Comparative Immunology of Allergic Responses

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Abstract

Allergic responses occur in humans, rodents, non-human primates, avian species, and all of the domestic animals. These responses are mediated by immunoglobulin E (IgE) antibodies that bind to mast cells and cause release/synthesis of potent mediators. Clinical syndromes include naturally occurring asthma in humans and cats; atopic dermatitis in humans, dogs, horses, and several other species; food allergies; and anaphylactic shock. Experimental induction of asthma in mice, rats, monkeys, sheep, and cats has helped to reveal mechanisms of pathogenesis of asthma in humans. All of these species share the ability to develop a rapid and often fatal response to systemic administration of an allergen—anaphylactic shock. Genetic predisposition to development of allergic disease (atopy) has been demonstrated in humans, dogs, and horses. Application of mouse models of IgE-mediated allergic asthma has provided evidence for a role of air pollutants (ozone, diesel exhaust, environmental tobacco smoke) in enhanced sensitization to allergens.

INTRODUCTION

Allergy is a term describing a state of hypersensitivity to an antigen. The immune system is structured to recognize and respond to pathogens for protection of the host. When the immune response becomes misdirected toward foreign materials (allergens) that are not potentially injurious to the host, the resultant immune response is usually detrimental. There are several different types of hypersensitivity, including types I–IV as originally described based on the immunological mechanism by Gell and Coombs (1). The term allergy or allergic response refers to type I hypersensitivity, which is mediated by antibodies of the immunoglobulin E (IgE) isotype, the topic covered herein.

Components of the Allergic Response and Mechanisms Involved

The allergic response is initiated by exposure to an allergen, which is usually one of the following: pollen, house dust mites, molds, animal danders, food components, venom, or saliva from insect bites. Chemical metabolites from drugs can also become allergens. Most allergens are small protein molecules that are highly soluble in mucus. On occasion a metabolite of a drug can act as a hapten, bind to a larger carrier protein in the body, and become an allergen. In several species, including humans, there is a genetic predisposition to develop allergy. Such individuals are called atopic.

An allergy is initiated when the allergen enters the host (which can be mouse, human, or one of many different mammalian species), often, but not always, through a mucosal surface. The allergen is taken up by dendritic cells, which transport the allergen to a local lymph node for processing and presentation to T lymphocytes. Within the dendritic cell in the lymph node, the allergen is digested into small peptides, bound to a class II major histocompatibility molecule, and then displayed on the surface of the cell for follicular T cells to recognize. Once a T cell with the appropriate T cell receptor has bound to the allergen peptide, the T cell becomes activated. The dendritic cell drives the type of response the T cell will make (which depends on molecular characteristics of the antigen/allergen). If the primary cytokine produced by the dendritic cell is IL-4, the T cell will become a T helper cell type 2 and make large amounts of IL-4 and IL-13. In contrast, if the dendritic cell makes mostly IL-12, the T cell will become a T helper type I cell and make mostly interferon γ. The B lymphocytes present in the lymph node germinal centers can bind the allergen by the immunoglobulin-type molecules that serve as B cell receptors on the cell membrane. Once a B cell has bound the allergen onto its B cell receptors, it receives additional signals: from binding co-receptors on the T cell and by binding the secreted T cell cytokines IL-4 and IL-13 to their respective receptors on the B cell. Binding of IL-4 and IL-13 to their respective receptors on the B cell further stimulates the B cell to develop into a plasma cell that makes IgE. The IgE produced by plasma cells is specific for the allergen that stimulated the B cell to become activated.

IgE is an antibody that consists of two heavy chains (epsilon) and two light chains. It is approximately 180 kDa, having one domain more than IgG. It is present in nanogram amounts in the blood. IgE does not fix complement or agglutinate with antigens. It binds tightly to FcεRI, the high-affinity IgE receptor, on tissue mast cells and blood basophils. There is a second IgE receptor, low-affinity receptor (FcεRII or CD23), a C-type lectin present on B lymphocytes; it has a role in feedback regulation of the immune response. Most of the IgE produced binds almost immediately to FcεRI on mast cells, and it stays on those cells for many months. The mast cell is then sensitized to the allergen. If the host is reexposed to the allergen and reaches the mast cells, the receptors to which the allergen is bound are cross-linked by the IgE-allergen, and degranulation of the mast cell

is triggered (**Figure 1**). The process of degranulation causes release of preformed mediators, including histamine, heparin, and serotonin, and stimulates arachidonic acid metabolism by phospholipase A2 activation in the cell membrane. Metabolism of arachidonic acid occurs by two pathways: cyclooxygenase and lipooxygenase, which leads to production of eicosanoids (prostaglandins, thromboxane, and leukotrienes). These mediators have a slower onset of action but are potent in eliciting inflammation in allergic diseases. Prostaglandin D2 recruits eosinophils and Th2 cells to the area; leukotrienes C4, D4, and E4 contribute to the inflammatory response.

The process of mast cell degranulation is immediate upon binding of the mast cell–bound IgE to its allergen. Histamine causes smooth muscle contraction, vasodilation, and increased vascular permeability—these physiological effects cause the clinical signs that are observed in diseases like hay fever, asthma, and systemic anaphylactic shock. The mast cell also plays a role in enhancing the allergic response by inducing further IgE synthesis by B lymphocytes. These cells express a molecule CD40 ligand, which binds to CD40 on the B cell, and they also produce IL-4—both of which stimulate the class switch to IgE by the B lymphocyte.

