Pathogenesis of Asthma

Mediators and Mechanisms

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Introduction

Asthma is a common lung disease defined by reversible airway obstruction, airway inflammation, and increased airway responsiveness to a wide variety of stimuli. It is characterized by paroxysmal bronchospasm, hypersecretion of mucus, airway wall edema, and bronchial hyperreactivity. There is substantial evidence for the role of inflammation in asthma and bronchial hyperreactivity. Early autopsy studies of patients who had died in status asthmaticus showed epithelial denudation, mucosal edema, glandular hypertrophy, and dense eosinophilic infiltration. More recently, bronchoalveolar lavage (BAL) studies in patients challenged with aeroallergens consistently reveal increased numbers of BAL fluid eosinophils, mast cell mediators, and products of other inflammatory cells (1,2). Furthermore, transbronchial biopsies, even of patients with mild, well-controlled disease, have shown significant inflammatory changes. Biopsies have not only shown inflammation, but also an association between the degree of inflammatory changes and measurements of nonspecific bronchial hyperresponsiveness (3,4). Finally, therapy directed toward airway inflammation has been most effective in the treatment of chronic asthma and in attenuating bronchial hyperreactivity.

In the pathogenesis of asthma, the mast cell and eosinophil continue to be regarded as central participants. However, appreciation of asthma as an inflammatory disease process has led to the recognition of the importance of other inflammatory cells and their respective products in a complex immunologic response. In recent years there has also been an explosion of knowledge with regard to cytokines and the potential role of neuropeptides. This chapter will focus first on immune effector cells and their mediators. We will then briefly discuss neural control of the airways, including our current understanding of neuropeptides. Finally, we will attempt to synthesize an overall construct of asthma pathogenesis and discuss therapeutic implications.
Mast Cells and Mast Cell Mediators

Mast cells are unique among cells present in the human respiratory tract in that they are capable of influencing most of the factors felt to underlie airway hyperreactivity (5). These factors include the smooth muscle itself, autonomic control of smooth muscle, bronchial mucosal permeability, and epithelial damage and inflammation. In addition to IgE-mediated degranulation, a number of other factors are now known to cause mast cells to release mediators, including complement fragments, neuropeptides, cell-derived releasing factors, cationic proteins, hypoxia, drugs, and cytokines from a variety of stimulated leukocytes and macrophages (Fig. 1). Many of the mediators that will be discussed under the label of mast cell mediators are also products of other cells. These cells are also likely to contribute to the pathogenesis of asthma, either directly or indirectly, through the release of mediators as a result of mast cell degranulation.

Mast cell mediators are typically divided into preformed and newly generated subgroups (see Table 1). Preformed mediators are contained in the granule matrix and include biogenic amines, various enzymes, chemotactic factors, and proteoglycans. Newly generated mediators are synthesized only on mast cell activation. These mediators include cyclooxygenase and lipoxygenase products of arachidonic acid, platelet-activating factor, adenosine, and several cytokines.

Role of Mast Cells

Mast cells are present in concentrations of 1–7 x 10⁶/g lung tissue and are distributed in physiologically strategic locations. These locations include beneath the basement membrane of airways, near blood vessels in the submucosa, adjacent to submucosal glands, throughout bronchial smooth muscle bundles, within the intra-alveolar septum, and in the bronchial lumen. Although comprising < 0.1% of the total BAL cell population, the number is severalfold higher in patients with allergic asthma. Lung tissue from patients who have died during an asthma attack shows decreased mast cell staining, indicating probable degranulation. Furthermore, in vitro studies have demonstrated the ability of specific antigen to contract sensitized airway smooth muscle and that the contraction is associated with the concomitant release of mast cell mediators.

The first direct in vivo evidence for the role of mast cells in allergic asthma comes from the work of Casale et al. (6). In this study, all of seventeen allergic asthmatics and none of nine normal subjects had both visible airway constriction and increased BAL histamine levels in response to bronchoscopic instillation of antigen. Moreover, increases in BAL histamine levels correlated with airway methacholine sensitivity.