

Rodent Models of Allergic Rhinitis: Relevance to Human Pathophysiology

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Rodent models of allergic airways disease employ a wide range of test allergens, sensitization and provocation protocols, animal strains, and experimental endpoints. Studies of experimental asthma, especially the use of murine models, have contributed significantly to the understanding of the genetics and immune-mediated pathophysiology of pulmonary airways during allergy. By comparison, rodent models of allergic rhinitis are less well developed. Recent interest in the potential mechanistic links between asthma and allergic rhinitis has increased the need for relevant animal studies directed at upper airways responses. Specifically, the nature of nasal airway remodeling in response to chronic activation of allergic pathways and its relationship to airway occlusion is not well described. This cursory review discusses current approaches to assessing nasal obstruction in rodent models, and how the histopathologic analysis might be improved to facilitate understanding of the pathogenesis of allergic rhinitis in humans.

Introduction

Allergic rhinitis (AR) is the most prevalent atopic disease in the world [1]. In a multi-year international study, reported symptoms of nasal congestion, irritation, and watery eyes were more common and had increased more rapidly than asthma in the last 15 years. AR is defined clinically as nasal obstruction, rhinorrhea, sneezing, and nasal pruritus. In the United States, more than 36 million people have AR that is directly related to seasonal stimuli, and even more have persistent symptoms year round.

AR is a common diagnosis in patients with allergic asthma, with comorbidity reported from 50% to 100% in the United States and Europe [2]. Conversely, an estimated 20% of individuals with AR have some manifestation of

lower airway symptoms, such as airway hyperreactivity. AR is believed to be a risk factor for developing asthma [3,4]. Given the occurrence of upper and lower airway allergic symptoms in the same patient, there is much speculation over the pathophysiologic linkages between asthma and AR [3,5]. Histopathologic comparisons of the nasal and bronchial mucosa from allergic airways reveal similar inflammatory and epithelial cell alterations in both tissues, suggesting that common mechanisms of pathogenesis may contribute to each condition [3,6]. Recognition of the clinical and pathologic commonalities of AR and asthma has led to the development of diagnostic and therapeutic strategies by clinicians participating in the workshop on Allergic Rhinitis and its Impact on Asthma (ARIA) [7]. Among the knowledge gaps identified were the nature of airway remodeling in rhinitis and how it may affect pulmonary function.

Clearly, the anatomic, morphologic, and functional differences in the nasal airways compared with the pulmonary airways render them uniquely sensitive to disparate allergic responses. For example, both upper and lower airways can contribute to airway obstruction, but by quite different mechanisms. Smooth muscle contraction can narrow pulmonary airways, whereas vasodilation of highly vascularized mucosa can narrow nasal airway openings. Mucus overproduction and hypersecretion may also contribute to airway occlusion and contribute to functional obstruction of both nasal and bronchial airways. In general, mucus can be more readily cleared from the nose, but mucus plugging in pulmonary airways is a prominent feature associated with mortality in status asthmaticus. Thus, although a “one-airway” approach may be a useful paradigm in which to frame AR-asthma relationships, animal models that describe each condition separately, as well as in tandem, are needed to understand the pathophysiology of allergic airways disease, and to inform the design of clinical intervention protocols and the development of new therapeutics.

Animal Models of Allergic Airways Disease: Lessons From Asthma Models

Considerable work using the ovalbumin-sensitized and challenged rodent has helped describe both the

acute, and more recently the chronic, immune-mediated inflammation and hyperreactivity of pulmonary airways. Studies using mice with either naturally occurring mutations or designed knockout models have been valuable in gaining understanding of the role of cytokines, adhesion molecules, and cell receptors in allergic inflammatory responses. Asthma is a chronic, often life-long, disease of episodic inflammation with extensive airway remodeling. By comparison, most rodent models of asthma have been relatively acute in nature, with several high-dose allergen challenges over a few days or weeks. Although airway hyperreactivity, eosinophilic and lymphocytic infiltration, and mucus overproduction are present during experimental asthma, other histopathologic features such as smooth muscle cell proliferation, myofibroblast involvement, subepithelial fibrosis, and epithelial proliferation and shedding are often absent in allergic rodent models. Other features that are not necessarily hallmarks of human asthma (eg, alveolar inflammation; downregulation of inflammatory and immunologic responses) can often develop in acute allergic models.