The presence of eosinophils is a hallmark of allergy, often showing up as elevated blood eosinophil counts as well as infiltration in tissues such as the lung. Chemokines, collectively referred to as eotaxins, are produced and released during the IgE-mediated allergic response. These include CCL11, CCL24, and CCL26 (eotaxins 1, 2, and 3, respectively). These eotaxins attract and activate eosinophils by binding to the eotaxin receptor CCR3 on the eosinophils. The eosinophil has a role in amplification of the allergic response, as they have been shown to downregulate the Th1 response

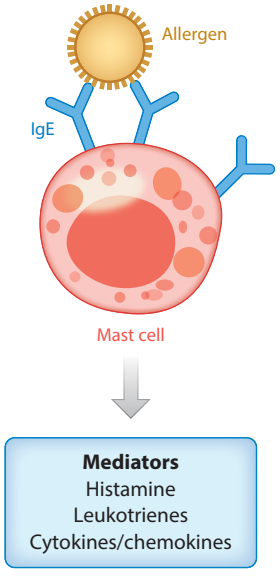

Figure 1

The mast cell, which is present in connective tissue throughout the body, has FcεR1 receptors that bind to immunoglobulin E (IgE) molecules. Once IgE has been produced in response to allergen by the immune system, it binds tightly to these mast cell receptors. When the allergen enters the body, it will bind to IgE molecules on the mast cell membrane, cross-linking them and triggering the cell to release its granule contents. The mediators contained in the granules, such as histamine, cause physiological effects (increased capillary permeability, smooth muscle contraction, and vasodilation), thus producing clinical signs of the allergic disease. Other mediators, such as leukotrienes, prostaglandins, and chemokines, are formed after the mast cell is activated and have effects similar to the stimulation of eosinophil chemotaxis.

and secrete Th2 cytokines. Eosinophils are also very capable of killing parasites (discussed below). In chronic allergic asthma, eosinophils are an important cell type in the remodeling of airways.

Allergy in Humans

It is estimated that approximately 40% of people have some type of allergy. Allergic rhinitis is present in 10–30% of adults, and 8% of children have a food allergy. Animal danders are an important allergen source, with up to 15% of the population documented as allergic to cats and 10% allergic to dogs. Many cases of fatal anaphylactic shock are induced by drug allergy. Allergy has increased in incidence over the past 20 years, with environmental factors often cited as a contributing cause. In 2009, 10% of children had asthma compared with 8% of adults (2).

The clinical syndromes caused by allergy include systemic anaphylaxis, acute urticaria (hives), seasonal rhinoconjunctivitis (hay fever), asthma, and food allergy. All of these are caused by the IgE-mediated mechanism described above. The route of entry of the allergen into the host varies. Anaphylaxis most commonly, but not always, is caused by injection (intravenous, intramuscular, or via insect bite). The respiratory tract is the major route for hay fever and asthma induction. Urticaria is caused by either skin or systemic allergen exposure, and asthma is initiated by inhalation. The oral route is the entry site for food allergens (1).

Anaphylaxis is instigated by a rapid and widespread degranulation of mast cells with resultant mediator release. The mediator-initiated smooth muscle contraction, vasodilation, and increased capillary permeability cause laryngeal edema and circulatory collapse. Anaphylactic shock can cause death if not treated immediately with epinephrine, an α-adrenergic receptor stimulant, which reverses the physiological effects (1).

Allergic rhinoconjunctivitis, or hay fever, is generally caused by inhaled pollens. The clinical signs include a runny nose, excessive lacrimal secretion, itchy eyes, sneezing, and increased mucus production in the upper respiratory tract. Most people with hay fever respond well to antihistamines (3).

The development of raised swellings on the skin, hives, can occur after contact with allergens (such as holding a dog or cat). They can also result from a systemic contact, such as a food or drug. They are pruritic and variably responsive to antihistamines (4).

Asthma is an IgE-mediated condition, which is initiated by sensitization to allergen, but in which chronicity airways become remodeled and the lung undergoes changes in structure that include hyperplasia of mucus-secreting cells and alterations in airway submucosal structures. Asthmatics have hyperresponsive airways, which cause constriction and difficulty in breathing. Exposure to allergen causes immediate airway constriction—the asthma attack—but several hours after allergen challenge, the leukotrienes produced often cause a resurgence of airway constriction that has a longer duration than that instigated by the release of histamine. Tissue inflammation is a hallmark, particularly the presence of eosinophils in the lung (5).

Detection and Measurement of IgE and Other Homocytotopic Antibodies

The very low concentration of IgE in the blood makes it difficult to measure this antibody isotype by methods such as gel diffusion. Because IgE neither precipitates with antigen nor fixes complement, these types of assays cannot be used to detect IgE. In the initial days of IgE's discovery in humans, and later in other species, in vivo assays were used to detect and quantitate the antibody. These early methods took advantage of the cytophilic nature of IgE. The Prausnitz-Küstner test was performed by injecting serum from a patient suspected of having allergy into the skin of a nonallergic person. After 24 h, the allergen was injected into the same site. If the injected site developed a wheal-and-flare reaction, it was determined that the person from whom the serum

came was allergic to that allergen. To differentiate IgE from other antibody classes that might also bind to mast cells, the serum was first heated for at least 30 min at 56°C (6). The ability of IgE to bind to mast cells is destroyed by such treatment. As research on IgE progressed to mouse models, a test called passive cutaneous anaphylaxis (PCA) was developed. The PCA reaction is like the Prausnitz-Küstner test in the sensitization phase, but the allergen is injected by the intravenous route along with Evans blue dye. Within 10–15 min after such an injection, blue wheals are apparent where the sensitization injections were made. It is possible to determine a PCA titer by making serial injections of diluted serum (1:4, 1:8 . . . 1:256). Mouse IgE was generally titered by PCA on the dorsal skin of a rat, as the homology between mouse and rat is sufficiently close to allow mouse IgE to sensitize rat mast cells. In more recent years, the radioallergosorbent test was used to test for IgE by using an antibody against the IgE (available for human IgE detection long before other species). Current assays for serum IgE are usually done by using the enzyme-linked immunosorbent assay (ELISA) method.

