Rodent Allergens

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Rodent allergens play a significant role in the pathogenesis of asthma and allergic rhinitis, and are potent causes of acute and chronic symptoms. This has long been apparent in occupational settings, particularly in the laboratory, but has been most recently studied and found to be important in home environments. These allergens have been suggested as uniquely important among inner-city children with asthma. Furthermore, rodents have become increasingly popular as pets. With recent awareness of significant exposure in a variety of settings, hypersensitivity to rodents has become increasingly important. This review focuses on the importance of rodent allergens, concentrating on mouse and rat, but including other potentially important rodents such as gerbil, hamster, and rabbit. It also discusses the pathogenesis, diagnosis, prevention, and management of rodent allergy.

Introduction

Rodent allergens have been noted as significant causes of asthma and allergic disease. The most studied exposure has been in occupational settings among workers exposed to laboratory animals. Epidemiologic studies show that up to one third of those exposed to laboratory animals will develop symptoms of laboratory-animal allergy, such as rhinitis, conjunctivitis, and contact urticaria, and one in 10 of those exposed may develop asthma [1–3]. In recent years, rodent allergens have been studied in home environments and other populations outside the laboratory [4••,5••]. Mouse allergens were recently found to be highly prevalent in inner-city homes of children with asthma [4••]. It was learned that this prevalent exposure contributed to sensitization [5••], suggesting that these allergens may be uniquely important among this population. While less is known about other rodent allergens in general populations, we do know that rodents such as gerbils, hamsters, and rabbits have become increasingly popular as household pets. Because of the increased prevalence of exposure and sensitization to these allergens, it is important to identify them and to discuss methods of environmental control. These methods may help prevent the development of rodent allergy. This review focuses on rodent allergens and evaluates the etiology, pathogenesis, diagnosis, management, environmental control, and prevention of rodent-allergen hypersensitivity which may be important in the development of allergic and atopic disease.

Etiology

Allergens

Many of the rodent allergens have been identified and characterized [6] (Table 1). The most studied and well described are mice and rat allergens. Three mouse allergens have been identified. Mus m 1, or MUP (mouse urinary protein), has a 19 kd molecular weight as determined by dodecylsulfate-polyacrylamide gel electrophoresis. This allergen is found in the rodents' urine as well as hair follicles and dander. Mus m 1 is four times higher in male mice than in females because gene expression is testosterone-dependent. A second allergen, Mus m 2, is a glycoprotein with a molecular weight of 16 kd that is found in hair and dander, but not in urine [7,8]. A final allergen is albumin, which is allergenic in about 30% of mice-sensitive individuals [7–10].

Previously, two rat allergens had been identified in urine, saliva, hair, and dander. Rat n 1A has a molecular weight of 20 to 21 kd and Rat n 1B has a molecular weight of 16 to 17 kd. Rat n 1A was originally thought to be a prealbumin, but more recent studies have demonstrated that both allergens are variants of $\alpha_2\mu$-globulin and have been determined as members of the lipocalin family of proteins [11]. More recently, rat fur and saliva have been further studied. Rat fur contains five major allergens of relatively high molecular weights (>22 kd), while salivary glands demonstrate at least five other major allergens with lower molecular weights (<22 kD). Several more minor or intermediate allergens have been identified, although not well characterized [12]. As it does in mice, rat albumin also possesses some allergenic activity, with about 24% of rat-allergic individuals showing sensitivity to rat albumin.

Although allergens from guinea pigs have not been fully characterized, two antigenic fragments, termed Cav p 1 and Cav p 2, have been identified and are found in the animals' urine, hair, and dander [13]. Likewise, rabbit allergens are not well characterized, but at least two specific allergens, Ory c 1 and Ory c 2, have been identified. Ory c 1 is a glycoprotein with a molecular wieght of 17 kd that is found in saliva, hair, and dander. Ory c 2 is found in hair, dander, and