Given the imperfect pathology observed in acute disease in rodents, significant effort has gone into developing more realistic models of chronic asthma, in which frequent exposures to lower allergen concentrations are used to better portray exposure histories of allergic subjects to seasonal and episodic encounters with allergens. Airway remodeling in these recent models of chronic disease in mice includes more relevant features of human asthma (ie, intraepithelial eosinophils, intramural collagen deposition, epithelial hyperplasia and metaplasia, smooth muscle hyperplasia and hypertrophy, and increases in myofibroblasts) [8–10].

Besides the mouse, rats and guinea pigs have also been used to model different aspects of human asthma. Regardless of the strain, the method to induce allergic airways is similar across species and allergens. Sensitization or immunization to an antigen can be accomplished by using either systemic (intraperitoneal or dermal) or airway (aerosol or intranasal) routes of exposure, with and without adjuvant, and using single or multiple immunizations. Sensitized animals are then challenged by either dermal, inhalation, intranasal, or intratracheal instillation, and with varying vehicle volumes and antigen doses. The benefits and disadvantages of these protocols are discussed in detail elsewhere [11,12•,13]. Clearly, disparate experimental approaches have yielded different results, making interpretation and comparisons across animal models challenging.

Animal Models of Allergic Rhinitis

Compared to rodent models of human asthma, experimental AR is less developed. Reliance on short-term protocols predominates in the literature, and therefore

present the same weaknesses (ie, focus on acute inflammation, less attention to airway remodeling) as acute asthma models discussed above. Studies using the guinea pig, and to a lesser extent the Brown Norway rat, have provided most of the data describing the inflammatory and vascular responses to allergic stimuli in the nose. Occlusion of nasal passages, and the necessity for oral breathing, is the most common complaint from patients with AR. Nasal obstruction in response to an allergic stimulus is characterized by early and late phases of inflammation [14,15••]. Within seconds, a transient episode of itching and sneezing begins; this episode lasts for 5 to 30 minutes, and then wanes. A secondary phase of rhinorrhea and obstruction begins minutes later and can last for hours. Evidence from both animal and human clinical studies shows that preformed mediators released from mast cells and basophils—specifically histamines, tryptase, cysteinyl leukotrienes (cysLTs), and platelet-activating factor (PAF)—promote the initial irritation and sneeze reflex. During the secondary phase, other preformed and synthesized mediators, predominately prostaglandins, interleukins, and chemoattractants, elicit the recruitment of eosinophils and neutrophils into nasal tissues.

In the allergic guinea pig, enumerating the frequency of nasal rubbing and sneezes is a subjective but useful measure, especially for testing the early phase mechanisms and therapies involving histamine- and leukotriene-dependent pathways [14,16,17]. However, the associated histopathology as it relates to nasal obstruction in both early and late phase responses is not fully understood. Findings from acute disease studies in rodents disagree with responses documented in humans, notably with vasoconstrictors and leukotriene modifiers. Therefore, airway remodeling in chronically exposed rodents may be more relevant to understanding the pathophysiologic mechanisms in humans.

Nasal Obstruction

Nasal airflow and acoustic rhinometric measurements that are used in humans are not easily adapted to rodents [18]. However, at least two techniques have emerged, and have been refined in recent years, that appear to provide a reproducible physiologic approach to determine nasal obstruction. The first method employs a novel use of whole-body plethysmography (WBP) which, by virtue of obligate nose-breathing in rodents, also would detect contributions of flow and pressure changes from upper airways (Fig. 1). Rodent WBP has been used extensively to measure lower airway function in allergic rodents, and relies on a unit-less parameter called enhanced pause (Penh), the physiologic meaning of which is controversial [19,20]. Briefly, part of the derivation of the Penh parameter utilizes the change in expiratory flow pattern, which some interpret as bronchoconstriction.