Detection of IgE that is already bound to mast cells in a patient's skin is done by intradermal skin testing, either by injection of 0.1 ml of allergen or sometimes by a prick test. Once allergen is injected into the skin, it rapidly binds mast cell IgE; if there is IgE present that is specific for the allergen, the presence of a wheal indicates that the patient is allergic to that allergen. It should be noted that because IgE stays on mast cells for months and the half-life of IgE in the blood is short (2.3 days for humans), the results of the in vivo and in vitro assays do not necessarily always agree. This is particularly true if the allergen is present seasonally and no longer in the environment when the blood sample is taken. Development of reagents to detect IgE in species such as dog, horse, cattle, and cat has taken longer owing to the difficulty in collecting sufficient amounts of IgE for immunization of rabbits or mice to make antibody reagents. However, in recent years the availability of monoclonal antibody technology and use of synthetic peptide antigens have eliminated the problem.

Interaction of Allergy and Helminth Infection

As stated above, the IgE response is important for immunity to parasites, particularly helminths. Animals and people with helminth infestations, such as *Ascaris*, have high levels of IgE specific to antigens of the worm. In schistosomiasis, the development of IgE to worm larvae is critical to ultimately cure the infestation. IgE binds to eosinophils by the low-affinity receptor (FcεII, also known as CD23) and provides the eosinophil with a means to identify antigens on the parasite cuticle. This process is called antibody-dependent cellular cytotoxicity, and the eosinophil releases several toxic proteins: major basic protein and eosinophil cationic protein, which mediate parasite destruction. Thus, the presence of eosinophils is a hallmark of both allergy and parasitism (1, 7).

There have been many theories on the relationship of allergy and parasitism. The increase in allergy in the industrialized nations is accompanied by better sanitation and health care, which translates into less parasitism. There is some support for the theory that IgE response has become misdirected owing to these changes (8). However, there is accumulating evidence that environmental pollutants, such as diesel exhaust, sidestream smoke, and ozone, enhance the IgE response and promote allergic lung disease (9). Clearly, factors other than decreased parasitism contribute to the development of allergy.

MOUSE MODELS OF THE ALLERGIC RESPONSE

Mouse models have been used extensively to study allergy (10). Mice can produce IgE in response to injected and aerosolized antigens. Intravenous injection of a sensitized mouse with antigen will

result in anaphylactic shock. Sera from mice sensitized to produce IgE have homocytotropic function; i.e., they will sensitize mouse or rat mast cells for antigen-induced degranulation. Like human IgE, mouse IgE is heat labile. The mouse also has an IgG subclass, IgG1, which is capable of sensitizing mast cells for a shorter duration (less than 24 h) and is not heat labile.

A variety of inbred mouse strains have been developed, some of which are T helper type 2 skewed in their immune response and consequently are high IgE responders (Balb/c); other strains (C57BL) are not Th2 skewed and make IgE less readily. These mice are useful for studies on allergy and IgE (11).

Mouse and Rat Models of Asthma

Most studies on asthma performed during the past 20 years have used mouse models. The availability of reagents and inbred strains and ease of handling have been contributing factors. Although the mouse is not exactly like a human, this species has contributed toward our understanding of mechanisms of asthma and has demonstrated mechanisms of airway remodeling that are a result of the asthmatic response (12, 13). In addition, mouse models have helped to decipher the interaction of environmental factors with lung immunity (14). The standard mouse model of asthma involved multiple rounds of parental sensitization, usually with ovalbumin in alum adjuvant. This is followed by aerosol exposure to ovalbumin. Ovalbumin-sensitized mice have been used to document cytokine profiles in asthma models. Our group used ovalbumin sensitization of Balb/c mice to demonstrate the adjuvant effect of environmental tobacco smoke on allergic sensitization (15) and, in another study, the effect of progesterone on allergic asthma (16).

One of the earliest models used to study airway inflammation and hyperresponsiveness was the Brown Norway rat (17). This strain of rat is atopic and thus resembles the human asthmatic in sensitization and elicitation of allergic reactions in the lung. Much of the knowledge we now have about induction of IgE production, elicitation of the allergic response, and the development of airway remodeling after repeated aerosol exposure to allergen has been provided by these species. That said, neither the mouse nor the rat has a clinical syndrome that develops naturally like asthma does in the human patient.

The ability to create gene knockout mice and mice that overexpress certain genes has enhanced our understanding of the role of certain molecules in asthma (18). For example, mice lacking IL-5 show decreased peribronchial fibrosis and a decrease in eosinophil infiltration. In contrast, mice that overexpress eotaxin show enhanced airway remodeling (19). Mice deficient in IL-13, a Th2 cytokine, show decreased airway inflammation and mucus cell hyperplasia (20).

Studies performed in the mid-1970s by our group showed that Swiss-Webster mice exposed to ozone and aerosolized ovalbumin without prior parenteral sensitization were sensitized for systemic anaphylaxis after intravenous ovalbumin administration compared with mice similarly exposed to ovalbumin but not to ozone (21). IgE-containing cells in the lungs of ozone/ovalbumin-exposed mice were significantly more numerous than those from filtered air/ovalbumin-exposed mice (21). This was the first demonstration of the effect of intermittently inhaled ozone on sensitization to an inhaled allergen.