Table 1. Rodent allergens

Animal	Allergen	MW (kd)	Source	Biologic function
Mouse (*Mus musculus*)	Mus m 1 (prealbumin)	19	Hair, dander, urine	Lipocalin-odorant binding protein
	Mus m 2	16	Hair, dander, urine	Unknown
	Albumin		Serum	Serum protein
Rat (*Rattus norvegicus*)	Rat n 1A/Rat n 1 B ($\alpha_{2\mu}$-globulin)	16–21	Hair, dander, urine, saliva	Lipocalin-pheromone binding protein
Guinea pig (*Cavia porcellus*)	Cav p1		Hair, dander, urine	Unknown
	Cav p2		Hair, dander, urine	Unknown
Rabbit (*Oryctolagus cuniculus*)	Ory c 1	17	Hair, dander, saliva	Unknown
	Ory c 2		Hair, dander, urine	Unknown

MW—Molecular weight.

urine [14]. Other common rodents in laboratory and home-pet settings, such as gerbils and hamsters, have been reported to cause allergic reactions, but their specific allergens have not been well studied or clearly characterized.

Aerodynamics and environmental distribution

The aerodynamic and environmental properties of many of these allergens have been well characterized and have been most studied in occupational laboratory settings. Rodent allergens are found in a wide range of particle sizes, and it has been shown that small and large particles can migrate throughout a facility. For example, Ohman *et al.* [15] studied mouse allergen in public areas of an animal facility, and found that rooms connected to the animal facility, but not actually containing mice, had detectable allergen on particles ranging in size from 0.4 to 3.3 μm. In free-standing, independently ventilated areas such as a cafeteria not connected to a mouse facility, the allergen was predominantly greater than 10 μm in size [15]. This suggests that mouse allergens can be carried substantial distances in animal facilities.

Airborne mouse allergen levels in the Ohman study ranged from 16.6 to 563 ng/m^3 in rooms with mice and 1.2 to 2.7 ng/m^3 in rooms without mice, the highest levels associated with direct mouse contact, as would be expected [15]. Another study showed that levels varied with both the number of mice and degree of work activity in the rooms, suggesting that in addition to the number of rodents, disturbance and activity of the allergen may increase airborne allergen levels [16].

Airborne rat allergens are carried on particles ranging from 1 to 20 mm with the majority on particles less than 7 μm. These allergens can remain airborne 60 or more minutes after disturbance. Allergen levels have been studied in different settings, and the level of exposure has been shown to be primarily dependent on activity, with the highest exposures occurring among cage changers, room cleaners, and animal feeders [17,18]. Levels are also increased with higher animal density and decreased relative humidity [19].

Guinea pig allergen has been measured by radioallergosorbent test (RAST) inhibition, and a high percentage of this allergen is found on particles less than 0.8 μm in diameter, which remains airborne for long periods. Urine and pelt allergen levels in laboratory facilities ranged from 17 to 90 ng/m^3 in one facility [13].

While these allergens have been well studied and found to be highly prevalent in laboratory occupational settings, only recently have mouse allergen levels been evaluated in home environments [5••,6]. My colleagues and I had the opportunity to evaluate the prevalence of mouse allergen in eight major inner-city areas as a follow-up to the National Cooperative Inner-City Asthma study. In that study of 608 inner-city homes, we found that 95% of all homes had detectable mouse allergen, with levels as high as 618,000 ng/gm in the kitchen, consistent with a high prevalence of mouse allergen exposure [5••]. This was one of the first studies to describe the potential importance of mouse allergens in home environments, particularly among inner-city children with asthma.

Furthermore, it has been observed that as rodents such as hamsters, gerbils, rabbits, and even mice and rats have become increasingly popular as pets, significant exposures to these allergens in home environments could be important in the development of atopic disease.

Pathogenesis and Diagnosis

Pathogenesis

Not unlike many of the other inhaled allergens, the development of rodent allergy is related to both individual susceptibility and exposure. Individual susceptibility by history of allergy and genetic tendency of an individual toward atopy are clearly important risk factors. One suggested factor that may increase the risk of developing allergy to rodents is a tendency toward hypersensitivity to other animal allergens such as cat and dog [20]. Therefore, it may be important to determine which patients may be more susceptible to developing rodent allergy, and to aid in early intervention for prevention and control [20].