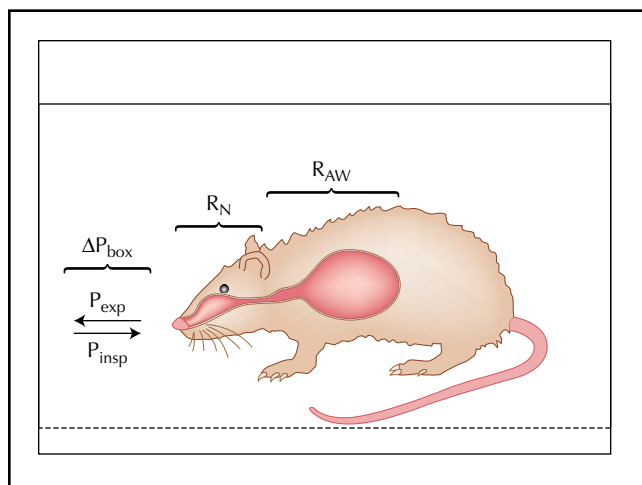


Figure 1. Schematic of whole body plethysmography to estimate nasal obstruction in rodents. Total box pressure (P_{box}) fluctuates with inspiration (P_{insp}) and expiration (P_{exp}) as the animal breathes. Changes in box pressure over time (ΔP_{box}) can be used to calculate enhanced pause (Penh). Alternatively, respiration rate can be directly measured. Rodents are obligate nose breathers. Protocol and dosing regimens assume that nasal resistance (R_N) is greater than lower airway resistance (R_{AW}). If $R_N \gg R_{AW}$, then changes in Penh or respiration rate are interpreted as changes in R_N .

It has been used to estimate lower airway reactivity in asthmatic rodents, and therefore a central criticism is that any upper airway obstruction (ie, nasal) is ignored in most interpretations in experimental results. Some studies have taken advantage of WBP in rhinitis models where intranasal challenge protocols are designed for allergen delivery to be limited to the nose, and not to reach the deep lung (discussed in greater detail later). For example, Nakaya et al. [21•] used allergic BALB/c mice to measure increases in Penh after intranasal histamine or allergen challenge. Although nasal challenge induced modest histologic evidence of inflammation in pulmonary tissues, there were no allergen-induced changes in lower airway resistance when analyzed by separate, invasive techniques that bypassed the nose. Given the lack of lower airway changes in this protocol, they concluded that changes in Penh were due solely to nasal obstruction. However, other direct methods, such as making pressure measurements in the isolated nasal cavity, were not used to corroborate these conclusions. Furthermore, this approach does not address another central criticism of Penh, that it simply represents ventilatory timing, rather than airway obstruction [20,22].

A change in respiratory frequency as measured in WBP is a physiologically relevant parameter that has recently been used to estimate nasal obstruction [23••,24]. In allergic BALB/c mice, direct nasal cavity pressure and flow measurements were taken during forced oscillation maneuvers at constant volume to determine total resistance. Calculations from ventilatory oscillations in rodents are a powerful method to measure

lower airway function, so its use in the upper airways provides a comparable and accurate measure for nasal resistance. Cannulated at the level of the nasopharynx in a retrograde direction, animals were ventilated through the nasal cavity to measure pressure and flow changes. In these studies, allergen-induced increases in nasal resistance were strongly correlated with separate WBP data that showed decreases in respiratory frequency. Analysis of lower airway reactivity in this study showed no allergen-induced changes in lung resistance, nor was lavage cellularity different in allergic rats. Breathing rate has also been used recently as an index of nasal obstruction in guinea pigs with AR, and is correlated well with histamine-dependent responses [25]. Thus respiratory frequency, which could be interpreted as an index of ventilatory timing, appears to be an accurate indicator of nasal obstruction.

It is important to note that the contribution from lower airways or from neurogenic control of breathing is assumed to be negligible in these rhinitis protocols that exploit WBP. Many AR models target the upper airways by minimizing the instilled volume or by conducting intranasal challenges in awake animals. Kinetic studies show that with instilled volumes of 10 μ L or less, 70% is retained in the nasal cavity of anesthetized mice, while 15% to 20% reaches the lung [11]. In awake animals, similar nasal retention can be achieved with volumes as large as 25 μ L, but only 5% or less makes it to the lung. Although delivery to the nose is optimized with these approaches, subtle effects in the lung, either direct or indirect, cannot be completely discounted. Indeed, the premise of the “united airway” hypothesis linking AR to asthma suggests that immunogenic responses in upper and lower airways are connected [26]. To illustrate, Li et al. [27] optimized allergen delivery to either upper or lower airways in mice, and induced localized inflammation in either upper or lower airways, but not both. However, serum eotaxin, interleukin (IL)-5, and eosinophils were equally elevated in all protocols, regardless of preferential inflammation in either nose or lung [27]. Thus, even though airway allergen delivery may be preferentially targeted within the respiratory tract, circulating mediators present during experimental AR and asthma could affect pulmonary airway reactivity or blood flow to the nasal mucosa.