PRIMATE MODELS OF THE ALLERGIC RESPONSE

Primates housed in zoos occasionally suffer from allergy. In one case report, a chimpanzee that showed clinical signs of seasonal rhinitis and conjunctivitis tested positive by skin test to inhalent allergens (22). Testing of Rhesus macaques housed in outside pens at a primate facility revealed

sensitivity to several tree and grass pollens (L.J. Gershwin, unpublished data; 23). However, the greatest body of information on primates and allergy comes from the use of monkeys as models of asthma for humans. In many ways, the rhesus macaque monkey is a more superior asthma model for human asthma than the mouse. The anatomy of the lung is more similar, and the immunology, including mast cell mediators, is identical (24, 25).

Several primate models have been developed to study human asthma. Many groups used *Ascaris* antigen, as most monkeys are sensitized to it naturally owing to roundworm infestation (26). Aerosol of *Ascaris* antigens can induce an asthmatic response in most species that have such sensitization. Studies on the pathogenesis of allergic lung inflammation have been performed using this naturally sensitized model of asthma (26). It is an interesting manipulation of the natural protective role of IgE in intestinal parasitism. In this model, the *Ascaris* antigen is aerosolized, and respiratory disease results. Several dust mite models of asthma have been developed in the Rhesus macaque (27, 28) and in the cynomolgus monkey (29). Our group developed a house dust mite asthma model in the Rhesus macaque; sensitization was accomplished with injections of house dust mite allergen in alum adjuvant accompanied by heat-killed *Bordetella pertussis*, which facilitates induction of an IgE response. These sensitizations resulted in skin-test positivity and airway hyperreactivity following aerosol exposure to the allergen (27). The model was quite successful for studying the pathophysiology and immunology of asthma (30–33).

ALLERGIC RESPONSES OF LIVESTOCK (CATTLE, SHEEP, HORSES, AND PIGS)

Type I hypersensitivity responses of food-producing animals have been reviewed previously (34). Although cattle do not develop asthma naturally as a clinical syndrome, they produce IgE to a variety of allergens. Similarly, IgE is also produced by sheep, goats, swine, and horses. All of these species are capable of undergoing anaphylactic shock.

Bovine/Cattle Allergy

Bovine IgE has been studied extensively, including documentation of its role in parasite infestation, its response to inhalant allergens, and its role in bovine respiratory disease caused by viral and bacterial pathogens (35). All cattle produce IgE antibodies in response to parasite antigens, and total IgE levels correlate with parasite load (36). In general, naturally occurring type I hypersensitivity/allergy in cattle is rare. This species does not develop asthma. We studied an occurrence of apparent allergic rhinitis in a group of cattle and found some positive skin-test reactivity to several inhalant allergens (37). Anaphylactic shock has been observed in cattle after some vaccinations; one report characterized the reagnic (mast cell sensitizing) antibody/IgE response to antigens present in the foot-and-mouth disease vaccine that elicited the adverse response (38, 39). Antigens from baby hamster kidney cells used to grow the vaccine virus were shown to be the target for IgE (reagnic) antibodies present in vaccinated cattle (40). Anaphylaxis has also been shown to occur in response to diethylstilbestrol implants used to promote growth in feedlot cattle (L.G. Gershwin, unpublished data) and in response to other medications. Anaphylaxis in cattle occurred after vaccination for leptospirosis; removal of the causative antigens by washing the *Leptospira* cultures was successful in preventing further incidence of anaphylaxis in vaccinated cattle (41). An experimental vaccine for bovine pneumonia caused by *Mannheimia haemolytica* (previously known *as Pasteurella haemolytica*) consisted of capsular polysaccharide; anaphylaxis occurred in vaccinated cattle (42). Heat-inactivated *Mycoplasma mycoides* has also been reported to induce anaphylaxis in calves (43).

In one study, cattle vaccinated with *Haemophilus somnus* bacterin were found to have made an IgE antibody response (44). In calves vaccinated with formalin-inactivated, alum-adjuvanted bovine respiratory syncytial virus (BRSV), BRSV-specific IgE was found to be present in serum of calves with vaccine-enhanced disease (45, 46). Hypersensitivity to mold spores has been associated with chronic cough in several species, and our group showed that BRSV infection, together with inhalation of *Alternaria* (47) or *Micropolyspora faeni* (48), enhanced this response. These aerosol exposures induced some clinical signs of increased respiratory effort, but not the typical syndrome of asthma as defined in humans and cats.

The immune response of calves to BRSV infection often involves an IgE response to one or more viral antigens, even in the absence of previous exposure by vaccination (49). A synergy has been described between BRSV and *Histophilus somni* (formerly *H. somnus*) in disease pathogenesis. In experimental dual infection, *H. somni*–specific IgE is produced, and the bacteria show enhanced survival in the lung as compared with singly *H. somni*–infected cattle (50, 51).

Anaphylaxis. In ruminants (sheep, goats, and cattle), the respiratory tract is the primary shock organ. Animals cough, have difficulty breathing/dyspnea, and collapse. Upon necropsy, lung edema, emphysema, and hemorrhage are observed. Seratonin (5-hydroxytryptamine), leukotrienes, and kinins are reported to be the mediators of importance (7). In the early 1970s, Eyre et al. (52) described bovine anaphylaxis and the role of histamine and other mediators. In that report, the mediator SRS-A (slow-reacting substance of anaphylaxis) was implicated—currently those mediators are described as leukotrienes (1, 7).

