,[35] 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,[44] are cytotoxic to the respiratory epithelium[45] and could therefore account for the denudation of the epithelium seen in asthma.[46] Because airway epithelium elaborates a smooth muscle relaxant factor that remains to be identified,[47 48] epithelial denudation may underlie the exaggerated response of the muscle to bronchoconstrictor substances. Eosinophils have the capacity to generate sulphidopeptide leukotrienes, notably leukotriene C4,[49] and also the potent inflammatory mediator PAF.[50] 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,[51] the dog,[52] and man.[53] 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.[15 54] 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.[55]

Platelets

A role for the platelet has also been suggested because platelet depletion prevented PAF induced airways hyperreactivity in guinea pigs,[51] 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,[56] and are activated in the circulation.[57] 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[58] 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.[59]

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 F_{2a}[60]—may act directly. Cyclo-oxygenase metabolites have been implicated in ozone induced hyperreactivity in dogs because it is blocked by indomethacin.[61] 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.[62] 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.[63] Direct potentiation of airway smooth muscle contraction in vitro by inflammatory mediators, such as 5-HETE[64] and leukotrienes C4 and D4,[65] 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 reactivities in vivo are similar,[66 67] 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 serotonin[68] or thromboxane A_2[69] 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,[72] 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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