The only certain physiologic measure of nasal obstruction in rodents, therefore, is to isolate the nasal cavity from the lower airway and perform modified pulmonary function techniques. Though presently in limited use, models with retrograde ventilation of the nose and forced oscillations to derive resistance hold the most promise for understanding the airway mechanics of upper airway obstruction in rodents. Related techniques are also used that simply measure the pressure changes in the nose which, as a component of resistance (pressure/flow), also correlated with allergen-induced nasal rubbing, sneezes,

and histamine release in guinea pigs [17,28]. Although the invasive methods provide more direct measurement of nasal cavity physiology than noninvasive approaches, one limitation is the need for euthanasia after measurements are taken.

Although the techniques for directly measuring nasal obstruction have been refined, the data from these studies are only as relevant as the protocol used to induce AR. For example, in guinea pigs, allergen-induced nasal resistance was reversed by antihistamines, but not by an adrenergic agonist [29]. These results disagree with the ameliorative effects of commonly used vasoconstrictors in humans. Furthermore, in results from mouse models described previously [23••], nasal resistance was dependent on immunoglobulin (Ig) E-mediated pathways but not on eosinophil accumulation. This is at odds with a putative, causative role for eosinophils in the late response of airway obstruction [30]. Thus, the newer approaches to measuring airway obstruction appear to reveal some limitations of acute models, further illustrating the need for the development of chronic protocols that may better represent human responses.

Airway Remodeling

In general, animal models of AR are less developed and lack the diversity of asthmatic rodent models. Most of the experimental models of AR involve acute rodent studies ranging from days to weeks, with at most 12 exposures to allergen before measuring endpoints. Although these models have provided much insight into the early and late inflammatory and obstructive responses, accompanying histopathologic descriptions have been either vague or inaccurate. Like asthma, AR is a chronic disease, marked by episodic rounds of inflammation, yet few rodent AR studies have been designed to examine long-term alterations in the nasal mucosa. This void might easily have been filled, in part, by examining the nose from mice used in chronic asthma studies [8–10]. Either the nasal tissues were not collected in these studies, or the data have yet to be reported. Some of the disagreement in rodent and human data could be explained by long-term alterations in airway wall in human nasal tissue that are not present in acute AR models.

The rodent and human nose share similar types of nasal epithelium, but have distinct gross structural differences and distribution of epithelium. Interspecies variability in nasal gross anatomy has been emphasized in previous reviews [31,32••]. Marked differences in airflow patterns among mammalian species are primarily due to variation in the shape of nasal turbinates. The human nose has three turbinates: the superior, middle, and inferior (Fig. 2). These structures are relatively simple in shape compared to turbinates in most laboratory animals that have complex folding and branching patterns. In laboratory rodents, evolutionary pressures

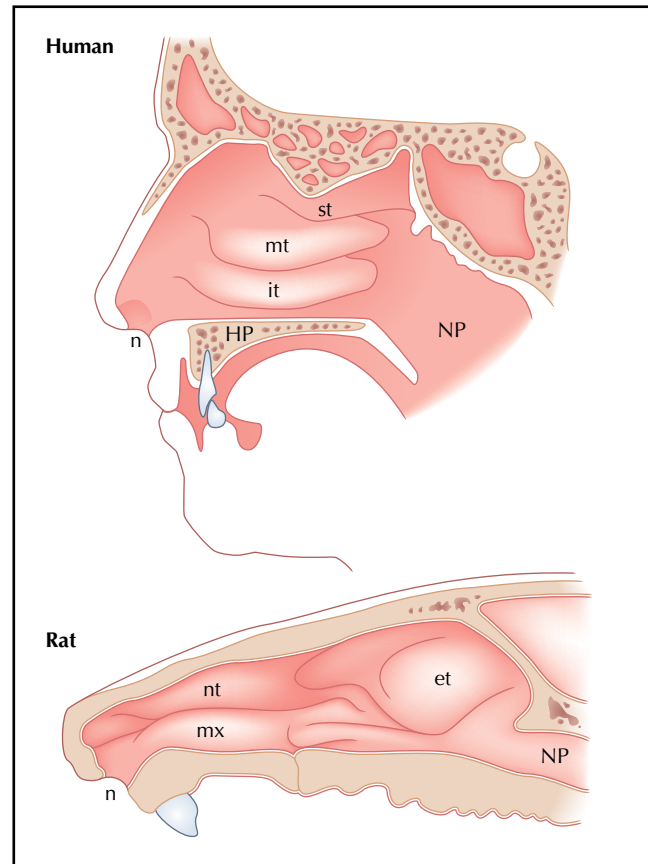


Figure 2. Diagrammatic representation of the exposed mucosal surface of the lateral wall and turbinates in the nasal airways of human and rat. The nasal septum has been removed to expose the nasal passage; illustrations are not to scale. et—ethmoturbinate; HP—hard palate; it—inferior turbinate; mt—middle turbinate; mx—maxilloturbinate; n—naris; NP—nasopharynx; nt—nasoturbinate; st—superior turbinate.