Ovine/Sheep and Caprine/Goat Allergy

Nasal bot hypersensitivity. Sheep and goats are afflicted with a nasal bot ectoparasite, *Oestrus ovis*, which causes nasal-sinusal myiasis. The parasite causes physical trauma in the nasal cavity with its hooks and spines, but it also elicits a local hypersensitivity reaction. Affected tissue contains mast cells, eosinophils, macrophages, and lymphocytes in far greater abundance than normally seen in nasal mucosa of uninfested animals (53). The allergens causing this local reaction are molecules excreted or secreted by the parasite larvae (54).

Allergic asthma (experimentally induced). Asthma is not a natural disease exhibited by sheep. Sheep have been used as an animal model for asthma, initially by aerosolization of antigen from *Ascaris suum*, an intestinal parasite to which the sheep naturally develops IgE antibodies (55), and later by sensitization with other allergens, such as ovalbumin, house dust mite extract, or peanut allergen (56, 57). Some of the early information on mediators of asthma pathogenesis came from studies using the sheep model. There are advantages of sheep over mouse asthma models: They are larger and can thus supply a greater variety of samples over time. Sheep studies have contributed significantly to knowledge of the pathogenesis of allergic asthma. Sheep IgE and hypersensitivity have been reviewed (58).

Porcine/Swine Allergy

Swine have been used as a model for food allergy (59), asthma (60), and allergic dermatitis (61). However, reports of naturally occurring allergic disease in the pig are rare. Porcine IgE and its role in health and disease were reviewed (62). Wilkie and his group (59, 63) have used neonatal pigs as a model for food allergy in humans. Like humans, pigs are large monogastric animals with similar gastrointestinal physiology, which makes them a particularly good model for studies on food

allergy. However, reports in the literature on food allergy in swine are related to allergens that are used to experimentally induce the hypersensitivity. Most commercially raised swine have a regulated diet, and the paucity of reports on naturally occurring food allergy in this species is likely related to the lack of a diverse diet of complex proteins in commercial US swine. Elsewhere, a more diverse diet is often fed to pigs, indicating that this species may show a stronger downregulation of the IgE response to food antigens than other species.

Anaphylaxis. Swine, like the other species, can undergo anaphylactic shock. The main shock organs are the respiratory and intestinal tracts (7). A pig in anaphylaxis will become cyanotic and collapse with systemic hypotension. Histamine is the major mediator. Affected pigs may show dyspnea, coughing, ataxia, patchy erythema, vomiting, and edema of the face and eyelids (58, 64). On necropsy there is pulmonary edema, gastric edema, and effusion into body cavities. As in other species, anaphylaxis in the pig occurs most frequently in response to injected antigen, such as vaccine components. Anaphylaxis has been described in pigs following injections of bacterins for *Bordetella bronchiseptica* and *Haemophilus* and in pigs treated with chloramphenicol (64).

Equine/Horse Allergy

The role of IgE in equine health and disease has been reviewed recently (65). The horse, like other species described herein, produces a strong IgE response to gastrointestinal nematodes. However, respiratory, skin, and food allergy are also seen commonly in this species.

Recurrent airway obstruction. Recurrent airway obstruction (RAO), also known as chronic obstructive pulmonary disease (heaves), is an important allergic disease of stabled horses. Affected horses develop airway inflammation after exposure to moldy hay and straw. Clinical signs include cough, dyspnea, and decreased exercise tolerance. There is a long-standing debate about the role of IgE in this disease (66). IgE antibodies against *Aspergillus fumigatus*, a common fungus, and against mite extracts have been detected in serum of RAO-affected horses, but control horses have also been shown to produce IgE to these antigens (67). Skin testing of RAO-affected horses in some studies has shown positive reactivity early in the course of the disease, indicative of an IgE pathogenesis, but in other studies horses have shown primarily late phase reactions more typical of a type III (IgG-mediated) or intravenous (T cell–mediated) reaction (67). There appears to be a genetic susceptibility to IgE-mediated respiratory responses to environmental antigens in horses and also to the development of RAO (68). Interestingly, warmblood horses with inherited susceptibility to RAO appear to be more resistant to strongylid parasites (69, 70).

Horses with RAO present with coughing and nasal discharge, which escalates over time to difficulty breathing owing to lung inflammation. Lung provocation testing and evaluation of lung lavage fluid for evidence of eosinophils and neutrophils are important diagnostic criteria. Horses with RAO respond to treatment with aerosolized bronchodilators. Removal of stabled horses from the allergenic environment to pasture has also proven to be helpful in management of this condition.

Genetic studies on several warmblood horse families with RAO have shown the genetic link to development of RAO. One study examined several families of warmblood horses and concluded that inheritance most likely followed a mixed pattern (71). In another study, a single-nucleotide polymorphism in the interleukin 4 receptor gene (IL-4R) was significantly associated with RAO (72). Further observations in two warmblood horse families, one healthy and one with high RAO incidence, showed that there were significant differences between mRNA expression of IL-4R in peripheral blood mononuclear cells from RAO-affected horses in the RAO-associated family but

not in the control horse family (72). That IgE-mediated responses, strong Th2 responses, are associated with immunity to parasites creates an intriguing link between mechanisms for RAO development and parasite resistance.