Environmental exposure is also another important risk factor in the pathogenesis of developing rodent allergy. In laboratory occupational settings, epidemiologic studies have shown that the greater the exposure to rodent allergens, the more likely one will become sensitized and have symptoms related to work [21]. For example, animal handlers and caretakers develop allergic symptoms more frequently than those who do not work in direct contact with the animals [22]. Hollander *et al.* [21] noted a 42-fold higher prevalence of symptomatic rat allergy among heavily exposed atopic individuals. Therefore, identifying those with increased exposure is important in estimating risk and implementing measures for prevention.

Different job descriptions are associated with vastly different exposures to animal allergens [23]. The highest exposures typically occur in handlers who are responsible for cage cleaning and feeding of the animals. "Users" are defined as persons involved in daily experimental use of the animals. These include technicians, students, and investigators. These people have intermittent contact with the animals, and therefore have lower levels of exposure. Unexposed workers are secretaries and administrators who have no direct contact with the animals. When specific tasks are considered, cleaning cages or manipulating active animals is associated with significantly higher levels of airborne rat allergen exposure [24]. Further, it has been shown that symptomatic inflammatory responses in sensitized workers correlates with airborne allergen concentrations, and that more symptoms occur with active cage cleaning than with quiet activity [24,25].

When looking at a combination of risk factors for development of sensitization to rodent allergens, exposure appeared to be of most importance. Cullinan *et al.* [26] evaluated a cohort of 342 employees at a laboratory animal facility. The researchers analyzed the risk factors of allergen exposure, atopy, and smoking. Atopy to other allergens increased the odds ratio of developing sensitization and symptoms to rodent allergens, as did cigarette smoking, but exposure appeared as the most important determinant. In addition, Heederik *et al.* [27] analyzed cross-sectional data from 1062 animal laboratory workers and found that rat allergen sensitization risk increased with increasing exposure intensity and that workers who were atopic had clearly elevated sensitization risk related to exposure.

Another interesting observation is that even those who do not have direct contact with animals can have work-related symptoms. Such symptoms were reported in one study in 56% of workers who had no direct contact with animals [22]. Furthermore, study has suggested that even children of parents occupationally exposed to rodent allergens present with a significantly higher incidence of sensitization to rodents compared with children of non-exposed parents [28•]. This suggests that any exposure in environments where rodents are present may induce disease, and that this exposure can even be spread to the home environments of these employees. This is not surprising given the data regarding the widespread distribution of these allergens in animal facilities.

In home environments, recent evaluation of mouse allergens among inner-city homes of children with asthma found a relationship between atopy, exposure, and sensitization, not unlike what has been found in laboratory occupational settings [5••]. Furthermore, a recent study evaluating Japanese patients who kept hamsters as pets, found that those being studied developed earlier onset of bronchial symptoms and elevated IgE levels to these animals, and demonstrated rapid remission and cessation of symptoms after removing these pets from the home [29]. Although other rodent allergens have not been evaluated extensively, it is reasonable to predict from these preliminary studies that high levels of exposure and atopy are significant risk factors for developing sensitization in home environments as well as in occupational settings. Further study is desirable to fully evaluate the role of rodent allergens in home environments.

Diagnosis

Diagnosis begins with a thorough history of symptoms and precipitating factors. Often, the diagnosis becomes clear, such as when an individual who works around rodents develops acute symptoms in the work environment. However, as is often in the case of pet owners of rodent as pets, patients often experience chronic, low-grade symptoms, and the history may be difficult to correctly interpret, especially if other indoor allergens cloud the diagnosis. Furthermore, many patients deny that symptoms arise from their beloved household pets, which can make the history inconclusive to the diagnosis.

The next step in the diagnosis of rodent allergy involves determining allergen-specific IgE, either by skin tests or in vitro RASTs. Although extracts are available for mouse, rat, rabbit, gerbil, hamster, and guinea pig, little is known about their standardization and predictability. In addition, other tests such as correlating pulmonary function tests with exposure, bronchial, nasal or conjunctival provocation challenges may help with diagnosis, but most of these challenge procedures should generally be viewed as research tools, and logistically are not appropriate for clinical use. A simple diagnostic tool may be a trial of avoidance of the presumed offending rodent.