concerned chiefly with olfactory function and dentition have defined the shape of the turbinates and the type and distribution of the cells lining the turbinates. In the proximal nasal airway, the complex nasoturbinate and maxilloturbinate of small laboratory rodents probably provide better protection of the lower respiratory tract than the simple middle and inferior turbinates of the human nose. Mucosal swelling in turbinates, especially where they are in close opposition to the septum and lateral wall, can impede both airflow and mucus drainage through the nasal cavity.

Another major difference is the distribution of epithelial types in rodents and humans. Gross et al. [33] morphometrically determined that approximately 50% of the nasal cavity surface area in rats is lined by sensory neuroepithelium. By comparison, olfactory epithelium in humans is limited to an area of about 500 mm², which is only 3% of the total surface area of the nasal cavity. The majority of the nonolfactory nasal epithelium of laboratory animals and humans is ciliated respiratory epithelium. Although this pseudostratified nasal epithelium

is similar to ciliated epithelium lining other proximal airways (ie, trachea and bronchi), it also has unique features. Nasal respiratory epithelium in the rat is composed of six morphologically distinct cell types: mucous, ciliated, nonciliated columnar, cuboidal, brush, and basal. We have identified the nasal transitional epithelium, which consists of simple cuboidal cells and lines the proximal airways and maxilloturbinates of rodents, as a sensitive epithelium to undergo metaplastic responses to inhaled stimuli, including allergens [34]. It is unknown if similar metaplastic changes occur during human AR.

Most of the histopathologic analyses in both humans and rodents have been in regions with respiratory epithelium, where the character of the mucus-secreting apparatus and underlying mucosa are evaluated. The anterior portion of the middle and inferior turbinates are common sampling sites for biopsies in humans, partly because of their accessibility (Fig. 2). In rodents, by comparison, analyses are usually in the nasal septum and lateral wall, as well as sites that unfortunately are not clearly identified in the methodological descriptions. Thus, when responses in respiratory epithelium of rodents and humans are compared, the surface epithelium may be similar, but the cellularity and vascularization of the underlying mucosa may be quite different and belie inaccurate pathologic conclusions. For example, the septal mucosa overlies cartilage, whereas the mucosa of turbinates overlies bone. From a review of the literature, examples of the limitations of histopathologic descriptions in both human and experimental AR include the following: 1) inconsistency in site-specific selection for evaluation; 2) misidentification of nasal anatomy; and 3) use of subjective quantitative and qualitative analyses (eg, number of goblet cells versus amounts of stored mucosubstances). There is no common approach for histologic evaluation by clinicians or by researchers in AR models, and thus comparisons are relatively limited.

The lack of detailed anatomic descriptions of nasal remodeling in rodent AR may reflect the lack of similar detailed reports from human AR. Early analyses of human responses focused on goblet cell enumeration, where modest increases during seasonal allergic rhinitis were not statistically significant [35]. Using an acute challenge protocol, we have documented a similar lack of hyperplasia in allergic Brown Norway rats, but also have measured a profound increase in the amounts of intraepithelial mucosubstances [34]. Thus, hypertrophy and hyperproduction of mucus, rather than goblet cell hyperplasia, may underlie the mucus hypersecretion associated with human AR. Supporting this notion is our observation of secreted mucosubstances in the nasal lumen of allergic rats, which parallels the findings of Berger et al. [36], who found more actively secreting goblet cells in AR patients than in healthy controls. These features are likely overlooked with routine examination,

and can be underestimated if mucus detection relies on only a single stain, rather than both periodic acid–Schiff (PAS) and alcian blue, which stain for neutral and acidic mucosubstances, respectively.