Skin allergy: *Culicoides* hypersensitivity and urticaria. Skin allergy in horses can be caused by a variety of allergens that induce IgE. However, the most common example is hypersensitivity type I/allergy to insect bites, of which salivary antigens of the *Culicoides* mite are the most common allergens. Insect bite hypersensitivity (IBH), also called summer itch, occurs in a variety of breeds and is both seasonal and genetic. It is a chronic/recurrent allergic dermatitis that occurs in affected horses when they are exposed to bites of the *Culicoides* mite. One study examined Swedish-born Icelandic horses and Exmoor ponies—two distinct horse breeds—to evaluate genetic traits that might contribute to IBH. Major histocompatibility class II variants were found to be linked to IBH (73). There have also been studies reporting involvement of non–MHC associated genes. Single-nucleotide polymorphisms in genes coding for interferon γ, transforming growth factor β, and CD14 showed differences between horses affected by and unaffected by IBH (74). The incidence of IBH in Icelandic horses was found to be associated with a change in IL-4-producing T cells, such that during the summer, when horses are symptomatic, interferon γ in peripheral blood mononuclear cells (PBMC) was low and IL-4 was high, whereas during the winter this was not true. Horses not afflicted with IBH had increased production of IL-10 from PBMC (75). There was a higher proportion of IL-4^+ and a lower percentage of $CD4^+$, $CD25^+$, $FoxP3^+$, and IL-10^+ cells in IBH-affected horses, indicating that T regulatory cells may have a role in preventing development of IBH (76). Results of intradermal skin testing for *Culicoides* allergen reactivity in affected versus normal horses showed that sensitization to *Culicoides* allergens occurs frequently in horses in the absence of clinical disease (77).

Recurrent urticaria (hives). Urticaria occurs fairly commonly in horses. Often the inciting cause is not determined. Allergies to feeds, topical applicants (e.g., fly spray, shampoo), or inhalants are often incriminated by evaluation of case history. In one study, the inflammatory infiltrate in recurrent urticaria–affected skin and the cytokine profiles were evaluated (78). The presence of cells and cytokines associated with a T helper type 2 response (eosinophils, tryptase positive/mast cells, IL-4) in skin with lesions compared with unaffected skin provided evidence of an allergic etiology for this condition.

Anaphylaxis. Systemic anaphylaxis occurs in horses, usually after injection of an antigen for which the horse has IgE. In the horse, the shock organs are the respiratory system and the intestine. A horse with anaphylaxis will manifest with respiratory distress and collapse if not treated immediately with epinephrine. Less severe anaphylaxis often presents with colic-like clinical signs. The primary early mediators that are involved are histamine and serotonin (7). Eyre & Lewis (79) made one of the first descriptions of mediators that induce anaphylaxis in horses.

It is not a common occurrence, but some horses become sensitized to constituents of vaccines. When these horses are vaccinated frequently, particularly with vaccines that share the antigens to which the IgE is directed, anaphylaxis can occur. The clinical signs are often subtle initially while sensitization is developing (colic, injection site swelling), but continued vaccination can result in fatal fulminant shock. Our group has demonstrated the presence of IgE antibodies specific to bovine serum albumin, a common protein in viral vaccines (80). The presence of serum IgE specific for proteins in a vaccine, detected by a sensitive ELISA, was not always correlated with clinical signs of anaphylaxis. Although serum from horses that had undergone an allergic response had much higher levels of antibody than that from nonreactive horses, IgE antibodies specific to other

proteins in vaccines, particularly ovalbumin in egg-derived vaccines, have been cited as causing anaphylaxis in vaccinated horses. Off-label treatment of horses with intravenous ivermectin has been associated with anaphylactic shock leading to death in horses, as reported in a Dutch publication (81). Other associations between drugs and equine anaphylaxis include procaine penicillin (82).

ALLERGIC RESPONSES OF COMPANION ANIMALS

Canine Allergy

Canine atopic dermatitis. Allergic skin disease is common in dogs. Atopic dermatitis, one type of allergic dermatitis, is very common and occurs in some dog breeds more than in others. Breeds most commonly affected include Retrievers, Lhasa Apsos, Wire Fox Terriers, West Highland White Terriers, Dalmatians, Poodles, Cocker Spaniels, Setters, Boxers, and Bulldogs; however, mixed breeds can also develop the condition. Atopic dermatitis generally begins fairly early in life and worsens over time. The allergens that cause atopic dermatitis are from the environment and can include molds, pollens, dust mite antigens, feathers, and plants. When the allergens are present only during specific seasons (such as certain weeds and tree pollens), the clinical signs improve on the off season, only to return later when the allergens are again prevalent. Face rubbing and paw licking are the first signs that appear. These are followed by development of erythema, with hair loss, scabs, crusts, and often secondary bacterial or yeast infection. Sometimes there is involvement of the ear canal as well. The allergens may be inhaled and/or absorbed via the percutaneous route. Biopsy of lesions shows accumulation of mast cells and Langerhans cells. Intradermal skin testing is often performed to determine what allergens are causing the disease. This method is usually quite effective—a wheal results at the site of injection of an allergen for which the dog has specific IgE attached to skin mast cells. Many allergic dogs are desensitized with frequent injections of the identified allergens. For many dogs, pruritus is so intense that owners may consider euthanasia. A newly developed drug, a Janus kinase inhibitor, controls the intense itching associated with this condition and has been a great asset to treatment regimes (83). Atopic dogs (those with a genetic predisposition for allergy) have been used as models for human asthma, particularly for studies on neonatal sensitization to ragweed. Young dogs, like children, are more susceptible to aerosol sensitization early in life (84).