Control of rodent allergens

Currently, less is known about the control of rodent allergens than some of the other indoor allergens such as dust mite. For rodents in the laboratory setting, maintaining adequate ventilation and filtering systems in the building should aid in reducing exposure. Studies have shown that newer individually ventilated cage systems may prevent allergen exposure compared with conventional, less ventilated systems [30•,31]. Allergen exposure may also be minimized if rodents are housed in sealed

individual ventilation systems under negatively pressurized cages [32,33•]. Furthermore, personal protection may include adequate cleaning facilities and protective clothing such as masks and gloves for susceptible workers. In addition, waste and soiled bedding require appropriate removal, and care should be made to avoid contact with rodent urine because urine is one of the major sources of allergen. Finally, periodic medical surveillance and monitoring should be implemented to determine highly susceptible individuals at risk for developing rodent allergy. Appropriate protection and medical intervention may then be implemented in a timely fashion [33•,34].

In home environments, control of rodent allergens have not been well studied, and there are no studies to date evaluating the potential role of environmental intervention in reducing rodent allergens, and pest control among at-risk homes in both urban and suburban areas. There is some literature on environmental control measures using mouse extermination [35], but these have not been applied to homes of patients with atopic disease and asthma. This author is currently involved in a project investigating the role of environmental intervention in mouse allergens among inner-city homes of children with asthma. The hope is that through this and other projects, we will further understand the role of rodent allergens in home environments.

For rodents that are household pets, little is known about control of these allergens. In general, we can apply principles used in control of other well-studied allergens such as cat. The first-line treatment in control of rodent allergens is removal of the animal from the home. Specifically, if a patient has significant symptoms related to pet exposure, this recommendation must be stressed. While it is not known how long it can take for rodent allergen levels to decrease after removal from the home, studies of cat allergens suggest that it may take 4 to 6 months before allergen levels are significantly reduced to perceive clinical benefit. The allergen levels can fall more quickly if extensive environmental control measures are taken, such as removal of carpets, curtains, upholstered furniture, and other reservoirs for allergen. Thorough, aggressive, and repeated cleaning will obviously help decrease allergen levels faster as well.

Unfortunately, a high proportion of patients is reluctant and unwilling to remove their household pets. Many people view pets as members of the family, and would refuse to even keep them out of the bedroom or outside, let alone get rid of them completely. If the rodent can't be removed, there are several environmental control measures that can be implemented. Keeping the animal out of the bedroom or only outdoors may decrease allergen exposure. It is unclear whether washing the rodent or using high-efficiency particulate air (HEPA) filters would be helpful, but studies have suggested that these are helpful in reducing cat allergen, and may be considered for families who refuse to remove the rodent from the home [36–38].

Medical Management

While medical management of rodent allergy should begin with attempts to reduce exposure as outlined above, appropriate allergy and asthma medications may be administered prior to exposure to help control symptoms. Oral antihistamines, B_2 agonists, and allergy eye medications may be used prior to short acute exposure (*ie*, visiting a relative who owns a rodent, or visiting a laboratory animal facility) and may help mask the allergic symptoms. However, it should be stressed that none of these medications are curative, and it is not recommended that these medications be used instead of environmental control measures. Furthermore, it should be noted that the highly sensitive individual with continued symptoms despite reduced exposure may require absolute avoidance of the animal allergen.

Uncontrolled studies of immunotherapy to other animals such as mice, rats, and rabbits have shown some improvement [39], but the long-term effects on chronically exposed sensitized individuals remain to be determined. Although rare, a person allergic to an animal may experience a life-threatening reaction from an animal bite, scratch, or needle contaminated with animal allergens. If this ever arises, epinephrine kits may be implemented. Such patients should be instructed on how to carry and use these devices if they are determined to be susceptible to life-threatening reactions.

Conclusions

Rodent allergens are important in the pathogenesis of allergic disease. The major rodent allergens include mouse and rat, but atopic disease has been implicated in other animals such as gerbils, hamsters, rabbits, and guinea pigs. Environmental control measures should be the first-line treatment in prevention and medical management of disease. In summary, while rodent allergens are potent triggers for allergic disease, environmental control measures and avoidance are important in preventing morbidity from these allergens. Medications and immunotherapy may also be considered when necessary.

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