Infiltrations of eosinophils, neutrophils, and mast cells are commonly reported in both AR models and in clinical studies [21•,24,34]. Eosinophils in biopsies and in nasal lavage fluid are highly correlated with most symptoms in AR patients [30,37]. Nitric oxide, leukotrienes, and interleukins derived from eosinophils are potential mediators of nasal obstruction and goblet cell responses during AR. However, at least two animal studies have found no causative role for eosinophils in AR responses. Blockade of IL-5 in guinea pigs inhibits eosinophil accumulation in nasal mucosa, but mucus secretion and nasal airway obstruction are unaffected after chronic allergen exposure [38]. Furthermore, in IgE-receptor-deficient mice, nasal obstruction was independent of eosinophil recruitment into nasal tissues [23••]. Although these results appear to disagree with conventional thought on eosinophils in AR responses, it should be noted that eosinophils are strongly associated, but not clinically proven, to mediate late responses that lead to obstruction in human AR [30,37]. These results from animal studies of AR are not unprecedented, as eosinophil-independent pathways of airway hyperreactivity and mucus cell metaplasia have also been demonstrated in murine asthma models [39,40]. More studies with chronic models of AR are needed to clarify the role of eosinophils in both allergic asthma and AR.

Histamine-dependent pathways initiated from activated mast cells are well defined in AR. Histologically, increased numbers of degranulated mast cells are detected and identified in turbinate biopsies from patients with AR [41,42]. Kinetic studies in response to allergen provocation in human AR demonstrate mast cell migration from the lamina propria into nasal epithelium where degranulation occurs [43]. However, descriptions of nasal mast cell numbers or their histopathology are rarely reported in AR models. After 2 weeks of allergen challenge, mast cell migration, but not increased numbers or degranulation, was detected in the nasal airways of allergic guinea pigs [44]. Longer time periods were not examined to determine if mast cell numbers eventually would increase. In a more recent report from a chronic mouse model of fungal AR, descriptions of mast cell kinetics into the epithelium and mucosa are more reminiscent of human AR [45•]. Despite the subjective evaluation and misidentification of nasal anatomy, this model reproduces many key features of human AR besides mast cell pathology. Specifically, the lesions include epithelial injury, shedding, invaginations, hyperplasia, and secretions, as well as thickening of lamina propria and progressive infiltration of eosinophils. However, this report is primarily descriptive, as numeric density of mast cells or morphometry of other histologic features were not evaluated.

Conclusions

There is a critical need for more detailed descriptions of airway mucosal and epithelial alterations in both human and rodent AR. Clinical studies in humans provide suggestive evidence that hallmarks of asthmatic airway remodeling are also present in the nose: epithelial damage; basement membrane thickening; mesenchymal changes (including the transformation of mucosal myofibroblasts); eosinophilic infiltrates; mast cell migration; and alteration in the mucus-secreting apparatus [3,46••]. However, these findings are few and inconsistent, and are practically absent in rodent models of acute AR. Without a common methodological approach for the collection and analysis of both rodent and human tissues, relevant comparisons and meaningful conclusions will be difficult.

The first step to creating a relevant AR model in laboratory animals is to focus on the development of models of chronic disease. Acute protocols have served well to describe inflammatory cell infiltration and reorganization of the mucus-secreting apparatus. It is not clear if the nasal structures in rodent AR exhibit notable tissue remodeling, such as neovascularization in mucosa, collagen deposition, or submucosal gland development. Thus, more studies using weekly challenge regimens and extended low-dose exposures, similar to those used in mouse models of chronic asthma, may result in more clinically relevant alterations in nasal mucosa.

With regard to evaluating nasal pathology in rodents, more systematic and thorough approaches are needed. Strategies for histopathologic analyses should begin by consulting nasal diagrams generated by Mery et al. [47], or using the approach proposed by Young [48]. We have also identified sensitive sites to evaluate respiratory epithelial populations in nasal septum, lateral wall, turbinates, and nasopharynx, where we have detected consistent epithelial responses in both allergic rats and mice [34,49]. Analysis of the nasolacrimal duct as a sensitive site for allergic rhinoconjunctivitis is almost completely ignored in rodent AR models. Similarly, little attention is given to rodent sinus airways during experimental AR, though both structures are easily identified in rodent nasal maps. A more thorough approach, preferably combining subjective descriptions with quantitative morphometric approaches, would greatly strengthen the utility of animal models of AR.

AR is a disease that is on the increase, without satisfactory therapies or strong animal models. A translational approach that unifies histopathologic and physiologic data from human and animal AR is needed to understand and clarify mechanisms of chronic responses in the allergic nose. Extension and incorporation of existing research on rodent asthma would greatly benefit progress in improving the design and analysis of rodent models of AR.

Acknowledgments

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