Respiratory allergy in dogs. Manifestation of type I hypersensitivity in dogs is more common as a skin disease than as a respiratory allergy. However, in atopic dogs respiratory allergy can occur in response to pollens and other inhalants. It appears that development of type I hypersensitivity to inhaled allergens, such as ragweed, is facilitated by aerosol exposure during neonatal life. This early-life sensitization of atopic canine neonate models is thought to occur in human infants (84).

Food allergy. In dogs, allergy to food constituents can manifest as either gastrointestinal or dermatological signs. The skin allergic response is highly pruritic (itchy) and can become chronic. Allergens involved often include dairy, fish, chicken, and eggs. Determination of the allergen source of a food allergy is best done by performing a food trial using a hypoallergenic diet. The mechanism of IgE-mediated food allergy is as described for other allergic diseases. Sometimes dogs may have an intolerance to a food component, which is not an IgE-mediated allergy. This parallels quite closely the situation in humans. In both species, true allergy must be differentiated from food intolerance. Food allergy has been reviewed recently for both dogs and cats (85).

Anaphylaxis. As with other species, dogs can undergo anaphylaxis. It is most often the result of an injected antigen for which the dog has IgE. However, venoms from insects, drugs, and food components can also act as antigens that elicit anaphylaxis. Anaphylaxis has been reviewed recently in the dog and cat (86). The main shock organ for the dog is the liver; this differs from other species in which the respiratory tract and/or intestine are the primary organs affected. A dog in anaphylaxis will collapse, often after vomiting and having diarrhea. The constriction of hepatic blood vessels causes portal hypertension and pooling of blood in the viscera. On necropsy, the liver is engorged, and there is visceral hemorrhage. Histamine, leukotrienes, and prostaglandins are mediators of anaphylaxis in the dog (7).

Feline Allergic Disease

Feline asthma. Feline IgE has been described, induced experimentally, and evaluated in experimental and actual cases of feline asthma (87). Cats are the only domestic animal to develop asthma spontaneously, experiencing airway inflammation and hyperreactivity just as humans do (88). The allergens that elicit asthma are often identical in both species: Pollens, house dust mites, and cockroaches are some of the more common shared allergens (89). Asthma in the cat often begins with coughing, sometimes referred to as allergic bronchitis; it progresses to episodes of dyspnea, which may be sufficiently serious for use of inhaled drugs to dilate airways. Upon tracheal lavage, there is evidence of eosinophils in airway secretions and increased amounts of mucus. Feline asthma is a significant cause of cat morbidity and a problem for cat owners, but it also provides an excellent model for testing various modalities of treatment that can be applied to both cats and humans. For example, in a recent study, feline asthma was treated with a tyrosine kinase inhibitor (90), demonstrating the utility of using feline asthma to test drugs that might be useful for treating human asthma. Of the many asthma models that have been developed, the cat is the most useful, as it is not a contrived model but shares a parallel clinical syndrome with human asthma.

Feline allergic/atopic dermatitis. Allergy is a common cause of skin disease in cats, as it is in dogs. In one study, the prevalence of atopic dermatitis was 12.5% in the cat population examined (91). The head, face, neck, and ventral abdomen are most commonly affected with pruritic lesions that may develop scabs, erosions, and alopecia. Affected cats are usually allergic to environmental allergens, such as pollens and insects. They are intensely itchy (pruritic), licking and biting at the skin, which results in erythema (raised reddened areas), areas of hair loss, and often secondary infection with bacteria or fungi. Cats, like dogs, can also become allergic to the bite of the flea; this condition is called flea allergy dermatitis. In the latter case, eliminating fleas from the animal and his environment is the most important part of treatment.

Anaphylaxis. In the cat, anaphylaxis resembles more closely that of the horse and pig than the dog. The shock organs are the respiratory tract and the intestines. A cat with anaphylaxis will usually have trouble breathing and may also defecate and vomit. Upon necropsy, the lungs and intestines show edema. The major mediators are histamine, leukotrienes, and serotonin (7).

Feline eosinophilic granuloma complex. Some cats develop a severe debilitating ulcer on the upper lip, which is also referred to as an indolent or rodent ulcer. Upon histology there is an eosinophilic infiltrate in the affected tissue. The exact etiology is not known, but this is thought to be an allergic condition, primarily owing to the tissue eosinophilia (92). Allergy to food or even to fleas has been associated with these ulcers. They respond to elimination of the allergens and corticosteroid treatment. Other manifestations of this condition occur elsewhere on the body—all

part of the eosinophilic granuloma complex. Cats that develop these lesions are usually young to middle age. Oral eosinophilic granulomas have been documented in 16 tigers (*Panthera tigris*), and in some of those cases the lesions were responsive to corticosteroid therapy (93).

ALLERGIC RESPONSES IN OTHER SPECIES

The literature on the occurrence of homocytotropic antibodies and allergic reactivity in a variety of animal and avian species was reviewed 36 years ago (94). For some species, there has been little added to the literature since then.

Marsupials

The Australian marsupial *Setonix brachyurus* (quokka) is reported to have a homocytotropic antibody of the IgG subclass, which can sensitize mast cells for mediator release, causing an allergic-type response (95). However, there is a paucity of information in the literature on hypersensitivity responses in marsupials.

Birds

Reports of type I hypersensitivity are rare in birds but not nonexistent. In one case report, two elf owls were treated successfully with leuprolide acetate for several years to prevent egg laying. After these several years, the annual injection caused the almost immediate death of both birds. The compound was evaluated and found to be potent. The conclusion was that anaphylaxis was a probable cause (96).

