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Review

Rat models of asthma and chronic obstructive lung disease ☆

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Abstract

The rat has been extensively used to model asthma and somewhat less extensively to model chronic obstructive pulmonary disease (COPD). The features of asthma that have been successfully modeled include allergen-induced airway constriction, eosinophilic inflammation and allergen-induced airway hyperresponsiveness. T-cell involvement has been directly demonstrated using adoptive transfer techniques. Both CD4+ and CD8+ T cells are activated in response to allergen challenge in the sensitized rat and express Thelper2 cytokines (IL-4, IL-5 and IL-13). Repeated allergen exposure causes airway remodeling. Dry gas hyperpnea challenge also evokes increases in lung resistance, allowing exercise-induced asthma to be modeled. COPD is modeled using elastase-induced parenchymal injury to mimic emphysema. Cigarette smoke-induced airspace enlargement occurs but requires months of cigarette exposure. Inflammation and fibrosis of peripheral airways is an important aspect of COPD that is less well modeled. Novel approaches to the treatment of COPD have been reported including treatments aimed at parenchymal regeneration.

Keywords: Early airway responses; Late airway responses; Cysteinyl leukotrienes; Proliferating cell nuclear antigen; Bromo-deoxyuridine; Adoptive transfer; Anti-oxidants; Emphysema

Contents

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1. Introduction

Early studies of the regulation of airway function and its potential relationship to asthma and chronic obstructive pulmonary disease (COPD) employed large animals such as the dog, cat and monkey. The detailed study of respiratory system mechanics was easily performed in these animals whereas equipment to study smaller animals was not generally available. In the past 20 years the techniques available for small animals have improved substantially and have undergone extensive testing. Furthermore the focus has shifted from the investigation of the neural control of airway smooth muscle (ASM) tone and of neurogenic causes of airway hyperresponsiveness (AHR) to the study of airway inflammation. Small animals such as the rat have proven to be very useful for such studies. Although there have been a substantial number of studies employing murine models of asthma the measurement of pulmonary function in the mouse is somewhat more difficult to make than in the rat. Non-invasive techniques for the mouse have been developed to facilitate the assessment of pulmonary function but are associated with a substantial degree of uncertainty. The range of experimental techniques that can be practiced on the mouse will no doubt lead to further growth of the considerable enthusiasm for this animal for the modeling of respiratory disease. However, the rat is still an important species for drug testing so that it should continue to enjoy popularity for the study of experimental asthma and COPD.

Asthma has three defining features, namely AHR, airway inflammation and airway obstruction that is at least partly reversible. All of these characteristics have been successfully reproduced in the rat. AHR can be induced by a variety of stimuli such as allergen challenge of actively or passively sensitized animals, through viral infections or irritant substances. However, AHR may also be innate, occurring without any particular trigger. The mechanisms of AHR are still unresolved. However, the phenomenon of AHR is a reflection of excessive airway narrowing for a given dose of contractile agonist administered. It is generally believed that changes in ASM properties may be important [1]. Post-receptor mechanisms must be important because responses to different agonists that employ distinct cell surface receptors reveal the hyperresponsiveness. Changes in contractile proteins (myosin isoforms, myosin light-chain kinase) or in signaling (inositol phosphate metabolism) causing increased smooth muscle contraction (force or velocity) could cause AHR. Alternatively, changes in mechanical impedances to airway narrowing such as the elastic properties of the lung parenchyma or local changes in the parenchyma adjacent to the airways causing mechanical uncoupling could also be a potential explanation [2]. Indeed it is likely that there are several mechanisms that account for AHR in different pathologies.

Airway inflammation is usually studied after allergic challenge; it is pleiomorphic but it has a substantial eosinophilic component when triggered by allergen. The eosinophilia is caused by cytokines and chemokines that are associated with the Th2 pattern of T-cell cytokines. Antigen presentation by dendritic cells to ovalbumin (OVA) specific T cells, predominantly CD4+ cells, is responsible for the generation of activated Th2 cells expressing interleukin (IL)-4, IL-5 and IL-13 [3]. Non-allergenic stimuli such as ozone are accompanied by neutrophilic inflammation. The role of T cells in these responses has not been well studied.

Airway obstruction has generally been induced by allergic challenge. Allergen-induced bronchoconstriction involves an ''immediate response'' within minutes, also named the early response, and a delayed airway narrowing termed the late response. The latter is more strongly associated with airway inflammation than the isolated early airway response. Airway narrowing can also be evoked by dry gas hyperpnea, a model for exercise-induced asthma and various other non-allergic stimuli.

2. Innate airway hyperresponsiveness

A comparison of agonist (serotonin or methacholine)-induced airway responsiveness in the rat was made many years ago and demonstrated strain-related differences [4,5]. Fisher 344 rats have demonstrated consistent AHR compared to other strains, of which the Lewis was chosen as the most suitable for comparison. Several differences in the properties of ASM tissue have been identified that could contribute to or account for the differences. A greater amount of muscle has been shown by morphometry in airways of the Fisher rats compared to Lewis rats [6]. The volume sensitivity of induced bronchoconstriction is less marked in the Fisher rat than the Lewis rat. Tracheal responses to agonists are greater in the Fisher and also demonstrate increases in both sensitivity and maximal responses [7]. The increase in maximal response is consistent with the increase in muscle mass. However, the greater response seems to be in part related to nitric oxide production by epithelium; the Fisher rats have less cyclic guanosine monophosphate synthesis following treatment with a nitric oxide donor, nitroprusside, suggesting reduced guanylyl cyclase activity in the airway [8]. Inhibition of nitric oxide synthase by administration of L-NAME diminishes the differences in airway responsiveness between F344 and Lewis rats in vivo [9]. The Fisher rat retains the hyperresponsiveness of its ASM in vitro. Cultured explants from these rats have been used to show greater and faster contractions of the Fisher airways in situ to serotonin and methacholine [10,11]. The cells in culture show enhanced responses to serotonin and bradykinin in the form of calcium transients [12]. The greater calcium transients appear to be accounted for by reduced inositol trisphosphate phosphatase activity, resulting in larger IP3 transients in the Fisher rat [13]. Furthermore, the Fisher rat has greater expression of the 7 amino acid inserted myosin isoform associated with faster myosin contraction [14].