In a 1970 study, chickens were immunized with bovine serum albumin. The serum was used in a PCA test on 10-day-old chicks, and positive tests were elicited. The homocytotropic antibody had characteristics more similar to IgG1 of mammals than to IgE. In another study, chickens were administered compound 48/80 (which degranulates mast cells), and an anaphylaxis-type response occurred. Evaluation of tissues showed histamine levels indicating that this mediator was likely involved (96). Another study demonstrated what appeared to be a homolog of human IgE in domestic fowl, including performance of the PCA test and heat liability (97). The role of prostaglandin mediators in chicken anaphylaxis was studied using in vitro assays; effects on pulmonary vasculature were demonstrated (98). Anaphylaxis was also reported in elf owls (99).

Reptiles

Induction of anaphylaxis in the lizard *Caloides versicolor* by sensitization to egg albumen was reported. The performance of splenectomy prior to challenge appeared to have a sparing effect (100). There is also a very old report from 1927 of induction of anaphylaxis in the turtle after sensitization to mammalian serum. Precipitins were present in the serum, which produced a positive PCA response (101).

Comparative Biology of Homocytotropic Antibodies

Homocytotropic antibodies are defined as antibodies that are able to sensitize mast cells and basophils of the same species; this is compared with heterotropic antibodies, which can sensitize these cells in other species. One deviation from this definition is that homocytotropic antibodies can also sensitize very closely related species (rat/mouse; human/monkey; sheep/goat/cow). IgE

antibodies are homocytotropic. Many species also have homocytotropic antibodies that are of the IgG subclass. When IgG homocytotropic antibodies are present in a species (such as IgG1 in the mouse), they sensitize for a shorter time (a few hours), and the ability to sensitize cells is not heat labile. IgE antibodies are heat labile (56°C for 30 min). In one study, we evaluated the ability of bovine IgE to sensitize mast cells in vivo in several species, including the dog, rabbit, and rat. We found that only the sheep and goat served as recipients for the passive sensitization by bovine IgE-containing serum (102).

Environmental Factors that Interact with Genetic Predisposition to Enhance Development of Allergic Reactivity

Environmental air pollutants and allergy. Allergy in the human population has been increasing during the past several decades, particularly in the industrialized nations. Many theories have been proposed to explain the cause of this disproportionate increase in allergy. Causal factors that enhance allergy have emerged. These include ozone, environmental tobacco smoke, and diesel exhaust. Mice have served well as models for the effects of environmental pollutants on allergic reactivity of humans. Experimental evidence from studies in the mouse has shown for each of these that a T helper type 2 immune response is fostered by inhalation of the pollutants and that IgE antibodies to allergens present concurrently are made more readily than in filtered air.

Exposure of mice to 0.5–0.8 ppm ozone enhanced the IgE response to ovalbumin inhaled by mice several days after continuous pollutant exposure. When challenged with intravenous ovalbumin, mice in ozone died from anaphylaxis, compared with those in filtered air, most of which were able to survive despite having received the same allergen inhalation (103). Upon examination, the lungs of ozone- and ovalbumin-treated mice showed significantly more IgE-producing cells than the lungs of mice receiving ovalbumin inhalation after being housed in filtered air (21).

Exposure of Balb/c mice to environmental tobacco smoke (sidestream smoke) and ovalbumin similarly stimulated a strong IgE response to the ovalbumin compared with that in mice exposed to ovalbumin in the filtered air environment (15). In a similar model, we found that the female hormone progesterone exacerbated allergic asthma, including IgE responses to house dust mite allergen, when mice were exposed to sidestream smoke during sensitization (16).

Other pollutants of significance are diesel exhaust particles (DEP), which have been shown to enhance sensitization to allergen. A recently reported study used a mouse model of asthma to demonstrate that exposure of pregnant mice to DEP enhanced development of allergic asthma following ovalbumin sensitization in neonates (104). Affected mice showed enhanced airway inflammation, production of Th2 and Th17 cytokines, and ovalbumin-specific IgE (105). Another example of comparative model usage in allergic disease research used the mouse to study the effect of size of DEPs on induction of the allergic response (106). The fine particles were the ones most inductive of the IgE response.

Viral Infection and Allergy

Animals have been used as models to investigate the hypothesis that infection with RSV predisposes infants to future development of asthma. In one study, BRSV infection of calves was compared with sham infection while calves were exposed to aerosolized ovalbumin for six days. In this study, viral-infected calves not only made a greater ovalbumin-specific IgE response but also showed enhanced production of the Th2 cytokines IL-4 and IL-13 early in infection, with a peak occurring on the fourth day post infection (107). Epidemiological data from human cases showed

that hospitalization with RSV as an infant is a risk factor for development of asthma in childhood (108). Mouse models have also been used to show a relationship between early-life RSV infection and development of allergic asthma (109).

SUMMARY

Allergic responses of the type I hypersensitivity mechanism occur in mammals and birds. The presence of a homocytotropic antibody class is important for elicitation of the mast cell degranulation and mediator release that cause the clinical signs. The studied nonmarsupial mammals all appear to have an IgE-type antibody class, although some have an additional homocytotropic antibody of an IgG subclass. These are distinguishable from IgE by their shorter duration on mast cell receptors and by a lack of heat sensitivity. Naturally occurring allergic syndromes of humans are similar to those in many animal species, with identical mechanisms of sensitization and elicitation. However, researchers have created similar clinical syndromes in several species that do not naturally develop the disease (e.g., asthma in species other than the cat). These animal models have been useful for comparative biology and to address research hypotheses that cannot be tested on human subjects. Overall, the allergic response, as stated earlier, uses the same mechanism as that required for defense against helminth parasites; as such, it is not surprising that the similarity of the response spans many species.

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